ELSEVIER

International Journal of Pharmaceutics 130 (1996) 203–212

international journal of pharmaceutics

An investigation into physical and chemical properties of semi-solid self-emulsifying systems for hard gelatin capsules

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Received 26 June 1995; accepted 24 August 1995

Abstract

Semi-solid systems for hard gelatin capsules, based on polyethyleneglycol 400/non-ionic surfactants/corn oil mixtures, have been examined as an eventual alternative to the classical liquid self-emulsifying systems. A combination of 15% of polyoxyethylene (20) cetyl ether and 15% of polyoxyl (60) hydrogenated castor oil was used as surfactant. The PEG 400/corn oil ratio has been modified and the ability of both surfactants to promote the emulsification of corn oil, at 37°C and under conditions of gentle agitation, has been investigated by a conductimetric method. The water was added at constant flow rate and during emulsification the conductance of the dispersion was monitored continuously which enabled the processes of emulsification to be compared. Fine emulsions were obtained from quaternary systems containing 10–45% of corn oil added to the detriment of PEG 400. When a greater quantity of PEG 400 was substituted by corn oil the efficiency of the surfactants decreased considerably, and very coarse emulsions were obtained. The behaviour of the encapsulated formulations when placed in contact with water at 37°C was in agreement with these observations. The self-emulsifying deficiency observed for these most lipophilic systems has been attributed firstly to the unfavourable PEG 400/corn oil ratio and secondly to an initial restriction in the performance of the surfactants.

Keywords: Self-emulsifying system; Semi-solid mixture; Capsule; Emulsion; Conductimetric method

1. Introduction

Self-emulsifying systems have been described as mixtures of oil and surfactant which emulsify in water under the condition of gentle agitation. A representative composition for oral administration is the mixture of 70% w/w Migliol 812 and 30% w/w Tween 85 (Pouton, 1985). For this purpose efficient self-emulsifying formulations can also be produced by combining hydrophilic and hydrophobic surfactants, such as Tween 80/Span 80 mixtures, in appropriate ratios in suitable oils (Groves and de Galindez, 1976). More complex formulations containing Labrafil M2125 CS, Tween 80 and propylene glycol have also been described (Craig et al., 1993).

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SSDI 0378-5173(95)04296-M

It has been suggested (Pouton, 1985) that these liquid systems can be administered in gelatin capsules and subsequently result in the formation of a fine emulsion within the gastric space. This process may favourably influence the bioavailability of lipophilic drugs or help to avoid the irritancy which can be caused by high concentration of certain drugs.

Recently, Kinget and Van Roelen (1994) have found that a combination of PEG ether of cetyl alcohol (non-ionic surfactant) with PEG 400, added with a small amount of corn oil, increases the bioavailability in rabbits of a poor water-soluble drug, 8-methoxypsoralen, when administered by the oral route. The formulation described is a semi-solid paste suitable for filling hard gelatin capsules. It was therefore of interest to determine whether or not self-emulsifying vehicles with semi-solid aspect could be prepared from the combination of these excipients. Such formulations could be considered as an eventual alternative to the liquid self-emulsifying systems.

However, in our recent study (Halbaut et al., 1995) it has been shown that the initial mixture composed of PEG 400 and PEG ether of cetyl alcohol, both water soluble, was unlikely to be suitable for the incorporation of high percentages of corn oil. A second surfactant, polyoxyl (60) hydrogenated castor oil was therefore added to the formulation, in order to incorporate sufficient quantities of corn oil. The final step of the development of quaternary systems led to the study of the incorporation of corn oil (from 10 to 70% with detriment to PEG 400) to the initial hydrophilic mixture containing 15% of both surfactants and 70% of PEG 400.

In the present study, the ability of both surfactants to promote the emulsification of corn oil in water at 37°C has been examined. The effects of changing the formulation via the variation of PEG 400/corn oil ratio have also been studied.

As a preliminary experiment, the efficiency of the encapsulated formulations was assessed following two criteria: the disintegration time of the capsules and the microscopic appearance of the resulting emulsions. A more detailed investigation of the emulsification process was carried out using a more objective and comparative method which allowed the conductance variations of the systems to be monitored continuously during the addition of water to the emulsifiable materials.

This work also included drop point determination of the pasty bases and microscopic examination of the mixtures before and after water addition. This allowed us to relate the structure of the pasty bases and their melting properties with the aspect of their corresponding emulsions.

2. Conductimetric method: previous considerations

It has been shown (del Pozo and del Pozo, 1982; del Pozo and del Pozo, 1985) that the gradual dilution of the emulsifying concentrate (surfactants + oil) with water added at constant temperature and flow rate, produces conductimetric variations of the system which can be related with the ability of surfactants mixture to promote the emulsification of an oil.

The interpretation of the conductimetric records have been discussed in detail by Barbé et al. (Barbé et al., 1990a; Barbé et al., 1990b). The authors have shown theoretically (1990a) and experimentally (1990b) through equilibrium phase diagrams that the conductimetric records were in accordance with the theoretical basis involving the formation of mesomorphic phases at the oil/water interface. These mesomorphic phases would provide some stabilisation against coalescence to a certain extent by a form of steric hindrance (Tadros and Vincent, 1983).

The essential features of the conductimetric analysis are summarised as follows:

The conductivity of the emulsifying concentrate in practice remains near zero until the addition of a fixed volume (a_i) of water. This volume corresponds to the minimum amount of water required for the initial mixture to disrupt the oil phase into droplets within a condensed ordered phase consisting of molecular associations of surfactant and water.

Thereafter, as the sample is diluted with water the variations in conductivity would reflect the result of two different effects. On the one hand, assuming that the ions supplied by the water with low conductivity can be neglected, the conductiv-

Table 1
Composition of the quaternary systems

Quaternary mixtures	Composition (% w/w)			
	PEG 400	Corn oil	Polyoxyethylene 20 cetyl ether	Polyoxyl 60 hydrogenated castor oil
60/10	60	10	15	15
55/15	55	15	15	15
45/25	45	25	15	15
35/35	35	35	15	15
25/45	25	45	15	15
15/55	15	55	15	15
10/60	10	60	15	15
00/70	00	70	15	15

ity of the system tends to decrease on dilution, whereas the concentration of ions initially present within the mixture decreases. On the other hand, since the thickness of the water layer between the surfactant sheets increases and the viscosity of the mesophase decays, the ions may move more freely within the systems, whereby the conductivity tends to increase.

As a result of these opposite effects, the conductance rises to a maximum as the maximum expansion of the mesophase is reached. This stage of dilution obtained for a volume (a_M) of added water leads to an equilibrium state which corresponds to the saturation of the hydratation capacity of the surfactants and, in this way, to the maximum stabilisation of the system against coalescence.

With further addition of water the conductivity of the system falls. This subsequent increase of the aqueous bulk may be considered as 'free water', forming, with the excess of surfactant, an isotropic media which dilutes the primary emulsion, in principle without interacting with the basic structure of the primary emulsion.

In summary, the overall aspect of the conductimetric records can be related to the ease with which the combination of compounds will form mesomorphic phases at the oil/water interface and also to the ease with which water molecules will penetrate within these mesomorphic phases.

For a number of self-emulsifying systems the ability of an oil solution or dispersion of surfactants to form emulsions spontaneously when added to a considerable excess of water is also connected with these two mechanisms (Groves and Mustafa, 1974; Groves and de Galindez, 1976). It was therefore of interest to examine the conductimetric behaviour of the quaternary mixtures during water addition.

3. Materials and methods

3.1. Materials

The quaternary mixtures were prepared using corn oil (pharmaceutical quality), polyethyleneglycol 400 (PEG 400, USP Grade), polyoxyethylene 20 cetyl ether (Brij 58^R, ICI Atlas) and polyoxyl 60 hydrogenated castor oil (Cremophor RH 60^R, BASF). Polyoxyethylene 20 cetyl ether contains 0.01% of BHA and 0.005% of acid citric as antioxidants. For the emulsification study, water was double-glass distilled.

3.2. Composition and preparation of quaternary mixtures

All quaternary mixtures contained 15% of each non-ionic surfactant, but the remaining (70%) was formed by different PEG 400/corn oil ratio (Table 1). For the sake of better understanding the compositions are repeated in this article by a four-figure reference which indicates, for each mixture, the proportion of PEG 400 and corn oil, respectively.

The mixtures were prepared as follows: the compounds of each formulation were heated together to 60°C. The resulting mixture was placed in a bath at 19°C, under constant stirring (first 10 s at 200 rpm and then at 20 rpm), to cool the mixtures to room temperature. Samples were stored at room temperature in closed glass recipients.

3.3. Conductimetric study

3.3.1. Description of the emulsification device

The emulsification device for the study of conductimetric variations during the process of O/W emulsion formation was mainly based on the apparatus previously described by Barbé et al. (1992), except a few modifications (del Pozo et al., 1992). A sketch of the overall apparatus in horizontal cross-section is shown in Fig. 1.

The emulsification assembly includes a glass recipient, consisting of a water-jacketed, round-bottom vessel, where the oily emulsifiable material is placed. Above, in a fixed position there is a water-jacketed glass column where the aqueous phase will be situated and added at constant flow rate to the emulsifiable material through a calibrated pipette provided with a stopcock. The emulsification vessel and the water supply recipient are both warmed by means of a thermostatic bath kept at constant temperature by a heater unit (Heto mod. T 623). A linear response electronic thermometer (Julabo LC 5) with a PT 100 temperature sensor was used for temperature control.

The stirring of the dispersion was performed by an anchor-shaped paddle (9.5 cm diameter o.d.), rotated at a constant speed by a synchronous motor (Heidolph RZR 1) with adjustable rotational speed.

The conductimetric measurements are carried out in a sampling circuit consisting of a glass tube connected to the bottom of the emulsification vessel and prolonged with a silicone tube (diameters i.d. 6 mm; o.d. 9 mm). The glass tube is located between the two shells of the emulsification vessel. It forms an elbow for removing the possible air bubbles and has a tube-shaped opening for the location of the conductimetric cell (Radiometer PP1042) in a fixed position. The product in process circulates by means of a peristaltic pump and is finally poured again into the emulsification vessel to complete the circuit.

In this way, the conductance of the dispersion was measured continuously during the water addition. The data were processed by the computer provided with a suited software and connected to the conductimeter (Radiometer CDM 3) through an interface (Julabo IF 1).

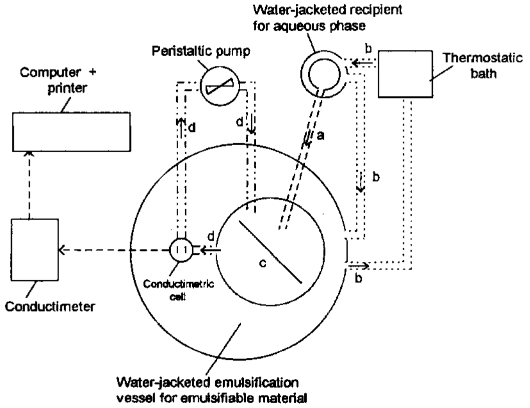

Fig. 1. Sketch in vertical cross-section of the assembly used to examine the conductimetric behaviour of emulsifiable materials during water addition. (a) Calibrated pipette. (b) Warming circuit. (c) Anchor-shaped paddle. (d) Sampling circuit.

3.3.2. Emulsification procedure

Emulsifiable material (120 g, 48 h old), for feeding the sampling circuit, was placed in the emulsification vessel. When the temperature of the product reached 37°C (± 0.1°C), the paddle was rotated at 120 rpm and the peristaltic pump was started at a flow rate of 50 ml/min. Once the temperature and initial conductance of the emulsifiable concentrate were stable, the water at 37°C was added at a constant flow rate of 73 ml/min for 8 min. These experimental conditions were considered to be satisfactory to achieve reproducible conductimetric measurements.

The conductance of the mixture was displayed as a function of time during the emulsification process and the recorded data were printed out at the end of the experiment.

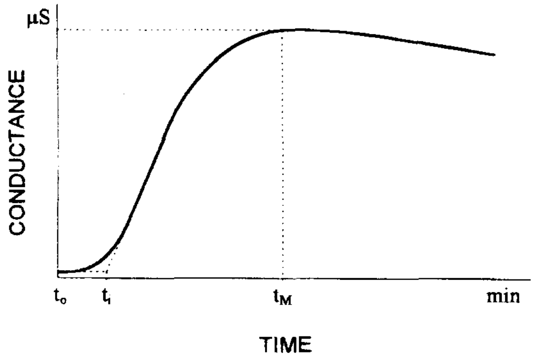

Fig. 2. Typical shape of conductimetric curves associated with the process of dilution of emulsifiable materials.

3.3.3. Determination of conductimetric parameters

Typically, the conductance/time curve (Fig. 2) consists of a lag phase followed by a pseudo-linear phase where the conductance gradually rises to a maximum and finally a linear phase where the conductance progressively decreases.

Mathematical modelling of the conductance curve as a function of time has been considered inappropriate, since the value of the conductance is not a direct measure of the number of particles present or their particle size. However, the conductimetric parameters shown in Fig. 2 give an indication of the ability of the surfactant mixture to produce the emulsification of oil. These characteristic parameters t_i and t_M are, respectively, the beginning of the conductivity increase and the time taken to reach the maximum of conductance. They would correspond to the two above-mentioned stages of dilution and dispersion in the emulsification process, obtained with a_i and a_M millilitres of added water, respectively.

The conductimetric parameters t_i and t_M were expressed as means and standard deviations of triplicates.

3.4. Photomicrographic study

A Zeiss Jenamed microscope was fitted with an automatic device for photomicrographs including an Electronic mod. B100M camera.

Samples of each mixture were examined before and after water addition, by polarized light for emulsifiable masses or light microscopy for their respective emulsions, and photomicrographs were taken in each case.

3.5. Capsule disintegration

The quaternary bases (48 h old) were manually filled into size 2, clear hard gelatin capsules (Elanco, Qualicaps) using glass syringes. The fill mass was set to 250 mg.

Disintegration time of the capsules were determined using an Erweka Z T3 apparatus, fitted with Erweka P control heater, as in Eur. Ph. (monograph V.5.1.1., 1980). 950 ml of distilled water at 37 °C was employed as disintegration medium. Considering the turbidity of the systems, only two capsules were used instead of six, in order to facilitate the determination. All studies were repeated three times, with good agreement between measurements (difference between values < 13 s).

Photomicrographs of the disintegration media were taken at the end of the same experiments but carried out with six capsules, which enabled the microscopic appearance of the resulting emulsions to be compared.

3.6. Drop point determination

Drop point of the mixtures was determined using a Mettler FP 900 apparatus. Samples (48 h old) placed in the device were initially heated to 27°C, held at this temperature for 1 min, then heated at 1°C/min. Drop point values were automatically displayed by the device.

Each drop point represents an average of three measurements and repeat studies showed good reproducibility (difference between values < 0.3°C).

4. Results and discussion

4.1. Preliminary studies

Preliminary studies were conducted as a first approach to the physical and chemical properties of quaternary mixtures. They included drop point assessment and capsule disintegration experiments. The results are listed in Table 2.

In the preliminary study of capsule disintegration, it was found that in all cases the capsules were ruptured within 1 min 10 s (±10 s) after immersion in distilled water and subsequently the contents began to empty out and emulsify. However, comparison of disintegration times gave the first evidence that the emulsifying properties of the quaternary systems depended on the PEG 400/corn oil ratio. For the bases containing 10–45% of corn oil, the disintegration time was about 2 min 30 s and it was approximately 1 min longer for those containing more than 50% of corn oil, due to the slower dispersion and emulsification of the contents of the capsules.

Microscopic examination of emulsions formed by quaternary bases showed that only those containing 10–45% of corn oil were efficient self-emulsifying systems since the bulk of the oil was dispersed as fine droplets (< 1–3 μm). The other mixtures, in contrast, produced visibly poor emulsions with droplets > 10–50 μm and high polydispersity.

The examination of the results of drop point determination (Table 2) gives an additional evidence emphasizing the influence of PEG 400/corn oil ratio on the properties of the quaternary mixtures.

For mixtures containing 10–45% of corn oil added to detriment of PEG 400 the drop point remains close to 36°C, whereas for the others (>45% of corn oil) it is approximately 1°C higher than the former. These results are in close agreement with those obtained previously from DSC study and could be attributed to the difference between the structure of the pasty bases (Halbaut et al., 1995).

Table 2
Results of preliminary studies

Quaternary mixtures	Capsule disintegration time (min, s)	Mixture drop point (°C)
60/10	2′20″	35.7
55/15	2′20″	35.8
45/25	2′25″	36.0
35/35	2′25″	36.1
25/45	2′30″	36.1
15/55	3′35″	37.0
10/60	3′45″	36.9
00/70	3′45″	37.2

On the other hand, drop point values indicate that although the quaternary systems under study are semi-solid at room temperature they become mobile at 37°C. As a result, since these emulsifying materials are composed of PEG 400 as the hydrophillic liquid, corn oil as the lipophilic liquid and a high percentage (30%) of hydrophilic emulsifiers, they turn into fluid non-aqueous emulsions at 37°C under stirring. This is under the conditions of the conductimetric study prior to water addition.

4.2. Conductimetric study

Further evidence in support of the above-mentioned findings concerning the different behaviour of the pasty mixtures was obtained from the results of conductimetric study summarised in Table 3. Quaternary compositions containing 10–45% of corn oil when added with water spontaneously formed an emulsion at 37°C: there was no lag time t_i. Assuming that prior to water addition the bulk of corn oil was already dispersed in the water-soluble medium consisting of PEG 400/surfactants mixture, it was not surprising that the water tended to penetrate rapidly into such oil/polyol systems.

On the other hand, for these oil/polyol systems when the concentration of corn oil was increased from 10 to 45% to the detriment of PEG 400, the values of t_M decreased. The composition of the resulting emulsions at t_M was determined (see Table 2) and transferred to a pseudoternary diagram (Fig. 3). As the ratio water/PEG 400 + surfactants remained approximately constant for the emulsions concerned, the corresponding points appear aligned on the normal to the base water/PEG 400 + surfactants in the triangle of Fig. 3. This result indicates that as the hydrophilic content was decreased in the initial mixture, proportionally less water (a_M) was required to reach the equilibrium state corresponding to maximum hydratation of the systems. This is in agreement with the previous study of Barbé et al. (1990b).

Table 3
Values of the parameters t_i and t_M (mean ± S.D., n = 3) associated with the conductimetric response of quaternary mixtures containing different proportion of PEG 400 and corn oil, when gradually diluted with water at 37°C, and composition of the resultant dispersions at times t_i and t_M

Quaternary mixtures	Parameters (s)		Dispersion composition at t_i (% w/w)				Dispersion composition at t_M (% w/w)			
	t_i	t_M	PEG 400	Corn oil	Surfactant mixture	Water	PEG 400	Corn oil	Surfactant mixture	Water
60/10	—	234 ± 15	—	—	—	—	17.8	3.0	8.9	70.3
55/15	—	239 ± 10	—	—	—	—	16.1	4.4	8.8	70.7
45/25	—	219 ± 9	—	—	—	—	14.0	7.8	9.2	69.0
35/35	—	196 ± 9	—	—	—	—	11.7	11.7	10.1	66.5
25/45	—	175 ± 11	—	—	—	—	9.0	16.2	10.8	64.0
15/55	23 ± 3	181 ± 12	12.2	44.6	24.3	18.9	5.3	19.4	10.6	64.7
10/60	114 ± 6	254 ± 11	4.6	27.8	13.9	53.7	2.8	16.8	8.4	72.0
00/70	132 ± 14	286 ± 16	0.0	29.9	12.8	57.3	0.0	17.9	7.7	74.4

(—) lag time not detected.

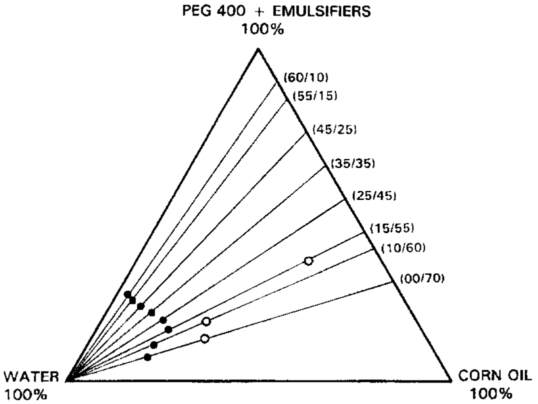

Fig. 3. Pseudoternary diagram showing the dilution line for systems containing different proportions of PEG 400 and corn oil, gradually diluted with water at 37°C, and the composition of the resultant dispersions at t_i (○) when detected and at t_M (●). The remaining 30% is accounted for by surfactants.

However, for quaternary systems containing more than 50% of corn oil, lag time t_i was detected during water addition. Moreover, t_i lengthened considerably as the oil percentage was increased (Table 3). These effects together with the increase in viscosity observed at the beginning of the dilution provided clear evidence of phase inversion in these cases (Rhodes, 1990). Therefore, the quaternary bases containing more than 50% of corn oil can be considered, before dilution, as polyol/oil systems. In addition, for these systems time t_M also lengthened as the oil content was increased to the detriment of PEG 400, that is to say, as the mixture became more lipophilic and the proportion of the compound that facilitated the water penetration was decreased. Under these circumstances, the lengthening of both t_i and t_M reflects the increasing difficulty of emulsification through phase inversion. As a result, the corresponding points are displaced towards a more aqueous area in the pseudoternary diagram (Fig. 3). Such conductimetric effects have been previously reported for other emulsifying mixtures (Barbé et al., 1990b).

4.3. Photomicrographic appearance before and after water addition

When the oil/polyol systems were examined by microscopy at room temperature under polarised light, those containing 10–25% of corn oil had a homogeneous appearance (Fig. 4, upper). Under the conditions of the conductimetric study, these systems provided fine emulsion with particles < 3 μm in diameter (Fig. 5, upper).

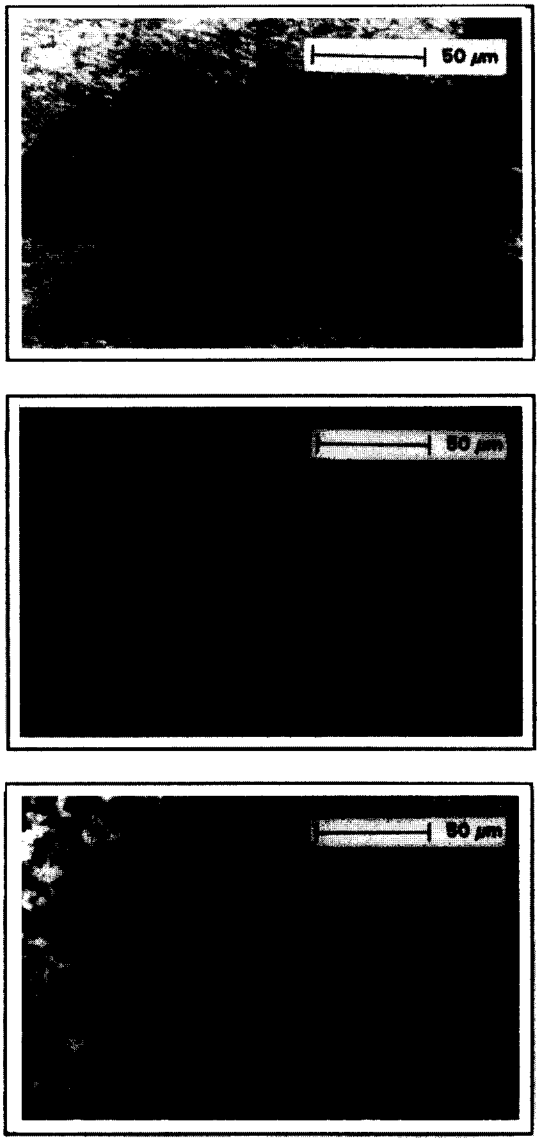

Fig. 4. Photomicrographs of quaternary mixtures containing 15% (upper), 35% (middle) and 55% (bottom) of corn oil, respectively.

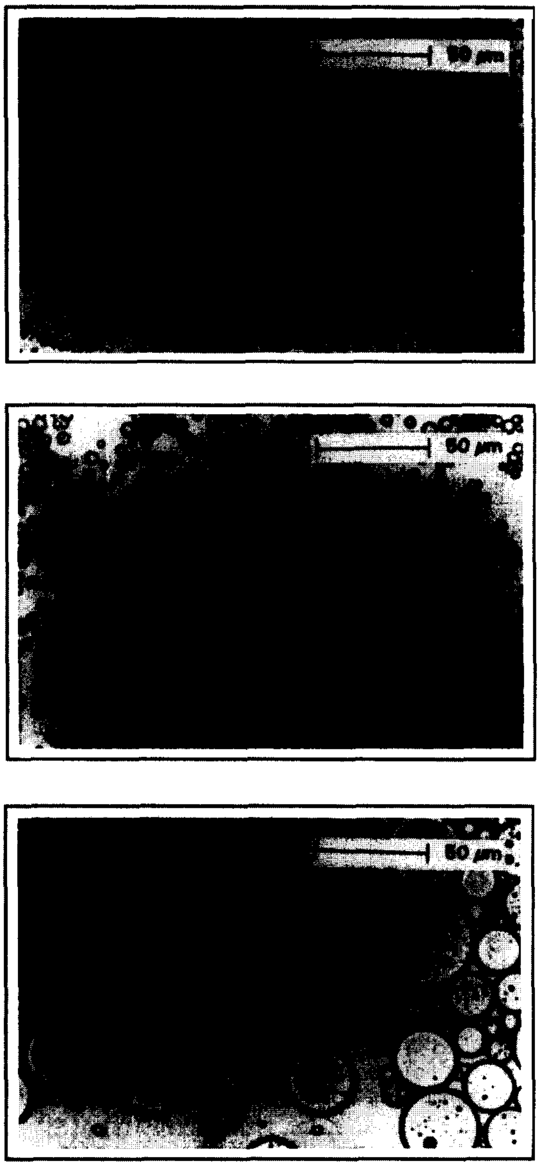

Fig. 5. Photomicrographs of emulsions produced by quaternary mixtures containing 15% (upper), 35% (middle) and 55% (bottom) of corn oil, respectively.

When the proportion of corn oil was increased from 35 to 45% to the detriment of PEG 400, the masses became more heterogeneous (Fig. 4, middle). The bulk of corn oil appears dispersed as fine droplets and finely dispersed solid aggregates can be distinguished. These solid formations have been identified as surfactant aggregates, mainly formed by polyoxyethylene 20 cetyl ether (Halbaut et al., 1995). These oil/polyol systems, which easily emulsified in the conductimetric device, as expected, were also capable of forming fine emulsion, though with a larger particle size (Fig. 5, middle).

All the polyol/oil systems had a heterogeneous appearance under polarised light, with numerous and large aggregates of surfactants (Fig. 4, bottom). These systems emulsified with difficulty in the emulsification device and, as expected, produced extremely coarse dispersion consisting of large particles (10–100 µm) (Fig. 5, bottom).

In summary, the microscopic examination of the quaternary mixtures before and after the water addition again emphasized the difference between the oil/polyol systems and polyol/oil ones.

Finally, the emulsions obtained at the end of the conductimetric analysis were compared with those formed previously by the self-emulsification of the encapsulated formulations. Obviously there were significant differences due to the different experimental conditions. However, both methods indicate that oil/polyol systems under study produce fine emulsions, while polyol/oil systems form coarse polydispersed emulsions.

These differences can be related not only to the PEG 400/corn oil ratio but also to the state of the surfactants within the systems prior to water contact. Taking into account the structure of the quaternary systems and their melting properties, it is reasonable to assume that the oil/polyol systems became practically melted at 37°C, a fact which would favour the self-emulsification process. In contrast, for polyol/oil systems, it is likely that aggregates of surfactants may remain partially unmelted. This may initially restrict the performance surfactants which represents an additional difficulty for self-emulsification. This is because the unmelted surfactant aggregates have to dissolve first in water.

5. Conclusions

Physical and chemical properties of PEG 400/non-ionic surfactants/corn oil mixtures have been assessed from conductimetric analysis, drop point determination and photomicrographic study before and after water addition. Data have been presented which demonstrate firstly the usefulness of the techniques in examining the properties of such semi-solid self-emulsifying systems and secondly the effects of changing the formulation on those properties.

On the basis of the results, it is concluded that the proposed conductimetric technique may allow a greater understanding of the self-emulsifying process, as the information gained from the composition of the resulting dispersion at different stages of dilution can explain, through the ternary diagram, the ease or difficulty with which water penetrates into the systems.

Finally, it should be emphasized that drug inclusion may modify the properties of the mixtures under study, as reported for other self-emulsifying systems (Craig et al., 1993). Further work is required in order to examine the problems that may be associated with the use of these mixtures, for instance toxicity and instability with particular regard to oxidation (Rhodes, 1990), since vegetable oils are liabled to undergo autooxidation.

References

Barbé, R.C., del Pozo, C.A., Faulí, T.C. and del Pozo, O.A., Sistemas emulsionados O/A en el diagrama ternario de equilibrio de fases (I). Interprétacion teórica del significado de los parámetros conductimétricos. *Circ. Farm.*, 307 (1990a) 209–220.

Barbé, R.C., del Pozo, C.A., Faulí, T.C. and del Pozo, O.A., Sistemas emulsionados O/A en el diagrama ternario de equilibrio de fases (II). Estudio experimental de los parámetros conductimétricos en la formación de emulsiones estables de parafina líquida elaboradas con emulsiones no iónicos. *Circ. Farm.*, 308 (1990b) 305- 318.

Barbé, R.C., Halbaut, B.L., del Pozo, C.A. and Faulí, T.C., Evolución de los procedimientos conductimétricos aplicados al estudio de emulsiones. *Circ. Farm.*, 313 (1992) 43–54.

Craig, D.Q.M., Lievens, H.S.R., Pitt, K.G. and Storey, D.E., An investigation into the physicochemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. *Int. J. Pharm.*, 96 (1993) 147–155.

del Pozo, C.A. and del Pozo, O.A., Aplicación de la conductimetría al estudio de formación y estabilidad de emulsiones fluidas O/A preparadas con emulgentes no iónicos. *Ci. Indust. Farm.*, 1 (1982) 309–314.

del Pozo, C.A. and del Pozo, O.A., Gráficas conductimétrica del proceso de formación de emulsiones de parafina formuladas con emulgentes no ionógenos. Paramétros conductimétricos y HLB requerido. *Ci. Indust. Farm.*, 4, (1985) 141–148.

del Pozo, C.A., Barbé, R.C., Halbaut, B.L. and Faulí T.C., Preformulation and design of pharmaceutical and cosmetic emulsions by conductimetric technique. *6th International Conference on Pharmaceutical Technology*. APGI. Paris 1992. Volum V, 102–110.

European Pharmacopoeia, 2nd edn. Maisonneuve S.A., 1990.

Groves, M.J. and Mustafa, R.M.A., Measurement of the 'spontaneity' of self-emulsifiable oils. *J. Pharm. Pharmac.*, 26 (1974) 671–681.

Groves, M.J. and de Galindez, D.A., The self-emulsifying action of mixed surfactants in oil. *Acta Pharm. Suec.*, 13 (1976) 361–372.

Halbaut, L., Barbé, C., Del Pozo C.A., Cadenato, A., Salla, J.M., Bases semi-solides destinées au remplissage de gélules contenant du PEG 400 et une huile végétale. Caractérisation physico-chimique. S.T.P. *Pharma Sci.*, 5 (1995) 208–215.

Kinget, R. and Van Roelen, R., The absorption of 8-methoxypsoralen from lipid-containing semisolid matrices for oral use: a prospective study in rabbits. *J. Dermatol. Treat.*, 5 (1994) 25–28.

Pouton, C.W., Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. *Int. J. Pharm.*, 27 (1985) 335–348.

Rhodes, C.T., Disperse systems. In Banker G.S. and Rhodes C.T. (Eds.), *Modern Pharmaceutics*, 2nd edition revised and expanded, Marcel Dekker, New York, 1990, pp. 327–354.

Tadros, T.F. and Vincent, B., Emulsion stability. In Becher, P. (Ed.), *Encyclopedia of Emulsion Technology*, Vol. 1, *Basic Theory*. Marcel Dekker, Inc., New York, 1983, pp. 129–285.