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Microcalorimetric study of microemulsions as potential drug delivery systems. II. Evaluation of enthalpy in the presence of drugs

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Summary

Two oil-in-water microemulsions with the same oil/water/co-surfactant (isopropylmyristate, water, 1-butanol), but differing in the surfactant (Aerosol OT or egg lecithin) were studied. The additions of butanolic solutions of two drugs at different lipophilicity (menadione and prednisone) to the same mixture of water/oil/surfactant were examined. The ΔH values were substantially similar to those obtained in the absence of any drug, except in the case of menadione which gave less endothermic values in the microemulsion containing lecithin as a surfactant.

Introduction

The use of microemulsions – clear systems at infinite stability – as therapeutic dosage forms was predicted by many authors (Friberg and Bothorel, 1987; Ziegenmeyer and Führer, 1980). Interesting results were obtained in vitro and in vivo (Martini et al., 1984). Microemulsions could allow a prolonged drug release, influence transdermal and topical absorption and could also be used for parenteral administration (Herrmann et al., 1984).

A question to be answered is whether the presence of a drug could influence the stability of a microemulsion. The evaluation of the enthalpies associated with the process of microemulsification can give information about stability.

In the first part of this work (Fubini et al., 1988) the calorimetric evaluation of the enthalpy changes when different amounts of co-surfactant were added to a fixed mixture of 3 other components up to the point of microemulsion formation and the above was performed. Two microemulsions with the same oil/water/co-surfactant but differing in the surfactant (lecithin or Aerosol OT) were examined. A linear relationship between ΔH and molar fractions of added co-surfactant was found at the molar ratios below the one required for microemulsion formation: a marked variation in endothermicity was found at the point corresponding to microemulsion formation.

The aim of the second part of the present work was to examine the influence that a drug, as the

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fifth component, can produce on the calorimetric behaviour of the microemulsions.

Two drugs with different lipophilicities (Leo et al., 1971), menadione and prednisone, were chosen. The calorimetric evaluation was performed as previously reported (Fubini et al., 1988), but now adding increasing amounts of butanolic solutions of the drug to the fixed mixture of the other 3 components (oil, water, surfactant).

Experimental

Materials

Isopropylmyristate (ISM) (98% pure), 1-butanol (reagent grade), menadione (2-methyl-1-4-naphtochinone) were from Merck; prednisone (17α,21-dihydroxy-pregna-1,4-diene-3,11,20-trione) was from Aldrich; water was freshly distilled; bis-2(ethyl-hexyl)sulphosuccinate sodium salt (AOT), wax-like (98% pure) was from Merck and was further purified (Eicke, 1979); lecithin from egg yolk (crude) was also from Merck and was purified as previously described (Gallarate et al., 1988).

Apparatus

A microcalorimeter Calvet type (C80 Setaram) was used, which was described in part I of the work.

Methods

Microemulsions

The oil-in-water type microemulsions described in the previous work were considered: the compositions were the following.

Microemulsion no. 1: ISM = 19.3% w/w (x_1 = 0.02011); water = 58.4% w/w (x_2 = 0.92518); AOT = 10.1% w/w (x_3 = 0.00644); 1-butanol = 12.2% w/w (x_4 = 0.04827).

Microemulsion no. 2: ISM = 7.5% w/w (x_1 = 0.00853); water = 53.3% w/w (x_2 = 0.92715); egg lecithin = 26.6% w/w (x_3 = 0.01137); 1-butanol = 12.6% w/w (x_4 = 0.05295).

The same microemulsions were also obtained in the presence of the drugs, prednisone and menadione, which were previously dissolved in butanol. The maximum achievable drug concentration in the systems was 1.4×10^{-3} M for prednisone and 1.8×10^{-2} M for menadione. The resulting microemulsions were tested for stability as previously described (Gallarate et al., 1987; Hansrani, 1980).

Experimental cells

Calorimetric cells were accurately described in part I (Fubini et al., 1988). The lower vessel of the cell, always filled with the emulsified system, was closed by a cover and the upper vessel contained a butanolic solution of the drug. The mixing of the reactants, initially separated, was possible by the automatic continuous alternative reversing of the calorimeter (Fournier et al., 1988).

Examined systems

In the description of the studied systems, the amount of every component was indicated as follows: molar fractions x^* were employed by considering equal to unity the sum of the molar fractions only at the microemulsion formation. The molar fraction of the drug was negligible by comparison with the other components.

The experiments were performed by adding increasing amounts of a butanolic solution of the drugs to the emulsified systems up to microemulsion formation. The experiments were planned in order to keep constant the concentration of the drug in each final system, i.e. menadione 1.8×10^{-2} M, prednisone 1.4×10^{-3} M.

Microemulsion no. 1

Addition of butanolic solutions of prednisone to the mixture: ISM (x_1^* = 0.02011), water (x_2^* = 0.92518), AOT (x_3^* = 0.00644): (a) in the amount exactly required to obtain the microemulsion (x_4 = 0.04827); and (b) in defect (x_4^* from 0.01460 to 0.03372). Final concentration of the drug = 1.4×10^{-3} M.

Addition of butanolic solutions of menadione to the same mixture: (a) in the amount exactly required to obtain the microemulsion (x_4 = 0.04827); and (b) in defect (x^* from 0.01460 to 0.03372). Final concentration of the drug = 1.8×10^{-2} M.

Microemulsion no. 2

Addition of butanolic solutions of prednisone to the mixture: ISM ($x_1^* = 0.00863$), water ($x_2^* = 0.92715$), lecithin ($x_3^* = 0.01137$), 1-butanol ($x_4^* = 0.01590$): (a) in the amount exactly required to obtain the microemulsion ($x_4 = 0.05295$); and (b) in defect (x_4^* from 0.02968 to 0.04558). Final concentration of the drug: 1.4×10^{-3} M.

Addition of butanolic solutions of menadione to the same mixture: (a) in the amount exactly required to obtain the microemulsion ($x_4 = 0.05295$); and (b) in defect (x_4^* from 0.02657 to 0.04558). Final concentration of the drug = 1.8×10^{-2} M.

A third of the total amount of butanol had to be added to the other 3 components of microemulsion no. 2 before mixing in the calorimeter, because of the lowering of the viscosity of the system.

All the experiments were performed at a fixed temperature: 37 ± 0.01° C.

Results

The presence of prednisone or menadione did not influence the stability of either of the microemulsions studied; besides, even the minimum amount of co-surfactant required to obtain transparent systems did not vary as a consequence of the presence of the drugs.

The addition of butanol (in which prednisone or menadione were previously dissolved) to the examined emulsified systems was an endothermic process for both microemulsions studied, i.e. the partial molar enthalpy, always referring to the added moles of butanol was above zero.

Microemulsion no. 1

In Fig. 1 the partial enthalpies obtained by addition of increasing amounts of butanolic solutions of prednisone or menadione to the system no. 1 (water/ISM/AOT) are reported as a function of the total number of moles of butanol in the system. The dotted line represents the trends of the ΔH values obtained when no drug was present in the system. An almost linear relationship between the measured ΔH and the moles of butanol added was noted at the molar fractions of co-surfactant below the one required for microemulsion formation. An identical trend could be noted for both drugs examined. The partial molar heat, obtained from the slopes of the straight lines was 1.32 kJ · mol^{-1} in the presence of prednisone and 1.30 kJ · mol^{-1} in the presence of menadione. The ΔH value corresponding to microemulsion formation deviated from linearity towards a lower endothermicity; respectively 26% and 23% for prednisone and menadione.

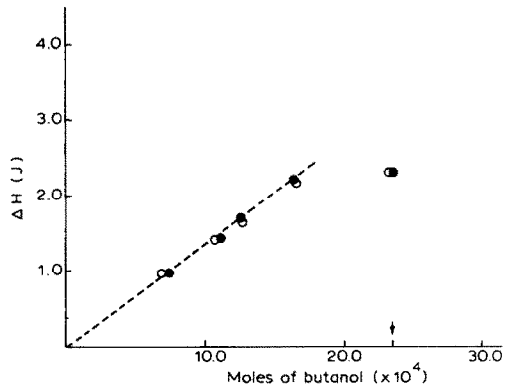

Fig. 1. Enthalpies of addition of butanolic solutions of drugs to a system: water/ISM/AOT. Abscissa: moles of butanol. Ordinate: enthalpies of addition. ------, in the absence of any drug; ●, in the presence of prednisone; ○, in the presence of menadione. ↓, moles of butanol required to obtain the microemulsion.

TABLE 1

Partial molar enthalpies of addition of butanolin solutions of prednisone and menadione to a system of water/ISM/AOT up to microemulsion formation

Moles of butanol in the microemulsion = 23.5×10^{-4} ($x_4 = 0.04827$). Molar fractions of butanol in the final systems: a = 0.01460; b = 0.02241; c = 0.02590; d = 0.03372; e = 0.04827.

Moles butOH ($\times 10^4$)	ΔH_m (kJ · mol^{-1} ± 0.05)	
	Prednisone	Menadione
7.1 a	1.34	1.36
10.9 b	1.28	1.29
12.6 c	1.33	1.27
16.4 d	1.34	1.28
23.5 e *	0.98	1.00

* Microemulsion formation.

When no drug was present in the system the partial molar heat of addition of butanol below the concentration required to reach the microemulsion was 1.35 kJ · mol^{-1}; in that case the deviation from linearity at microemulsion formation was 29% towards the lower endothermicity. The molar enthalpies obtained at any addition of increasing amounts of butanolic solutions of both drugs, yielding either concentrations below those for microemulsion formation up to the amount required to achieve the microemulsion, are reported in Table 1.

Microemulsion no. 2

In Fig. 2 the partial enthalpies obtained by addition of different amounts of butanolic solutions of prednisone or menadione to the emulsified system no. 2 (water/lecithin/ISM/butanol) to obtain the microemulsion are reported as a function of the total moles of butanol. The dotted line represents the trend of the ΔH values previously obtained in the same experimental conditions when no drug was present in the system (Fubini et al., 1988). For both drugs examined, as in the previous case, a linear relationship occurred between the measured ΔH and the moles of butanol added, as well as the expected deviation towards lower endothermicity.

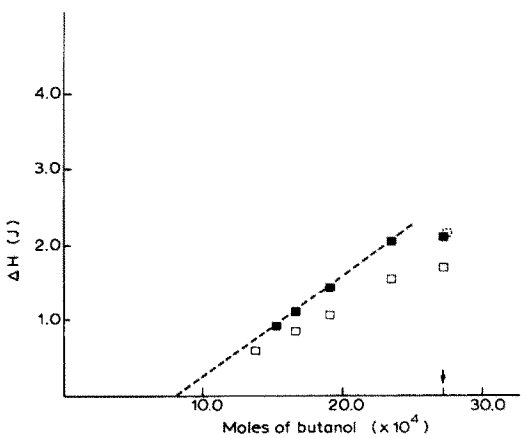

Fig. 2. Enthalpies of addition of butanolic solutions of drugs to a system: water/ISM/lecithin/butanol. Abscissa: moles of butanol. Ordinate: enthalpies of addition. ------, in the absence of any drug; ■, in the presence of prednisone;, □, in the presence of menadione. ↓, moles of butanol required to obtain the microemulsion.

TABLE 2

Partial molar enthalpies of addition of butanolic solutions of prednisone and menadione to a system of water/ISM/lecithin/butanol up to microemulsion formation

Moles of butanol in the microemulsion = 27.3×10^{-4}. Molar fraction of butanol in the initial system = ($x_4^* = 0.01590$) = 8.2×10^{-4}. Molar fractions in the final systems: a = 0.02657; b = 0.02968; c = 0.03181; d = 0.03704; e = 0.04558; f = 0.05295.

Moles butOH ($\times 10^4$)	ΔH_m (kJ·mol^{-1} ± 0.05)	
	Prednisone	Menadione
5.5 a	–	1.15
7.1 b	1.38	–
8.2 c	1.34	1.07
10.9 d	1.35	1.01
15.3 e	1.37	1.01
19.1 f *	1.11	0.91

* Microemulsion formation.

In the presence of prednisone (Fig. 2), the partial molar heat of addition of butanol "in defect" obtained from the slope of the straight line was 1.36 kJ · mol^{-1}; the ΔH value corresponding to the addition of butanol in the exact amount to obtain the microemulsion was 18% less endothermic than that value.

When menadione was present in the system, the partial molar heat of addition of butanol "in defect' was 1.06 kJ · mol^{-1} and the deviation from linearity occurring when the amount of butanol added caused microemulsion formation was 14%. By comparison with what was found in the absence of any drug, the partial molar heat of addition was definitely lower, 1.06 kJ · mol^{-1} as opposed to 1.39 kJ · mol^{-1}, whereas the percentage deviation at the microemulsion formation was more or less the same.

The molar enthalpies obtained at every addition of particular amounts of butanolic solution of both drugs are reported in Table 2.

Discussion

Two lipophilic drugs were chosen to observe the calorimetric behaviour of microemulsive sys-

tems. The lipophilicity of the drugs enabled the achievement of sufficiently high concentrations of drugs in the internal phases. Two drugs with different lipophilicity (log $P = 2.20$ for menadione and 1.46 for prednisone) (Leo et al., 1971) were chosen in order to emphasize possible differences in the calorimetric studies. Drugs without dissociable groups were studied to limit interactions with the surfactants. High concentrations of drugs in the internal phase were required to observe if the microemulsions were still formed in a drug-saturated system and if a variation in the calorimetric behaviour could be shown in the presence of a drug compared to a system in its absence. Both the drugs gave stable microemulsions: no change in the composition of the microemulsions was necessary. The concentrations obtained were near saturation.

Previously (Fubini et al., 1988), the addition of butanol to the other 3 components of the microemulsion showed that the molar enthalpy, ΔH, upon addition of butanol in defect was quite similar in both microemulsions; the differences between lecithin and AOT did not markedly influence the values of ΔH. A marked variation in the linearity (minimal in endothermicity) was found at the microemulsion formation in both cases.

As can be noted from Tables 1 and 2 and Figs. 1 and 2, a linear relationship between ΔH and molar fraction of added butanol were found at molar ratios below the one required for the microemulsion formation; a marked variation in the linearity was found at the microemulsion formation. The ΔH values obtained in the presence of the drugs were substantially similar to those obtained in their absence, except in the case of menadione in the microemulsion containing lecithin as a surfactant, which gave less endothermic values. In the microemulsion without any drug, the presence of different surfactants did not markedly influence the values of ΔH; the variation between the two different microemulsions, found only in the case of menadione, indicated that some exothermic phenomenon took place, alongside the other phenomena provoked by the addition of butanol.

As the linearity of the ΔH values vs butanolic solutions plot was maintained, the difference in the slope could be ascribed only to an interaction of the drug with some microemulsion components. This phenomenon could be therefore ascribed to formation of some complexes or aggregates between lecithin and menadione, as the other components did not vary from one case (Microemulsion no. 1) to another (Microemulsion no. 2).

The present work indicated, on the one hand, that the stability on the two microemulsions was not changed by the presence of the drugs, on the other, that microcalorimetry was able to evidence weak interactions between components not easily detectable with other techniques.

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References

Eicke, H.F., On the cosurfactant concept. *J. Colloid Interface Sci.*, 68 (1979) 440–450.

Fournier, J., Fubini, B., Bolis, V. and Pezerat, H., Thermodynamic aspects in the adsorption of polynuclear aromatic hydrocarbons on chrysotile and silica – possible relation to synergistic effects in lung toxicity. *Can. J. Chem.*, (1988) in press.

Friberg, S.E. and Bothorel, P.B., *Microemulsions: Structure and Dynamics*, CRC Press, Lancaster, 1987, pp. 153–172.

Fubini, B.,Gasco, M.R. and Gallarate, M., Microcalorimetric study of microemulsions as potential drug delivery systems. I. Evaluation of enthalpy in the absence of any drug. *Int. J. Pharm.*, 42 (1988) 19–26.

Gallarate, M., Gasco, M.R. and Trotta, M., Influence of octanoic acid on membrane permeability of timolol from solutions and from microemulsions. *Acta Pharm. Technol.*, 34 (1988) 102–105.

Hansrani, P.K., *Studies on Intravenous Fat Emulsions*, Ph. D. thesis, Nottingham University, 1980.

Herrmann, U., Voege, H., Andrews, P., Zembrod, A. and Klaas, M., *Pharmaceutical Microemulsions*, (Bayer-A-Q) Ger. Offen. DE 3, 315, 805 (CL A61K9/10) 08 Nov 1984, Appl. 30 Apr 1983.

Leo, A., Hantsch, C. and Elkins, D., Partition coefficients and their uses. *Chem. Rev.*, 71 (1971) 525–616.

Martini, M.C., Bobin, M.F., Flandin, H., Cailland, F. and Cotte, J., Role des microemulsions dans l'absorption percutanee de l'α-tocopherol. *J. Pharm. Belg.*, 39 (1984) 348–354.

Ziegenmeyer, J. and Führer, C., Mikroemulsionen als topische Arnzeiformen. *Acta Pharm. Technol.* 26 (1980) 273–725.