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Calorimetric investigation of the interaction between α,β-poly(*N*-hydroxyethyl)-DL-aspartamide and surfactants

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Summary

The enthalpic effect due to the interaction between α,β-poly(*N*-hydroxyethyl)-DL-aspartamide (PHEA) and sodium dodecyl sulfate, cetyltrimethylammonium bromide, and octylphenoxypolyethoxyethanol in aqueous solutions, as a function of the surfactant concentration, was measured by the calorimetric technique. Below the critical micellar concentration, no enthalpic effect was measured. At higher concentrations, the enthalpic effect, exothermic for the interaction of PHEA with the anionic micelles and endothermic for that with the cationic and nonionic micelles, was interpreted in terms of the binding of micelles to the polymeric chain. The influence of a simple electrolyte (sodium chloride) on the PHEA-micelle interaction was also investigated and is discussed here.

In recent years the synthesis of polymer-drug adducts has received increasing attention from numerous workers, since using these adducts as therapeutic agents, the side-effects of drugs, due to hyperdosage, can be minimized while ensuring a prolonged action and controlled drug delivery to target cells or tissues (Kydonieus, 1980; Anderson and Kim, 1986). In addition, attachment of drugs to hydrophilic macromolecular carriers can improve their biostability, biosolubility and pharmacokinetics (De Duve et al., 1974; Sinkula, 1978).

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The main properties that a polymeric carrier may possess are: biodegradability, water solubility and non-toxicity. In particular, hydrophilic polymers can be used in controlled release of drugs if they have special properties which include an adequate diffusion coefficient (mainly affected by its molecular weight) as well as a high degree of binding to the cell surface. Since, in many cases, at physiological pH, the cell surface bears a net negative charge, positively charged carriers are favoured (Wallach, 1969). It was also found that corneal uptake of liposome-associated radioactivity is greatest for positively charged liposomes (Scaeffer and Krohn, 1982).

A class of candidates as drug carriers are some synthetic polyamino acids. In particular, α,β-

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TABLE 1

Molar enthalpy of interaction between PHEA and SDS, CTAB and Triton X-100 in aqueous solutions at 25°C

[SDS] (M)	ΔH (kJ/mol)	[CTAB] (M)	ΔH (kJ/mol)	[Triton X-100] (M)	ΔH (kJ/mol)
0.005991	0.0	0.000821	0.0	0.000180	0.0
0.01371	−88.6	0.002638	10.0	0.03483	5.3
0.03509	−102.0	0.004774	30.0	0.04885	10.6
0.05834	−115.2	0.009866	50.0	0.08713	15.8
0.1197	−121.9	0.01656	55.2	0.1193	26.4
0.1895	−125.2	0.02807	48.5	0.2143	26.5
		0.03810	44.6		
		0.06113	33.8		
		0.08571	16.7		
		0.1185	0.0		
		0.1480	−35.2		

poly(*N*-hydroxyethyl)-DL-aspartamide (PHEA) seems to have ideal properties: it is nontoxic, nonantigenic, biodegradable in living systems and highly soluble in water (Neri et al., 1973; Haines and Alexander, 1975; Drobnik et al., 1979). The possibilities to link covalently some drugs to PHEA and to perform tests on the improved pharmaceutical efficiency of these adducts have been previously investigated (Giammona et al., 1987, 1989).

In spite of the great potentialities of PHEA, only a few studies of its physico-chemical properties have been performed (Antoni et al., 1974, 1980). In particular, studies concerning the binding ability of PHEA to biomembranes or more simply to model membranes, despite being of the utmost importance to explain the pharmaceutical efficiency of PHEA-drug adducts, are lacking in the literature.

With the aim of gaining more information on this subject, we have undertaken a systematic investigation of the interactions between PHEA and model membranes (i.e. vesicles, micelles, reversed micelles) (Castelli et al., 1990).

In this work, the results of a calorimetric investigation of the interactions between PHEA and micelles of anionic, cationic and nonionic surfactants in aqueous solutions are reported and discussed.

PHEA was prepared and purified following previously described methods (Neri et al., 1973; Giammona et al., 1987). After dialysis, the average molecular weight, as determined by viscosimetry using the Mark Houwink equation ($[\eta] = 2.32 \times 10^{-3} \cdot M^{0.87} = 13.9$ ml/g), was $M = 22\,000$ (Antoni et al., 1974). The IR and analytical data of PHEA were in agreement with those reported in the literature (Giammona et al., 1987 and references therein).

Sodium dodecyl sulfate (SDS), *N*-cetyl *N*,*N*,*N*-trimethylammonium bromide (CTAB), octylphenoxypolyethoxyethanol (Triton X-100) and sodium chloride were reagent grade Sigma products and were used without further purification.

The calorimetric measurements were carried out at 25°C by using an LKB 2107 flow microcalorimeter. Each calorimetric measurement was carried out by mixing inside the calorimeter an aqueous solution of PHEA (0.00005 M) with an aqueous solution of the surfactant. In order to cancel the thermal effect due to the dilution of the surfactant solution, the baseline was taken as the signal obtained by mixing into the calorimeter the same surfactant solution with water. No thermal effect due to the dilution of the aqueous solution of PHEA was observed.

The experimental molar enthalpies (ΔH) of interaction of PHEA with SDS, CTAB and Triton X-100 in aqueous solutions as functions of the surfactant concentration are reported in Table 1 and graphically depicted in Fig. 1. Considering that the critical micellar concentration (CMC) values of SDS, CTAB and Triton X-100 are 8.3×10^{-3}, 9.2×10^{-4} and 2.4×10^{-4} M, respectively

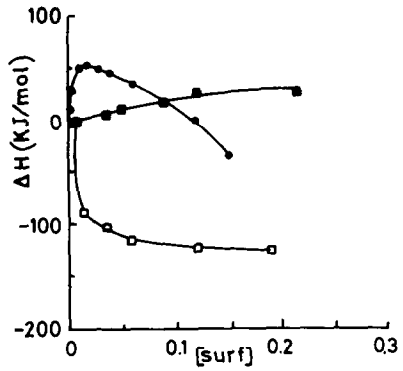

Fig. 1. Molar enthalpy of interaction between PHEA and SDS, CTAB and Triton X-100 as a function of surfactant concentration.

(Lindman et al., 1980), a perusal of the data reported in Table 1 demonstrates that, below the CMC of the surfactants, no thermal effect is observed. This result suggests that the interactions between PHEA and monomeric surfactant molecules are negligible. In contrast, above the CMC, an enthalpic effect is observed that is endothermic for the interaction of PHEA with the nonionic and cationic micelles whereas it is exothermic with the anionic micelles. Taking into account that the interactions between polymers and ionic surfactants are strongly exothermic when they are oppositely charged (Abuin and Scaiano, 1984; Skerianc et al., 1988), it it may be concluded that PHEA is positively charged. This conclusion was further directly confirmed in our laboratory by electrophoresis. On inspection of Fig. 1, it can also be observed that the molar enthalpies relative to SDS and Triton X-100 reach a nearly constant value at sufficiently high surfactant concentrations whereas the trend relative to CTAB is characterised by a maximum. In the case of SDS and of Triton X-100, the behaviour of ΔH indicates clearly that, at sufficiently high surfactant concentrations (i.e. when the molar enthalpy levels off), the PHEA polymer chain is completely saturated by the micellar aggregates. The saturation occurs at lower concentration in the case of SDS as a consequence of the favourable electrostatic effect (i.e. the binding constant of the negatively charged SDS micelles to the positively charged PHEA is greater than that of the neutral Triton X-100 micelles). The behaviour of ΔH shown by CTAB is less clear and probably additional processes must be invoked (for instance, conformational change in the polymeric chain induced by the positively charged CTAB micelles).

Given the pre-eminent role played by the charges transported by PHEA and micelles, further calorimetric measurements were carried out in order to explore, at least qualitatively, the influence of a simple electrolyte on the PHEA-micelle interactions. In Table 2 is reported the molar enthalpy of interaction of PHEA with SDS, CTAB, Triton X-100 micelles in the presence of a simple electrolyte (NaCl).

A perusal of Table 2 shows that the interaction between PHEA and SDS becomes less exothermic on increasing the NaCl concentration whereas the interaction between PHEA and CTAB or Triton X-100 becomes more exothermic. Both findings can be attributed to the effect of the screening of the charges existing on PHEA and the ionic micelles due to the sodium and chloride ions and demonstrate that the binding of PHEA to micelles is a consequence not only of electrostatic forces but also of dipolar and hydrophobic interactions.

TABLE 2

Molar enthalpy of interaction between PHEA and SDS, CTAB and Triton X-100 micelles, at fixed surfactant concentration, as a function of the NaCl concentration

[SDS] = 0.14 M		[CTAB] = 0.046 M		[Triton X-100] = 0.10 M	
[NaCl] (M)	ΔH (kJ/mol)	[NaCl] (M)	ΔH (kJ/mol)	[NaCl] (M)	ΔH (kJ/mol)
0.02778	−101.6	0.06624	−10.3	0.03679	10.6
0.1015	−68.5	0.1408	−31.6	0.05490	0.0
0.1260	−61.4			0.1179	−10.6
				0.1628	−26.7

Each set of data is headed with the surfactont concentration.

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