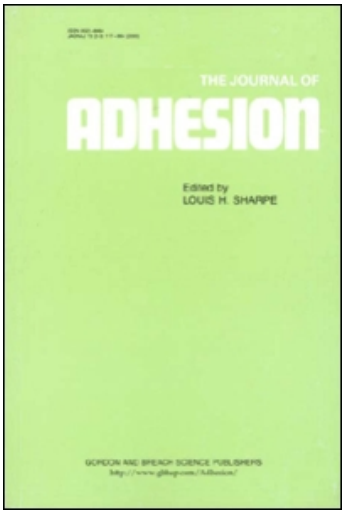

The Journal of Adhesion
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713453635

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To cite this Article Carthew, David L. , Buckton, Graham , Parsons, Gary E. and Poole, Stephen(1997) 'The Influence of a Phase Transition in Poly(oxyethylene)/Poly(oxypropylene)/Poly(oxyethylene) Block Copolymer Surfactants on the Properties of Material Adsorbed from Dilute Aqueous Solution', The Journal of Adhesion, 63: 1, 89 — 98
To link to this Article: DOI: 10.1080/00218469708015215
URL: http://dx.doi.org/10.1080/00218469708015215

J. Adhesion, 1997, Vol. 63, pp. 89–98
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The Influence of a Phase Transition in Poly(oxyethylene)/Poly-(oxypropylene)/Poly(oxyethylene) Block Copolymer Surfactants on the Properties of Material Adsorbed from Dilute Aqueous Solution*

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(Received 7 November 1995; In final form 26 March 1996)

In this study the adsorption of poloxamer block copolymer surfactants to polystyrene latex has been studied at a range of temperatures. It has been noted previously that the adsorption first falls, then rises and falls again as the temperature is increased, due to the existence of a phase transition in aqueous solutions of these surfactants at specific temperatures, which may be a critical micelle temperature. The present study shows that the hydrophobicity of the surface changes in a manner related to the amount of poloxamer adsorbed (*i.e.* is greatly influenced by the temperature of adsorption in relation to the transition temperature). The coating layer thickness, however, is essentially unchanged by the temperature of adsorption (*i.e.* not related to the amount adsorbed), but is influenced by the temperature at which the sizing was undertaken. This is due to dehydration of the poly (oxyethylene) with increasing temperature. The data presented here provide a possible explanation for the changes in biological distribution of poloxamer coated particles which occur when they are injected into animals.

*One of a Collection of papers honoring Robert J. Good, the recipient in February 1996 of *The Adhesion Society Award for Excellence in Adhesion Science, Sponsored by 3M.*

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Keywords: Poloxamers; hydrophobic interaction chromatography; adsorption; critical micelle temperature; phase transition; block copolymer surfactants; polystyrene latex

1 INTRODUCTION

Poloxamers (Pluronics and Synperonics) are nonionic surfactants which exist as aba block copolymers of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene). The general formula of the poloxamers is:

$$H(O—CH_2—CH_2)_a—(O—CHMe—CH_2)_b—(O—CH_2—CH_2)_a—CH$$

Many combinations of hydrophobe (poly(oxypropylene)) and hydrophile (poly(oxyethylene)) molecular weights exist such that a wide variety of structure and function are obtainable from the series. The uses of poloxamers are manifold, including inclusion in cream and aqueous suspension formulations, as well as a large literature concerning the role of adsorbed poloxamers in controlling organ distribution of colloidal particles which have been injected into animals (see for example Rudt and Muller [1]). Much remains to be understood about the structure and function of adsorbed poloxamers. It is known that poloxamers adsorb to hydrophobic surfaces by means of the poly(oxypropylene) region, which binds to the surface in a "loop and chain" structure. This form of adsorption results in practical irreversibility of the adsorption process (as all bonds with the surface are unlikely to break simultaneously). The hydrophilic chains then project some considerable distance from the surface of the solid (see below).

The physico-chemical properties of poloxamer solutions have been the subject of many publications in recent years (a substantial literature listing is given in the work of Penders *et al.* [2]). It has been shown from calorimetric measurements that the spontaneous adsorption is entropically rather than enthalpically driven [3], which relates to the ordering of the poloxamer and of water around both the hydrophobic surface of the adsorbent and the hydrophobe of the poloxamer. Latex coated with different poloxamers, which all have sufficiently large coating thickness to achieve steric stabilisation of the particles and which all apparently have similarly hydrophilic surfaces, are known to accumulate in different organs when injected into ani-

mals (*e.g.* Porter *et al.*[4]). There is considerable uncertainly about why different poloxamers will alter organ distribution of injected colloids on which they have been adsorbed. It is apparent that the organ distribution may relate to the poly(oxypropylene) molecular weight [1], which in turn may relate to the number of proteins which adsorb to the surfactant coated surface (which then function as triggers for removal to different sites by various phagocytic cells of the body) (*e.g.*, Blunk *et al.*[5]).

The phase behaviour of poloxamers has been investigated in dilute aqueous solution [6–9] and in more concentrated systems (*e.g.*, Linse [10], Wanka *et al.*[11]). It is clear that dilute aqueous solutions of the poloxamers undergo a reversible phase change, at a defined temperature (T_p). The T_p for this response is concentration dependent, with a higher T_p being seen with decreasing concentration [9]. It has been shown that the T_p, and thermodynamic parameters relating to this transition, correlate with the poly(oxypropylene) content of the surfactants, rather than with either total molecular weight or the poly(oxyethylene) content [7]. The involvement of the poly(oxypropylene) regions has also been identified by NMR studies [8], which revealed that the only region in the structure to show a change in properties at the T_p of the surfactant was the CH_3 group on the poly(oxypropylene). Recently [12] it has been argued that these phase transitions are in fact the onset of micellisation (a critical micelle temperature, for a given concentration) as a consequence of a highly temperature dependent micelle formation; such theories have been reviewed in detail elsewhere [13].

Previoulsy [14] we have shown that the amount of material adsorbing on a hydrophobic surface is related to the difference between the temperature at which adsorption takes place and that at which the phase transition (critical micelle temperature) occurs (T_p). This trend shows a decreasing amount of surfactant adsorbed (at any selected equilibrium surfactant concentration) with increasing temperature, until the transition temperature is approached, at which point the amount adsorbed increases. With further increases in temperature (above the transition point) the amount adsorbed falls (Fig. 1, for experimental details see Carthew *et al.*[14]). The falls in adsorption before and after the transition are indicative of typical exothermic adsorption behaviour; however, the major jump in adsorption

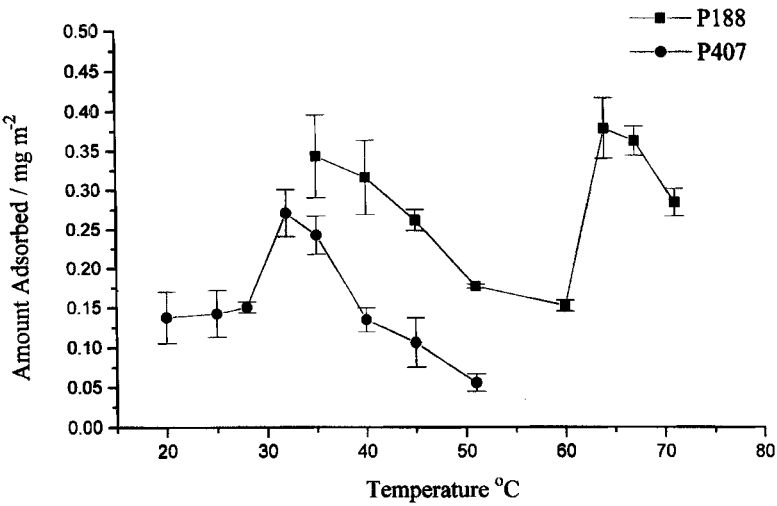

FIGURE 1 The amount of poloxamers P407 and P188 adsorbed to atovaquone as a function of temperature, showing a rise in the amount of adsorption at the phase transition. Error bars are ± standard deviation of the mean.

behaviour at the transition shows that the liquid state conformation of the surfactant affects adsorption. The increase in adsorption at the transition temperature is in keeping with the proposal that the hydrophobe dehydrates and contracts at this point, thus, more surfactant is able to adsorb to unit area of the solid surface. The adsorption process is essentially irreversible, as the multiple contact points between the poly(oxypropylene) and adsorbent do not break simultaneously. In our previous work [14] we were able to show that the amount adsorbed to a surface was not changed if the temperature was altered subsequent to adsorption being completed.

It is likely that the interaction between the solid and the densified hydrophobe will be different from that between the solid and the surfactant below the phase transition; this may well relate to the functionality of the surface coating. For example, the fact that the organ distribution of poloxamer-coated colloidal particles correlates with poly(oxypropylene) content [1, 15], as does the T_p, may well mean that the proximity to the phase transition has an influence on the structure of the coated surface, which in turn has the significant influence on functionality. It is possible that many unexplained occur-

rences, such as batch-to-batch variability on organ distribution following adsorpiton of P407 [4], are a consequence of adsorption at, or around, T_p.

It this study the surface nature of the adsorbed material is assessed using hydrophobic interaction chromatography to see whether the changes in amount of surfactant adsorbed are mirrored by changes in hydrophilicity of the adsorbed material. As the atovaquone particles were too large to be used in hydrophobic interaction chromatography experiements, hydrophobic polystyrene latex particles were substituted. It has been assumed that the adsorption trend around the CMC is the same for the latex as for the atovaquone (Fig. 1), which is reasonable as this trend is also observed for other hydrophobic materials studied [16].

MATERIALS AND METHOD

Three poloxamers (P407, P338 and P188, used as received from ICI, the details of which are given in Tab. I) were adsorbed onto a model hydrophobic surface (polystyrene latex spheres of diameter 0.06 μm, from Polysciences Inc., which have been used regularly in the literature in adsorption studies with poloxamer surfactants, for example Refs. 17–19). The poloxamers were prepared as aqueous solutions (250 mg/L), to 10 mL of which 0.1 mL of latex was added. This was equilibrated in a shaking water bath for 24 hours. The adsorption experiments were repeated at up to 9 different temperatures in the range 25–60°C.

TABLE I Properties of the surfactants

	POP units[a]	*POE units*[b]	T_p(°C)
P407	67	2 × 98	26.1 [9]; 26.5 [12]
P338	54	2 × 128	30.4 [9]; 31.5 [12]
P188	30	2 × 75	55.7 [7]; 52.5 [12]

[a]Approximate number of oxypropylene units each with molecular weight 58.

[b]Approximate number of oxyethylene units, each with molecular weight of 44, one at each end of the poly(oxypropylene).

Superscript numbers in T_p column refer to source references.

The coated latex was then removed and 600 µl injected into a column of propylagarose of 1 cm diameter and 10.3 cm length, using a rheadine. The flow rate of buffer (pH 6.8) solution through the column was 35.3 mL/h. The column was flushed after each experiment with Triton *X*–100 surfactant to remove any material which had been retained. All such experiments were undertaken at 37°C.

The size of the latex particles and of the particles after coating with poloxamer (250 mg/L, at a range of temperatures) was assessed using photon correlation spectroscopy (Malvern Autosizer 20°C). The adsorption was undertaken at 5 temperatures between 25 and 55°C and the sizing was undertaken at a temperature of 20°C. Samples which were adsorbed at one temperature (25°C) were assessed for size at different post-adsorption temperatures.

RESULTS AND DISCUSSION

As described above, the amount of poloxamer adsorbed to hydrophobic solids peaks at a certain critical temperature (see, for example, Fig. 1). The peak for adsorption is directly related to the concentration of surfactant used, thus the lower concentrations used for the adsorption studies [14] in each case yield maxima in the order of 8 degrees above T_p, reported by Mitchard *et al.* [7], and 6 degrees above the T_p values, reported by Armstrong *et al.* [9] (who each used a different concentration of surfactant). The rise in T_p with a decrease in concentration is in keeping with the observation reported by Armstrong *et al.* [9], and with the observations on temperature dependence of the critical micelle concentration reported by Alexandridis *et al.* [12].

The hydrophobic interaction chromatography (HIC) of the latex coated with the poloxamer at different temperatures on occasion yielded total retention on the column (*i.e.*, a hydrophobic surface), thus to allow comparison the reciprocal of the retention time has been plotted as a function of incubation temperature during adsorption (such that a retention time of infinity can be plotted as zero for the reciprocal plot). The data are shown in Figure 2, from which it can be seen that the three poloxamers yield surfaces with different hydrophobicities depending upon the temperature of adsorption. In each case the maximum (*i.e.*, highest reciprocal of retention time, which is the most

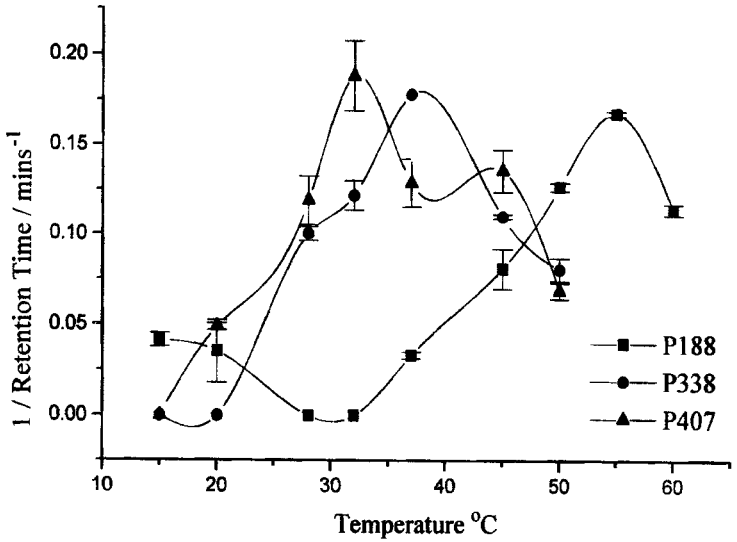

FIGURE 2 The inverse of retention times obtained by hydrophobic interaction chromatography as a function of temperature at which adsorption was carried out.

hydrophilic surface) is in the region of the T_p recorded by either scanning calorimetry [9] (ca.26 and 30°C for P407 and P338, respectively) or by solubilisation [12] (26.5, 31.5 and 52.5°C for P407, P338 and P188, respectively). Whilst we have not attempted to prove that the poloxamer remains adsorbed during transit through the HIC column, the multipoint adsorption behaviour makes adsorption practically irreversible in most circumstances, and this has been assumed to be the case here.

The sizing data for the latex after coating with poloxamer P407, P338 and P188 are shown in Figure 3. It can be seen that the size does not change to any great extent following adsorption over a wide range of temperatures. It follows that the coating layer thickness is essentially unchaged at different coating temperatures and, thus, the coating layer thickness does not correlate with the changes in hydrophobicity of the surface (which were seen when using HIC). The changes in hydrophobicity must relate to differences in packing density during adsorption, whilst the coating layer thickness shows that the poly(oxyethylene) regions of the molecules protrude a similar distance from the surface, irrespective of packing density of the hydrophobe

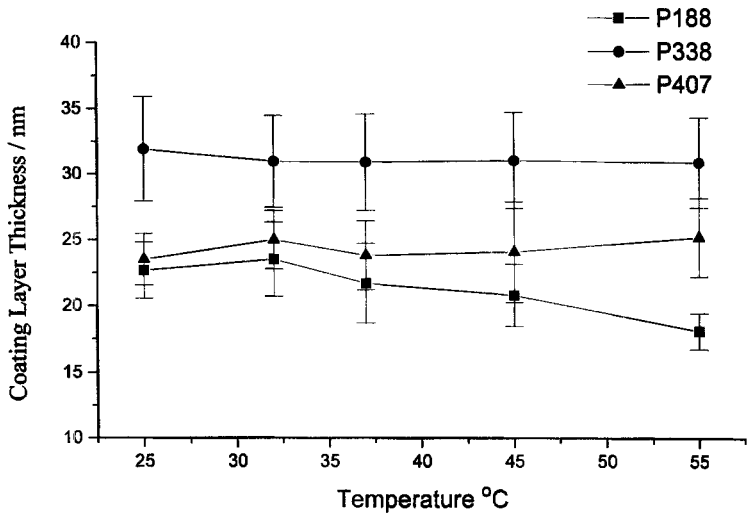

FIGURE 3 Coating layer thickness (measured at 20°C) as a function of temperature at which adsorption was carried out.

during adsorption. The factor which has the biggest influence on coating layer thickness is the temperature at which the sizing was undertaken, as shown in Figure 4. The size of the coating decreases as the temperature is increased (the data in Fig. 4 were all obtained from material adsorbed at 25°C, but sized at different temperatures) which is in keeping with the dehydration of the poly(oxyethylene). It can be seen (Fig. 4) that the coating layer thickness for P188 (for which each surfactant molecule nominally has 2 chains of 75 poly(oxyethylene) units) is smaller than that for both P338 and P407 (which have 2 chains of 128 and 98 poly(oxyethylene) units each, respectively). Thus, at any one temperature for the sizing experiments, there is an approximate link between the coating layer thickness and the poly(oxyethylene) chain length, this is, however, no more than a rank order, showing that the poly(oxyethylene) chains are not fully extended.

CONCLUSION

It has been shown that the amount of poloxamer adsorbed to hydrophobic materials falls with temperature until a critical temperature

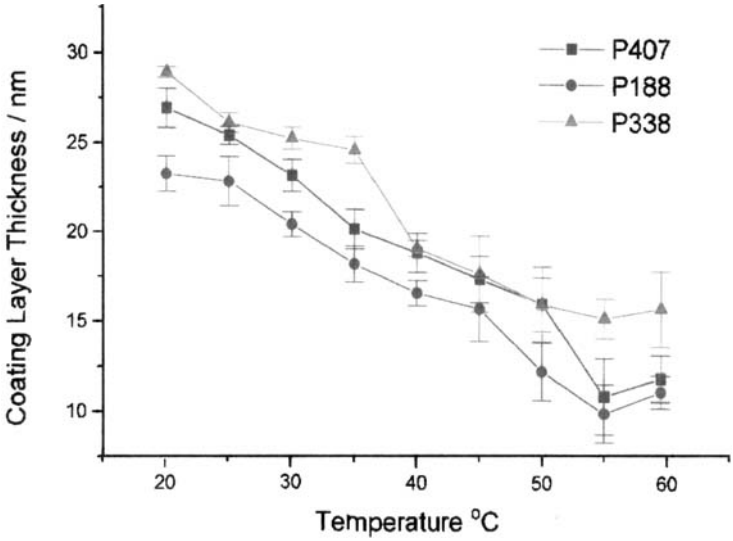

FIGURE 4 Coating layer thickness (difference between the size measured before and after surfactant adsorption) following adsorption at 25°C, measured at a range of temperatures (recorded on x-axis).

(for P407), or remains relatively flat (for P188). After reaching the critical temperature (which varies with concentration of surfactant in solution) adsorption is seen to show a sudden increase. Following this temperature, the amount adsorbed falls with temperature. This transition is due to the dehydration of the hydrophobe and aggregation of the surfactant in solution. The adsorption of the surfactants is essentially irreversible and is not altered by storage at different temperatures after adsorption is complete.

The hydrophobicity of the surface to which the poloxamer is adsorbed is affected by the temperature at which the adsorption was undertaken (and will also be influenced by the concentration of the surfactant used to perform the adsorption experiment). However, the coating layer thickness of the surfactants is linked to the poly(oxyethylene) chain length, and to the temperature at which the sizing was undertaken, but not to the temperature at which the adsorption was undertaken.

It is misleading to use coating layer thickness as a proof of surface coverage for these surfactants. These data have great significance for

work in, for example, drug targeting, where these differences in surface nature may well explain the differences seen in organ distribution following injection of poloxamer-coated latex particles into animals.

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