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International Journal of Pharmaceutics 160 (1998) 157–162

international journal of pharmaceutics

Osmotic behavior of poloxamer 407 and other non-ionic surfactants in aqueous solutions

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Received 4 October 1996; received in revised form 8 September 1997; accepted 9 September 1997

Abstract

Solutions of non-ionic surfactants were prepared in water and buffer. The osmotic behavior of these solutions were studied by measuring their osmolality, using the freezing point depression method. Graphical representation of osmolality versus concentration depicted non-linear parabolic curves that were applied to logarithmic and polynomial mathematical models. One such surfactant, poloxamer 407, was selected and studied in solutions of water and buffer. We observed curves of similar profile, which were attributed to its interaction and association in aqueous solution. In the liquid state the osmotic influence is due to the surfactant-water interaction. When the solution is warmed and converted to the gel state, the polymer is taken out of play and the osmotic influence is due to the aqueous solution only. This phenomenon was supported by in vitro red blood cell tonicity observations. © 1998 Elsevier Science B.V.

Keywords: Poloxamer; Non-ionic surfactants; Osmolality; Sol–gel phases; Curve fitting models

1. Introduction

Non-ionic surfactants are widely used in cosmetics and pharmaceuticals as solubilizers, emulsifiers, stabilizers and wetting agents. One such surfactant, poloxamer 407, is unique because its micellar rearrangement in solution will produce a change in viscosity with change in temperature (Schmolka and Bacon, 1967). This polyoxyethylene–polyoxypropylene block copolymer has an average molecular weight of 12 500 and is commonly used in toothpaste, mouthwash and ophthalmic contact lens solutions. Its complex micellar arrangement in water and electrolyte solutions was explained by Attwood et al. (1985). Micellar organization and behavior have been studied by different techniques, such as ultrasonic velocity and light scattering (Al-Saden et al., 1982; Rassing and Attwood, 1983; Zhou and Chu, 1988), photo-luminescent probing (Gilbert et al.,

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PII S0378-5173(97)00316-5

1987), surface tension (Prasad et al., 1979) and gamma irradiation (Al-Saden et al., 1980). The solution to gel transition phenomenon can be explained by thermodynamics (Vadnere et al., 1984), wide-angle X-ray diffraction (Tung, 1994) and by shear modulus kinetics (Miller and Drabik, 1984; Wang and Johnston, 1991). The effect of univalent and multivalent salts on the gelation properties of poloxamer 407 are explained by Juhasz et al. (1990) and Pandit and Kisaka (1996).

This paper focuses on the colligative property of osmotic pressure. Osmolality measurements, by the freezing point depression method, were used to study osmotic behavior. The osmolality of poloxamer 407 was compared against those of other block polymers and non-ionic surfactants. The effect of buffered poloxamer 407 solutions on the tonicity of bovine red blood cells was studied in the solution and gel states.

2. Materials and methods

Poloxamer 188 and 407 and Poloxamine 908 were obtained from BASF (Parsippany, NJ). Tween 60 and 80 were obtained from ICI America (Wilmington, DE). Polyoxyl (POE) 40 stearate was obtained from PPG Mazer (Gurnee, IL). Polyethylene glycol 400 was obtained from Union Carbide (Danbury, CT). Nonoxynol-9 was obtained from RhonePoulenc Surfactants (Danbury, CT). Sodium heparin was obtained from Sigma Chemical (St. Louis, MO). All buffer salts used were pharmaceutical grade.

Stocks solutions of 20% w/w surfactant were prepared by dissolving each of the non-ionic surfactants in de-ionized water. Mixing was accomplished with magnetic stir-bars and stirrers. In the case of the poloxamer surfactants, the cold method was employed to facilitate dissolution (Schmolka, 1977). Appropriate dilutions of the stock solution were made with de-ionized water. The osmolality of the diluted samples was measured using the freezing point osmometer (Advanced Digimatic, model 3D2).

Solutions of poloxamer 407 were similarly prepared in a Sorensen phosphate buffer (18.5 mM/kg) containing three levels of sodium chloride (51.28, 68.38 and 112.82 mM/kg). Appropriate dilutions of the stock solution were made, by weight, with solutions containing the buffer solutions of the corresponding ionic concentration. The osmolality of the diluted samples was measured just as before.

Blood was collected from a freshly slaughtered bull and transferred to a 1 l Erlenmeyer flask containing a solution of heparin sodium, 75 mg/10 ml of water, as an anticoagulant. The blood was stored at 4°C and used within 24 h of collection. Gel formulations containing 28% w/w poloxamer 407 were prepared in tromethamine (Tris)-maleate buffer systems and adjusted with sodium chloride to be either hyperosmotic, iso-osmotic or hypo-osmotic. Samples of each preparation weighing 25–30 g were placed in 100 mm diameter glass petri dishes and equilibrated as a liquid (4°C) or a gel (25°C). Aliquots (1 ml) of blood were added to each dish and mixed in gently. These samples were incubated for 2 h at these temperature conditions, and then examined at 100× magnification with a light microscope (Reichert Microstar IV).

3. Curve fitting

The relationship of osmotic pressure and concentration is described by the Van't Hoff equation (Jirgensons and Straumanis, 1962; Hammel, 1976).

$$p = RT\frac{c}{M} \tag{1}$$

where p is the osmotic pressure and is proportional to the molality or molarity of an aqueous solution having a concentration c in g/kg or g/l, respectively. R is the gas constant, T is the absolute temperature and M is the molecular weight. This equation is applicable to dilute solutions of spherocolloids and linear colloids with minimum interaction, such as egg albumen or glycogen. Although, in the case of highly interactive linear polymers like polyvinyl chloride, cellulose derivatives and the poloxamers, the Huggins and Flory modification of the Van't Hoff equation is applied

to account for the non-linearity in the osmotic pressure versus concentration curve (Jirgensons and Straumanis, 1962).

$$\frac{p}{c} = \frac{RT}{M} + bc + b_1c^2 + b_2c^3 + \ldots \quad (2)$$

where b, b_1 and b_2 are association or interacting constants. The measure of osmotic concentration in pharmacy is the 'osmole', which depends on the dissociation of a mole of solute in 1 kg of water. The osmolality (mOsm/kg) linearly increases with an increase in solute concentration and the number of particles in solution. The osmolality O, is described as

$$O = \phi n \frac{c}{M} \quad (3)$$

where ϕ is the osmotic coefficient that accounts for the degree of molecular dissociation and n is the number of particles or ions into which a molecule will dissociate. For non-ionic solutes such as dextrose and urea, n and ϕ are equal to 1. Although, in the case of non-ionic interacting molecules n can be a value less than 1 because of the 'take out of play' effect (Martin et al., 1969). On the other hand, ϕ can be of a value much greater than 1 because of the degree of molecular association. Combining Eq. (3) with Eq. (1), we have a correlation between osmotic pressure and osmolality:

$$O = \phi n \frac{p}{RT} \quad (4)$$

Eq. (2) can now be written as

$$\frac{O}{c} = \frac{\phi n}{M} + \frac{\phi nbc}{RT} + \frac{\phi nb_1c^2}{RT} \quad (5)$$

$$\frac{O}{c} = \frac{\phi n}{M} + \frac{\phi nbc}{RT} + \frac{\phi nb_1c^2}{RT} + \frac{\phi nb_2c^3}{RT} \quad (6)$$

The logarithm of Eq. (3) provides a logarithmic model.

$$\log O = \log \frac{\phi n}{M} - \log c \quad (7)$$

4. Results

Mathematical correlation data of osmolality (O) versus concentration (c) were generated for each surfactant. The non-linear polynomial calculations were made with the PCNONLIN 4.2A SCI software. Maximum correlation was obtained in each case, when the quadratic, cubic and the logarithmic models were applied, that is Eqs. (5)–(7), respectively. From these equations it was possible to calculate the different interaction constants to understand the degree of polymer–solvent interaction. The reference polyol, PEG 400, produces a linear profile in all of the curve fitting models used. This linearity suggests that this low molecular weight polymer has strong polymer–solvent interaction with adequate association in water ($\phi n = 1068.8$ and $b = 0.00252$). The parabolic shapes of the curves, in Fig. 1, depict strong polymer–solvent interaction and stronger intermolecular association, as in the case of poloxamine 908, poloxamer 188 and poloxamer 407. On the other hand, nonoxynol-9 has little to no polymer–solvent interaction and minimal association in water ($\phi n = 71.6$ and $b = -0.00652$).

Solutions of poloxamer 407 in a phosphate buffer (18.5 mM/kg) containing 51.28, 68.38 and 112.82 mM/kg of sodium chloride produced similar osmotic effects as observed with solutions in water (Fig. 2). We see an upward shift in the parabolic curve with an increase in sodium chloride concentration. At low non-gel concentrations of poloxamer 407, the curve is linear. Although, at concentrations above 60–80 g/kg, linearity is lost due to stronger polymer–solvent interactions and intermolecular association. The osmolality of these three poloxamer 407 solutions can be corrected, by subtracting the osmolality curve of the polymer in water from the osmolality curve of the polymer in the phosphated-saline solution. This correction will show that the above preparations are hypo-osmotic, iso-osmotic and hyperosmotic, respectively.

Examination of microscopic (100 × magnification) photographs of bovine red blood cells in hypo-osmotic, iso-osmotic and hyperosmotic buffered Tris-maleate gel (25°C) show that the cells appear to be either distended, normal to

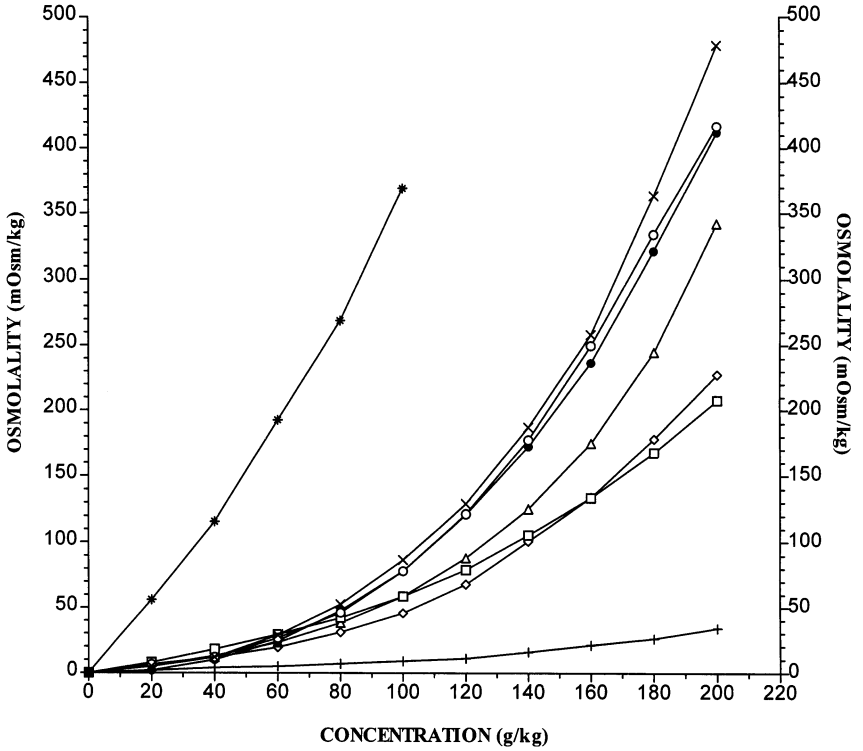

Fig. 1. Osmolality of non-ionic surfactant solutions in water. Key: (□) Tween 20, (△) Tween 80, (◇) Polyoxyl POE 40 stearate, (●) Poloxamine 908, (○) Poloxamer 188, (×) Poloxamer 407, (*) PEG 400 and (+) Nonoxynol-9.

slightly distended and crenated, respectively. Red blood cells incubated at 4°C were found to be partially crenated, distorted and stretched in all three formulations. This observation would suggest that the formulation in the cold liquid state, is hyperosmotic, adhesive or detergent-like. Incubation at 4°C for 2 h in a highly concentrated surfactant solution is extreme and not very practical.

5. Discussion

An observation has been made to correlate osmolality with the osmotic behavior of a non-ionic surfactant. One may suggest that the osmolality of a large molecular weight polymer in aqueous solution should be negligible, because osmolality is a measurement of the number of particles in a solution. Hence, the osmotic pressure would also be negligible, but, this is not so. This phenomenon was described by polynomial Eqs. (5) and (6) and the curves in Figs. 1 and 2. At low temperatures there is an increase in polymer–solvent interaction due to hydrogen bonding. The polymer-solvent interaction prevents the free flow of solvent molecules in the solution, thereby affecting osmosis. An interference with the heat of fusion of the crystal lattice in the frozen test solution is reflected by the resulting osmolality measurement. As the temperature and concentration are increased, there is an increased polymer–polymer interaction and decreased polymer–solvent interaction, resulting in the liberation of free water. This explanation is similar to the Newtonian versus non-Newtonian behavior described by Tung (1994).

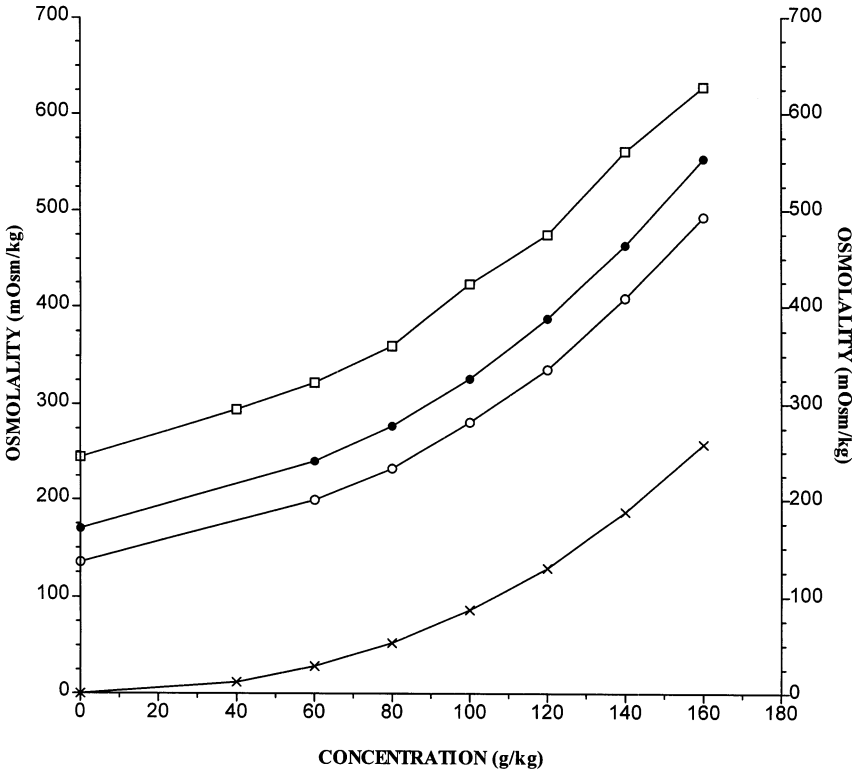

Fig. 2. Osmolality of poloxamer 407 in phosphated-saline buffer containing 18.5 mM/kg of phosphate and (○) 51.28, (●) 68.38 and (□) 112.82 mM/kg of sodium chloride. Poloxamer 407 solutions in water (×).

6. Conclusion

A few non-linear mathematical models have been proposed for determining the osmolality of strongly interacting non-ionic surfactants. Their association and interaction with the dispersion medium must be considered when incorporating them into pharmaceutical preparations. In the case of polyphasic systems, it may be important to consider the osmotic influence as a function of temperature. The measurement of red blood cell tonicity is an easy way to screen various injectable surfactant formulations.

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