ELSEVIER

International Journal of Pharmaceutics 165 (1998) 211–216

international journal of pharmaceutics

Adsorption of polysorbate 80 on pyrantel pamoate: effects on suspension stability

R. Duro, J.L. Gómez-Amoza, R. Martínez-Pacheco, C. Souto, A. Concheiro *

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

Received 6 August 1997; received in revised form 1 December 1997; accepted 17 December 1997

Abstract

Adsorption of polysorbate 80 in aqueous suspensions of 4% (w/v) pyrantel pamoate gave rise to an *L*-type adsorption isotherm that could be fitted by the Langmuir equation, allowing estimation of the amount of surfactant forming a monolayer ($\Gamma_{max} = 2.12$ mg g^{-1}), and of the adsorption activity ($a = 0.24$). The surfactant adsorption film slightly decreased the magnitude of the zeta potential of the system with respect to the mean value for the corresponding aqueous suspension (-60.34 mV). These results and the results of stability studies suggest that the polysorbate 80 was stabilizing the suspensions through a steric mechanism. At low surfactant concentrations this steric stabilization was only partial, however, and redispersion of sedimented particles became more difficult than in the absence of polysorbate 80. For the entire range of polysorbate 80 concentrations studied, sedimentation volumes were low and were not correlated with redispersability times. The rate of dissolution of aqueous suspensions of 4% (w/v) pyrantel pamoate increased upon adding polysorbate 80, which is attributable to the surfactant's having aided wetting of the drug particles.

Keywords: Pyrantel pamoate; Polysorbate 80; Interfacial adsorption; Pharmaceutical suspensions; Physical stability; Zeta potential

1. Introduction

Surfactants are frequently used in the formulation of pharmaceutical suspensions, to lower interfacial tension and facilitate wetting of suspended solids by the bulk external phase (Ofner et al., 1988). Their effects derive from their accumulation as an amphiphilic film at the solid-liquid interface (Martin, 1993), where they can alter the stability of the suspension through electrostatic, steric or electrosteric mechanisms (Napper, 1989; Lucks et al., 1990). The formation of this film is a complex process that is conditioned

* Corresponding author. Tel.: +34 981 594627; fax: +34 981 547148; e-mail: FFancon@usc.es

0378-5173/98/$19.00
PII S0378-5173(98)00015-5

by competition for adsorption sites between surfactant and solvent molecules, and by other factors such as the structure and conformational flexibility of the surfactant, its ionic or non-ionic character, and the presence of other ions with a tendency to adsorb at the solid-liquid interface (Denoyel and Rouquerol, 1991). Likewise, the nature and surface properties of the adsorbent also influences the adsorption mechanism and the structure of the adsorbed film (van den Boomgaard et al., 1987; Meguro et al., 1988).

Although there is a some information available about the adsorption of surfactants at the solid-liquid interface in model systems (Denoyel and Rouquerol, 1991; Böhmer et al., 1992; Steinby et al., 1993), there have been relatively few studies examining the implications of these phenomena for the stability of real, polydisperse pharmaceutical suspensions (Jovanovic and Djuric, 1985; Rawlins and Kayes, 1983). In the present work, we set about redressing this by examining the adsorption of polysorbate 80—a widely used pharmaceutical wetting-agent (Nash, 1988)—in aqueous suspensions of the antihelmintic pyrantel pamoate, which is customarily formulated as a suspension (Martindale, The Extra Pharmacopoeia, 1996). Particular attention was paid to the effects of polysorbate 80 on the electrical charge and dissolution rate of the pyrantel pamoate particles, and on the physical stability of the systems.

2. Materials and methods

2.1. Reagents

Pyrantel pamoate USP and polysorbate 80 USP (Tween® 80) were purchased from Sigma Chemicals (Batches 48F0042 and 90H0678, respectively). All suspensions and reagents were prepared using water of resistivity 18.2 MΩ cm obtained from a Millipore Milli-Q® reverse osmosis system (Millipore Corp.).

2.2. Particle size analysis of the pyrantel pamoate

Three representative samples of the drug were obtained using a Quantachrome® Rotary Microriffler and their particle size distributions were determined in Multisizer II Coulter® counter. The dispersant medium was the electrolyte solution ISOTON II (Coulter® Electronics), and all analyses were of 60 s duration. The proportion of particles (% v/v) in a series of particle volume diameter intervals were measured, and the resulting distributions were characterized in terms of the geometric mean volume diameter and the corresponding standard deviation.

2.3. Adsorption isotherms

The surfactant adsorption isotherm was obtained studying a series of suspensions of 4% (w/v) of pyrantel pamoate in a dispersion of between 6 and 50 mg dl^{-1} of polysorbate 80. Each suspension was equilibrated by stirring it at 25°C for 48 h, whereupon it was centrifuged at $85 \times 1000g$ for 15 min, the supernatant was decanted and filtered through a 0.45 μm pore-diameter nylon membrane (ref. NY501300; Lida). The unadsorbed surfactant in the supernatant was determined by the method of Clesceri et al. (1989). To avoid any bias in the results due to adsorption of the surfactant on the filter, the standards used to construct the calibration line were treated identically to the supernatant derived from the samples. The data obtained were fitted with the Langmuir equation (Eq. (1)) (Shaw, 1980):

$$\Gamma = \Gamma_{\max} \frac{c}{c + (1/a)} \quad (1)$$

where Γ is the amount of surfactant adsorbed per g of solid, Γ_{max} is the amount of surfactant per g of solid forming a monolayer, c is the equilibrium concentration of surfactant in the dispersion, and a is the adsorption activity, which is constant for a given system and set of conditions.

2.4. Characterization of the suspensions

Series of suspensions of 4% (w/v) pyrantel pamoate in solutions of polysorbate 80 (0.02, 0.04, 0.06, 0.08, 0.10, 0.30, 0.50, 0.70 and 0.90 g dl^{-1}) in water were prepared as described in Section 2.3, above. Each suspension was subjected to the following determinations.

2.4.1. Zeta potential

The zeta potentials for the suspensions were calculated from their electrophoretic mobilities by means of the Helmholtz–Smoluchowski equation (Nash and Haeger, 1966). Electrophoretic mobilities were measured in triplicate by Laser Doppler Anemometry (LDA) in a Zetasizer III apparatus (Malvern Instruments) equipped with an AZ4 4 mm-diameter capillary cell. Optimal particle concentrations were obtained by diluting the suspensions with 1 mM KCl solution. The electrode compartments of the measuring cell were filled with 2 mM KCl. The applied field strength was 150 mV.

2.4.2. Redispersability

Twenty milliliters of suspension were sealed in a 25 ml glass tube of diameter 15 mm and stored at 25°C for 15 days. Redispersability—the time (measured in blocks of 30 s) needed to completely redisperse the sediment formed during storage—was determined with a rotary mixer (model 34526; Breda Scientific), spinning the tubes end over end at 30 revs min^{-1}. The particle-size distribution of the redispersed sediment was determined as described in Section 2.2.

2.4.3. Sedimentation volume

For samples treated identically to those described in Section 2.4.2, the sedimentation volume was calculated as the ratio of the volume of the resulting sediment to the volume of the suspension (Tunçel and Gürek, 1992).

2.4.4. Dissolution rate

Dissolution rates were determined for (4% w/v) pyrantel pamoate suspensions in water containing 0, 0.1 or 0.9 g dl^{-1} of polysorbate. All assays were performed in a Turu-Grau apparatus (USP23, Method II) as follows. A 2.5 ml aliquot of the suspension (containing 100 mg of pyrantel pamoate) was introduced into the dissolution medium (900 ml of artificial enteric juice USP23 of pH 7.5, stirring at 25 revs min^{-1} and at 37°C) at a height of 5 cm above the vessel bottom. At pre-set intervals, the amount of drug dissolved was determined spectrophotometrically in a Shimadzu UV-240 instrument. Regression analysis was used to fit the resulting dissolution profiles with the equation of Higuchi and Hiestand (1963) (Eq. (2)):

$$W(F) = \sum_{i=1}^{n} [(a_{oi}^2 - Kt)/A_{oi}^2]^{3/2} F_i \quad (2)$$

where A_{oi} is the initial (i.e. at dissolution time = 0) mean volume diameter of interval i, F_i is the volume fraction of the particles in that interval (as determined by particle size analysis; Section 2.2), n is the total number of particle size intervals, and K is the dissolution rate coefficient.

Statistically significant effects of polysorbate 80 on the rate of drug dissolution were identified by means of the Kruskall–Wallis non-parametric test and, subsequently, a multiple comparisons test (Siegel and Castellan, 1988).

3. Results and discussion

The particle size data for the pyrantel pamoate were characterized by a geometric mean volume diameter of 9.53 μm, and a geometric standard deviation 1.73 μm. Fig. 1 shows the fit of the Eq. (1) to the isotherm for the adsorption of polysorbate 80 on these pyrantel pamoate particles obtained at 25°C, a standard value of temperature for the preparation and storage of these pharmaceutical systems. The shape of this isotherm (type L) and the goodness-of-fit of the equation suggest that adsorption occurs through non-specific, hy-

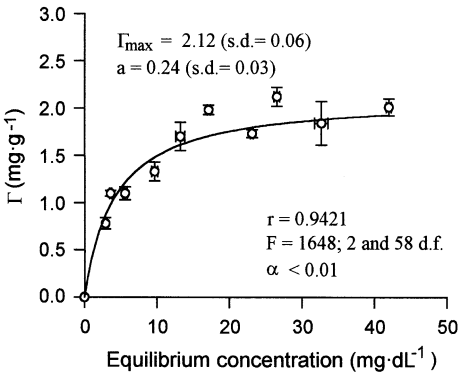

Fig. 1. Adsorption isotherm at 25°C of polysorbate 80 on pyrantel pamoate particles in aqueous suspension (4% w/v).

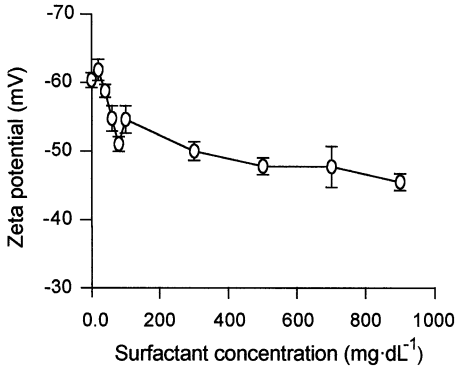

Fig. 2. Effects of polysorbate 80 on the zeta potential of suspended pyrantel pamoate particles.

drophobic interactions between the surface of the drug particles and apolar groups of the surfactant, until the latter forms a monolayer, at around 2.12 mg g^{-1}. The adsorption isotherm also shows that the critical micelle concentration (CMC) of the polysorbate 80 is between 10 and 15 mg dl^{-1} (Denoyel and Rouquerol, 1991), which agree with a previously published value; 13.1 mg dl^{-1} (Mandal and Moulik, 1982). Such type-*L* isotherms are typical of apolar adsorbents that do not adsorb further surfactant upon increasing surfactant concentration. By contrast, adsorption onto polar adsorbents is a two-stage process that gives rise to S-shaped isotherms (Denoyel and Rouquerol, 1991; Brahimi et al., 1992) that cannot be fitted by the Eq. (1); firstly, the surfactant attaches itself to the particle surface through its polar groups; then molecules still in solution form a second layer through hydrophobic interactions with the apolar groups of the adsorbed molecules (Rupprecht, 1978). For the polysorbate 80/pyrantel pamoate system, the magnitude of the adsorption activity ($a = 0.24$ dl mg^{-1}) indicates that, compared to non-ionic cellulose ethers (Duro et al., 1998), polysorbate 80 has relatively low affinity for pyrantel pamoate.

Fig. 2 shows the variation of the zeta potential of the pyrantel pamoate particles with polysorbate 80 concentration. At all concentrations, the particles were negatively charged owing to the presence of readily ionized phenol and carboxylic acid groups in pyrantel pamoate (Martindale, The Extra Pharmacopoeia, 1996). The magnitude of the zeta potential for the aqueous suspension (−60.34 mV) decreased upon addition of polysorbate 80, which is attributable to the interfacial film formed having increased the distance between the shear surface and the particle surface (Lucks et al., 1990). This decrease was smaller than for adsorption of polar non-ionic cellulose ethers because these polymers form much thicker interfacial films than polysorbate 80 (Duro et al., 1998). A similarly small decrease in zeta potential was noted by Jovanovic and Djuric (1985) in their study of aqueous suspensions of aluminium hydroxide and polysorbate 80.

Fig. 3 shows the results of the stability studies. In all cases, redispersion of the sediment formed during storage regenerated the original system, i.e. a suspension that had much the same particle size distribution as the original pyrantel pamoate. The variation of the redispersability of these systems with the concentration of surfactant is in keeping the adsorption results and similar to that described by Rawlins and Kayes (1983) for polystyrene latex suspensions containing other polyoxyethylene surfactants. Specifically, at concentrations of polysorbate 80 below that required for monolayer formation, sufficient surfactant molecules were adsorbed to produce partial steric stabilization of the system, allowing sedimentation of individual particles. However, the close

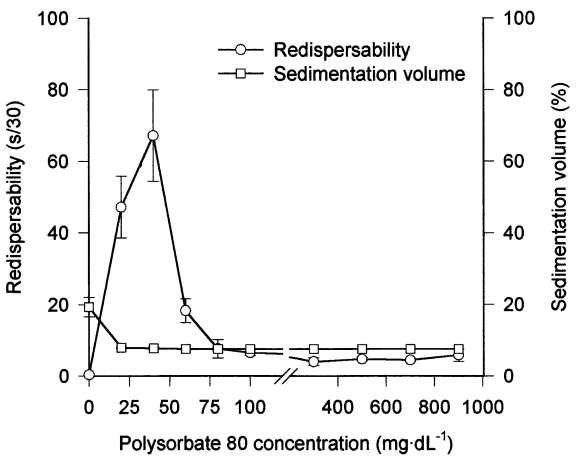

Fig. 3. Effects of polysorbate 80 on the redispersability and sedimentation volume of pyrantel pamoate suspensions.

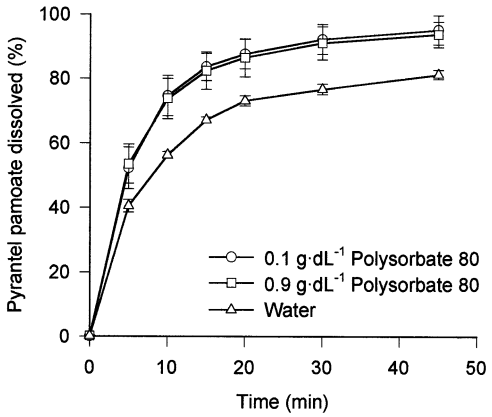

Fig. 4. Dissolution profiles for pyrantel pamoate in aqueous suspensions containing various concentrations of polysorbate 80.

proximity of the partially covered particles in the sediment favour the formation of crystalline bridges, as is reflected in the long redispersability times for these systems. By contrast, at slightly higher concentrations, the surfactants formed complete monolayers, surrounding the particle with their chains extended out into the bulk solution (Lucks et al., 1990), and redispersability times were shorter. Overall, the redispersability results indicate that incorporation of the surfactant transformed the flocculated pyrantel pamoate suspensions into partially or fully stabilized systems in which the particles sedimented individually (Napper, 1989). This was reflected in the formation of low-volume, compact sediments (Fig. 3) and the lack of any correlation between redispersability and sedimentation volume. As regards the mechanism of stabilization, in view of the small decreases induced in the magnitude of the zeta potential upon adding polysorbate 80 to the pyrantel pamoate suspensions in water, it would appear that electrostatic stabilization contributed only very slightly to stabilization.

Fig. 4 compares the dissolution profiles for the two systems containing polysorbate 80 and for the aqueous suspension of pyrantel pamoate. The assay conditions were elected having into account the higher solubility of the drug in the enteric medium with respect to gastric fluid and the physiological temperature conditions. Fitting of these

Table 1
Mean volume diameter (A_{oi}) and volume fraction (F_i) for each particle size interval used in fitting Eq. (2) to the dissolution profiles

Interval	A_{oi} (cm)	F_i
1	0.0015	0.0136
2	0.0045	0.1121
3	0.0075	0.3068
4	0.0105	0.1690
5	0.0135	0.1919
6	0.0165	0.1063
7	0.0195	0.0513
8	0.0225	0.0490

data with the Eq. (2), using the mean volume diameters and volume fractions listed for each particle size interval in Table 1, gave the dissolution rate coefficients in Table 2. Comparison of these rate coefficients by means of the Kruskall–Wallis test indicated that the polysorbate 80 had induced a significant increase in dissolution rate ($KW = 9.81$; 2 d.f., $\alpha < 0.05$). This rate increase can be attributed to the adsorbed surfactant film's having aided wetting of the pyrantel pamoate particles. Note that the low concentrations of surfactant added to these systems rule out the possibility that the increase in the rate of dissolution was due to micellization effects.

Subsequent application of the multiple comparisons test to the dissolution rate data indicated that increasing the concentration of polysorbate 80 had no significant effect on the rate of dissolution, in the range of concentrations studied. Addition of concentrations of polysorbate 80 above that needed for monolayer formation thus appear

Table 2
Dissolution rate coefficients (K) obtained by fitting Eq. (2) to dissolution profiles for aqueous suspensions of pyrantel pamoate containing various concentrations of polysorbate 80 surfactant

Surfactant concentration (g dl^{-1})	K 10^9 (cm^2 s^{-1})	r	F
0	0.98	0.8123	43.9*
0.1	1.27	0.9648	977*
0.9	1.31	0.9771	897*

*1, 46 d.f.; $\alpha < 0.01$.

to offer no advantages as regards increasing the rate of dissolution of the pyrantel pamoate.

Acknowledgements

This work was supported by grant FAR 91-0293 from CICYT, Spain.

References

Böhmer, M.R., Koopal, L.K., Janssen, R., 1992. Adsorption of nonionic surfactants on hydrophilic surfaces. An experimental and theoretical study on association in the adsorbed layer. Langmuir 8, 2228–2239.

Brahimi, B., Labbe, P., Reverdy, G., 1992. Study of the adsorption of cationic surfactants on aqueous laponite clay suspensions and laponite clay modified electrodes. Langmuir 8, 1908–1918.

Clesceri, L.S., Greenberg, A.E., Rhodes-Trussell, R., 1989. Standard methods for the examination of water and wastewater, 17th Ed., Port City Press, Baltimore.

Denoyel, R., Rouquerol, J., 1991. Thermodynamic (including microcalorimetry) study of the adsorption of nonionic and ionic surfactants onto silica, kaolin and alumina. J. Colloid Interface Sci. 143, 555–572.

Duro, R., Alvarez, C., Martínez-Pacheco, R., Gómez-Amoza, J.L., Concheiro, A., Souto, C., 1998. The adsorption of cellulose ethers in aqueous suspensions of pyrantel pamoate particles. Effects on zeta potential and stability. Eur. J. Pharm. Biopharm. 45, 181–188.

Higuchi, I.W., Hiestand, E.N., 1963. Dissolution rates of finely divided drug powders. I. Effect of a distribution of particle sizes in a diffusion-controlled process. J. Pharm. Sci. 52, 67–71.

Jovanovic, M., Djuric, Z., 1985. The effect of zeta potentials of aluminium and magnesium hydroxide particles on the viscosity of suspensions. Pharmazie 40, 498–499.

Lucks, J.S., Müller, B.W., Müller, R.H., 1990. Inorganic suspensions-interaction with salts and ionic surfactants. Int. J. Pharm. 58, 229–235.

Mandal, A.B., Moulik S.P., 1982. Interaction of cetyltrimethylammonium bromide with sodium dodecyl sulfate in electrolyte and nonelectrolyte enviroments. In: Mittal, K.L., Fendler, E.J. (Eds.), Solution behaviour of surfactants, Vol. 1, Plenum Press, New York.

Martin, A.M., 1993. Physical Pharmacy, 4th Ed., Lea and Febiger, London.

Martindale, The Extra Pharmacopoeia, 31th Ed., 1996. The Pharmaceutical Press, London.

Meguro, K., Adachi, T., Fukunishi, R., Esumi, K., 1988. Formation of multiple adsorption layers of surfactants on particle surfaces. Langmuir 4, 1160–1162.

Napper, H., 1989. Polymeric stabilization of colloidal dispersions, Academic Press, London.

Nash, R.A., 1988. Pharmaceutical suspensions. In: Lieberman, H.A., Rieger, M.M., Banker, G.S., (Eds.), Pharmaceutical dosage forms. Disperse systems, Vol. 1, Dekker, New York.

Nash, R.A., Haeger, B.E., 1966. Zeta potential in the development of pharmaceutical suspensions. J. Pharm. Sci. 55, 829–837.

Ofner, C.M., Schnaare, R.L., Schwartz, J.B., 1988. Oral aqueous suspensions. In: Lieberman, H.A., Rieger, M.M., Banker, G.S., (Eds.) Pharmaceutical dosage forms. Disperse systems, Vol. 2, Dekker, New York.

Rawlins, D.A., Kayes, J.B., 1983. Pharmaceutical suspension studies III The redispersability of suspensions. Int. J. Pharm. 13, 171–181.

Rupprecht, H., 1978. Sorption von Tensiden an Festkörperoberflächen und ihre Bedeutung im Bereich der Arzneiformen. Prog. Colloid Polymer Sci. 65, 29–44.

Shaw, D.J., 1980. Introduction to Colloid and Surface Chemistry, 4th Ed., Butterworth-Heinemann, London.

Siegel, S., Castellan, N.J., 1988. Non parametric statistics for behavioral science, 2nd Ed., McGraw Hill, New York.

Steinby, K., Silveston, R., Kronberg, B., 1993. The effect ot temperature on the adsortion of a nonionic surfactant on PMMA latex. J. Colloid Interface Sci. 155, 70–78.

Tunçel, T., Gürek, F., 1992. Studies on formulation of loperamide hydrochloride suspensions. Eur. J. Pharm. Biopharm. 38, 82–88.

van den Boomgaard, Th., Tadros, Th.F., Lyklema, J., 1987. Adsorption of nonionic surfactants on latices and silica in combination with stability studies. J. Colloid Interface Sci. 116, 8–16.