Effects of Interactions between Cellulose Ethers and Polysorbate 80 on the Stability of Pyrantel Pamoate Suspensions

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Viscometric and cloud-point data for aqueous dispersions of polysorbate 80 and a cellulose ether (one of two varieties of hydroxypropylmethylcellulose (HPMC) or sodium carboxymethylcellulose (NaCMC) which differ regarding molecular mass) indicated the existence of physico-chemical interactions between aggregated surfactant molecules and polymer macromolecules. The implications of these interactions for interfacial adsorption onto pyrantel pamoate particles suspended in various formulations of these polymer-surfactant dispersions were evaluated. Both HPMCs and also the NaCMC of a higher molecular mass were adsorbed, though in smaller amounts than in the absence of the surfactant owing to the weak adsorption activity of the polymer-surfactant associations. No adsorption of polysorbate 80 was detected in these suspensions. By contrast, in suspensions containing the lower molecular mass NaCMC, polysorbate 80 was adsorbed while the polymer apparently was not. The zeta potential and several indicators of physical stability varied among the various suspensions incorporating ionic polymers, and also among those incorporating non-ionic polymers, in a markedly different way from the corresponding formulations which incorporated a polymer or additive alone. Both polymers and also the polysorbate 80 strongly promoted rapid dissolution of the pyrantel pamoate.

Key words pyrantel pamoate; aqueous suspension; physical stability; cellulose ether; polysorbate 80; interfacial adsorption

The administration of drugs in suspensions has a long and important history. Although this mode of administration is used less frequently nowadays, it continues to provide effective solutions to formulation problems which technologically simpler systems cannot always solve. However, the formulation of suspensions presents its own problems, most of which are associated with the physical stability of the system. Among the factors affecting the physical stability of pharmaceutical suspensions is the use of different additives.[1)]

Research in this area has focused largely on thickening agents and surfactants, which may affect stability through interfacial adsorption.[2—5)] The solution interactions of surfactants and hydrophilic polymers (commonly used together in pharmaceutical suspensions) have been shown to occur mainly between the polymeric macromolecules and aggregated surfactant molecules.[6,7)] If neither or only one of these additives has ionizable groups, their interactions are generally hydrophobic in nature and, consequently, the length of the polymer and surfactant chains is a major factor determining their strength.[6,8)] By contrast, when both the polymer and the surfactant are ionic, it is mainly electrostatic factors which promote or impede aggregation processes.[6,7,9)]

The effects of polymer-surfactant solution interactions on interfacial adsorption have been studied in model systems. In this regard, among the most important contributions are Saunders' study[10)] of methylcellulose–surfactant systems, Sperry *et al.*'s work[11)] on the hydroxyethylcellulose-*tert*-octylphenoxypolyethoxyethanol (Triton® X-405) system, Claesson *et al.*'s work[12)] on the ethylhydroxyethylcellulose–sodium dodecylsulfate system, and Ma and Li's and Otsuka and Esumi's research[13,14)] on systems containing polyvinylpyrrolidone and anionic surfactants. By contrast, there has been relatively little work on the implications of these phenomena for the design and formulation of pharmaceutical suspensions.

In a recent paper we examined how the adsorption of cellulose ethers or the surfactant polysorbate 80 alone affected the physical stability of pyrantel pamoate aqueous suspensions.[4,5)] In the present work, we examined the solution interactions between polysorbate 80 and a cellulose ether (one of two varieties each of hydroxypropylmethylcellulose and sodium carboxymethylcellulose) to determine how this phenomena affects the interfacial adsorption of both additives, as well as their joint effects on the zeta potential and physical stability of pyrantel pamoate suspensions. The effects of these additives on the dissolution rate of the pyrantel pamoate were also evaluated.

Experimental

Drug and Excipients The drug used was pyrantel pamoate USP (batch 48F0042; Sigma Chemical, Madrid, Spain). The excipients were hydroxypropylmethylcelluloses with nominal viscosities of 4000 cPs (HPMC K4M) and 15000 cPs (HPMC K15M) (batches 88760708 and 89760708, respectively; Colorcon, Orpington, U.K.), and sodium carboxymethylcelluloses with nominal viscosities of 400—800 cPs (hereinafter, NaCMC I) (batch 71H0397, Sigma Chemical, Madrid, Spain) and 1000 cPs (hereinafter, NaCMC II) (batch 012, J. Escuder, Barcelona, Spain). The surfactant was polysorbate 80 (Tween® 80, batch 90H0678, Sigma Chemical, Madrid, Spain). Details of determination of the particle size distribution analysis (Coulter® Multisizer II) and specific surface area (Micromeritics ASAP 2000) of pyrantel pamoate have been published previously.[4)] The geometric mean volume diameter of the pyrantel pamoate was 9.53 μm (geometric standard deviation 1.73 μm) and its specific surface area was 1.237 $m^2 \cdot g^{-1}$. All suspensions and reagents were prepared using water with a resistivity of 18.2 M$\Omega \cdot$cm obtained from a Millipore Milli-Q® reverse osmosis system (Millipore Corp.).

Characterization of Polymers The degree of substitution (DS) and the content (% w/w) of methoxyl and hydroxypropoxyl (HPMCs) and carboxymethoxyl groups (CMCNas) of the polymeric chains were determined by ^{13}C-NMR spectroscopy. Samples were hydrolyzed as per Parfondry and Perlin,[15)] and the NMR spectra were recorded at 75 MHz in a Bruker AMX 300 spectrometer with chromium(III) acetylacetate in dimethyl sulfoxide (3 mg·ml) as an external reference. Characteristic peaks were identified by comparison of these spectra with those of methyl and hydroxypropyl glucopyranose derivatives in the case of the HPMCs,[16,17)] and that of carboxymethyl glucopyranose derivative in the case of the NaCMCs.[15,18)] The mean molecular weight of the polymers was estimated from their intrinsic viscosity as described in a previous paper.[4)]

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Characterization of Solution Surfactant–Polymer Interactions Capillary Viscometry: Series of dispersions were made up containing 0.2, 0.4 or 0.6 g·dl^{-1} of cellulose ether, 0.1, 0.5 or 0.9 g·dl^{-1} of polysorbate 80, and both the polymer and the surfactant in these concentrations. The kinematic viscosities of these dispersions were determined at 25 °C in Canon–Fenske viscometers (Afora refs. 5354/1-6). The viscosities relative to water (η_{rel}) were calculated and used to estimate polymer–surfactant interaction parameters (IP) for each dispersion by means of the equation of Lewis and Robinson,[19]

$$IP = \eta_{rel(P)} + \eta_{rel(S)} - \eta_{rel(P+S)} \quad (1)$$

where the subscripts P and S refer to polymer and surfactant, respectively.

Cloud Point: Cloud points were determined in triplicate for 2 g·dl^{-1} dispersions of the HPMCs made up in water and in aqueous solutions of 0.1, 0.5 and 0.9 g·dl^{-1} of polysorbate 80.

Experimental Design. Preparation of Suspensions Following the procedure outlined in an earlier paper,[4] series of suspensions of 4% (w/v) pyrantel pamoate were made up in dispersions containing three concentration levels of polymer and polysorbate 80, the combinations of concentration levels being chosen in accordance with a 3×3 factorial design. Each suspension was equilibrated by stirring it at 25 °C for 48 h. The suspensions are identified according to the polymer variety and the polymer and surfactant concentrations as follows: by a letter, where A=HPMC K4M, B=HPMC K15M, C=NaCMC I, and D=NaCMC II; and by two subscripts 1, 2 or 3, the first corresponding to a polymer concentration of 0.2, 0.4 or 0.6 g·dl^{-1}, respectively, and the second to a polysorbate 80 concentration of 0.1, 0.5 or 0.9 g·dl^{-1}, respectively.

Characterization of the Suspensions The suspensions prepared as described above were characterized as follows, in each case making replicate measurements.

Quantification of Polymer and Surfactant Adsorption: The suspensions (five replicates of each formulation) were centrifuged at 85×1000 ***g*** for 15 min (Kontron Centrikon T-1075) and the supernatant was decanted and filtered through a 0.45 μm pore-diameter membrane (ref. NY501300; Lida). The unadsorbed polymer in the supernatant was determined by Mildwisky's method,[20] and the polysorbate 80 was determined by the method of Clesceri *et al.*[21] (the selectivity of these methods was confirmed in preliminary experiments). In order to avoid any bias in the results due to polymer or surfactant adsorption on the filter, the standards used to construct the calibration lines were treated identically to the supernatant derived from the samples. The amount of polymer or surfactant adsorbed was calculated as the difference of that added and that present in the supernatant.

Zeta Potential: The zeta potentials for the suspensions (three replicates of each formulation) were calculated from their electrophoretic mobilities by means of the Helmholtz-Smoluchowski equation.[22] 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.

Redispersability: Twenty ml of suspension (five replicates of each formulation) were sealed in a 25 ml glass tube 15 mm in diameter and stored at 25 °C for 15 d. Redispersability, the time measured in blocks of 30 s needed to completely redisperse the sediment formed during storage, was determined visually after spinning the tubes end over end at 40 rpm with a rotary mixer (model 34526, Breda Scientific).

Sedimentation Volume: For samples (five replicates of each formulation) treated identically to those in the Redispersability section (above), the sedimentation volume was calculated as the ratio of the volume of the resulting sediment to the volume of the suspension.

Sedimentation Rate: One ml samples (three replicates of each formulation) of freshly prepared suspensions were taken, and 20 ml of each suspension were stored at 25 °C for 6 h, whereupon a second set of 1 ml samples of the supernatants was taken. These samples were diluted to 50 ml with distilled water, and their transmittance (%) at 550 nm was measured in a Shimadzu UV-240 spectrophotometer. Relative turbidities were calculated as the ratio (%) of the transmittance after and before storage.

Dissolution Rate: Pyrantel pamoate (4% w/v) suspensions (six replicates of each formulation) were made up in water (blank) or in water containing 0.2 or 0.6 g·dl^{-1} of HPMC K15M or NaCMC II and 0.1 or 0.9 g·dl^{-1} of polysorbate 80, respectively. In a Turu-Grau apparatus (USP23, Method II), 900 ml of artificial enteric juice (USP23) of pH 7.5 was stirred at 25 rpm at 37 °C. A 2.5 ml aliquot of drug suspension (containing 100 mg of pyrantel pamoate) was introduced into this apparatus at a height of 5 cm above the vessel bottom. At pre-set intervals, the amount of drug dissolved was determined spectrophotometrically, at 300 nm in a Shimadzu UV-240 instrument. The resulting dissolution profiles were fitted with the equation of Higuchi and Hiestand,[23]

$$W(F) = \sum_{i=1}^{n} \left[(A_{0i}^2 = Kt) / A_{0i}^2 \right]^{3/2} \cdot F_i \quad (2)$$

where $W(F)$ is the undissolved drug fraction, n is the total number of particle size intervals into which the distribution is divided (8 in this case), A_{0i} 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), and K is the dissolution rate coefficient.

Statistical Analysis The results obtained under the 3×3 factorial design were subjected to analysis of variance (ANOVA) to establish the statistical significance of the effects of the two factors, proportion of polymer (P) and proportion of surfactant (S), on the following properties of the drug suspension: amount of polymer adsorbed (Γ), zeta potential (ζ), redispersability (R), sedimentation volume (V), and relative turbidity (T). To identify whether the response to the factors was linear or quadratic, the sums of squares were divided into first- and second-order terms by reference to tables of orthogonal coefficients.[24] Quantification of the effects of the factors and their significant interactions ($\alpha<0.05$) on the response variables was done by multiple regression analysis.

Results and Discussion

Table 1 lists the results of the structural characterization of the polymers studied. The two HPMCs have appreciably different mean molecular weights but are very similar regarding substitution. By contrast, the two NaCMCs differ considerably regarding both their mean molecular weights and their substitution characteristics. The higher degree of substitution of the CMCNa I with respect to the CMCNa II and the lack of substituents at the 3-position of the anhydroglucose units detected for the latter one would be expected to be reflected in the hydrophilicities of these polymers, which was confirmed by the appreciably different hydration enthalpies determined previously for these polymers (127.7 J·g^{-1} for NaCMC I, as against 107.9 J·g^{-1} for NaCMC II).[4]

The IP obtained by viscometric characterization of the polymer-surfactant solutions (Eq. 1) are included in Table 2,

Table 1. Structural Characteristics of the Polymers

Polymer	Molecular weight	Degree of substitution				Total substituent content (%)		
		C-2	C-3	C-6	Total	Methoxyl	Hydroxypropoxyl	Carboxymethoxyl
HPMC K4M	92500	0.73	0.23	0.69	1.65	22.9	8.27	—
HPMC K15M	141000	0.72	0.24	0.73	1.69	23.3	8.62	—
CMCNa I	125000	0.42	0.21	0.40	1.03	—	—	26.1
CMCNa II	164000	0.31	n.d.	0.40	0.71	—	—	19.8

n.d.=not detectable.

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Table 2. Mean (Standard Deviation) Results of the Viscometric Study of the Polymer–Surfactant Solutions and Characterization of the Drug Suspensions

Formulation	IP	Γ (mg·g^{-1})	ζ (mV)	R (s/30)	V (%)	T (%)
A_{11}	1.01 (0.01)	1.37 (0.58)	−11.23 (0.44)	3.9 (0.2)	7.5 (0.0)	59.03 (4.13)
A_{12}	0.99 (0.01)	0.78 (0.21)	−25.00 (0.16)	2.0 (0.0)	7.5 (0.0)	59.27 (9.02)
A_{13}	0.94 (0.02)	0.72 (0.11)	−26.71 (1.01)	3.2 (0.2)	7.5 (0.0)	54.09 (0.42)
A_{21}	1.07 (0.03)	3.08 (0.98)	−6.99 (0.99)	3.6 (0.2)	7.9 (0.2)	73.30 (7.18)
A_{22}	0.96 (0.02)	2.50 (0.65)	−24.16 (0.85)	2.2 (0.0)	8.8 (0.0)	65.84 (4.19)
A_{23}	0.37 (0.08)	1.75 (0.18)	−26.73 (0.70)	3.4 (0.6)	8.0 (0.0)	65.53 (0.56)
A_{31}	0.91 (0.08)	4.00 (0.25)	−2.91 (0.44)	5.1 (0.5)	8.8 (0.0)	88.47 (6.26)
A_{32}	0.65 (0.06)	2.77 (0.41)	−21.91 (0.18)	4.4 (0.5)	8.8 (0.0)	76.92 (1.45)
A_{33}	−1.32 (0.11)	2.65 (0.49)	−26.37 (1.00)	4.5 (0.6)	8.8 (0.0)	59.23 (3.02)
B_{11}	0.82 (0.01)	1.90 (0.22)	−9.40 (1.11)	7.2 (1.9)	8.0 (0.0)	75.88 (2.81)
B_{12}	0.84 (0.01)	1.85 (0.29)	−21.68 (1.24)	2.8 (0.0)	7.5 (0.0)	71.35 (5.45)
B_{13}	0.79 (0.01)	0.90 (0.38)	−23.44 (0.87)	3.0 (0.0)	7.5 (0.0)	59.52 (4.21)
B_{21}	−0.14 (0.02)	4.75 (0.50)	−8.58 (0.71)	7.8 (2.1)	8.3 (0.3)	84.93 (6.44)
B_{22}	−0.29 (0.01)	5.40 (1.34)	−17.74 (0.56)	5.2 (0.6)	8.5 (0.7)	75.01 (2.46)
B_{23}	−0.50 (0.02)	2.55 (0.89)	−22.39 (0.91)	4.0 (0.0)	9.0 (0.0)	70.00 (5.68)
B_{31}	−2.07 (0.10)	5.30 (0.60)	−6.42 (0.50)	7.4 (0.0)	10.0 (0.0)	95.91 (2.04)
B_{32}	−3.44 (0.04)	4.70 (1.21)	−17.18 (0.62)	8.6 (0.6)	9.0 (0.0)	96.00 (2.83)
B_{33}	−5.36 (0.07)	4.40 (1.32)	−23.62 (0.31)	6.2 (0.6)	10.0 (0.0)	94.62 (0.86)
C_{11}	1.26 (0.01)	n.d.	−55.01 (1.41)	14.6 (2.4)	7.0 (0.0)	0.50 (0.16)
C_{12}	1.06 (0.02)	n.d.	−53.03 (0.82)	3.6 (1.2)	7.5 (0.0)	0.17 (0.08)
C_{13}	0.98 (0.01)	n.d.	−53.89 (2.72)	2.0 (0.0)	7.5 (0.0)	0.34 (0.08)
C_{21}	1.73 (0.03)	n.d.	−54.54 (0.34)	16.8 (2.1)	7.5 (0.0)	0.42 (0.02)
C_{22}	1.51 (0.03)	n.d.	−53.97 (1.54)	2.0 (0.0)	7.5 (0.0)	0.28 (0.09)
C_{23}	1.26 (0.04)	n.d.	−53.17 (0.71)	2.0 (0.0)	7.5 (0.0)	0.49 (0.10)
C_{31}	2.67 (0.18)	n.d.	−55.53 (0.31)	24.8 (1.2)	7.5 (0.0)	0.79 (0.13)
C_{32}	2.57 (0.03)	n.d.	−54.50 (1.04)	2.4 (0.6)	7.5 (0.0)	0.51 (0.14)
C_{33}	1.82 (0.07)	n.d.	−51.50 (1.02)	2.2 (0.3)	7.5 (0.0)	0.80 (0.15)
D_{11}	1.00 (0.01)	0.70 (0.32)	−53.60 (1.17)	36.8 (6.0)	8.7 (0.4)	0.98 (0.05)
D_{12}	1.58 (0.01)	n.d.	−49.57 (0.70)	4.0 (0.6)	7.5 (0.0)	0.95 (0.10)
D_{13}	1.64 (0.02)	n.d.	−48.21 (0.42)	2.4 (0.6)	8.5 (0.0)	1.28 (0.27)
D_{21}	1.00 (0.06)	0.80 (0.45)	−53.87 (1.01)	68.4 (5.8)	12.5 (0.0)	1.84 (0.13)
D_{22}	2.57 (0.06)	n.d.	−47.95 (1.72)	5.8 (1.5)	15.0 (0.0)	1.93 (0.13)
D_{23}	2.50 (0.14)	n.d.	−48.21 (0.87)	3.8 (0.0)	12.5 (0.0)	1.73 (0.11)
D_{31}	1.00 (0.07)	4.50 (0.94)	−52.48 (2.13)	68.6 (17.3)	19.5 (1.1)	6.06 (1.66)
D_{32}	2.90 (0.14)	3.00 (0.53)	−50.87 (0.94)	7.6 (0.0)	19.0 (1.4)	6.98 (1.28)
D_{33}	5.16 (0.08)	0.65 (0.42)	−49.82 (1.31)	7.4 (0.6)	18.0 (1.1)	7.51 (2.25)

IP=interaction parameter, Γ=adsorbed polymer, ζ=zeta potential, R=redispersability, V=sedimentation volume, T=relative turbidity. n.d.=not detectable.

together with the results of the characterization of the drug suspensions.

The observed deviations of the IPs from the reference value of 1 (unity) suggest the existence of polymer–surfactant interactions. For the suspensions containing the non-ionic HPMCs, the regression equations obtained were:

HPMC K4M: $IP = -0.42 + 6.49 \cdot P + 3.75 \cdot S - 6.70 \cdot P^2 - 2.30 \cdot S^2 - 6.74 \cdot P \cdot S$

$r^2 = 0.93$, 5, 21 d.f., $F = 52.9$, $p > 0.99$

HPMC K15M: $IP = -1.63 + 15.9 \cdot P + 3.25 \cdot S - 27.4 \cdot P^2 - 0.70 \cdot S^2 - 10.2 \cdot P \cdot S$

$r^2 = 0.98$, 5, 21 d.f., $F = 259.2$, $p > 0.99$

The IP, in all cases, was <1, and it decreased steadily with an increasing concentration of polymer or surfactant, most notably in the case of the higher molecular weight HPMC (Fig. 1). This behavior has been observed previously for similar systems[25,26] and was attributed to changes in polymer conformation following the formation of hydrophobic links with the non-ionic surfactant, and to the formation of macromolecule–hemimicelle–macromolecule bridges.[27] By contrast, the IP for the NaCMCs was >1 (Table 2) and increased with polymer concentration, as shown in the regression equations:

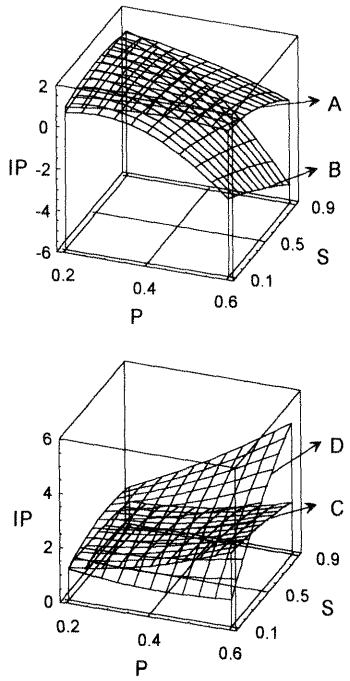

Fig. 1. Response Surfaces Describing the Effects of Polymer (P) and Surfactant (S) Concentrations on the Interaction Parameter (IP)

A=HPMC K4M, B=HPMC K15M, C=NaCMC I, D=NaCMC II.

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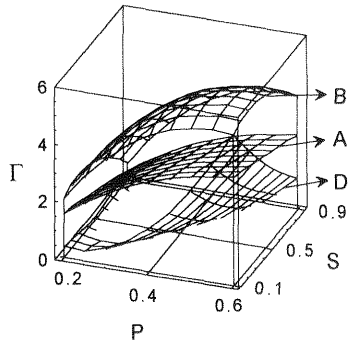

Fig. 2. Response Surfaces Describing the Effects of Polymer (P) and Surfactant (S) Concentrations on the Amount of Polymer Adsorbed (Γ, $mg \cdot g^{-1}$)

A=HPMC K4M, B=HPMC K15M, D=NaCMC II.

Table 3. Mean (Standard Deviation) Cloud-Point Temperatures for $2\,g \cdot dl^{-1}$ Dispersions of HPMC Containing the Indicated Amounts of Polysorbate 80

Polysorbate 80 concentration ($g \cdot dl^{-1}$)	Cloud point (°C)	
	HPMC K4M	HPMC K15M
0	71.44 (0.06)	71.97 (0.06)
0.1	70.97 (0.13)	71.61 (0.07)
0.5	70.12 (0.07)	71.11 (0.06)
0.9	64.71 (0.68)	61.27 (0.22)

NaCMC I: $IP=1.03-0.45 \cdot P+0.64 \cdot S+5.59 \cdot P^2-0.59 \cdot S^2-1.79 \cdot P \cdot S$

$r^2=0.97$, 5, 21 d.f., $F=144.0$, $p>0.99$

NaCMC II: $IP=1.79-5.25 \cdot P+0.09 \cdot S+4.73 \cdot P^2-1.86 \cdot S^2+11.0 \cdot P \cdot S$

$r^2=0.95$, 5, 21 d.f., $F=89.7$, $p>0.99$

and the corresponding response surfaces (Fig. 1). For the systems with NaCMC I, increasing surfactant concentration decreased the IP, suggesting that this polymer has no tendency to form aggregates with the polysorbate 80.[25] Given the fundamental role which hydrophobic interactions must play in the association of this ionic polymer and the non-ionic polysorbate, this behavior must have its origin in the especially high hydrophilicity of NaCMC I. By contrast, for NaCMC II (less hydrophilic than NaCMC I), the IP increased with surfactant concentration (Fig. 1) suggesting that the observed interaction has its origin in the formation of aggregates by means of hydrophobic associations between the nonsubstituted portions of the polymer molecule and the surfactant aliphatic chains.[26]

Further information on the interactions between the HPMCs and the polysorbate 80 was obtained by determining cloud points for selected dispersions.[28,29] For both HPMC varieties, the cloud-point temperature for a $2\,g \cdot dl^{-1}$ dispersion decreased with increasing the polysorbate 80 concentration (Table 3). Other authors have attributed this behaviour to the formation of hydrophobic aggregates,[29] which would support the explanation put forward to account for the IPs <1 obtained for the HPMCs in the viscometric studies.

Adsorption of the polymer onto the pyrantel pamoate particles was detected for the suspensions containing either of the HPMCs or NaCMC II. The low affinity of NaCMC I for the hydrophobic particle surface is attributable to the high hydrosolubility of this polymer.[4] The response surfaces for these experiments (Fig. 2) corresponding to the regression

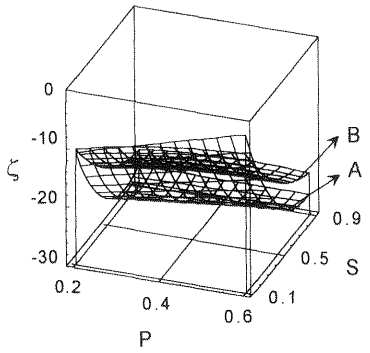

Fig. 3. Response Surfaces Describing the Effects of HPMC (P) and Surfactant (S) Concentrations on Zeta Potential (ζ, mV)

A=HPMC K4M, B=HPMC K15M.

equations:

HPMC K4M: $\Gamma=-0.76+14.3 \cdot P-1.48 \cdot S-10.8 \cdot P^2$

$r^2=0.83$, 3, 41 d.f., $F=64.6$, $p>0.99$

HPMC K15M: $\Gamma=-2.95+29.1 \cdot P+2.43 \cdot S-26.5 \cdot P^2-4.27 \cdot S^2+0.31 \cdot P \cdot S$

$r^2=0.76$, 5, 39 d.f., $F=23.9$, $p>0.99$

NaCMC II: $\Gamma=1.93-14.0 \cdot P+0.82 \cdot S+34.38 \cdot P^2+1.70 \cdot S^2-13.0 \cdot P \cdot S$

$r^2=0.91$, 5, 39 d.f., $F=79.03$, $p>0.99$

show that polysorbate 80 (S) generally hinders the adsorption of all three polymers (P). This reduction in polymer adsorption activity is attributable to the formation of polymer–surfactant aggregates in solution. Similar behavior observed for other surfactant/cellulosic polymer systems has been attributed to the occupation of polymer adsorption sites in polymer–surfactant aggregation.[11] Analogously, aggregate formation leads to a nondetectable adsorption of polysorbate 80 which, in absence of polymer, was significantly adsorbed.[5] Adsorption of polysorbate 80 was only appreciable in the suspensions with NaCMC I. There were no statistically significant differences among the amounts adsorbed in the various NaCMC I formulations. The mean amount adsorbed was $1.7 \pm 0.2\,mg \cdot g^{-1}$, which is close to the value obtained for monolayer adsorption in pyrantel pamoate suspensions containing polysorbate 80 alone.[5] It might be expected that in these formulations, the polymer would interfere less with adsorption of the polysorbate 80 since there was no polymer adsorption or polymer–surfactant solution aggregation.

The regression equations for the zeta potential of the suspensions with the non-ionic polymers:

HPMC K4M: $\zeta=-9.64+22.3 \cdot P-57.4 \cdot S+42.9 \cdot S^2-24.9 \cdot P \cdot S$

$r^2=0.99$, 4, 22 d.f., $F=978.6$, $p>0.99$

HPMC K15M: $\zeta=-11.3+25.4 \cdot P-34.9 \cdot S-18.0 \cdot P^2-20.15 \cdot S^2-9.89 \cdot P \cdot S$

$r^2=0.98$, 5, 21 d.f., $F=170.0$, $p>0.99$

are graphically represented in Fig. 3. This figure shows that increasing the polysorbate 80 concentration increases the negative charge of the particles, and that this effect may be related to the surfactant's tendency to impede adsorption of the polymer (Fig. 2). Other mechanisms must also be involved, however, since no clear relationship could be established between the zeta potential and the amount of polymer adsorbed; the only significant correlation between these parameters ($r=0.60$, $F=14.1$, 1, 25 d.f., $\alpha<0.05$) was found for

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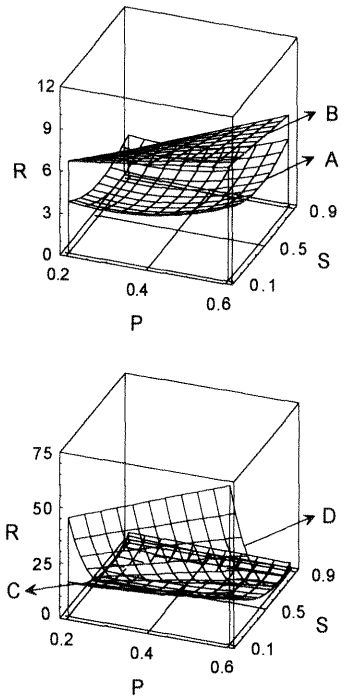

Fig. 4. Response Surfaces Describing the Effects of Polymer (P) and Surfactant (S) Concentrations on Redispersability Time (R, s/30)

A=HPMC K4M, B=HPMC K15M, C=NaCMC I, D=NaCMC II.

the suspensions with HPMC K4M. A further factor affecting the zeta potential in these systems may have been the conformational changes induced in the polymer upon association with the surfactant, which would have altered the properties of the adsorbed film.[30]

The zeta potentials of the suspensions containing ionic polymers differed only slightly among the various formulations. ANOVA showed that the surfactant concentration significantly affected the zeta potential, linearly in the case of NaCMC I, and linearly and quadratically in the case of NaCMC II. Although the corresponding data could not be adequately fitted with the regression model, it is clear that the absolute value of the zeta potential decreased slightly with increasing surfactant concentration, possibly due to the adsorption of the latter in the suspensions with NaCMC I, or to the masking of the ionic groups of the adsorbed macromolecules by polysorbate 80 in the suspensions with NaCMC II.

The response surfaces for the redispersability of the suspensions obtained from the equations:

HPMC K4M: $R=5.91-11.7\cdot P-7.52\cdot S+19.6\cdot P^2+6.77\cdot S^2+0.31\cdot P\cdot S$

$r^2=0.80$, 5, 39 d.f., $F=31.4$, $p>0.99$

HPMC K15M: $R=6.53+2.98\cdot P-7.58\cdot S+9.38\cdot P\cdot S$

$r^2=0.61$, 3, 41 d.f., $F=21.5$, $p>0.99$

NaCMC I: $R=20.8-4.00\cdot P-58.6\cdot S+33.3\cdot P^2+49.6\cdot S^2-30.0\cdot P\cdot S$

$r^2=0.94$, 5, 39 d.f., $F=126.1$, $p>0.99$

NaCMC II: $R=48.2+76.6\cdot P-189\cdot S+157\cdot S^2-88.1\cdot P\cdot S$

$r^2=0.90$, 4, 40 d.f., $F=87.7$, $p>0.99$

are shown in Fig. 4. The redispersability times for suspensions with HPMCs increased slightly with polymer concentration, probably due partly to polymer adsorption and the accompanying increases in the viscosity of the bulk phase.[4] In all cases, redispersion of the sediment formed during storage regenerated the original system, *i.e.* created a suspension that had much the same particle size distribution as the original pyrantel pamoate. By comparison, the redispersability of the suspensions with NaCMCs showed wider variation among the various formulations, and it was strongly affected by changes in surfactant concentration. For the suspensions with NaCMC I, this effect was probably due to partial steric stabilization of the suspension through adsorption of the polysorbate 80.[5,31] In the case of the suspensions with NaCMC II, these produced sediments comprising two layers: a readily redispersable, flocculated upper layer, and an unflocculated lower layer that determined redispersability. The two-layer nature of this sediment suggests that its formation involved the depletion flocculation of the smallest particles and steric stabilization of the largest particles.

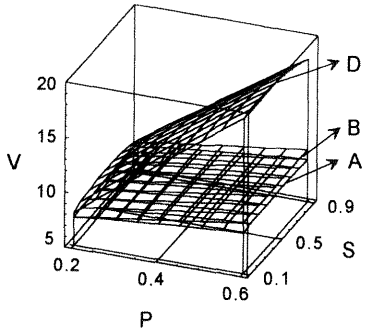

Fig. 5. Response Surfaces Describing the Effects of Polymer (P) and Surfactant (S) Concentrations on Sedimentation Volume (V, %)

A=HPMC K4M, B=HPMC K15M, C=NaCMC I, D=NaCMC II.

The variations in the sediment volume with the proportion of polysorbate 80 and HPMC or NaCMC II are shown in Fig. 5, and were characterized by the following equations:

HPMC K4M: $V=6.76+4.39\cdot P-2.08\cdot P^2-0.45\cdot S^2+1.05\cdot P\cdot S$

$r^2=0.85$, 4, 40 d.f., $F=53.2$, $p>0.99$

HPMC K15M: $V=6.53+5.17\cdot P+0.34\cdot S^2-0.33\cdot P\cdot S$

$r^2=0.81$, 3, 41 d.f., $F=57.8$, $p>0.99$

NaCMC II: $V=1.92+28.5\cdot P+4.35\cdot S-3.44\cdot S^2-4.06\cdot P\cdot S$

$r^2=0.95$, 4, 40 d.f., $F=203$, $p=0.99$

The HPMCs and NaCMC I gave rise to compact sediments (Table 2) whose volumes were not significantly affected (NaCMC I) or barely affected (HPMCs) by changes in the surfactant or polymer concentration. These observations, together with the results obtained in the redispersability experiments, suggest that the mechanisms involved in the formation of these sediments are more complex than simple flocculation.[1,32]

The sedimentation volumes of the suspensions with NaCMC II increased markedly with polymer concentration (Fig. 5). This increase was most evident for the flocculated layer of sediment. Since the degree of polymer adsorption was relatively low in these suspensions (Table 2), it would appear that nonadsorbed polymer molecules played an important role in flocculation, presumably through a depletion mechanism. The fact that a similar effect was not observed for the suspensions with NaCMC I is attributable to the ad-

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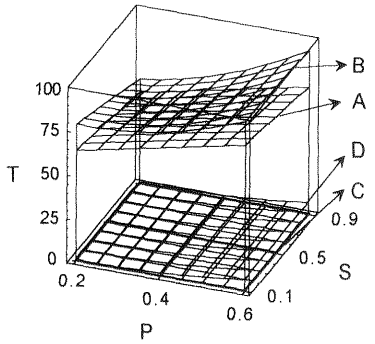

Fig. 6. Response Surfaces Describing the Effects of Polymer (P) and Surfactant (S) Concentrations on Relative Turbidity (T, %)

A=HPMC K4M, B=HPMC K15M, C=NaCMC I, D=NaCMC II.

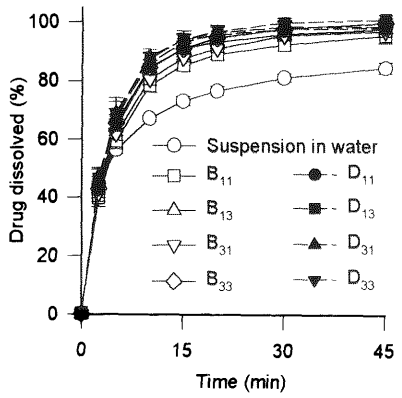

Fig. 7. Dissolution Profiles for Pyrantel Pamoate in Aqueous Suspensions Formulated as Indicated

B=HPMC K15M, D=NaCMC II.

sorption of polysorbate 80 in these formulations, and to the lower molecular weight of NaCMC I compared to NaCMC II, the degree to which the depletion mechanism influences the behaviour of suspensions being dependent on this parameter.[33,34]

The sedimentation rate varied widely among the various suspensions (Table 2). The regression equations:

HPMC K4M: $T=54.2+51.3\cdot P-13.6\cdot S$

$r^2=0.78$, 2, 24 d.f., $F=43.2$, $p>0.99$

HPMC K15M: $T=88.5-68.4\cdot P-32.4\cdot S+139\cdot P^2+47.1\cdot P\cdot S$

$r^2=0.92$, 4, 22 d.f., $F=60.0$, $p>0.99$

NaCMC I: $T=0.54-1.64\cdot P+3.14\cdot P^2+0.04\cdot S^2$

$r^2=0.52$, 3, 23 d.f., $F=8.29$, $p>0.99$

NaCMC II: $T=4.56-28.1\cdot P+53.2\cdot P^2$

$r^2=0.89$, 2, 24 d.f., $F=93.8$, $p>0.99$

and the response surfaces (Fig. 6) show the effect of the independent variables. The HPMC formulations had high relative turbidities, characteristic of stabilized systems in which the particles sediment individually. These high T were undoubtedly due to the effects of interfacial adsorption and to the strong thickening action of the HPMCs. By contrast, the relative turbidities of the suspensions with NaCMCs were typical of flocculated systems.[35] In the case of NaCMC I, flocculation appears to be favoured by the moderate stabilizing capacity of the surfactant film coating the pyrantel pamoate particles.[29] However, the forces responsible for flocculation are not strong enough to hold the particles together in the sediment, as is reflected in the small sedimentation volumes of these formulations (Table 2).

The kinetics of dissolution of the pyrantel pamoate were in all cases well fitted ($R^2>0.95$, Fig. 7) by Eq. 2. The dissolution rate coefficients for the systems containing additives (Table 4) were all larger than for the system containing no polymer or surfactant ($K=9.8\cdot10^{-10}\pm1\cdot10^{-11}$ cm$^2\cdot$s^{-1}), which is attributable to the formation of a film of adsorbed additive at the particles' surface which facilitated wetting by the dissolution medium.[4,5] The formation of a more compact film, which would have slowed dissolution, was probably prevented because polymer adsorption was curbed by polymer–surfactant interactions.

The differences among the rate coefficients for the various HPMC K15M and NaCMC II formulations were relatively small. Slightly faster dissolution rates were obtained for the NaCMC II formulations, which is attributable to the tendency of this polymer to form discontinuous adsorption films.[4] In this regard, because NaCMC II is more hydrophilic than HPMC K15M, it would also have been easier to be desorbed than the non-ionic polymer under the conditions used in the dissolution assay.

Table 4. Mean (Standard Deviation) Dissolution Rate Coefficients (K) for the Indicated Systems, as Obtained by Fitting the Higuchi and Hiestand Model[23] to the Kinetic Data

Formulation	K (cm$^2\cdot$s^{-1})	Formulation	K (cm$^2\cdot$s^{-1})
B_{11}	$1.46\cdot10^{-9}$ ($1.6\cdot10^{-10}$)	D_{11}	$1.98\cdot10^{-9}$ ($1.6\cdot10^{-10}$)
B_{13}	$1.73\cdot10^{-9}$ ($1.7\cdot10^{-10}$)	D_{13}	$2.12\cdot10^{-9}$ ($1.7\cdot10^{-10}$)
B_{31}	$1.55\cdot10^{-9}$ ($1.2\cdot10^{-10}$)	D_{31}	$2.03\cdot10^{-9}$ ($1.2\cdot10^{-10}$)
B_{33}	$1.75\cdot10^{-9}$ ($1.1\cdot10^{-10}$)	D_{33}	$2.52\cdot10^{-9}$ ($1.1\cdot10^{-10}$)

B=HPMC K15M, D=NaCMC II.

In conclusion, polysorbate 80 and the two cellulose ethers studied interact in solution, with the result that the adsorption of each additive in suspensions of pyrantel pamoate particles is different in the absence or in the presence of the other. These interactions thus affect the physical stability of the suspension, and so could have important technological implications. In particular, by careful adjustment of the amounts of HPMC and polysorbate present in a pyrantel pamoate suspension, it should be possible to obtain a suspension that is readily redispersable but which has a sedimentation velocity slow enough for correct dosification of the active ingredient.

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