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# Adsorption of non-ionic water-soluble cellulose polymers at the solid–water interface and their effect on suspension stability

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## Summary

The adsorption of a number of non-ionic water-soluble cellulose polymers onto polystyrene lattices and ibuprofen has been investigated. Plateau adsorption was obtained but was followed by multilayer formation at higher concentrations. Differences in the amount of polymer adsorbed at the two solid-solution interfaces was attributed to their different hydrophobicities. Sedimentation and redispersability studies indicate that the adsorbed layers produce a steric stabilizing effect the magnitude of which depends on the composition and thickness of the adsorbed layer.

## Introduction

Non-ionic water-soluble cellulose polymers are widely used in the formulation of pharmaceutical suspensions to control stability, because of their surface-active, suspending and steric stabilizing effect on the suspended particles. Most of the published work has been concerned with the suspending effect (Lesshafft and Dekay, 1954; Pienta et al., 1954; Garding and Sperandio, 1954; Farley and Lund, 1976) and there appears to be no reported investigation of steric stabilization by these polymers. Steric stabilization depends on the presence and characteristics of an adsorbed layer of polymer at the particle surface. This work reports an investigation

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into the adsorption characteristics of 3 cellulose polymers onto polystyrene latex and the drug ibuprofen and the effect that they have on suspension stability.

## Materials and Methods

### *Cellulose polymers*

Three groups of water-soluble cellulose polymers were used: hydroxyethylcellulose (HEC), Natrosol 250R low viscosity grades L and J; hydroxypropyl cellulose (HPC), Klucel low viscosity grades E and L, (Hercules, U.S.A.); and hydroxypropylmethylcellulose, Pharmacoat low viscosity grades 603, 606 and 615, (Shin-Etsu Chemicals, Japan). All products were used as received without further purification. Molecular weights and adsorbed layer thicknesses were determined using an Ostwald type U tube viscometer, to BS188, with a flow time in excess of 100 s for the reference liquid, at a constant temperature of 25 ± 0.1°C. For molecular weight determinations 5 solutions of concentrations up to 1% w/v were used for each polymer. The correlation coefficients for the plots used to obtain the intrinsic viscosities were better than 0.99 in each case. The viscometer was preconditioned with test solution before use.

The molecular weights of the polymers were evaluated using the following Mark-Houwink equations.

HEC in water at 25°C (Brown et al., 1963)

$$[\eta] = 9.49 \times 10^{-5}\ M^{0.87} \tag{1}$$

and

HPC in ethanol at 25°C (Wirick and Waldman, 1970)

$$[\eta] = 2.6 \times 10^{-5}\ M^{0.915} \tag{2}$$

TABLE 1

INTRINSIC VISCOSITIES AND MOLECULAR WEIGHTS OF THE CELLULOSE POLYMERS HEC, HPC AND HPMC

| Cellulose polymer | Intrinsic viscosity $[\eta]$ ($g^{-1} \cdot dl$) | Molecular weight M |
|---|---|---|
| HEC L | 1.400 | 62,000 |
| HEC J | 2.041 | 95,000 |
| HPC E | 1.139 | 120,000 |
| HPC L | 1.379 | 146,000 |
| HPMC 603 | 0.483 | 4000 |
| HPMC 606 | 1.089 | 10,000 |
| HPMC 615 | 1.554 | 15,000 |

and from this was established
HPC in water at 25°C

$$[\eta] = 6.25 \times 10^{-5}\ M^{0.84} \tag{3}$$

HPMC in water at 20°C (Dow Chemicals, 1975)

$$[\eta] = 3.39 \times 10^{-4}\ M^{0.88} \tag{4}$$

In all cases $[\eta]$ is the intrinsic viscosity. The molecular weights are given in Table 1.

For adsorption studies, solid with polymer solution was equilibrated in a shaking water bath at a temperature of $25 \pm 0.5$°C for 4 days, this being the time found necessary to establish equilibrium. For polystyrene latex the pH of the suspension was adjusted to 6.0 and for ibuprofen 4.0. All containers and glassware were preconditioned with the polymer solution being studied. Estimation of polymer concentrations was made by the method of Milwidsky (1973), where treatment of the polymer solution with phenol and concentrated sulphuric acid produces a brown colour, the intensity of which was measured using a Pye Unicam SP600 spectrophotometer at 490 nm. High concentrations of polymer were diluted as necessary. Calibration curves were linear over the concentration range studied.

*Polystyrene latex*

Polystyrene latex dispersions were prepared by the method of Chung-Li et al. (1976). Particle size distributions were obtained using an electron microscope (Joel Jem 100B).

Latex A, used for adsorption studies, mean diameter $4.34 \pm 0.32$ μm.
Latex B, used for suspension and adsorbed layer thickness studies, mean diameter $2.11 \pm 0.06$ μm.
Latex C, used for flocculation studies, mean diameter $1.18 \pm 0.04$ μm.
Latex D, used for adsorbed layer thickness studies, mean diameter $0.17 \pm 0.01$ μm.

*Ibuprofen*

Ibuprofen, a gift (Boots, Nottingham), was used as supplied by the manufacturer. Data supplied, melting point 78–80°C, mean particle diameter determined by Coulter Counter 24.6 μm and surface area (Quantasorb) of $0.58\ m^2 \cdot g^{-1}$.

## Results and Discussion

*Adsorption on polystyrene latex*

The non-ionic water-soluble cellulose used were HEC L and J; HPC E and L and HPMC 603, 606 and 615; results are shown in Figs. 1, 2 and 3, respectively.

All curves show a similar pattern of rapid initial adsorption with increasing concentration, the plateau then levels off to give a plateau region, which may represent monolayer adsorption, with further increase in adsorption at higher concentrations indicating multilayer adsorption.

Fig. 1.

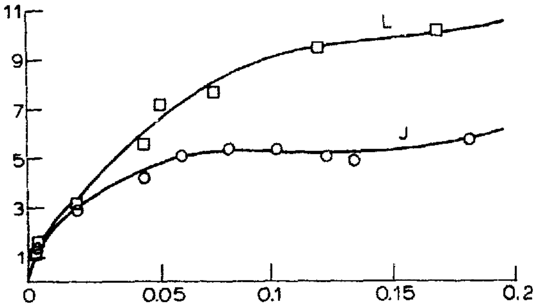

Fig. 2.

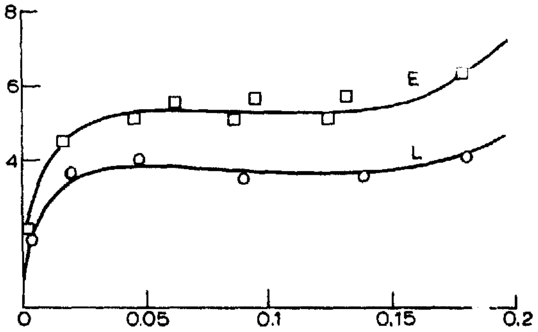

Fig. 1. Adsorption isotherms of hydroxyethyl cellulose: HEC J, ○; HEC L, □, on polystyrene latex at 25°C and pH 4.0. Ordinate: adsorption ($mg \cdot g^{-1}$); abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

Fig. 2. Adsorption isotherms of hydroxypropyl cellulose: HPC E, □; HPC L, ○, on polystyrene latex at 25°C and pH 4.0. Ordinate: Adsorption ($mg \cdot g^{-1}$); abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

Data for plateau adsorption are shown in Table 2.

Adsorbed layer thicknesses of the celluloses on polystyrene latex, obtained from both latex D (0.17 μm) and latex B (2.11 μm) are also given in Table 2. These results were obtained by viscometry, thus:

$$\eta r = 1 + 2.5\phi \tag{5}$$

where $\phi$ the volume fraction of solid in the dispersion is equal to fV, and

$$f = \left( \frac{\text{radius of particle + adsorbed layer thickness}}{\text{radius of particle}} \right)^3$$

and V = solids volume fraction.

Thus a plot of $\eta r$, the relative viscosity, versus V is linear and the slope of the line enables the adsorbed layer thickness to be evaluated.

The results for the different size lattices indicate that, within the limits of

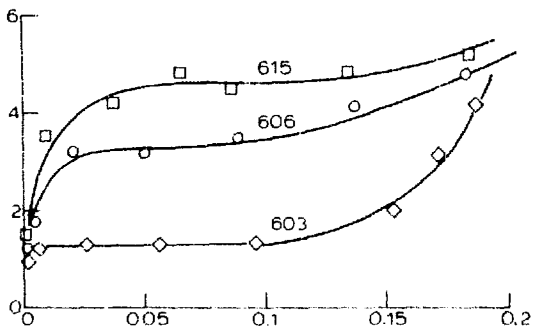

Fig. 3. Adsorption isotherms of hydroxypropylmethyl cellulose: HPMC 603, ◇; HPMC 606, ○; HPMC 615, □; on polystyrene latex at 25°C and pH 4.0. Ordinate: adsorption ($mg \cdot g^{-1}$); abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

TABLE 2

DATA FOR ADSORPTION OF CELLULOSE POLYMERS ON POLYSTYRENE LATEX

| Cellulose polymer | Plateau adsorption ($mg \cdot g^{-1}$) | Area occupied per molecule ($nm^2$) | Adsorbed layer thickness (nm) | |
|---|---|---|---|---|
| | | | Latex B | Latex D |
| HEC L | 9.10 | 14.82 | – | 53.6 |
| HEC J | 5.10 | 41.00 | – | 52.8 |
| HPC E | 5.30 | 49.41 | 51.2 | 42.8 |
| HPC L | 3.70 | 86.47 | 29.8 | 32.1 |
| HPMC 603 | 1.25 | 6.98 | 22.9 | 17.0 |
| HPMC 606 | 3.20 | 6.83 | 24.8 | 27.9 |
| HPMC 615 | 4.55 | 7.20 | 41.3 | 36.4 |

experimental error, the thickness of the adsorbed layer is not dependent on particle size.

The conformation of polymers in the unadsorbed states can be used as a guide for the investigation of the conformation of the adsorbed polymers. In solution the conformation of polymers is affected by intramolecular and intermolecular interactions and solvent conditions. The molecular dimensions of the polymers used here were obtained by viscometric means using the equations of Simha (1945)

$$[\eta] = 0.207 \cdot f^{1.732} \tag{6}$$

where $[\eta]$ is the intrinsic viscosity and f the axial ratio equal to $\ell/d$ and $\ell$ is the length and d the diameter of the molecule, and Kraemer (1941)

$$\ell = \left( \frac{6f^2MV_2}{N_A} \right)^{1/3} \tag{7}$$

where M is the molecular weight, $V_2$ the partial specific volume and $N_A$ Avogadro's number, respectively. Results are shown in Table 3 together with the results obtained from Catalin models.

Adsorption of non-ionic polymeric material may occur by hydrogen bonding, van der Waals interaction, ion dipole interaction (Vincent, 1974) and the hydrophobic effect (Tanford, 1980). In the absence of specific adsorption of a particular group of the polymer it is likely that the functional groups of both the anhydroglucose and substituted units of the cellulose polymer will be involved in the adsorption, i.e. adsorption will occur via both the backbone and substituted branches.

Jenckel and Rumbach (1955) have proposed a model for the conformation of a polymer adsorbed at the surface. They suggested that the polymer molecules will be only partially adsorbed, each molecule being anchored at one point or a few points of the adsorption sites forming 'wrinkles' or loops with the remainder extended out

TABLE 3

MOLECULAR DIMENSIONS OF CELLULOSE POLYMERS OBTAINED FROM VISCOMETRY AND CATALIN MODELS

| Cellulose polymer | Length (nm) | Diameter (nm) | Molecular area ($nm^2$) |
|---|---|---|---|
| | | Viscometry | |
| HEC L | 76.3 | 1.8 | 137.2 |
| HEC J | 100.7 | 1.9 | 191.3 |
| HPC E | 83.7 | 2.2 | 184.1 |
| HPC L | 95.7 | 2.2 | 210.5 |
| HPMC 603 | 30.3 | 1.3 | 39.4 |
| HPMC 606 | 50.4 | 1.4 | 70.6 |
| HPMC 615 | 63.6 | 1.4 | 89.0 |
| | | Catalin model | |
| HEC L | 195.1 | 2.0 | 390.2 |
| HEC J | 292.6 | 2.0 | 585.2 |
| HPC E | 220.7 | 1.6 | 353.1 |
| HPC L | 260.6 | 1.6 | 417.0 |
| HPMC 603 | 44.3 | 1.4 | 62.0 |
| HPMC 606 | 79.3 | 1.4 | 111.0 |
| HPMC 615 | 106.1 | 1.4 | 148.5 |

into the liquid phase. The results reported here show a significant difference between the experimental values of the area occupied per molecule (Table 2) and the values obtained for the molecular areas in the unadsorbed state (Table 3), indicating that partial adsorption of the molecule may have occurred. Support for this suggestion is given by the differences between the adsorbed layer thicknesses (Table 2) and the length of the molecule (Table 3).

The dependence of adsorption on molecular weight for HEC, HPC and HPMC is shown by the adsorption isotherms Figs. 1, 2 and 3, respectively. For HEC and HPC the amount adsorbed decreases with increasing molecular weight whilst for HPMC an increase in the amount adsorbed is shown.

The area per molecule (Table 2) for HEC and HPC increases as mol. wt. increases whilst for HPMC there is no significant variation. This indicates that HEC and HPC molecules adopt a flatter absorption conformation at the particle surface and this is confirmed by the results for the adsorbed layer thickness (Table 2).

For HPMC presumably the different mol. wt. molecules adsorb by the same points of attachment which are common to the different molecules, thus the area per molecule stays the same but the adsorbed layer thickness increases with the additional segments of the polymer extending into the solution. This results in an increase in adsorption as the molecular weight increases.

Fig. 4.

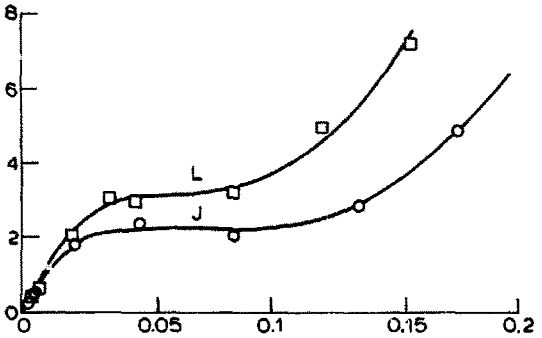

Fig. 5.

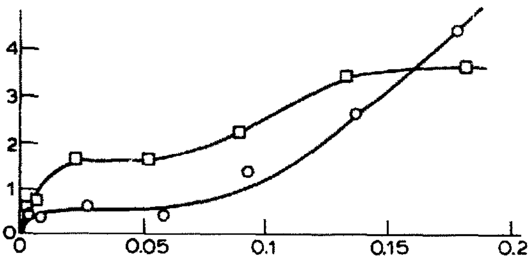

Fig. 4. Adsorption isotherms of HEC J, ○; HEC L, □, adsorbed on ibuprofen at 25°C and pH 6.0. Ordinate: adsorption ($mg \cdot g^{-1}$); abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

Fig. 5. Adsorption isotherms of HPC E, □; HPC L, ○, adsorbed on ibuprofen at 25°C and pH 6.0. Ordinate: adsorption ($mg \cdot g^{-1}$); abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

### *Adsorption on ibuprofen*

Adsorption isotherms for HEC, HPC and HPMC are shown in Figs. 4, 5 and 6, respectively. Similar patterns of adsorption are shown to those found with polystyrene latex, plateau adsorption amounts and molecular adsorbed areas are given in Table 4. Generally amounts adsorbed at plateau adsorption on ibuprofen are lower than those found with polystyrene latex, this being probably due to the fact that the latex surface is more hydrophobic than the ibuprofen — contact angles determined using a Goniometer (Precision Tools and Instruments) and solid films of polystyrene (prepared by evaporating a solution in dioxan) and ibuprofen (prepared by melting), being 93 ± 2°C and 83 ± 2°C, respectively. Scanning electron microscope examination of these films showed them to be quite smooth within the limits of resolution. The results show that polystyrene latex is a suitable model system for predicting results with ibuprofen. Similar results were found by Rawlins and Kayes (1982a) for polyvinyl alcohol fractions on similar solid substrates.

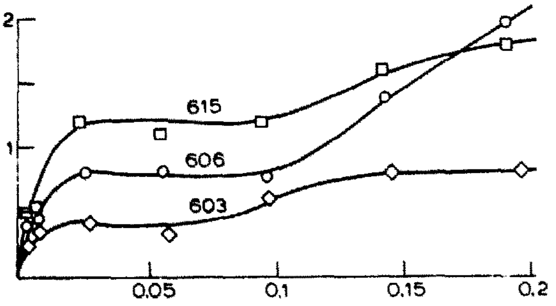

Fig. 6. Adsorption isotherms of HPMC 603, ◇; HPMC 606, ○; and HPMC 615, □, adsorbed on ibuprofen at 25°C and pH 6.0. Ordinate: adsorption ($mg \cdot g^{-1}$); abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

TABLE 4

DATA FOR ADSORPTION OF CELLULOSE POLYMERS ON IBUPROFEN

| Cellulose polymer | Plateau adsorption ($mg \cdot g^{-1}$) | Area occupied per molecule ($nm^2$) |
|---|---|---|
| HEC L | 3.20 | 18.66 |
| HEC J | 2.10 | 43.46 |
| HPC L | 1.60 | 72.19 |
| HPC E | 0.55 | 255.0 |
| HPMC 603 | 0.40 | 9.60 |
| HPMC 606 | 0.80 | 12.21 |
| HPMC 615 | 1.20 | 12.03 |

## *Suspension stability*

### *(a) Polystyrene latex suspensions*

Polystyrene latex suspensions were prepared containing 3.25% w/v of latex B and varying concentrations of HEC, HPC and HPMC, respectively, at pH 4. Stability characteristics were examined after allowing the suspensions to stand for 7 days when sedimentation was complete.

Sedimentation volumes were of the same magnitude, about 14%, for all concentrations of cellulose studied. However, redispersibility values (RV) obtained as described by Rawlins and Kayes (1982b) increased with increasing concentration of cellulose. Typical results are shown for HPMC 603 in Fig. 7 where it is seen that the RV increases at about the concentration where monolayer adsorption occurs, then stays constant for the region of plateau adsorption and again increases where multilayer adsorption occurs.

It appears likely that below the plateau concentration that flocculation of the system has occurred this may be due to a bridging effect as discussed generally by La Mer and Healy (1963) or specifically for the flocculation of lattices by methyl cellulose Saunders and Sanders (1956) and hydroxyethyl cellulose Miyata et al. (1974) or by the mechanism proposed by Sperry et al. (1981) for flocculation

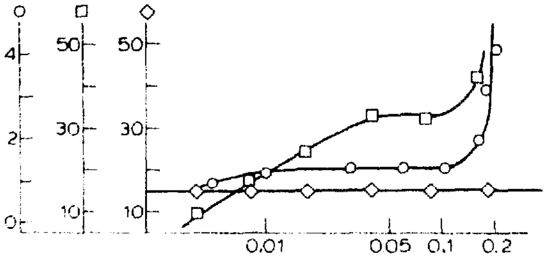

Fig. 7. Characteristics of polystyrene latex dispersion containing hydroxypropylmethylcellulose HPMC 603. (a) Adsorption isotherm, ○; (b) redispersibility value RV, □; (c) sedimentation volume SV, ◇. Ordinate: (a) adsorption ($mg \cdot g^{-1}$); (b) redispersibility value; and (c) sedimentation volume (%). Abscissa: equilibrium concentration ($g \cdot dl^{-1}$).

induced by hydroxyethyl cellulose where it is suggested that attractive forces between latex particles are induced by non-adsorbed soluble polymer.

At greater than plateau adsorption it is suggested that the particles are sterically stabilized but aggregated due to residual van der Waals forces of attraction between the polymer adsorbed layers, the thickness of the adsorbed layer being such as to allow an attractive energy minimum of such magnitude that aggregation occurs, as discussed by Rawlins and Kayes (1980) for certain non-ionic surface-active agents on diloxanide furoate. Where multilayer adsorption occurs this attractive minimum will be reduced thus leading to a deflocculated system which would tend to cake and thus give a higher redispersibility value.

Turbidity studies carried out with latex C using a Pye Unicam SP600 spectrophotometer and various concentrations of celluloses, confirmed that below the plateau value flocculation occurred, whilst above the value stable dispersions were produced.

### *(b) Ibuprofen suspensions*

Ibuprofen suspensions containing 2.5% w/v of drug were prepared similar to those made with polystyrene latex. These were assessed after standing for 24 h by which time sedimentation was complete. Results for HPMC 603 are shown in Fig. 8. At low concentrations a loosely aggregated inelegant high SV suspension was produced, and as the concentration of cellulose is increased a more elegant aggregated system is produced. At concentrations above that necessary to form a monolayer low SV caked systems occur. Redispersion values tend to a minimum at the concentration necessary to form a monolayer and it would appear, as with polystyrene latex, that an adsorbed layer of the correct characteristics is obtained. At high concentrations where redispersion is difficult it is likely that deflocculation and caking have occurred, although an alternative suggestion is that, under these conditions, the solubility limit of the polymer at the point where adsorbed layers meet is surpassed, leading to the polymer molecules cohering one to the other such that a gel structure is produced which would be difficult to disperse.

The results for these systems suggest that suspensions containing substituted celluloses are sterically stabilized in a similar manner to those containing non-ionic surface-active agents.

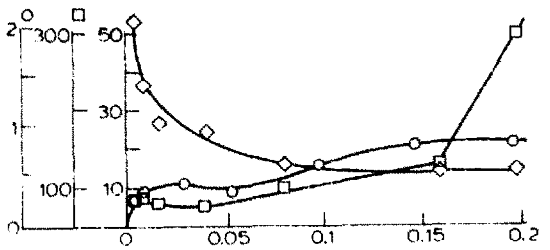

Fig. 8. Characteristics of ibuprofen suspensions containing HPMC 603. (a) Adsorption isotherm, ○; (b) redispersibility value RV, □; (c) sedimentation volume SV, ◇. Ordinate: (a) Adsorption (mg·g$^{-1}$); (b) redispersibility value; (c) sedimentation volume (%). Abscissa: equilibrium concentration (g·dl$^{-1}$).

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