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STABILITY OF SUSPENSIONS IN THE PRESENCE OF NONIONIC WATER SOLUBLE CELLULOSE POLYMERS

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ABSTRACT

The effect of three groups of nonionic water soluble cellulose polymers, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, on the stability or polystyrene latex suspensions and suspensions of the ibuprofen has been investigated.

Results of sedimentation volume, redispersibility and suspension appearance indicated that at low cellulose polymer concentrations suspensions were flocculated whereas at high concentrations suspensions were deflocculated. For hydroxyethyl-cellulose-ibuprofen suspensions flocculation was also observed at high concentrations. Flocculated suspensions obtained were not

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correlated with the energy diagrams. This was attributed to the flocculation energy involved in the interaction.

INTRODUCTION

The formulation of pharmaceutical suspensions which will not cake remains a challenging problem to the formulator.

Polymeric materials are frequently used in suspension formulation as a means of retarding sedimentation, but these substances are also absorbed at the particle interface. Earlier work with nonionic surface active agents[1] and polyvinyl alcohol[2] has examined the adsorption of these materials onto polystyrene latex and the durg diloxanide furoate and their steric stabilizing effect.

The adsorption of a number of nonionic water soluble cellulose polymers onto polystyrene latex and the drug ibuprofen has also been studied[3]. The present work investigates the stability of suspensions produced from these materials. An attempt is made to correlate the results of sedimentation volume, redispersibility and suspension appearance with potential energy diagrams.

MATERIALS AND METHODS

Cellulose Polymers

Three groups of nonionic water soluble cellulose polymers were used as previously described[3]: hydroxyethylcellulose (HEC), Natrosol 250R low viscosity grades L and J; hydroxypropylcellulose (HPC), Klucel low viscosity grades E and L

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(Hercules Inc., U.S.A.); and hydroxypropylmethylcellulose (HPMC), Pharmacoat low viscosity grades 603, 606 and 615 (Shin-Etsu Chemical Co., Japan).

Polystyrene Latex

Polystyrene latex was prepared as previously described[3]. The latex used in these studies was Latex B, monodisperse with number average diameter of 2.11±0.06 μm. Characterization of surface groupings by conductometric titration showed the presence of carboxyl and sulphate surface groups.

Ibuprofen

Ibuprofen (Boots Ltd., England) 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 $m^2 g^{-1}$ [3].

Preparation of Suspensions

3.3% w/v polystyrene latex suspensions were formulated by addition of water, cellulose polymer stock solutions and electrolyte stock solutions so as to give the desired concentration when the total volume was 10 ml. All suspensions were made in 10^{-3} M sodium chloride solution in order to give a suspending medium of suitable conductivity. The pH of the suspensions was adjusted to 6.0 by means of hydrochloric acid and/or sodium hydroxide solutions. The suspensions were equilibrated in a constant shaking water bath at 25 ± 0.5°C for four days which was the time required for equilibrium adsorption.

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Cellulose polymer-ibuprofen suspensions were prepared by dispersing 2.5 g of ibuprofen in water and stock solutions of cellulose polymers by means of a Whirlimixer (Fison Ltd., England) and sonicated for 25 minutes. The final volume of the suspensions was made to 25 ml. The suspensions were allowed to equilibrate in a constant shaking bath at 25 ± 0.5°C for four days. All suspensions were made in 10^{-3} M sodium chloride solution. The pH of the suspensions was 4.0. As mixing procedures may affect the suspension stability, the above mixing order was adopted for all suspensions.

Sedimentation Volume Measurements

Sedimentation volumes (SV) were recorded as ultimate settled volume relative to the total volume expressed as a percentage, after allowing the suspension to stand at 25 ± 0.5°C for seven days (polystyrene latex) and one day (ibuprofen). In some cases, particles floated on the top of the suspension as well as settled and here the combined volumes were taken for the ultimate settled volume.

Redispersibility Measurements

Redispersibility measurements were carried out by rotating the container through 360° at a constant speed of 60 rpm which was found to be the optimum rate to cause redispersion. The number of revolutions was recorded as redispersibility value (RV).

Potential Energy Diagrams

(1) Attraction. Calculation of attractive energy was made according to Vincent's equations[4] which allow for the attraction

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of the adsorbed layer on particle interaction and the retardation effect between particles. For two spheres of radii a_1, a_2, and Hamaker constants A_{p1}, A_{p2}, having adsorbed layers of thickness δ_1, δ_2, and Hamaker constants A_{s1}, A_{s2}, in a medium of Hamaker constant A_m, at a distance of d, the van der Waals attractive energy is given by

$$-12V_a = H_{s1s2}(A_{s1}^{\frac{1}{2}} - A_m^{\frac{1}{2}})(A_{s2}^{\frac{1}{2}} - A_m^{\frac{1}{2}}) +$$

$$H_{p1p2}(A_{p1}^{\frac{1}{2}} - A_{s1}^{\frac{1}{2}})(A_{p2}^{\frac{1}{2}} - A_{s2}^{\frac{1}{2}}) +$$

$$H_{p1s2}(A_{p1}^{\frac{1}{2}} - A_{s1}^{\frac{1}{2}})(A_{s2}^{\frac{1}{2}} - A_m^{\frac{1}{2}}) +$$

$$H_{p2s2}(A_{p2}^{\frac{1}{2}} - A_{s2}^{\frac{1}{2}})(A_{s1}^{\frac{1}{2}} - A_m^{\frac{1}{2}}) \qquad \text{(Eq. 1)}$$

where H is the geometric function. For short range interaction,

$$H_s = a'\left(\frac{y}{u} + \frac{y}{y+u} + 2\ln\left(\frac{u}{u+y}\right)\right) +$$

$$\frac{8br_1^2}{c}\left(2y + (2u + y)\ln\left(\frac{u}{u+y}\right)\right) \qquad \text{(Eq. 2)}$$

and for long range interaction,

$$H_L = \frac{a''}{10c}\left(\frac{y(1+y)^2}{u^2} + \frac{y(1-y)^2}{(u+y)^2} - \frac{2(y^2+y+1)}{u} +\right.$$

$$\frac{2(y^2-y+1)}{u+y} + 4\ln\left(\frac{u+y}{u}\right)\Big) + \frac{b''}{60r_1^2}\left(\frac{2}{u+y} -\right.$$

$$\left.\frac{2}{u} + \frac{y^2+y+1}{u^2} - \frac{y^2-y+1}{(u+y)^2} - \frac{y(1+y)^2}{u^3} - \frac{y(1-y)^2}{(u+y)^3}\right) \qquad \text{(Eq. 3)}$$

in which $y = \frac{r_2}{r_1}$, $u = x^2+xy+x$, $x = \frac{\Delta}{2r_1}$, $c = r_1+r_2+\Delta$,

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$a' = 1.01$, $b' = 0.14(2\pi/\lambda)$, $a'' = 245(\lambda/2\pi)$, $b'' = 2.04(\lambda/2\pi)$;

where for H_{s1s2}: $\Delta = d$, $r_1 = a_1+\delta_1$, $r_2 = a_2+\delta_2$;

H_{p1p2}: $\Delta = d+\delta_1+\delta_2$, $r_1 = a_1$, $r_2 = a_2$;

H_{p1s2}: $\Delta = d+\delta_1$, $r_1 = a_1$, $r_2 = a_2+\delta_2$;

H_{p2s1}: $\Delta = d+\delta_2$, $r_1 = a_1+\delta_1$, $r_2 = a_2$.

H_s is valid at a distance not greater than the critical separation of two particles i.e. $\Delta<\Delta^*$; whereas, for $\Delta>\Delta^*$, H_L should be used. The critical separation can be determined by

$$\Delta^* = 109 - 107 \log a + 3.75(\log a)^2 - 4.5(\log a)^3 \qquad \text{(Eq. 4)}$$

(2) Repulsion. The repulsion between two spheres with adsorbed polymer layers was calculated using the equations derived by Smitham and Napper[5]. Their equations give allowance for the interpenetration and the compression effects for adsorbed layer interactions and also take into account the density distribution of the adsorbed segments which is very important for high molecular weight polymers and thick adsorbed layers. For polymers adsorbed in a loop form on the sphere surface, the potential energy is given by

$$V_s = 2\pi a\omega^2 N_a(\nu_2^2/V_1)(0.5-\chi_1)KTS^m \qquad \text{(Eq. 5)}$$

where ω is the weight of stabilizing loops per unit area, N_a is the Avogadro number, ν_2 is the partial specific volume of the polymer, V_1 is the molecular volume of the solvent and χ_1 is the polymer-solvent interaction parameter. For the interpenetrational domain,

$$S_i^m = (e^{-2bL} + e^{-bd_o}(2bL - bd_o - 1))/(1 - F)^2 \qquad \text{(Eq. 6)}$$

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where d_o is the minimum separation between two spheres, L is the contour length of the polymer chains in the adsorbed layer and $F = e^{-bL}$ is the fraction of segment where b is the scaling constant. Smitham and Napper[5] found that F = 0.01 is appropriate for an exponential distribution function. For the interpenetrational-plus-compressional domain,

$$S^m_{i+c} = bL(e^{-2bL} + 2e^{-bL} - 1 + 2e^{-bL}(e^{-bL} - 1)/bL + (e^{-2bL} + 2e^{-bL} - 1) \ln L_o + (1 - e^{-2bL})L_o)/2(1 - F) \quad \text{(Eq. 7)}$$

where $L_o = d_o/L$.

The electrostatic repulsion between spheres was calcualted by[5]

$$V_e = \frac{\varepsilon a \psi_o^2}{2} \ln\{1 + \exp(-\kappa d)\} \quad \text{(Eq. 8)}$$

where ε is the dielectric constant, κ is the reciprocal Debye Hückel thickness of the diffuse double layer and ψ_o is the surface potential which is approximately identical to the zeta potential.

Hamaker Constsnts

The determination of Hamaker constants was carried out by the method of Fowkes[7]. The surface tensions of the cellulose polymer solutions were measured by the Wilhelmy plate technique in conjuntion with a microforce balance (CI Electronics Ltd., MK2B, England). Contact angles were obtained using a Goniometer (The Precision Tool and Instrument Ltd., England). The solid surfaces used in the contact angle measurements were hard paraffin and soft paraffin. The Contact liquids of the polymer solutions were of such strength as to give complete adsorbed layer coverage.

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Polymer-Solvent Interaction Parameters

The polymer-solvent interaction parameters were obtained by a light scattering method using the relation derived by Debye[8].

RESULTS AND DISCUSSION

Calculations of the total potential energy (V_t) were made by summing the attractive energy (V_a), the steric repulsive energy (V_s) and the electrostatic repulsive energy (V_e).

The results for the Hamaker constants of the cellulose polymers are given in Table 1. For most organic substances A values are within the range of 10^{-20} J[9] and literature values are inconsistent and vary quite widely. For example, the A value for polystyrene-water found by Watillon and Joseph-Petit[10] is $4\text{-}22\times10^{-21}$ J, by Ottewill and Shaw[11] is $1\text{-}11\times10^{-21}$ J and by Schenkel and Kitchner[12] is 9.0×10^{-20}J.
Fowkes[7] found that the A value for polystyrene-water is

TABLE 1

Cellulose Polymer	Hamaker Constant 10^{-19}J
HEC L	1.61
HEC J	1.71
HPC E	1.25
HPC L	1.34
HPMC 603	1.21
HPMC 606	1.30
HPMC 615	1.34
Ibuprofen	1.03

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5×10^{-21} J which is in good agreement with the calculated value of 5.5×10^{-21} J from dispersion data[9]. However, it was pointed out by Gregory[9] that the good agreement of the data is coincident because the interactions of the molecules operating at the interface are short range and have no additive effects to contribute to longer range forces such as those between colloidal particles. Although the results obtained here, due to the above reasons and also the complexity arising from the structure of the polymer and solvent at the interface, is difficult to justify, it does provide some semiquantitative information of the A values for the cellulose polymers used. For the V_a calculations here, the A_p for polystyrene latex was taken as 7.8×10^{-20} J[13] and A_m for water as 3.7×10^{-20} J[14].

For the V_s calculations, the χ_1 values given in Table 2 were used. The adsorption data were taken from the previous study[3]. An attempt to obtain V_s using the equation described by Ottewill and Walker[15] was made but it was not successful. The zeta potentials for V_e were obtained from the microelectrophoretic mobility results[16].

The total potential energy diagrams of HPMC-polystyrene latex suspensions are given in Figure 1 as representative of the cellulose polymer-polystyrene latex systems. A very sharp increase in energy is shown at high concentrations i.e. above the complete adsorbed layer concentration. It is suggested that the particles are sterically stabilized. At low concentrations, a maximum energy peak is given. These curves are similar to that obtained from bare polystyrene latex although lower potential energy is given which

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TABLE 2

Cellulose Polymer	χ_1
HEC L	0.471
HEC J	0.473
HPC E	0.499
HPC L	0.478
HPMC 603	0.446
HPMC 606	0.482
HPMC 615	0.481

is due to the adsorption of small amounts of cellulose polymer slightly reducing the zeta potential. It would be expected that this is a deflocculated system.

The results of redispersibility , sedimentation volume and suspension appearance are shown in Tables 3, 4 and 5 for HEC, HPC and HPMC suspensions respectively. At high concentrations, high redispersibility values and opalescent supernatants were obtained and at low concentrations, low redispersibility values and clear or slightly hazy supernatants were found, although sedimentation volumes gave no significant difference throughout the concentration range studied. At high concentrations, particles were deflocculated whereas at low concentrations it was interesting to find that particles were flocculated.

In the study of polystyrene latex in the presence of nonionic

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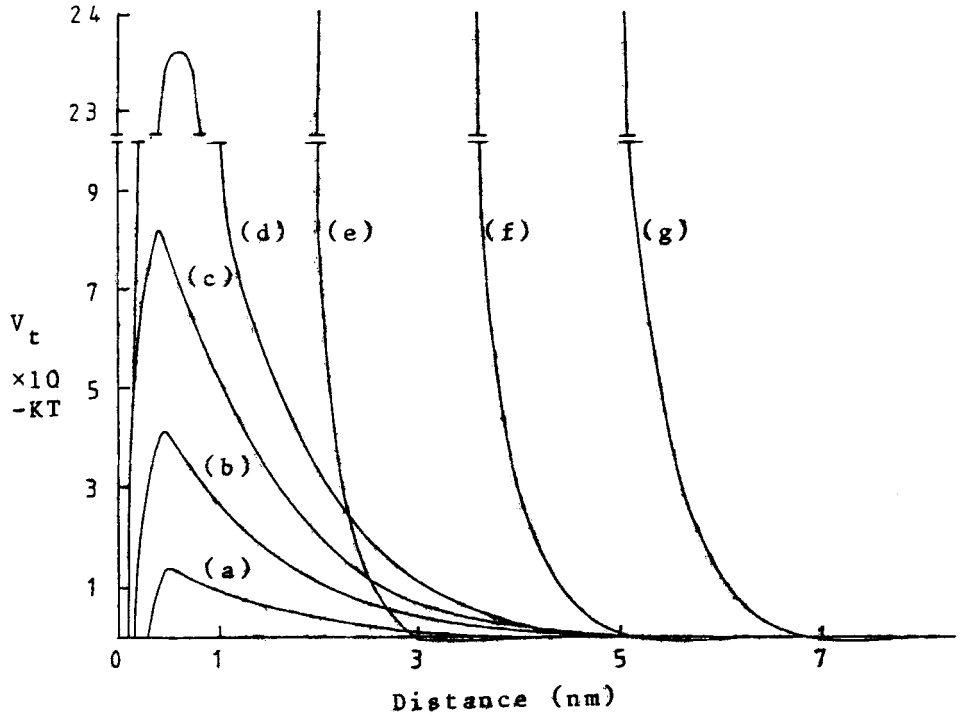

FIGURE 1

Total potential energy curves for polystyrene latex in the presence of HPMC. (a) at 0.004 g/dl HPMC 615 (b) at 0.004 g/dl HPMC 606 (c) at 0.004 g/dl HPMC 615 (d) bare latex (e) at 0.08 g/dl HPMC 603 (f) at 0.08 g/dl HPMC 606 (g) at 0.08 g/dl HPMC 615.

surface active agents of polyoxyethylene glycol monoethers of n-hexadecanol[17], similar energy diagrams to those of Figure 1 were found. At concentrations below the complete adsorbed layer concentration suspensions were deflocculated, since V_e was strong enough to maintain the stability of the particles. This was in accord with the high redispersibility and opalescent supernatant appearance results. For the case here, flocculated suspensions were found at concentrations below the complete adsorbed layer

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TABLE 3

Characteristics of Suspensions of Polystyrene Latex in the Presence of HEC.

Cellulose Polymer	Conc^{n} g/dl	SV	RV	Supernatant Appearance	Sediment Appearance
HEC L	0.16	14	27	Opalescent	Soft Caked
	0.08	14	23	Opalescent	Soft Caked
	0.04	14	23	Opalescent	Soft Caked
	0.016	14	25	Opalescent	Soft Caked
	0.008	14	16	Slightly Hazy	Soft Aggregated
	0.004	15	10	Clear	Soft Aggregated
HEC J	0.16	14	39	Opalescent	Soft Caked
	0.08	14	27	Opalescent	Soft Caked
	0.04	14	21	Opalescent	Soft Caked
	0.016	14	26	Opalescent	Soft Caked
	0.008	15	4	Clear	Soft Aggregated
	0.004	15	5	Clear	Soft Aggregated

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TABLE 4

Characteristics of Suspensions of Polystyrene Latex in the Presence of HPC.

Cellulose Polymer	Conc^{n} g/dl	SV	RV	Supernatant Appearance	Sediment Appearance
HPC E	0.16	14	29	Opalescent	Soft Caked
	0.08	14	28	Opalescent	Soft Caked
	0.04	14	20	Opalescent	Soft Caked
	0.016	14	25	Opalescent	Soft Caked
	0.008	14	4	Opalescent	Soft Caked
	0.004	14	10	Slightly Hazy	Soft Caked
HPC L	0.16	14	26	Opalescent	Soft Caked
	0.08	14	26	Opalescent	Soft Caked
	0.04	14	19	Opalescent	Soft Caked
	0.016	14	5	Opalescent	Soft Caked
	0.008	14	5	Opalescent	Soft Caked
	0.004	14	10	Slightly Hazy	Soft Caked

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TABLE 5

Characteristics of Suspensions of Polystyrene Latex in the Presence of HPMC.

Cellulose Polymer	Conc^{n} g/dl	SV	RV	Supernatant Appearance	Sediment Appearance
HPMC 603	0.16	14	42	Opalescent	Soft Caked
	0.08	14	32	Opalescent	Soft Caked
	0.04	14	33	Opalescent	Soft Caked
	0.016	14	24	Opalescent	Soft Caked
	0.008	14	17	Opalescent	Soft Caked
	0.004	14	9	Slightly Hazy	Soft Caked
HPMC 606	0.16	14	34	Opalescent	Soft Caked
	0.08	14	27	Opalescent	Soft Caked
	0.04	14	26	Opalescent	Soft Caked
	0.016	14	26	Opalescent	Soft Caked
	0.008	14	11	Opalescent	Soft Caked
	0.004	14	11	Slightly Hazy	Soft Caked
HPMC 615	0.16	14	30	Opalescent	Soft Caked
	0.08	14	29	Opalescent	Soft Caked
	0.04	14	27	Opalescent	Soft Caked
	0.016	14	16	Opalescent	Soft Caked
	0.008	14	5	Opalescent	Soft Caked
	0.004	14	6	Slightly Hazy	Soft Caked

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concentration although similar interaction energies to those of the deflocculated systems in the previous study were obtained[17] Therefore, the flocculation of the particles may be as a result of the bridging effect or the volume restriction effect of the polymers leading to a low redispersibility and clear supernatant suspension . The low sedimentation volumes may be due to the slow rate of flocculation[17]. It is suggested that a term of flocculation energy, V_f, should be added to the total potential energy.

For cellulose polymer-ibuprofen systems, as given in Tables 6, 7 and 8 for HEC, HPC and HPMC suspensions respectively, at low concentrations, aggregated sediments, clear supernatants and low redispersibility values were obtained. As pointed out in the polystyrene latex systems, cellulose polymers may have a flocculating effect and flocculation energy may play a role in the interaction between particles. In this case, at low concentrations, the flocculation energy in conjunction with the van der Waals attractive energy may completely overwhelm the electrostatic repulsive energy and no steric energy is involved in the interaction therefore causing a flocculated suspension.

At complete adsorbed layer concentrations, particles were restricted in the steric energy minimum leading to a flocculated suspension as given in Figure 2 in which typical results of HPMC suspensions are shown. Sedimentation volumes (Tables 6, 7 and 8) showed a value greater than 14% which was the ultimate sedimentation volume of the suspensions. Clear supernatant and easy redispersion suspensions were obtained. Also, in the case here, it is expected

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TABLE 6

Characteristics of Suspensions of Ibuprofen in the Presence of HEC

Cellulose Polymer	Conc^{n} g/dl	SV	RV	Superantant Appearance	Sediment Appearance
HEC L	0.2	50	600+	Clear	Loose Aggregated
	0.16	54	600+	Clear	Loose Aggregated
	0.08	55	280	Clear	Loose Aggregated
	0.04	59	600+	Clear	Loose Aggregated
	0.016	51	600+	Clear	Loose Aggragated
	0.008	55	300	Clear	Loose Aggregated
	0.004	60	500	Clear	Loose Aggregated
HEC J	0.2	45	600+	Clear	Loose Aggregated
	0.16	48	600+	Clear	Loose Aggregated
	0.08	50	600+	Clear	Loose Aggregated
	0.04	48	260	Clear	Loose Aggregated
	0.016	49	600+	Clear	Loose Aggregated
	0.008	51	530	Clear	Loose Aggregated
	0.004	53	520	Clear	Loose Aggregated

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TABLE 7

Characteristics of Suspensions of Ibuprofen in the Presence of HPC

Cellulose Polymer	Conc^{n} g/dl	SV	RV	Supernatant Appearance	Sediment Appearance
HPC E	0.2	15	200	Hazy	Caked
	0.16	15	147	Hazy	Caked
	0.08	21	111	Hazy	Aggregated
	0.04	20	110	Hazy	Aggregated
	0.016	25	120	Clear	Aggregated
	0.008	30	95	Clear	Loose Aggregated
	0.004	35	100	Clear	Loose Aggregated
HPC L	0.2	14	94	Hazy	Caked
	0.16	14	90	Hazy	Caked
	0.08	19	76	Hazy	Aggregated
	0.04	19	74	Clear	Aggregated
	0.016	23	84	Clear	Aggregated
	0.008	30	80	Clear	Aggregated
	0.004	49	60	Clear	Loose Aggregated

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TABLE 8

Characteristics of Suspensions of Ibuprofen in the Presence of HPMC

Cellulose Polymer	Conc^{n} g/dl	SV	RV	Supernatant Appearance	Sediment Appearance
HPMC 603	0.2	15	300	Hazy	Caked
	0.16	15	130	Hazy	Caked
	0.08	16	100	Hazy	Caked
	0.04	25	74	Hazy	Aggregated
	0.016	27	80	Clear	Aggregated
	0.008	36	89	Clear	Aggregated
	0.004	53	86	Clear	Loose Aggregated
HPMC 606	0.2	15	200	Hazy	Caked
	0.16	15	120	Hazy	Caked
	0.08	18	90	Hazy	Caked
	0.04	25	73	Hazy	Aggregated
	0.016	25	82	Clear	Aggregated
	0.008	25	79	Clear	Aggregated
	0.004	49	38	Clear	Loose Aggregated
HPMC 615	0.2	14	100	Hazy	Caked
	0.16	14	89	Hazy	Caked
	0.08	15	73	Hazy	Caked
	0.04	15	67	Hazy	Caked
	0.016	22	57	Clear	Aggregated
	0.008	25	52	Clear	Aggregated
	0.004	49	23	Clear	Loose Aggregated

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INTRODUCTION

Indomethacin was first synthesized in 1963 by Shen and his co-workers. It has anti-inflammatory, antipyretic and analgesic effects (Hort et al., 1965; Hodgkinson et al., 1973; Norcross et al., 1965; O'Brien, 1968; Smyth, 1965; Thompson et al., 1966; Wright et al., 1973; Zachariae, 1966). Unfortunately, like other anti-inflammatory agents it carries the risk of gastrointestinal irritation and a number of other side effects, e.g., nausea, vomiting, headaches, etc.

Relatively little information appears in the literature with regard to the *in vitro* release rate of indomethacin from ointments and the *in vivo* bioavailability. The purpose of this investigation was to examine the influence of different indomethacin-containing ointment bases on its *in vitro* release and *in vivo* availability in rabbits, and thus to correlate, if possible, the *in vitro* and *in vivo* data.

EXPERIMENTAL

Chemicals

The following reagents were used as received from the manufacturers. Indomethacin and 1-p-fluorobenzoyl-5-methyl-indole acetic acid (MSD, West Point, PA), emulsion base (hydrophilic ointment base, Clay-Park Labs, Bronx, N.Y.), absorption base (Acquaphor, Pharmaderm, Melville, N.Y.), cellophane membrane (M.W. cut-off point 1,000, Spectrum Medical Industries, L.A., Calif), and acetonitrile, acetic acid and methanol of chromatographic grade (Waters Associates, Millford, MA).

Preparations of Ointments

Indomethacin, previously reduced to a fine powder in a mortar, was incorporated at 1, 3, and 5% concentrations into two different bases by levigation. A 1% indomethacin suspension for oral use was also prepared by dissolving the appropriate amount of indomethacin in 0.1N HCl.

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TABLE 9

Concentrations of Cellulose Polymers in the Adsorbed Layer

Cellulose Polymer	HEC L	HEC J	HPC E	HPC L	HPMC 603	HPMC 606	HPMC 615
$Conc^{n}$	23.8	15.8	15.2	6.8	9.4	11.4	13.2

between the particles as shown in Table 9. This would lead to a high redispersion suspension. However, for HEC suspensions, at high concentrations, clear supernatants and voluminous sediments were found. Flocculated suspensions were obtained. It is likely that the flocculation of the particles may be due to the steric energy minimum and/or the polymer attractive energy, or polymer bridging energy or polymer volume restriction energy.

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