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Preparation and characterization of a new controlled release ibuprofen suspension for improving suspendability

Yoshiaki Kawashima [1], Taro Iwamoto [1], Toshiyuki Niwa [1], Hirofumi Takeuchi [1] and Yoji Itoh [2]

[1] *Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502 (Japan) and* [2] *A-H-Robins-Showa Co., Ltd, 1-5-6 Syoken, Chikusa-ku, Nagoya 464 (Japan)*

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Summary

A new controlled release suspension of ibuprofen was developed by using ibuprofen microspheres with an acrylic polymer (Eudragit RS-PM™). Uniform dispersibility of the microspheres for a period of more than 6 months could be obtained in a low viscous acidic solution of sodium carboxymethylcellulose (CMC) by the addition of D-sorbitol. The presence of D-sorbitol in the acidic medium increased the adsorbed amount of CMC on the microspheres and contributed to build the loose three-dimensional networks of CMC. The coarse microspheres covered with CMC were considered to be held in the networks. This structure of CMC made it possible to maintain the long-term uniform dispersibility. An in vitro drug release test showed no influence of the adsorbed CMC on the release rate. Leakage of drug from the microspheres in the suspension was not found to occur on storage for 6 months.

Introduction

An oral pharmaceutical suspension has long been one of the most favorable dosage forms for pediatric patients or patients unable to tolerate solid dosage forms (Howard, 1981; Sugihara, 1989). The liquid form is preferred because of the ease of swallowing and flexibility in the administration of doses. More therapeutic and commercial advantages (i.e., high patient compliance, reduction of side effect and improvement of bioavailability) could be expected by incorporating a function of controlled drug release into the suspension (Smith et al., 1960; Kawano et al., 1986; Moldenhauer and Nairn, 1990). Therefore, it is desirable to develop a well-formulated controlled release suspension.

There are many physical and chemical considerations in the development and preparation of a suspension which satisfies pharmaceutical requirements (Howard, 1981): uniform dispersibility of drug particles in suspension for concentration uniformity; no caking upon gentle shaking; low viscosity of the dispersion medium for ease of

Correspondence: Y. Kawashima, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502, Japan.

pouring; no adverse interaction between drug and additives for physicochemical stability and bioavailability. Some suspending agents are generally added to the dispersion medium in order that its structure helps to maintain uniform dispersibility (Farley and Lund, 1976; Iwata et al., 1982; Hashem et al., 1987) or to prevent caking of drug particles during shelf-life (Zatz et al., 1979). However, the adjustment of particle dispersity simply by the addition of a suspending agent, such as a water-soluble polymer, is likely to render the suspension too viscous to pour or to swallow. Due to these seemingly opposite requirements (i.e., high and prolonged dispersibility vs low and fluid viscosity), there are few suitable suspensions available that not only ensure physical and chemical stability but also possess the controlled release property of an active agent.

The authors have been developing a preparation suitable for suspensions containing controlled release microspheres of ibuprofen with an acrylic polymer (Eudragit RS-PM™). The microspheres were prepared by the emulsion diffusion method devised by the present authors (Kawashima et al., 1989a,b). In this paper, the preparation of a controlled release suspension possessing long-term uniform dispersibility (> 6 months) and low viscosity (60 cp) was developed by utilizing an acidic dispersion medium composed of sodium carboxymethylcellulose (CMC) with coexisting polyols, such as D-sorbitol. The factors determining the dispersibility and physicochemical properties of the suspension were investigated. The mechanism of stabilization of coarse microspheres in low-viscosity vehicle was also elucidated.

Materials and Methods

Preparation of microspheres of ibuprofen with acrylic polymer

Microspheres were prepared by the emulsion solvent diffusion method (Kawashima et al., 1989a,b): ibuprofen (150.0 g; Taito Koeki Co., Japan) and Eudragit RS-PM (Eudragit) (50.0–75.0 g; Rhom Pharma GmbH, Germany) were dissolved in ethanol (300.0 ml). The ethanolic solution thus prepared was poured into a 0.025–0.05% w/v aqueous solution (3000.0 ml) of a sucrose ester (DF-K70, Daiichi Kogyo Seiyaku Co., Ltd). The system was thermally maintained at 25 °C with agitation (50–150 rpm) by using a three-propeller stirrer in a vessel (5000 ml). After 60 min, the resultant spherical matrices were withdrawn by filtration and dried in a vacuum oven at 40 °C.

Preparation of suspensions

Microspheres (400.0 mg) were suspended in pH-adjusted aqueous solutions of CMC with an ester number of 0.69 per glucose residue (0–1.0% w/v), and the appropriate amount of D-sorbitol or other polyols was added. The total volume of each suspension was 15.0 ml when the pH of the suspensions was readjusted with 0.1 M HCl or 0.1 M NaCl solution. After the suspensions had been formulated, they were gently shaken at appropriate intervals during storage for 1 week.

Sedimentation volume

The sedimentation volumes were described in terms of the ratio of the equilibrium settled height (H_u) to the original height (H_0), as described by Su et al. (1984).

Redispersibility

The number of revolutions necessary to restore the suspension to homogeneity was recorded by the method described by Matthews and Rhodes (1968). The redispersibility was measured by rotating a test tube of 20 ml with a diameter of 1 cm. The test tube was filled with 15.0 ml of the suspension.

Rheology

The apparent viscosities were measured by using a rotation viscometer with a no. 1 rotor (Tokyo Keiki Seisakusho Co., Ltd, Japan). The flow curves were obtained by using a rheometer equipped with a corn of 92 mm diameter (NRM 120-0, Japan Rheology Co., Ltd, Japan) at 20 °C.

Zeta potential

The zeta potentials (Z-potential) were measured at 25 °C using a streaming potential analyzer (ZP-10B, Shimadzu Seisakusho Co., Ltd,

Japan). Values of the Z-potential were calculated from the Helmholtz-Smoluchowski equation (Vercammen and Janssens, 1984). Measurements were carried out in water, as described by Vercammen and Janssens (1984): the viscosity term in the equation exerts a pronounced effect upon the Z-potential. In a non-Newtonian suspension, the viscosity depends on the shear velocity and therefore will change during the measurements.

Determination of adsorption

The amount of CMC or D-sorbitol was measured separately, after dialysis of a supernatant obtained by centrifugation of a suspension at $1000 \times g$ for 1 min. The supernatant (1.0 ml) and 5.0 ml water were packed into a dialysis tube (seamless cellulose tubing, Viskase Sales Corp., U.S.A.) and incubated for 120 h at 25 °C in 1000 ml water (outer water phase), which was replaced daily by a fresh quantity. CMC remained in the tube, and D-sorbitol was dialyzed to the outside. The amounts of CMC and D-sorbitol adsorbed onto the microspheres were determined indirectly from the difference between the initial concentration and the amount found at equilibrium upon analysis after dialysis.

(A) CMC analysis The CMC concentration of the residue in the tube was assayed by the anthrone reaction. 2 ml of 0.1% w/v anthronesulfuric acid was added to 1.0 ml of the residue, and incubated for 15 min at 90 °C. After cooling, it was diluted with 60% sulfuric acid aqueous solution. This sample was analyzed photometrically at 625 nm. Adsorption of CMC on the membrane was negligible.

(B) D-Sorbitol analysis D-Sorbitol concentration in the dialyzate was assayed by gas chromatography (NF XVI, sorbitol assay). After dilution of 1.0 ml of the dialyzates with methanol, it was evaporated to dryness at 40 °C. 1 ml of the internal standard solution was added to the residual solid. The solution obtained was injected into a gas chromatograph.

Drug release test

Drug release tests on the suspension with microspheres and the original microspheres were carried out by using the paddle method specified in USP XXI. The samples were placed in 900.0 ml of phosphate buffer (pH 6.8). The dissolved drug was assayed spectrophotometrically at 220 nm.

Results and Discussion

Stabilization of suspension by formulation of D-sorbitol and CMC and pH adjustment of the medium

Table 1 shows the physical stabilities of microspheres in media of CMC in the presence of different concentrations of D-sorbitol. At a CMC concentration of 1.0%, there was a steady increase in sedimentation volume with increasing D-sorbitol concentration up to 21.0%. Above this concentration, the suspension was found to be stable even after standing for 4 weeks, i.e., the sedimentation volume was 1.0. Without D-sorbitol, the suspensions could not be stabilized by CMC (1.0%) alone. In this system, the microspheres settled rapidly within 1 h. At a CMC concentration of 0.5%, the suspension was stabilized when the concentration of D-sorbitol was increased to more than 28.0%. The increase in concentration of D-sorbitol did not result in a corresponding increase in the sedimentation volume of the 0.5% CMC system, as found in the suspension of 1.0% CMC.

TABLE 1

Effect of the amount of D-sorbitol in suspensions (pH 2.0) on their sedimentation volumes

CMC (% w/v)	D-Sorbitol (% w/v)	Sedimentation volume	
		After 1 week	After 4 weeks
1.0	0	0.1	0.1
	7.0	0.5	0.2
	14.0	0.9	0.7
	21.0	1.0	1.0
	28.0	1.0	1.0
0.5	0	0.1	0.1
	7.0	0.1	0.1
	14.0	0.1	0.1
	21.0	0.1	0.1
	28.0	1.0	1.0

Since the effect of D-sorbitol (a polyol) on the physical stability of the suspension has been evaluated, the effects of coformulating other polyhydric alcohols such as propylene glycol, ethylene glycol, glucose or glycerine, upon the suspensions at pH 4.0–1.0 were investigated (Table 2). Suspensions with four different polyols showed sufficient stability below pH 3.0 for the glycerine system and below pH 2.0 for the others, showing that the sedimentation volume was 1.0. Although the suspension (CMC = 0.5%, pH 2.0) was stabilized by the addition of 28.0% D-sorbitol, higher concentrations (more than 40.0%) were required for other polyols.

The effect of CMC on the physical stability of the suspension was evaluated as shown in Table 3. As the concentration of CMC in the suspensions increased, the sedimentation volumes reached 1.0 at a higher pH, namely, pH 2.0 for the 0.5% CMC system, pH 2.2 for the 0.8% and pH 2.6 for the 1.0% CMC systems. Suspensions without CMC were not stabilized even at pH 1.0.

The studies concerning the sedimentation volume of the suspensions clearly indicated that the coexistence of D-sorbitol with CMC at the optimum concentration and an acidic pH in the dispersion medium are prerequisites for making coarse microspheres stable in the suspension.

TABLE 2

Effect of addition of different types of polyol into suspensions (CMC = 0.5%) on their sedimentation volumes

Polyol (% w/v)	pH	Sedimentation volume (After 1 week)
Propylene glycol (40.0%)	1.0	1.0
	2.0	1.0
	3.0	0.1
	4.0	0.1
Ethylene glycol (40.0%)	1.0	1.0
	2.0	1.0
	3.0	0.1
	4.0	0.1
Glucose (40.0%)	1.0	1.0
	2.0	1.0
	3.0	0.1
	4.0	0.1
Glycerine (40.0%)	1.0	1.0
	2.0	1.0
	3.0	1.0
	4.0	0.1

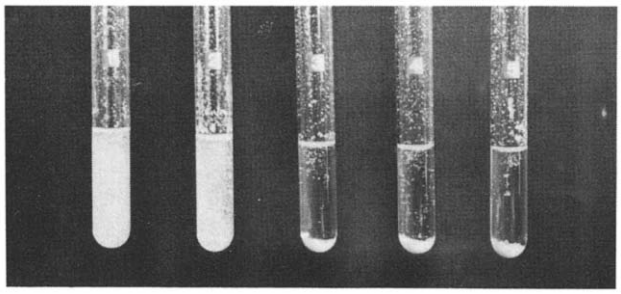
TABLE 3

Effect of the amount of CMC and the pH of the medium of suspensions containing D-sorbitol (28.0% w/v) on their sedimentation volumes

CMC (% w/v)	pH	Sedimentation volume	
		After 1 week	After 4 weeks
0	1.0	0.1	0.1
	2.0	0.1	0.1
	3.0	0.1	0.1
0.5	1.8	1.0	1.0
	2.0	1.0	1.0
	2.2	0.6	0.2
	2.4	0.1	0.1
0.8	2.0	1.0	1.0
	2.2	1.0	1.0
	2.5	0.1	0.1
	3.0	0.1	0.1
1.0	2.0	1.0	1.0
	2.4	1.0	1.0
	2.6	1.0	0.7
	3.0	0.1	0.1

Coarse microspheres (105 μm in weight average diameter) of ibuprofen with an acrylic polymer were uniformly suspended for more than 6 months in an acidic dispersion medium (< pH 2.0) composed of 0.5% w/v CMC by the addition of D-sorbitol (> 28.0% w/v), as shown in Fig. 1. The viscosity of the suspension (pH 2.0) was only 60 cp, which shows good fluidity. There has been no report that such coarse particles can be uniformly suspended in a readily fluidizable medium for more than 6 months. In contrast, caking was observed in media in which the pH had been adjusted to more than 3.0. The number of revolutions necessary to restore these caked suspensions to homogeneity was more than 40 according to the method described by Matthews and Rhodes (1968), indicating the difficulty of redispersibility for practical use.

The sedimentation volume of a suspension (medium pH, 2.0; CMC = 0.5%; D-sorbitol = 28.0%) was 0.7 after standing for 2 years at room



pH 1.0 2.0 3.0 4.0 5.0

* Suspension Medium = CMC (1.0%, w/v) + D-Sorbitol (28.0%, w/v)

Sedimentation volumes of each suspensions after standing 6 months

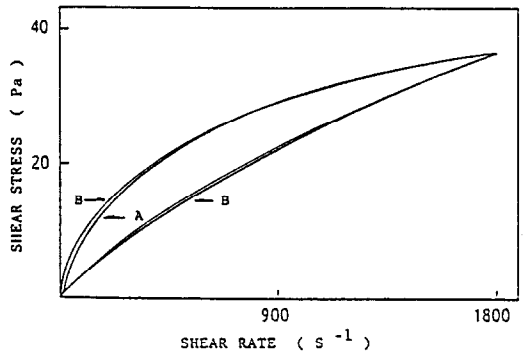
pH	1.0	2.0	3.0	4.0	5.0
Sedimentation volume	1.0	1.0	0.1	0.1	0.1

Fig. 1. Physical stability of microsphere suspension after standing for 6 months.

temperature. This suspension could readily be redispersed upon shaking: the number of revolutions required to make it homogeneous was only one.

Physicochemical properties of the stabilized suspension

Rheological properties The rheological properties of stabilized and unstabilized suspensions were precisely investigated in order to clarify the relationship between the viscosity and suspendability by using a rotation viscometer and a rheometer. Fig. 2 shows the apparent viscosities and flow curves of stable and unstable suspensions of medium pH 1.8 and 2.2, respectively (Table 3). Both suspensions were composed of 0.5% CMC and 28.0% D-sorbitol. As shown in Fig. 2a, the dispersion media of both suspensions



a, Shear stress - shear rate curves of suspension A and B

b, Apparent viscosities - shear rates of suspension A and B

Shear Rate (S^{-1})	Viscosity (cp) A	B
0.07	700	700
0.14	500	500
0.35	328	400
0.70	220	340
1.40	160	240
2.80	110	135
6.99	64	84
13.98	60	73

Fig. 2. Rheological properties of stabilized (A) and unstable (B) suspensions. Suspension A (microspheres uniformly suspended after standing for 6 months), pH 1.8; suspension B (microspheres begin to sediment within 24 h) pH 2.2. The formulation of both suspensions was the same: CMC 0.5% w/v; D-sorbitol 28.0% w/v.

were non-Newtonian liquids and showed a shear thinning property with identical hysteresis loops. Their apparent viscosities at shear rates of 0.07 and 0.14 s^{-1} were 700 and 500 cp, respectively (Fig. 2b). The stable suspension exhibited slightly lower apparent viscosities at 0.35–13.98 s^{-1} as compared to the unstable one.

At extremely low shear rates, the rates of disentanglement and alignment of polymer chains under the influence of shear are negligible compared to the rates of entanglement and randomization of polymer chains. Hence, the flow units are neither noticeably deformed nor reduced in size by shear, and the systems exhibit Newtonian flow, with a constant and high viscosity designated as the zero-shear viscosity (Umeya et al., 1970; Schott, 1985). The same apparent viscosity (700 cp) of two suspensions at the extremely low shear rate (0.07 s^{-1}) and the same shear-thinning property suggested that both the suspensions were of equal viscosity and of equal structural strength of the media on standing.

The results indicated that the physical stability of the suspensions studied could not be explained simply on the basis of the rheological properties. It was therefore considered that other mechanisms were operative in bringing about the considerable degree of physical stability so that the coarse microspheres could be uniformly suspended in the medium for over 6 months.

Zeta potential Fig. 3 shows the effect of the pH on the Z-potentials of ibuprofen, Eudragit and microspheres composed of ibuprofen and Eudragit in water. The Z-potential of ibuprofen increased proportionally to the pH and reached zero at pH 2.0. This Z-potential–pH profile agreed well with that of drugs possessing carboxylic acid groups (Law, 1984). The positive charge of Eudragit increased with decreasing pH. Below pH 3.0, the curve showed a steep increase while a moderate rise was indicated over the pH range 5–3. At the higher pH, the quaternary ammonium groups on the surface of Eudragit particles became slightly ionized, showing a low Z-potential value. As the pH decreased, the degree of ionization increased so as to cause an increase in Z-potential. Microspheres composed of ibuprofen and Eudragit showed a gradual decrease in negative charge until becoming zero at pH 3.2. A further decrease of pH gave a reversal of sign towards a positive charge, which followed a rapid increase in positive charge. At pH 2.0, the positive charge of microspheres reached 60 mV/g. The pH where the positive charge of microspheres began to rise was consistent with that where the charge of Eudragit steeply increases. These data indicated that Eudragit in microspheres gave microspheres with a high positive charge (60 mV/g) at pH 2.0.

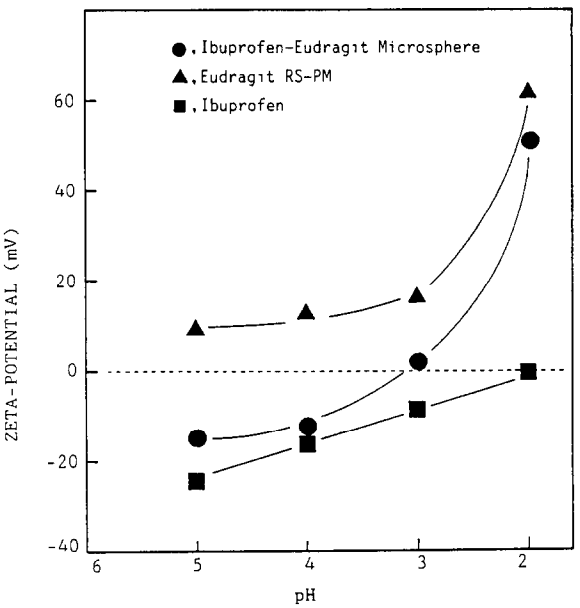


Fig. 3. Influence of pH on Z-potentials of microspheres and their components.

Adsorption and sedimentation The addition of positively charged ibuprofen-Eudragit microspheres to an aqueous solution of an anionic polymer may cause an electrostatic interaction, since there may exist an attractive force between the cationic groups of quaternary ammonium on the surface of microspheres and the anionic groups of the polymer.

The adsorption of CMC on microspheres in the presence of D-sorbitol was investigated as a function of pH in the dispersion medium as shown in Fig. 4A. The decrease in pH had no substantial effect on adsorption until the pH became 3.0. As the pH decreased below 3.0, the curve of the

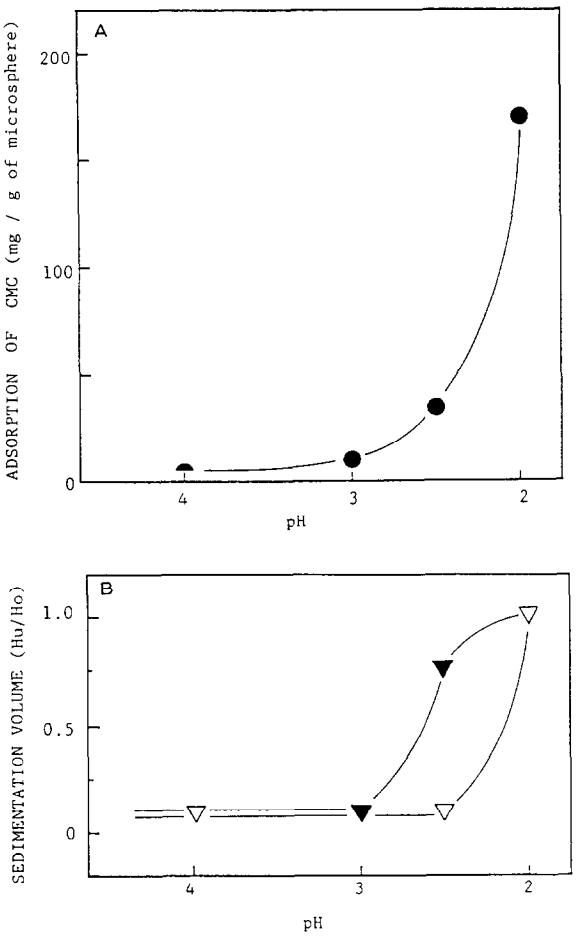


Fig. 4. (A) Dependence of the amount of CMC adsorbed per g of the microsphere on the pH of the suspension medium. Suspension formulation: CMC, 0.5% w/v; D-sorbitol, 28.0% w/v. (B) Dependence of sedimentation volume of suspensions on pH [storage after (▼) 1 h, (▽) 6 months].

adsorption showed a steep increase, which reached 150 mg/g of microspheres at pH 2.0. The sedimentation volume after 1 h began to rise at pH 3.0 where a marked increase in adsorption was observed, as shown in Fig. 4B. When the pH of the medium was 2.0, a suspension was physically stabilized, indicating a sedimentation volume of 1.0 even after 4 weeks. It was interesting to compare the results on the Z-potential with the adsorption behavior of CMC. The curve for the Z-potential of microspheres (Fig. 3) and that for adsorption (Fig. 4A) showed a similar trend with increasing acidity of the medium. The settling of microspheres changed and was prevented from pH 3.0. At this point, the adsorption as well as the Z-potential started to increase significantly. The findings shown in Figs. 3 and 4A suggested at least that the interaction of positively charged microspheres with the anionic polymer contributed to the extent of adsorption. It appeared to depend on the initial charge density on the surface of microspheres. The existence of CMC anions has been proved in the aqueous solution of pH 2.0 by the following experiments: (1) The 0.5% CMC (ester number per glucose residue = 0.20) solution showed precipitation at pH 2.0, since all sodium carboxymethyl groups of the glucose residues are converted to free acids under acidic conditions, whereas such precipitation was not found in any of the present systems, in which CMC with an ester number of 0.69 was employed. (2) Precipitation of the calcium salt of CMCs (ester number 0.69) was confirmed in its 0.5% solution (pH 2.0) by the addition of calcium chloride.

To achieve long term physical stability, the addition of the polyol to the dispersion medium was indispensable (Table 1), as well as the decrease in pH of the medium. These findings are consistent with the results reported by Zatz and Lue (1987), who studied a suspension of sulfamerazine prepared with polysorbate 80. The addition of sorbitol changed the adsorption properties of polysorbate on sulfamerazine due to the dehydration of the polyoxyethylene groups of polysorbate, resulting in an increase in sedimentation volume of the suspension.

Fig. 5A and B shows the effect of D-sorbitol on the adsorption of CMC on the microspheres and the sedimentation volume at pH 2.0. The curves for both the amount of adsorption and the sedimentation volume gradually increased in slope with increase in concentration of D-sorbitol in the medium. There is no steep increase in Fig. 5A at the specific point, which was found at around pH 3 in Fig. 4A. It was also confirmed that no adsorption of D-sorbitol on the microspheres was detectable in the present study. Fig. 6 shows the results for the sedimentation volume replotted in terms of the adsorption volume. The physical stability of the suspension was enhanced by in-

creasing the adsorption of CMC on microspheres. It was indicated that the stability of the suspension depended on the amount of CMC adsorbed. This dependency could explain the difference in stability of two suspensions (Fig. 2) composed of the same formulation but with different pH values. The pH values of stable and unstable suspensions were 1.8 and 2.2, respectively. The amount of adsorbed CMC (75 mg/g of microsphere) on the microspheres at pH 2.2 was insufficient to render them stable for 4 weeks. Adsorption was more strongly in evidence at pH 1.8 than at 2.2. Therefore, the physically stable suspension was considered to be obtained at pH 1.8, even after standing for 4 weeks.

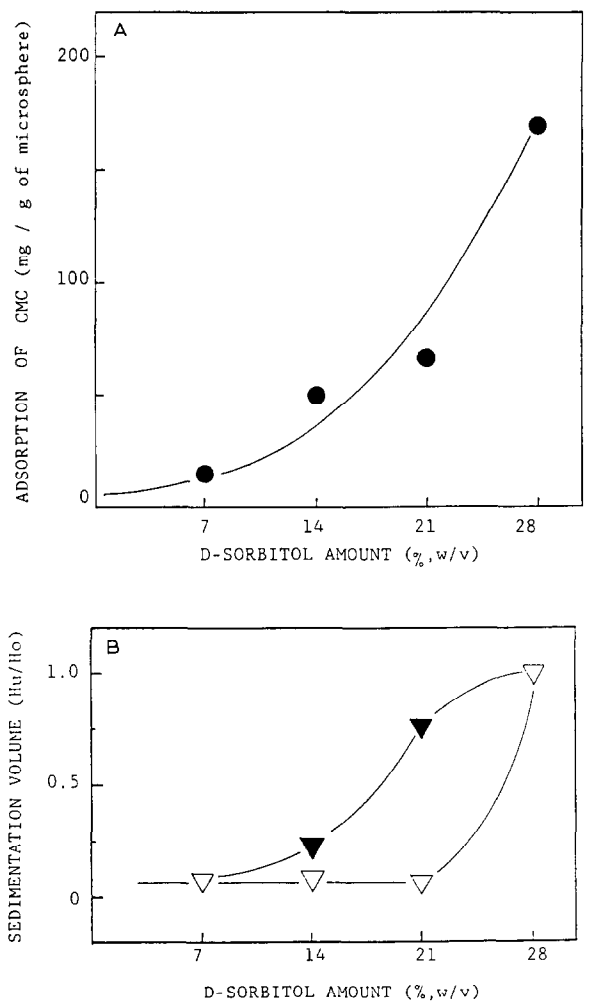


Fig. 5. (A) Dependence of the amount of CMC adsorption per g of the microsphere on D-sorbitol coexisting in the system. Suspension formulation: CMC, 0.5% w/v; pH 2.0. (B) Dependence of sedimentation volume of suspensions on the amount of D-sorbitol [storage after (▼) 1 h, (▽) 6 months].

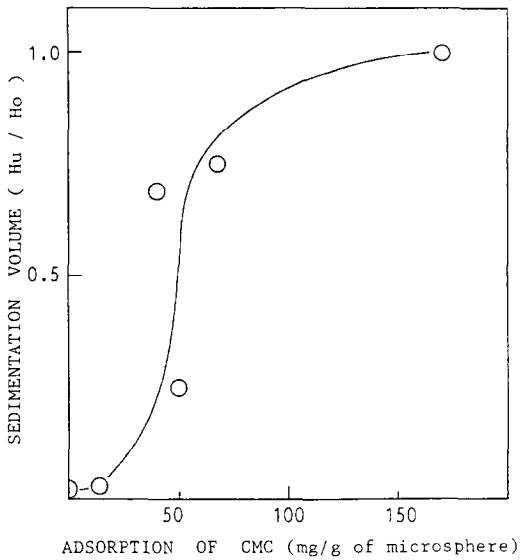


Fig. 6. Relationship between the adsorption amount of CMC on microspheres and the sedimentation volume of the suspension. Sedimentation volume: measured after standing for 1 h.

Mechanisms of stabilization and lower viscosity at high shear rate

The positive charge of microspheres which was exerted in an acidic medium acted as the initial driving force to adsorb CMC on the microspheres. After the slight, initial adsorption, the positive charge might be diminished to some degree by shielding of the microsphere surface (Tempio and Zatz, 1981). The amount adsorbed via the electrical attraction, however, was not enough to suspend microspheres uniformly in a low-viscosity medium for long periods. As reported by Hirai (1968), the extent of hydrogen bonding among CMC molecules was enhanced by the addition of D-sorbitol to an aqueous CMC system because CMC was subjected to dehydration by the strongly hydrating action of D-sorbitol itself. Consequently, in the presence of D-sorbitol, a proportion of the excess CMCs (not involved in the initial adsorption) in the system was forced to bind the CMCs already adsorbed on the micro-

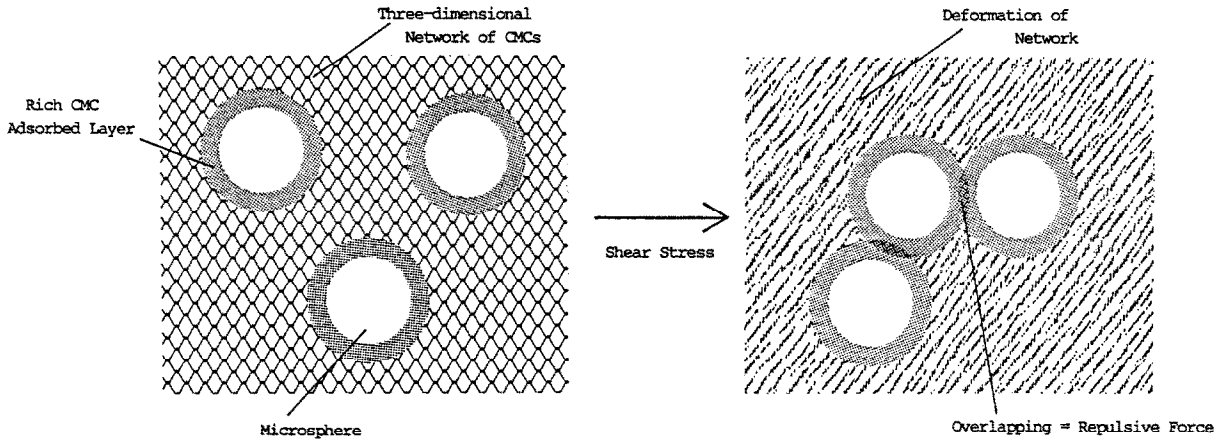


Fig. 7. Generation of mutual repulsive forces among microspheres by overlapping of layers rich in CMC adsorbed under shear stress.

spheres. This bonding led to a greater increase in the amount of CMC adsorbed on the microspheres: coverage of the dispersed microspheres by polymer molecules made it possible that the polymer could attach more extensively to the microspheres. At the same time, the hydrogen bonding among all CMC molecules caused by D-sorbitol resulted in the build up of a loose, three-dimensional network of CMC in the system. Microspheres covered with CMC were suspended in the loose structure of CMC. The phenomenon of hydrogen bonding among CMCs adsorbed on the microspheres building up the structure might contribute to making the suspension more stable. When a particular amount of urea was added to this stabilized system, instability resulted. Urea is well known to disrupt hydrogen bonding among polymers (Aoki and Nagai, 1978; Miyajima, 1990). This finding strongly suggested that the CMC network built up in the system was brought about by the hydrogen bonding among CMCs. A similar mechanism for the stabilization of coarse suspensions was discussed previously only on the basis of a theory of polymer stabilization of disperse systems by Hiestand (1972). The adsorption process postulated in this section is fairly consistent with the results: (1) the amount of CMC adsorbed in the presence of D-sorbitol rapidly increased at pH values below the isoelectric point where microspheres were positively charged; and (2) with increase in concentration of D-sorbitol, the amount of CMC adsorbed on the microspheres gradually increased. Therefore, a physically stable suspension of coarse microspheres can be achieved by controlling the degree of adsorption via the optimum concentration of D-sorbitol and the acidity of the dispersion medium.

The suspension stabilized via the formation of a three-dimensional network of CMC showed non-Newtonian flow. It was interesting to note that a stable suspension gave lower apparent viscosities at high shear rates than did an unstable

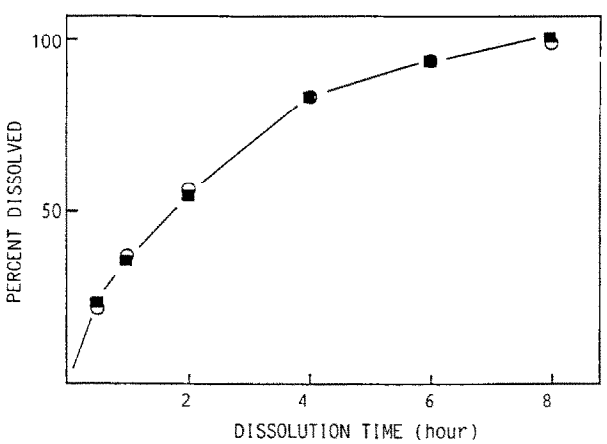


Fig. 8. Ibuprofen release profiles from microspheres and their suspension. (○) Microspheres; (■) suspension of microspheres. Suspension formulation: CMC, 0.5% w/v; D-sorbitol, 28.0% w/v; pH 2.0.

suspension, as found in Fig. 2b. The microspheres in the stable suspension were rich in CMC-adsorbed layers. After the three-dimensional structure had been broken down by high shear stress, the microspheres were forced to approach each other more closely. They were brought so close together that their polymer-rich layers began to overlap. Mutual repulsion was brought about by such overlapping (Tamai, 1990). Thus, the suspension was a more fluidizable liquid, giving a lower viscosity, as shown by the model in Fig. 7.

In vitro drug release profile from microspheres dispersed in suspension

The drug release rates of the ibuprofen–microsphere suspension (pH, 2.0; CMC, 0.5%; D-sorbitol, 28.0%) after standing for 6 months and microspheres alone were investigated in pH 6.8 phosphate buffer (JPXI disintegration test solution), as shown in Fig. 8. The ibuprofen release rate from the microsphere suspension was consistent with that from microspheres alone. This result indicated that no leakage of drug occurred from the microspheres in the suspension on storage for 6 months and that the adsorbed CMC exerted no influence on the drug release rate of microspheres. The acidity of the suspension medium was attributed as the cause of drug leakage being prevented from the microspheres. Because of the low solubility of ibuprofen (pK_a 5.2) in the acidic medium, it was unable to diffuse out from the microspheres to the medium.

In conclusion, the controlled release suspension developed in this study could satisfy the expected qualities in the pharmaceutical suspension: (1) uniform dispersibility; (2) no leakage of the drug from the microspheres during storage; and (3) no negative effect of the additives on the drug release property.

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