

Aqueous dispersion behavior of drug particles by addition of surfactant and polymer

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Abstract

The effect of surfactant and polymer on dispersion stability of aqueous suspensions of 5-(3-ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112) was investigated by measuring the adsorbed amount of surfactant and polymer, ζ potential, particle size, and sedimentation rate of CT112. The addition of celluloses rather than sodium dodecyl sulfate (SDS) provided a high stable suspension of CT112. In addition, mixed systems of celluloses and SDS enhanced CT112 dispersion more effectively. The mechanism of dispersion stability of CT112 by addition of SDS and celluloses is discussed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Aqueous dispersion of drug; Adsorption of surfactant and polymer; Cellulose; Sodium dodecyl sulfate

1. Introduction

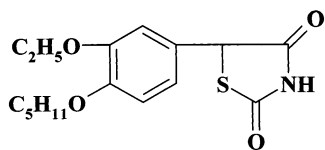
Drug particles are usually hydrophobic and are hardly dispersed in aqueous solution. Surfactants or polymers have been often added to dispersion systems to obtain a high stable dispersion of drug particles. As a result, the repulsion forces between drug particles are enhanced due to electrostatic forces and steric hindrance forces. We have studied the aqueous dispersion behavior of 5-(3-

ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112) particles, known as an enzymatic inhibitor, using water-soluble polymers such as poly(vinyl pyrrolidone) and celluloses and found that the conformation of polymer adsorbed on CT112 is an important factor to obtain a stable dispersion [1]. Further, since CT112 is soluble in alkaline solution a stable aqueous dispersion of CT112 has been prepared by neutralization of CT112 alkaline solution in the presence of polymer with addition of acid [2]. It is also expected that usage of both surfactant and polymer can enhance dispersion stability of drug particles because surfactant can adsorb effectively on CT112

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particles for controlling the nucleation process, while polymer may act as protective colloid. Thus, it is interesting to study the role of surfactant and



Scheme 1. Chemical structure of CT112.

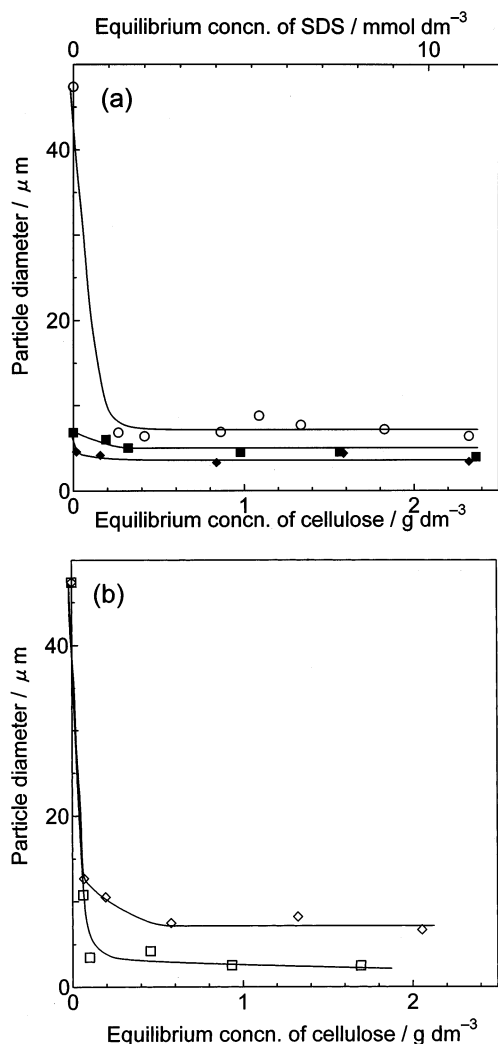


Fig. 1. Variation in particle diameter of CT112 by addition of (a) SDS (\circ), SDS-SH-50 (\blacklozenge), and SDS-SM-100 (\blacksquare); (b) SH-50 (\diamond) and SM-100 (\square). The feed concentration of SDS for SDS-SH-50 and SDS-SM-100 systems is $2\ mmol\ dm^{-3}$.

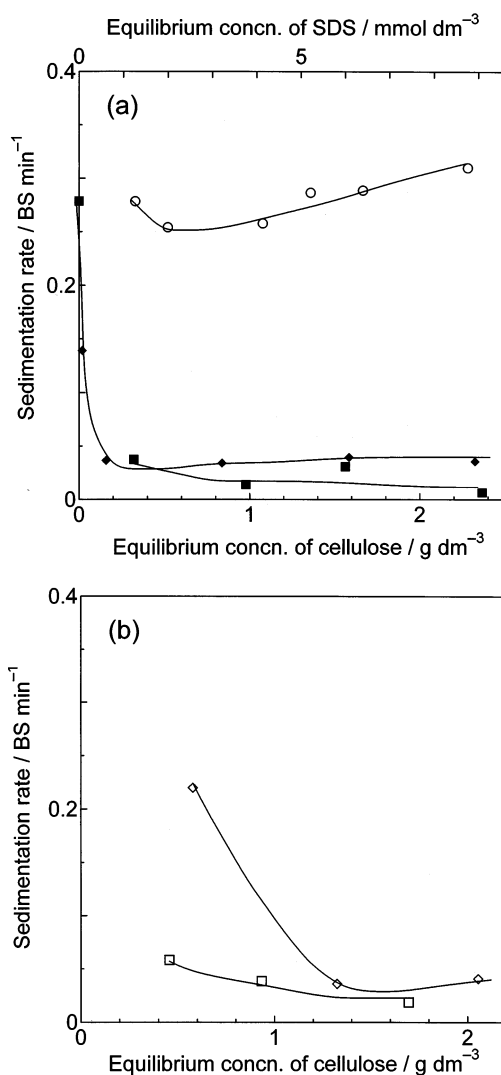


Fig. 2. Variation in sedimentation rate of CT112 by addition of (a) SDS (\circ), SDS-SH-50 (\blacklozenge), and SDS-SM-100 (\blacksquare); (b) SH-50 (\diamond) and SM-100 (\square). The feed concentration of SDS for SDS-SH-50 and SDS-SM-100 systems is $2\ mmol\ dm^{-3}$.

polymer for preparation of stable dispersion of drug particles. It is known [3] that adsorption of surfactant and polymer on solid particles depends on aqueous properties of surfactant and polymer as well as on surface properties of solids. Generally, if both polymer and surfactant are favorable for adsorption of solids, their competitive adsorption will occur. On the other hand, if the interactions between polymer and surfactant are strong

in aqueous solution, one of them can induce the adsorption of the other, which will not adsorb. These simultaneous adsorptions of surfactant and polymer will affect aqueous dispersion of CT112.

The aim of this work was to investigate the effect of surfactant and polymer for preparation of stable aqueous drug particle dispersion by measuring the dispersion stability of CT112, amount adsorbed of surfactant and polymer, and ζ potential of CT112.

2. Experimental

2.1. Materials

5-(3-Ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112) was kindly supplied by Senju Pharmaceutical Co. The chemical structure of CT112 is shown in Scheme 1. Sodium dodecyl sulfate (SDS) was obtained from Tokyo Kasei Kogyo and used after recrystallization from the mixture of isopropanol/hexane. 2-Hydroxypropyl methyl ether cellulose (SH-50, $M_w = 100\,000$) and methyl ether cellulose (SM-100, $M_w = 160\,000$) were obtained commercially. The water used was purified with a Milli-Q Plus system. The other chemicals were of analytical grade.

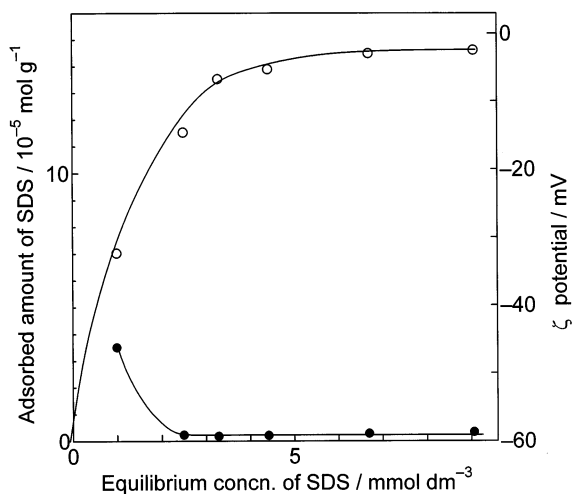


Fig. 3. Adsorption isotherm of SDS (○) on CT112 and ζ potential (●) of CT112 by adsorption of SDS.

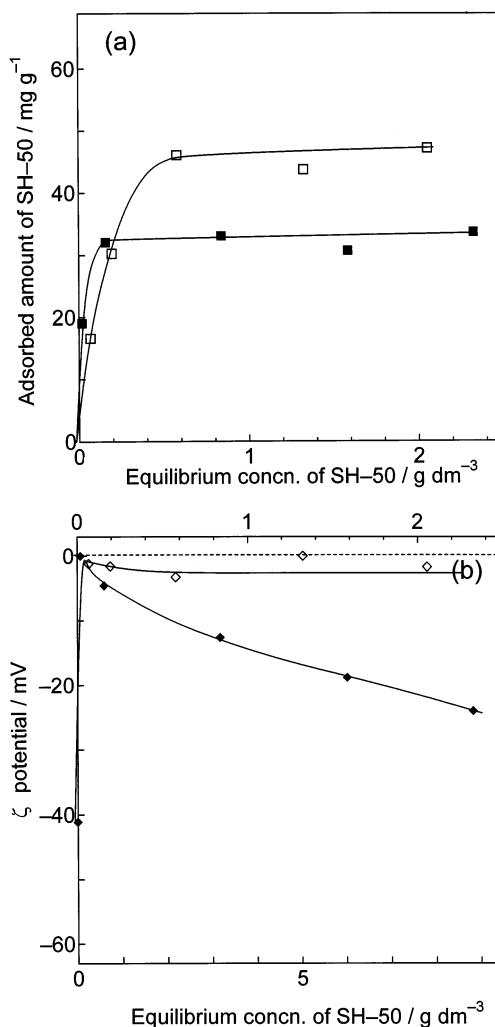


Fig. 4. (a) adsorption isotherms of SH-50 on CT112 in the absence (□) and in the presence (■) of SDS; (b) ζ potential of CT112 by addition of SH-50 in the absence (◇) and in the presence (◆) of SDS. The feed concentration of SDS is 2 mmol dm^{-3} .

2.2. Methods and measurements

5-(3-Ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112, 0.2 g) was dissolved in NaOH solution in the presence of surfactant/polymer and sodium acetate. To 8.6 ml of these basic solutions in vials, 1.4 ml of aqueous 0.5 N-HCl solution was added dropwise under agitation. The final pH

of the aqueous dispersions was found to be about 5, and then the vials containing the suspensions were shaken in a water bath at 25°C for 1 day. The dispersion stability was estimated by using a Turbiscan MA2000 (Formulation, France); it detects concentration variation in the mixture by scanning the whole height of the sample in transmission and in backscattering. The sedimentation rate was evaluated from the change of backscattering intensity at top portion of sample with running time. The particle size of CT112 was

measured with a laser scattering particle-size distribution analyzer (Horiba, LA-920). The amounts of polymer and surfactant adsorbed were calculated from the difference in their concentrations in the supernatant before and after the adsorption. The concentration of celluloses was determined by means of a spectrophotometric assay based on anthrone [4,5] and that of SDS using a high-performance liquid chromatography (Toso Co.) equipped with an RI-8012 RI detector, column, CAPCELL PAK C18 UG 4.6 mm i.d. × 250 mm (Shiseido Co., Ltd); temperature at 40°C. ζ Potential of CT112 suspensions was measured with an electrophoretic apparatus (Pen Kem 500); ζ potential was converted from mobility using the Smoluchowski relation.

Most of the experiments were carried out at 25°C.

3. Results and discussion

It has been confirmed previously [2] that aqueous dispersions of CT112 by neutralization of CT112 with acid in the presence of poly(vinyl pyrrolidone) or celluloses depend on the additive concentration of the polymer. The stability has been estimated by measuring the turbidity of CT112 suspensions.

In this study, the dispersion stability of CT112 was estimated by measuring the particle size of CT112 and sedimentation rate. Fig. 1 shows the change in the particle diameter of CT112 after neutralization. Here, the particle diameters were measured by diluting CT112 suspensions using mother solutions including SDS/polymer. Without any additives, the particle size of CT112 was at around 47 μm . By addition of low concentration of SDS or cellulose, the particle size of CT112 decreased significantly and it became constant with a further addition of SDS or cellulose. In particular, the systems of SDS–SH-50 (mixed), SM-100 (only), and SDS–SM-100 (mixed) showed diameters below 5 μm . The concentration of 2 mmol dm^{-3} SDS in the mixtures was employed by considering the effect of irritation of eyes with SDS.

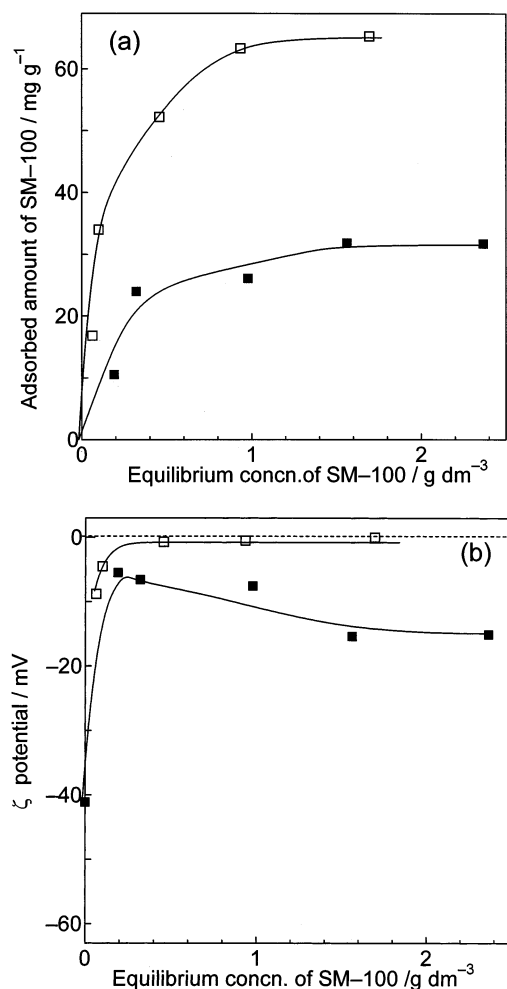


Fig. 5. (a) adsorption isotherms of SM-100 on CT112 in the absence (□) and in the presence (■) of SDS; (b) ζ potential of CT112 by addition of SM-100 in the absence (□) and in the presence (■) of SDS. The feed concentration of SDS is 2 mmol dm^{-3} .

Fig. 2 shows the sedimentation rate of CT112 using a Turbiscan. Without additive, CT112 particles were flocculated, showing a large sedimentation rate. By addition of SDS, any flocculation was not observed and the sedimentation rate was at around $0.25\text{--}0.30 \text{ BS min}^{-1}$ over a whole SDS concentration. On the other hand, the sedimentation rate by addition of SH-50 or SM-100 decreased compared with that by SDS. In addition, a remarkable low sedimentation rate was observed for SDS–SH-50 and SDS–SM-100. This result suggests that mixed systems of cellulose and SDS provide a reasonable stable dispersion of CT112.

To study the effect of additives such as SDS and celluloses on aqueous dispersion of CT112, the amount adsorbed of SDS/celluloses on CT112 and ζ potential of CT112 suspensions were measured. Fig. 3 shows the adsorption isotherms of SDS on CT112 in the absence of cellulose. One can see that the adsorbed amount of SDS increases and reaches saturation with SDS concentration. It seems that SDS molecules adsorb on CT112 surface, orienting their hydrocarbon chains to the surface because parent CT112 shows hydrophobic property. This adsorption mechanism of SDS can be supported by a change in ζ potential; ζ potential of CT112 without SDS could not be measured due to flocculation of CT112, but the addition of SDS renders the ζ potential negative, as shown in Fig. 3. In the two mixed systems containing a feed concentration of SDS (2 mmol dm^{-3}) the adsorbed amount of SDS was enhanced at low cellulose concentrations compared with that in the absence of cellulose and became a saturation with an increase of the cellulose concentration (data not shown). This enhancement in the adsorption of SDS caused by the cellulose adsorption is probably due to the interaction between SDS and celluloses. The adsorbed amount of celluloses was also affected by the coadsorption of SDS (Figs. 4 and 5); the

adsorbed amount of SM-100 was lower in the presence of SDS than that in the absence of SDS over a whole SM-100 concentration, whereas the adsorbed amount of SH-50 in the presence of SDS was greater than that in the absence of SDS at low SH-50 concentrations, but at high SH-50 concentrations, the trend was opposite. Thus, it is found that in the SDS–cellulose system, the adsorption of both SDS and SH-50 is enhanced at lower SH-50 concentrations. Interestingly, in such low concentration regime of SDS–cellulose system, the particle diameter of CT112 became small and the sedimentation rate was reasonably low. Further, the ζ potential of CT112 by addition of celluloses became zero, while it showed negative values for SDS–SH-50 and SDS–SM-100 systems. According to the previous study [2], it has been suggested that since the conformation of SH-50 and SM-100 adsorbed on CT112 takes mainly tails or loops, a high dispersion stability at relative high polymer concentrations occurs as a consequence of high steric hindrance between the adsorbed polymer layers. On the other hand, in the SDS–SH-50 and SDS–SM-100 systems a stable CT112 dispersion may occur due to steric hindrance caused by polymer adsorbed as well as electrostatic repulsion forces caused by SDS adsorbed. These results suggest that a combination of SDS and cellulose provides more stable aqueous dispersion of CT112 than SDS alone or cellulose alone.

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