

Effect of dilution on aqueous dispersion of drug particles

Hideo Terayama^a, Kozue Hirota^b, Tomokazu Yoshimura^b, Kunio Esumi^{b,*}

^a Chemical Development, International division, Senju Pharmaceutical Co. Ltd, 2-5-8 Hiranomachi, Chuo-ku, Osaka 541-0046, Japan

^b Department of Applied Chemistry, Institute of Colloid and Interface Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

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Abstract

Aqueous suspensions of 5-(3-ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112) have been prepared by neutralization of alkaline solutions of CT112 in the presence of surfactant/polymer with HCl. Sodium dodecyl sulfate (SDS) and celluloses have been used. The effect of dilution of water on the aqueous CT112 dispersion has been studied by measuring the amount adsorbed of surfactant and polymer, ζ -potential, particle size, and sedimentation behavior. The dispersion stability of aqueous CT112 suspension in the presence of polymer or SDS by dilution of water depends on the initial concentration of polymer or SDS. On the other hand, the dispersion stability of aqueous CT112 suspension in the presence of both polymer and SDS is stable even by dilution of water. The mechanism for the effect of dilution of water has been discussed.

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1. Introduction

Drug particles are known to be usually hydrophobic and hardly dispersed in aqueous solution. Surfactants or polymers have been often added to obtain a stable aqueous dispersion of drug particles.

Recently we have intensively studied the aqueous dispersion behavior of 5-(3-ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112) particles, known as an enzymatic inhibitor, using

surfactants and water-soluble polymers [1–4]. It has been found [3] that the aqueous dispersion stability of CT112 particles is enhanced by neutralization of CT112 alkaline solution in the presence of cellulose/sodium dodecyl sulfate (SDS) with the addition of HCl. The kinetics of neutralization for formation of CT112 particles has also been investigated [4].

Aqueous dispersions of particles are often used by diluting concentrated dispersions. Accordingly it is vital to study the effect of dilution on the dispersion stability of CT112 particles.

The objective of this study is to investigate the effect of water dilution on CT112 aqueous dispersions by measuring sedimentation rate, ζ -potential

* Corresponding author. Tel.: +81-3-3260-4271; fax: +81-3-3235-2214

E-mail address: kuesumi@ch.kagu.sut.ac.jp (K. Esumi).

and adsorbed amount of additives such as surfactants and water-soluble polymers.

2. Experimental

2.1. Materials

5-(3-Ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione (CT112) was kindly supplied by Senju Pharmaceutical Co. SDS was obtained from Tokyo Kasei Kogyo and used after recrystallization from the mixture of 2-propanol/hexane. 2-Hydroxypropylmethyl ether cellulose (SH-50, Mw = 100 000) and methyl ether cellulose (SM-100, Mw = 160 000) were obtained commercially. Water used was purified with a Milli-Q Plus system. The other chemicals were of analytical grade.

2.2. Methods and measurements

CT112 (0.2 g) was dissolved in NaOH solution in the presence of surfactant/polymer and sodium acetate. Then 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 6,

and then the vials containing the suspensions were shaken in a water bath at 25 °C for 1 day. Subsequently 30 ml of deionized water was added to the suspensions in the vials and the vials were shaken again at 25 °C for 1 day. Accordingly the initial dispersions of CT112 were diluted four times. 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. The particle size of CT112 was measured with a laser scattering particle-size distribution analyzer (Horiba LA920, Japan). The amounts of polymer and surfactant adsorbed were obtained 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 [5,6] and that of SDS using a high-performance liquid chromatography (Toso Co., Japan) equipped with a RI-8012 RI detector, column, CAPCELL PAK C18 UG 4.6 mm I.d. × 250 mm (Shiseido Co., Ltd, Japan); temperature at 40 °C. ζ -potential of CT112 suspensions was measured with an electrophoretic apparatus (Pen Kem 500, USA).

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

Table 1

Physicochemical properties of CT112 suspension in the presence of polymer or SDS before and after dilution

Polymer or surfactant	Average particle size (μm)	ζ -potential (mV)	Polymer adsorption (mg g^{-1})	SDS adsorption ($\times 10^{-5} \text{ mol g}^{-1}$)
<i>SH-50</i>				
1.5 g dm^{-3}	7.5	0	59.2	–
Dilution	6.1	0	44.6	–
0.4 g dm^{-3}	9.5	0	20.0	–
Dilution	9.5	0	19.9	–
<i>SM-100</i>				
1.5 g dm^{-3}	6.4	0	49.2	–
Dilution	9.7	0	24.4	–
0.4 g dm^{-3}	13.8	0	19.9	–
Dilution	25.4	0	19.9	–
<i>SDS</i>				
7.2 mmol dm^{-3}	5.3	–61.0	–	12.9
Dilution	5.7	–25.9	–	8.7
2.4 mmol dm^{-3}	6.6	–29.3	–	12.1
Dilution	27.3	–45.7	–	12.0

3. Results and discussion

3.1. Single systems of SDS-CT112 and polymer-CT112

After neutralization of CT112 in the presence of SDS or polymers with HCl, deionized water was added to the suspensions, resulting in four times dilution. The results are given in Table 1, where the initial concentrations added are 1.5 and 0.4 g dm⁻³ for polymer and 7.2 and 2.4 mmol dm⁻³ for SDS, respectively.

It has been reported [3] that the amount of polymer adsorbed on CT112 obtained by neutralization of CT112 with HCl in the presence of polymers depends on the initial concentration of the polymers. Actually, in both two initial concentrations the amount of polymer adsorbed at 1.5 g dm⁻³ is larger than that at 0.4 g dm⁻³. When the suspensions were diluted by addition of deionized water, the amount of polymer adsorbed decreased considerably in the case of initial concentration of 1.5 g dm⁻³, while in the case of 0.4 g dm⁻³ it hardly changed for both polymers. Probably polymer adsorbed weakly on CT112 particles at the high initial concentration of polymers will desorb by the dilution. On the other hand, polymers adsorbed strongly on CT112 particles at the low initial concentration of polymers show a strong resistance against the dilution. By the dilution, no distinct changes in the average particle size of CT112 particles are observed except SM-100 (0.4 g dm⁻³). It is conceivable that by the

dilution SM-100 molecules adsorbed on CT112 particles operate as bridge between CT112 particles at the initial concentration of 0.4 g dm⁻³, resulting in the increase of the average particle size.

In the case of SDS, the dilution effect on the average particle size of CT112 particles at the initial concentration of 7.2 mmol dm⁻³ SDS was hardly observed, while the average particle size at 2.4 mmol dm⁻³ SDS increased markedly by the dilution. However, from the data of amount adsorbed of SDS and ζ -potential a reasonable explanation for large average size of CT112 cannot be given at the present time.

3.2. Mixed systems of SDS-polymer-CT112

A previous study shows [3] that mixed systems of SDS and celluloses enhance CT112 dispersions more effectively than that of SDS or celluloses alone. A dilution effect was also studied for the mixed systems. At the present study, the initial SDS concentration was fixed at 0.3 mmol dm⁻³ and those of polymers were 0.4 and 1.5 g dm⁻³, respectively. The result is given in Table 2. One can see that the polymers adsorbed are hardly desorbed by the dilution except SH-50 (1.5 g dm⁻³), while the SDS adsorbed is significantly desorbed by the dilution. However, it is very interesting to note that after the dilution the average particle size of CT112 particles is below 8 μ m. This small particle formation is due to coadsorption of SDS and celluloses on CT112. When the alkaline

Table 2

Physicochemical properties of CT112 suspensions in the presence of polymer and SDS before and after dilution

Polymer and SDS ^a	Average particle size (μ m)	ζ -potential (mV)	Polymer adsorption (mg g ⁻¹)	SDS adsorption ($\times 10^{-5}$ mol g ⁻¹)
<i>SH-50 + SDS</i>				
1.5 g dm ⁻³	5.5	0	70.0	1.0
Dilution	5.9	0	55.2	0.2
0.4 g dm ⁻³	6.1	0	19.9	1.1
Dilution	6.7	0	19.8	0.2
<i>SM-100 + SDS</i>				
1.5 g dm ⁻³	6.6	0	45.2	1.0
Dilution	7.7	0	42.6	0.3
0.4 g dm ⁻³	4.0	0	19.8	1.0
Dilution	4.2	0	19.8	0.4

^a The initial concentration of SDS is 0.3 mmol dm⁻³.

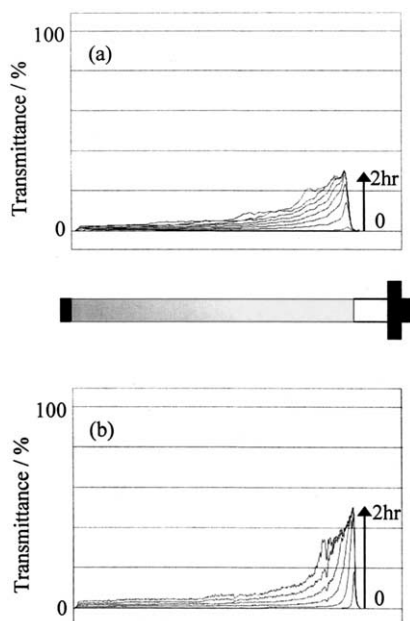


Fig. 1. Change in the transmission of CT112 suspension in the presence of SM-100 and SDS with running time before (a) and after (b) dilution. The initial concentrations of SM-100 and SDS are 0.4 g dm^{-3} and 0.3 mmol dm^{-3} , respectively.

solution of CT112 in the presence of SDS and cellulose is neutralized by addition of HCl, the growth of CT112 particles will be prevented by adsorption of SDS rather than cellulose. Stabilization of CT112 particles is enhanced by coadsorption of cellulose on the preadsorbed SDS. In addition, the cellulose molecules adsorbed are more extended to the aqueous phase than cellulose alone, resulting in an increase of steric hindrance which polymers plays an important role for stabilization of suspensions [7]. Even by the dilution, the structure of polymer-surfactant adsorbed layer on CT112 is not so changed, although some desorption of SDS is observed. Accordingly, a combination of SDS and celluloses provides stable aqueous dispersion of CT112 even after the dilution.

To clarify the dispersion stability of aqueous suspensions of CT112, the change in the transmission of CT112 suspensions with elapsed time was measured using a Turbiscan MA2000. The result for the mixed system of SDS-SM-100-CT112 as a typical example is shown in Fig. 1. The CT112

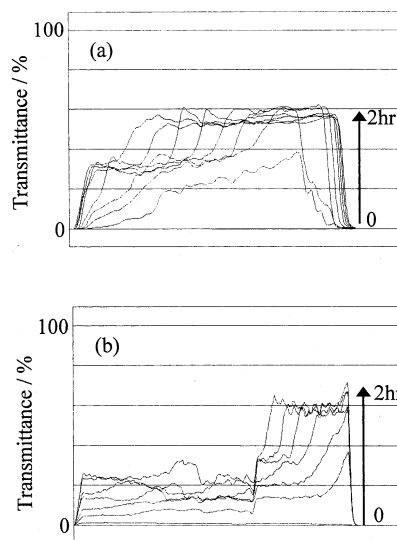


Fig. 2. Change in the transmission of CT112 suspension in the presence of SM-100 with running time before (a) and after (b) dilution. The initial concentration of SM-100 is 0.4 g dm^{-3} .

particles gradually sediment before dilution, while after the dilution they sediment a slightly faster. For comparison, the result for SM-100-CT112 system is also shown in Fig. 2. It is seen that before the dilution the CT particles sediment quite fast and they sediment considerably with a short time after the dilution. These transmission changes with the elapsed time clearly demonstrate that the mixed systems of SDS-SM-100 provide more stable CT112 dispersion than the single system of SM-100 even after the dilution.

References

- [1] K. Esumi, T. Mizusaki, H. Terayama, *Colloids Surf. B: Biointerf.* 9 (1997) 269.
- [2] K. Esumi, T. Wake, H. Terayama, *Colloids Surf. B: Biointerf.* 11 (1998) 223.
- [3] H. Terayama, K. Okumura, K. Sakai, K. Torigoe, K. Esumi, *Colloids Surf. B: Biointerf.* 20 (2001) 73.
- [4] H. Terayama, M. Funakoshi, K. Torigoe, K. Esumi, *Colloids Surf. B: Biointerf.* 23 (2002) 65.
- [5] L.H. Koehler, *Anal. Chem.* 24 (1952) 1576.
- [6] E.W. Yemm, A.L. Willis, *Biochem. J.* 57 (1954) 508.
- [7] K. Esumi, in: K. Esumi (Ed.), *Polymer Interfaces and Emulsions* (Chapter 12), Marcel Dekker, New York, 1999.