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Research paper

Evaluation of ophthalmic suspensions using surface tension

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Abstract

Uniformity and precision of single dose are required for ophthalmic suspensions including water-insoluble ingredients. Solid sediments formed after standing still must be immediately re-dispersible and distributed homogeneously before use. However, selection of an appropriate water-soluble polymer as suspending agent is a challenging problem. In this report, the relationship between the surface tension and the re-dispersibility of suspensions was investigated. The surface tension of 0.1 w/v% fluorometholone suspensions began to decline from 74 mN/m at 0.0001 w/v% of hydroxypropylmethylcellulose (HPMC) and became almost constant at 52 mN/m at 0.01 w/v% of HPMC. Re-dispersion time was less than 4 s when HPMC was present at concentrations between 0.0001 w/v% and 0.01 w/v%. At these concentrations, aggregation of suspended particles was not observed. When indomethacin suspensions at 1.0 w/v% concentration were used, the surface tension began to decline from 73 mN/m at 0.0005 w/v% HPMC and became constant at 50 mN/m at 0.005 w/v% HPMC. The suspension also showed good re-dispersibility, and a uniform suspension was obtained between 0.0005 w/v% and 0.005 w/v% of HPMC. The time required for re-dispersion was less than 17 s. The change of surface tension showed a good correlation with the concentration of HPMC in ophthalmic suspensions having good re-dispersibility. Measurement of the surface tension of suspensions provided the optimal concentration of the water-soluble polymers for the suspensions of well re-dispersible characteristics. Evaluation of ophthalmic suspension using surface tension is a good strategy for formulation of suspending pharmaceutical products in the ophthalmic area.

Keywords: Ophthalmic suspension; Surface tension; Redispersibility; Water soluble polymer; Fluorometholone; Indomethacin

1. Introduction

Aqueous ophthalmic formulations often contain water-insoluble pharmaceuticals. Dose uniformity of ophthalmic suspensions critically depends upon their homogeneity for their precise administration. Many dosing errors occur because of flocculation and caking, and also poor re-dispersibility of the suspensions after standing still for a long time. Therefore, ophthalmic suspensions should be easily re-dispersible by shaking [1–3] when the ingredients are flocculated in the suspensions.

Controlled flocculation of suspensions can be accomplished by the addition of electrolytes, ionic detergents, non-ionic detergents [4–8] or water-soluble polymers to the suspensions [9–14]. Electrolytes are added to increase the surface electrostatic repulsion of the suspended particles [15]. Water-soluble polymers, ionic detergents, and non-ionic detergents are added to increase wettability of the solid particles by adsorbing to the particles [16,17].

Of these additives, a water-soluble polymer such as hydroxypropylmethylcellulose (HPMC) is often used for ophthalmic suspensions to get uniform dispersion of the water-insoluble particles in water. Selecting appropriate water-soluble polymers and their concentrations is, however, difficult because the behavior of the suspensions changes with combination of the drug and polymer characteristics, polymer concentrations, coexisting electrolytes and other additives. In some cases, selection of inappropriate polymers and their concentrations may increase flocculation and caking of the suspension. Water-soluble polymers may sterically inhibit water-insoluble particles from approaching each other in the suspensions that would otherwise form flocculation or caking [18]. Moreover, the water-soluble polymers may adversely act as bridging agents [18] or mutually attract

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[19] between water-insoluble particles to accelerate flocculation or caking in the suspensions.

Water-soluble polymers such as nonionic water-soluble cellulose derivatives decrease the surface tension of solutions [20,21]. The polymers are adsorbed on the water-insoluble particles when the water-soluble polymers are added to the suspensions. The surface tension of suspensions may be influenced due to competition of adsorption and distribution between the surface of suspended particles and the water. Therefore, measuring the surface tension of suspensions is a good approach for predicting the flocculation of water-insoluble particles, and selection of appropriate water-soluble polymers and their concentrations.

In this report, we investigated the relationship between the surface tension and the re-dispersion time of the suspension to evaluate the usefulness of measuring the surface tension of suspensions. Fluorometholone (9-fluoro-11β,17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione) and indomethacin ([1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid) were used as model pharmaceuticals, and HPMC as the water-soluble polymer was used for preparing the ophthalmic suspensions.

2. Materials and methods

2.1. Materials

Fluorometholone and indomethacin active ingredients used were Japanese Pharmacopoeia (J.P.) grade. Hydroxypropylmethylcellulose (HPMC, TC-5E grade) was supplied by Shin-Etsu Chemical (Chiyoda-ku, Tokyo, Japan). Water was purified with a Milli-Q purification system (Millipore, Shinagawa-ku, Tokyo, Japan). Other reagents were the highest grade commercially available.

2.2. Suspensions

For the fluorometholone (0.05 w/v% and 0.1 w/v%) suspension without water-soluble polymer, 100 ml of water was placed in a 100-ml glass beaker. Fluorometholone (0.05 or 0.1 g) was added to the water, and the suspensions were mixed vigorously by a magnetic stirrer.

For the fluorometholone (0.1 w/v%) suspension and indomethacin (0.2 w/v% and 1.0 w/v%) suspension containing various concentrations of HPMC, 40 ml of water was placed in a 50-ml glass beaker. Fluorometholone (0.05 g) or indomethacin (0.1 or 0.5 g) was added to the water, and the suspensions were mixed by a magnetic stirrer. An aqueous solution of HPMC (10 w/v%) solution which was previously prepared was added to the suspensions to make final concentrations of 0.000005, 0.00001, 0.00005, 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, 0.1, 0.25 and 0.5 w/v%, and water was used to make it up to a fixed volume (50 ml).

2.3. Surface tension

The surface tension was determined on a K122 digital tensiometer (Krüss, Hamburg, Germany) using a Wilhelmy plate attachment in combination with an automatic dosing system (665 Dosimat (Metrohm, Herisau, Switzerland)) at controlled room temperature (25 °C). The surface tensions of 0.009 v/w% HPMC solution after 2, 32, 62 and 92 min required for equilibration were 44.1, 43.9, 43.8 and 43.7 mN/m, respectively. The time required for equilibration did not have a significant influence on the surface tension. Therefore, the time required for equilibration was set to 2 min. Fifty milliliters of water and fluorometholone (0.05 w/v% and 0.1 w/v%) suspensions without water-soluble polymer in a 100-ml glass vessel were used as the starting solution or suspension. The HPMC solution which was previously prepared at the concentration of 0.01 w/v% or 0.1 w/v% was added to the starting solution or suspension by automatic dosing system, and then the solution or suspension was mixed by magnetic stirring for 10 s. After 2 min required for equilibration, the surface tension of the water and the fluorometholone suspension containing each concentration of HPMC were measured. The surface tension of indomethacin suspensions containing various concentrations of HPMC which was prepared by the above method was measured using the same equipment. A 20-ml glass vessel was used. The Wilhelmy plate (dimensions 10.0 × 19.9 × 0.25 mm) was immersed in the dispersion to a depth of 1.0 mm. Measurement was repeated five times for every concentration, and the mean was obtained.

2.4. Re-dispersion time

Fluorometholone (0.1 w/v%) and indomethacin (0.2 and 1.0 w/v%) suspensions containing various concentrations of HPMC were filled in a 5-ml colorless polypropylene ophthalmic container. The time required for re-dispersion of the suspensions was measured after standing the containers in an upright position for 4 days at 25 °C. Re-dispersion time was defined as the seconds required to become a uniform suspension from the precipitated condition at the bottom of the container, when the container was rolled in a horizontal position using a Variable mix rotor VMR-5 at 60 rpm (AsOne Corporation, Kita-ku, Osaka, Japan). Measurement was repeated for three samples, and the mean was obtained.

2.5. Re-dispersion time for model formulations of fluorometholone ophthalmic suspension

The model formulations of fluorometholone ophthalmic suspension containing HPMC, sodium dihydrogen phosphate as a buffering agent, benzalkonium chloride as a preservative, and sodium chloride as a tonicity agent, were prepared (Table 1), and then poured into a 5-ml colorless polypropylene ophthalmic container. These samples were

Table 1
Model formulations of fluorometholone ophthalmic suspensions

Ingredient	Application	Formulation			
		#1	#2	#3	#4
Fluorometholone	Active ingredient	0.05 g	0.05 g	0.1 g	0.1 g
HPMC	Suspending agent	0.00125 g	0.5 g	0.0025 g	0.5 g
Sodium dihydrogen phosphate	Buffering agent	0.1 g	0.1 g	0.1 g	0.1 g
Benzalkonium chloride	Preservative	0.005 g	0.005 g	0.005 g	0.005 g
Sodium chloride	Tonicity agent	0.9 g	0.9 g	0.9 g	0.9 g
Sodium hydroxide	pH adjustment agent	Proper quantity (pH 7)	Proper quantity (pH 7)	Proper quantity (pH 7)	Proper quantity (pH 7)
Water	Medium	Total 100 ml	Total 100 ml	Total 100 ml	Total 100 ml

centrifuged at 200 × *g* for 10 min to sediment the suspended particles. After the precipitation process, the bottles were rotated by a Variable mix rotor VMR-5 at 60 rpm to observe the re-dispersion time.

3. Results and discussion

3.1. Surface tension

Fluorometholone and indomethacin are steroidal and non-steroidal anti-inflammatory drugs, respectively. Ophthalmic product containing these drugs is used for treatment of eye inflammation. These compounds which are hardly soluble in water are suited in this study as model pharmaceuticals. The particle sizes of fluorometholone and indomethacin used were 1.4 and 21.6 μm (median diameter), respectively. The contact angles for these compounds provide useful information to estimate their wettability. However, we could not measure in the present study, because the apparatus was not available. A cellulose derivative (HPMC) prepared by the introduction of hydroxypropyl and methyl groups, is a water-soluble polymer and is often used for ophthalmic suspensions as a suspending agent.

Surface tensions of water and fluorometholone suspensions containing various concentrations of HPMC are shown in Fig. 1. The *x*-axis of Fig. 1 for the concentration of HPMC is on a logarithmic scale. The initial surface tension of water was 71 mN/m. By adding HPMC, the surface tension of the solution began to decline at 0.00005 w/v% HPMC and became almost constant to 47 mN/m at 0.001 w/v% HPMC. It was indicated that HPMC has surface-active behaviour [20], and HPMC is distributed on the water surface by increasing the concentration to cause the decrease of the surface tension. The decrease of surface tension becomes constant over the critical polymer concentration (CPC) that is related to the critical micelle concentration (CMC) of low molecular weight surfactants [22].

The surface tension of 0.05 w/v% fluorometholone suspension began to decline from 65 mN/m at 0.0001 w/v% HPMC and became almost constant at 51 mN/m at 0.002 w/v% HPMC, according to the increase in the concentration of HPMC. The surface tension of 0.1 w/v% fluorometholone suspension also began to decline from 74 mN/m at 0.0001 w/v% HPMC and became almost constant at 52 mN/m at 0.01 w/v% HPMC. From comparison of the surface tension of water and suspension, the concentrations of HPMC at which the surface tension began to decline and at which the surface tension became constant shifted to higher concentrations due to the presence of suspended particles. The range of the shifted concentration became larger with an increase in the concentration of the fluorometholone suspension. It is considered that the adsorption of HPMC occurred on the surface of the suspended particles. Duro et al. reported that HPMC was adsorbed on a solid surface according to the Langmuir model [16]. The adsorption was proportional to the equilibrium polymer concentration in water. At the same time, HPMC was distributed on the water surface, then surface tension was decreased. When the water surface as well as the surface of suspended particles was filled up with

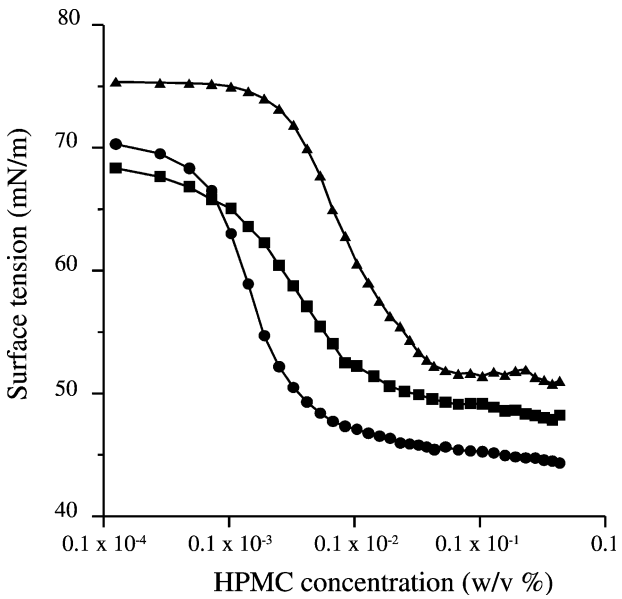

Fig. 1. Change of surface tension in water and fluorometholone suspensions containing various concentrations of HPMC. ●, water; ■, 0.05 w/v% fluorometholone suspension; ▲, 0.1 w/v% fluorometholone suspension.

HPMC, the decrease of surface tension became constant. Water surface tension is 72 mN/m at 25 °C under normal circumstances, and the fluorometholone suspension without HPMC should have shown the same surface tension because the medium was water. Although there was a small difference in the starting surface tension between water (71 mN/m) and 0.05 and 0.1 w/v% fluorometholone suspensions (68 and 75 mN/m, respectively) due to the effect of the adhesion of suspended particles to the Wilhelmy plate, it was necessary to measure the surface tension of suspensions. However, good reproducibility for the measurement of surface tension was given (RSD 1.8%, 0.1% fluorometholone suspension containing 0.0005 w/v% HPMC, $n = 10$), because the effect on adhesion of suspended particles to the Wilhelmy plate is constant. In this study, the surface tension was measured using whole suspension to obtain information from suspensions directly and to avoid the deviation due to adhesion of HPMC to glassware during subtraction of suspended particles, because of a very low concentration of HPMC.

3.2. Relationship between surface tension and re-dispersion time

Relationship between surface tension and re-dispersion time of 0.1 w/v% fluorometholone suspension is shown in Fig. 2. The *x*-axis of Fig. 2 for the concentration of HPMC is on a logarithmic scale. The surface tension began to decline from 74 mN/m at 0.0001 w/v% HPMC and became almost constant at 52 mN/m at 0.01 w/v% HPMC. On the other hand, the time required for re-dispersion was 2 s at the concentration with 0.0001 w/v% of HPMC (Table 2).

However, the suspended particles aggregated and floated, and a uniform suspension was not obtained in this concentration range. A uniform suspension was observed between 0.0001 and 0.01 w/v% HPMC. Re-dispersion time was less than 4 s, and the suspension did not accompany aggregation of suspended particles. When the concentration of HPMC was over 0.01 w/v%, the re-dispersion time exceeded 5 s, and re-dispersibility became worse. The concentration range of HPMC showing the short re-dispersion time (0.0001–0.01 w/v%) was well correlated to the HPMC concentration for the change of the surface tension (0.0001–0.01 w/v%). The evaluation for re-dispersibility in this study is well suited to compare the re-dispersibility for many samples of suspensions without measurement deviation by analyst, location and time, although the relationship between the method and the force exerted by patients when shaking a dropper bottle was not investigated.

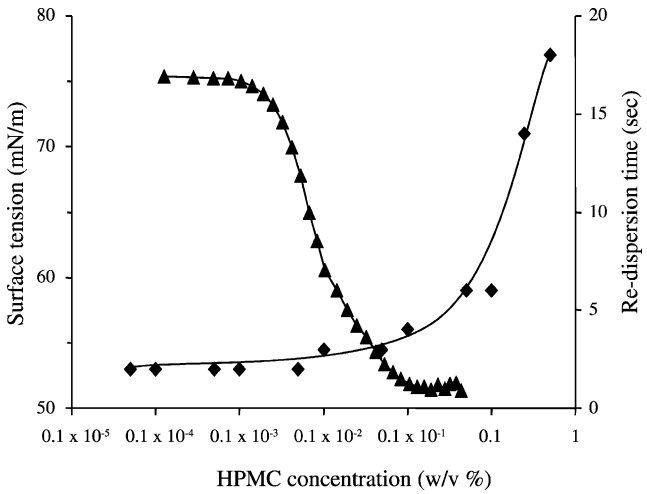

Fig. 2. Effect of HPMC concentration on surface tension and re-dispersion time of 0.1 w/v% fluorometholone suspension. ▲, surface tension (mN/m); ◆, re-dispersion time (s).

Table 2
Re-dispersion time of fluorometholone and indomethacin suspensions containing each concentration of HPMC

Pharmaceutical	HPMC concentration (w/v%)	Re-dispersion time (s)
Fluorometholone (0.1 w/v%)	<0.0001	= 2 (Non-uniformity)
	0.0001–0.01	<4
	>0.01	>5
Indomethacin (0.2 w/v%)	<0.0001	<7 (Non-uniformity)
	0.0001–0.01	<12
	>0.01	>12
Indomethacin (1.0 w/v%)	<0.0005	<7 (Non-uniformity)
	0.0005–0.005	<17
	>0.005	>20

When indomethacin suspension at 0.2 w/v% concentration was used, the surface tension began to decline from 72 mN/m at 0.0001 w/v% HPMC and became almost constant at 47 mN/m at 0.01 w/v% HPMC (Fig. 3A and Table 2). The *x*-axis of Fig. 3 for the concentration of HPMC is on a logarithmic scale. The time required for re-dispersion was 7 s or less below a concentration of 0.0001 w/v% HPMC. However, the suspended particles aggregated and floated without reaching a uniform suspension at this concentration. The suspension having good re-dispersibility and a uniform suspension was obtained between the concentrations of 0.0001 and 0.01 w/v% of HPMC. The time required for re-dispersion was not more than 12 s. When the concentration of HPMC was over 0.01 w/v%, the re-dispersion time became longer, and showed worse re-dispersibility. When indomethacin suspension at 1.0 w/v% concentration was used, the surface tension began to decline from 73 mN/m at 0.0005 w/v% HPMC and became constant at 50 mN/m at 0.005 w/v% HPMC (Fig. 3B and Table 2). The time required for re-dispersion was not more than 7 s below the concentration of 0.0005 w/v% HPMC. As indicated for the 0.2 w/v% indomethacin suspension, the suspended particles aggregated and floated without getting a uniform suspension at these concentrations. The suspension had a good redispersibility and a uniform

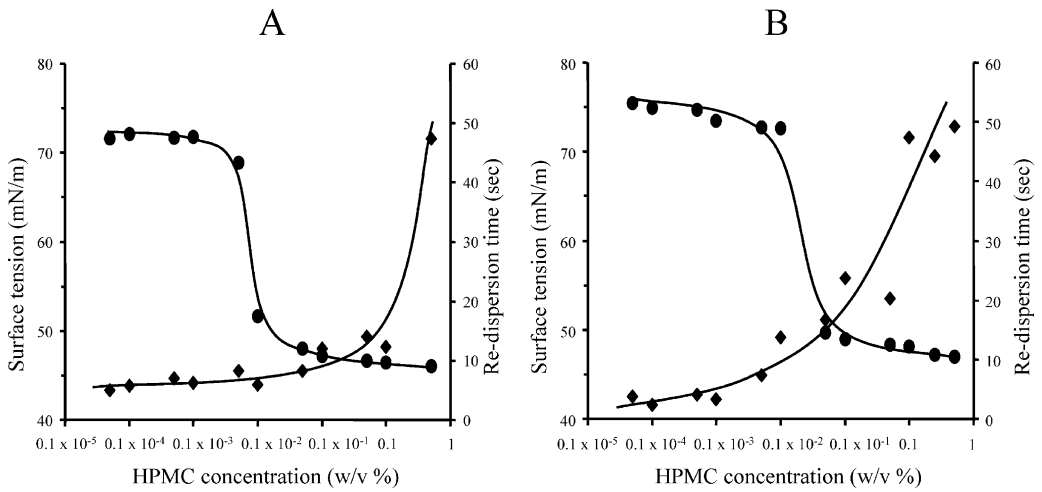

Fig. 3. Effect of HPMC concentration on surface tension and re-dispersion time of (A) 0.2 w/v% and (B) 1.0 w/v% indomethacin suspension. ●, surface tension (mN/m); ◆, re-dispersion time (s).

suspension was obtained between the concentrations of 0.0005 and 0.005 w/v% of HPMC. The time required for re-dispersion was less than 17 s. The concentration range of HPMC showing the short re-dispersion time for both 0.2 and 1.0 w/v% indomethacin suspensions (0.0001–0.005 w/v% and 0.0005–0.005 w/v%, respectively) corresponded well to the HPMC concentration for the change of the decreased surface tension (0.0001–0.005 w/v% and 0.0005–0.005 w/v%, respectively).

At the low concentration of HPMC, the suspended particles aggregated and floated without getting a uniform suspension. Wettability of the suspended particles was not improved at very low concentrations of HPMC in the suspension, although suspending agents such as HPMC improve the wettability of suspended particles. When the concentration of the water-soluble polymers increased in the suspension, the re-dispersibility time became exponentially longer, although a sufficient amount of HPMC would improve the wettability of the suspended particles in the suspension. Increasing re-dispersion time was reported to occur when HPMC was added in aqueous suspension of pyrantel pamoate, an antiparasitic agent [16]. The re-dispersibility is adversely affected by an excessive amount of water-soluble polymer. The fluorometholone and indomethacin suspensions containing the concentration of HPMC between the surface tension beginning to decrease and becoming constant had a good re-dispersibility without aggregation of suspended particles. These results indicate that there is a range for the appropriate concentration of water-soluble polymer to make a well re-dispersible suspension.

3.3. Re-dispersion time for the model formulations of fluorometholone ophthalmic suspension

We applied the optimized concentration of HPMC as described above to the model formulations of fluorometholone ophthalmic suspension to investigate the influence of common additives to the re-dispersibility. Formulation #1 contained 0.00125 w/v% HPMC which is in the range of the appropriate concentration between the surface tension beginning to decrease and becoming constant (0.0001–0.002 w/v%) for 0.05 w/v% fluorometholone ophthalmic suspension. Formulation #2 contained 0.5 w/v% HPMC, which had a much too high concentration compared to the optimized formulation. When 0.1 w/v% fluorometholone ophthalmic suspension was used, formulation #3 contained 0.0025 w/v% HPMC, which is in the range of the appropriate concentration (0.0001–0.01 w/v%). Formulation #4, containing 0.5 w/v% HPMC, was prepared for comparison of the optimized formulation. These formulations contained benzalkonium chloride as preservative, sodium dihydrogen phosphate as a buffering agent, and sodium chloride as a tonicity agent, which are usually used for ophthalmic preparations. Results are summarized in Table 3.

Re-dispersion times of formulations #1 and #2 were 6 and 119 s, respectively. Re-dispersion time of 0.05 w/v% fluorometholone ophthalmic suspension containing the optimized concentration of HPMC (formulation #1) was obviously shorter than that of the suspension containing higher concentration of HPMC (formulation #2).

Table 3
Re-dispersion time for the model formulations of fluorometholone ophthalmic suspensions

Formulation	Fluorometholone concentration (w/v%)	HPMC concentration (w/v%)	Re-dispersion time (s)
#1	0.05	0.00125	6
#2	0.05	0.5	119
#3	0.1	0.0025	4
#4	0.1	0.5	20

Re-dispersion times of formulations #3 and #4 were 4 and 20 s, respectively. As indicated for 0.05 w/v% fluorometholone ophthalmic suspension, re-dispersion time of 0.1 w/v% fluorometholone ophthalmic suspension containing the optimized concentration of HPMC (formulation #3) was shorter than that of the suspension containing a higher concentration of HPMC (formulation #4).

Benzalkonium chloride is the most common and useful preservative for ophthalmic preparations and many ophthalmic products contain benzalkonium chloride [23,24]. Benzalkonium chloride has a surface-active function [17] and it may affect the wettability of suspended particles and re-dispersibility of suspension. However, most ophthalmic suspensions containing benzalkonium chloride also contain surfactant and/or water-soluble polymer [24]. It seems that improvement of wettability of suspended particles and the re-dispersibility of suspension are not achieved by only benzalkonium chloride. Surface tension of various concentrations of HPMC solution containing 0.005 w/v% benzalkonium chloride was measured. However, the change of surface tension according to concentration of HPMC was not determined, because it was masked by the surface-active function of benzalkonium chloride. Sodium dihydrogen phosphate and sodium chloride are electrolytes that increase the surface electrostatic repulsion of the suspended particles [15]. Therefore, these additives should influence essentially the adsorption of HPMC on the suspended particles. However, no effect of these additives to the re-dispersibility of fluorometholone ophthalmic suspension was observed in this study. The influence of additives should be examined carefully in the development of ophthalmic solutions.

4. Conclusion

In the present study, we have reported the relationship between the surface tension and the re-dispersibility for ophthalmic suspensions. Selecting appropriate water-soluble polymers and their concentrations is important in making an ophthalmic suspension which does not result in flocculation and caking after standing for a long time. We found an appropriate range of concentrations of water-soluble polymer for a well re-dispersible suspension using fluorometholone and indomethacin as model pharmaceuticals. Measurement of surface tension is a good component of the physico-chemical characteristics of suspended particles in aqueous solutions, and it is a useful tool for the preparation of an ophthalmic suspension containing a suitable concentration of water-soluble polymers.

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