Adsorption of Actives in Ophthalmological Drugs for Over-The-Counter on Soft Contact Lens Surfaces

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Abstract: The adsorption of various kinds of ionic/nonionic actives, added in ophthalmological drugs (artificial tear, contact lens wetting solution, eye-drops, and eyewash) for over-the-counter (marketable drugs with no need of any medical prescription), on soft contact lens (SCL) surfaces has been studied as a function of hydrophobicity of the actives. The common logarithm of the 1-octanol/water partitioning coefficient ($AC_{log P}$) has been used in order to normalize the hydrophobicity of the actives employed in this study. No significant adsorption occurs for relatively hydrophilic actives, whereas the adsorption rate is gradually increased with an increase in the hydrophobicity of the actives. This suggests that the adsorption is predominantly governed by the hydrophobic interaction of the actives with the SCL surfaces, although an electrostatic interaction plays an additional role for the adsorption. The most effective adsorption occurs in the following active-lens combinations: cationic actives — the anionic and hydrated lens IV (methacrylic acid-based SCL); anionic actives — the nonionic and hydrated lens II (*N*-vinyl pyrrolidone-based SCL); and nonionic actives — the anionic and less-hydrated lens III (containing hydrophobic silicone monomers).

Key words: adsorption, actives in Eye-Drops, soft contact lens, hydrophobic interaction, partitioning coefficient

1 INTRODUCTION

A soft contact lens (SCL) is a polymerized hydrogel consisting of a base unit of 2-hydroxyethyl methacrylate (HEMA) and some monomer additives (such as *N,N*-dimethylacrylamide (DMA), *N*-vinylpyrrolidone (NVP), polyvinylalcohol (PVA) and methacrylic acid (MAA)). Recently, new SCL materials have been developed for SCL users in order to reduce drying of eye surfaces and hence to improve the feeling of a foreign body¹⁾. In particular, silicone hydrogel contact lenses have been of great interest because of their excellent oxygen permeability²⁾.

At present there are two types of ophthalmological drugs (including artificial tear, contact lens wetting solution, eye-drops, and eyewash) for over-the-counter (i.e.

marketable drugs with no need of any medical prescription) in Japan³⁾. One type is called either artificial tear or contact lens wetting solution: it is possible to use these drugs even when SCL is worn on the eyes. The other type is eye-drops and eyewash, which are not permitted to be dropped on SCL. The artificial tear (or contact lens wetting solution) generally contains inorganic salts, amino acids and water-soluble polymers and is able to reduce drying of eye surfaces (tear supplementation). At present, however, it is not permitted to add some active components (e.g. for itch, hyperemia and blurred vision) into the artificial tear because of some problems caused by the adsorption of the actives on SCL surfaces.

There are some reports concerning the adsorption of

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materials (including some base-components and preservative materials in natural/artificial tear) on SCL surfaces^{4,6)}. As expected, cationic actives (e.g. lysozyme in tear) are able to adsorb preferentially on anionic MAA-based SCL surfaces via an electrostatic interaction⁵⁾ and for hydrophobic actives (e.g. cholesterol in tear) the adsorption takes place more effectively on alkylmethacrylate with longer hydrocarbon chains than on shorter ones⁶⁾. As far as we know, however, adsorption of actives in the ophthalmological drugs for over-the-counter on SCL surfaces has not been characterized in detail yet.

In the current work we have studied the adsorption of 18 species of actives on SCL surfaces as a function of hydrophobicity of the actives. The actives have been classified by their ionic character (i.e. cationic, anionic and nonionic) and the hydrophobicity has been normalized using the common logarithm of the 1-octanol/water partitioning coefficient (AC_log P); the values of AC_log P are calculated using the ALOGPs 2.1 Program^{7,8)} based on the Actelion Property Explorer⁹⁾.

2 EXPERIMENTAL

2.1 Materials

Soft contact lenses are classified into four types, according to the report by the US Food and Drug Administration (FDA). In the current study we have used typical SCL products in Japan, selected from each group: Bausch & Lomb Medalist[®] Plus (type I), Precision UVTM (type II), Bausch & Lomb PureVision[®] (type III) and Acuvue[®] (type IV). The properties of these SCL products are given in Table 1.

The actives employed in this study are listed in Table 2, where the actives are classified by the ionic character (i.e. cationic, anionic and nonionic) at pH 7.4. Note that this pH is the same as the pH of tear¹⁰⁾. The AC_log P values shown in this table are calculated using the computer program given in reference 8. The surfactants used for enhancing the amount of hydrophobic actives dissolved (solubilized) in water were polyoxyethylenehydrogenated castor oil 60 (HCO60) (Nihon Surfactant Kogyo K.K., Japanese Pharmaceutical Excipients, medical purpose

Table 1 The Respective Properties in Various Aspects for the Different Types of Soft Contact Lenses.

FDA group	I	II	III	IV
	Nonionic (Less than 1 mol% ionic polymers)		Ionic (More than 1 mol% ionic polymers)	
	Low water content (Less than 50% water content)	High water content (More than 50% water content)	Low water content (Less than 50% water content)	High water content (More than 50% water content)
Lens name	Bausch & Lomb Medalist [®] Plus	Precision UV TM	Bausch & Lomb PureVision [®]	Acuvue [®]
Manufacture name	Bausch & Lomb Japan	Ciba Vision	Bausch & Lomb Japan	Johnson & Johnson
Material	Poly-HEMA	NVP, MMA	BalafilconA (TrisVC, NVP)	EtafilconA (Copolymer of 2- hydroxyethylmethacrylate and methacrylic acid)
Power	-3.00	-3.00	-3.00	-3.00
Water content (%)	38.6	74.0	36.0	58.0
Diameter (mm)	14.0	14.4	14.0	14.0
Base curve	8.7	8.7	8.6	8.8
Central thickness (mm)	0.035	0.14	0.09	0.07
Dry lens weight per slice (mg)	16.6	11.0	20.2	11.0
Oxygen transmissibility (Dk/L)*	27.1	27.1	110.0	40.0

* Unit Dk/L = $\times 10^{-9} (\text{cm}^2/\text{sec}) \cdot (\text{mLO}_2/\text{mL} \times \text{mmHg})$

Table 2 Principal Items of the Respective Actives Examined in the Present Study.

		Active name	Active abbreviation	Concentration of active (g/100 mL)	Manufacture name	Grade	AC_logP
Cationic active	Active ingredient	Berberine chloride hydrate	BCH	0.025	ALPS Pharmaceutical Ind. Co., Ltd.	The Japanese Pharmacopoeia	4.87
		Chlorpheniramine maleate	CPM	0.03	Kongo Chemical Co., Ltd.	The Japanese Pharmacopoeia	3.59
		Tetrahydrozoline hydrochloride	TZH	0.05	Okami Chemical Industry Co., Ltd.	Japanese Pharmaceutical Codex	2.06
		Neostigmine methylsulfate	NSM	0.005	Tokyo Chemical Industry Co., Ltd.	The Japanese Pharmacopoeia	3.03
		Lysozyme hydrochloride	RZH	0.5	Q. P. Corporation	The Japanese Pharmacopoeia	—
	Amino acid that make up lysozyme	L-Arginine	Arg	1.0	Wako Pure Chemical Industries, Ltd.	Special grade chemicals of Wako Pure Chemical Industries, Ltd.	-2.41
		L-Lysine hydrochloride	Lys	1.0	Wako Pure Chemical Industries, Ltd.	Special grade chemicals of Wako Pure Chemical Industries, Ltd.	-1.16
		L-Histidine hydrochloride monohydrate	His	1.0	Wako Pure Chemical Industries, Ltd.	Special grade chemicals of Wako Pure Chemical Industries, Ltd.	-1.64
Anionic active	Active ingredient	Sodium azulene sulfonate	AZS	0.02	ALPS Pharmaceutical Ind. Co., Ltd.	Japanese Pharmaceutical Codex	4.90
		Pranopfen	PPF	0.05	Toshin Chemical Co., Ltd.	The Japanese Pharmacopoeia	3.31
		Dipotassium glycyrrhizinate	GK2	0.25	Maruzen Pharmaceuticals Co., Ltd.	Japanese Pharmaceutical Codex	0.74
		Sodium cromoglicate	CG	1.0	Toshin Chemical Co., Ltd.	The Japanese Pharmacopoeia	1.48
	Additional ingredient	Potassium sorbate	SK	0.1	Daiichi Fine Chemical Co., Ltd.	Japanese Pharmaceutical Excipients	1.38
Nonionic active	Active ingredient	Retinol palmitate	VA	50000 unit/100 mL	DMS Nutrition Japan K. K.	The Japanese Pharmacopoeia	12.82
	Additional ingredient	Propyl parahydroxybenzoate	PPB	0.02	Midori Kagaku Co., Ltd.	The Japanese Pharmacopoeia	2.56
		Metyl parahydroxybenzoate	MPB	0.02	Midori Kagaku Co., Ltd.	The Japanese Pharmacopoeia	1.65
		1-Menthol	Men	0.01	The Suzuki Menthol Co., Ltd.	The Japanese Pharmacopoeia	2.76
	Active ingredient	Glucose	Glc	0.2	Nihon Shokuhin Kako Co., Ltd.	The Japanese Pharmacopoeia	-2.32

Table 3 Examination Methods and Analytical Conditions Employed for Different Actives.

Active abbreviation	Method	Detector	Measurement wavelength	Column	Mobile phase	Flow rate (mL/min)
BCH	HPLC	Spectrophotometric detector (SPD-M20A, Shimadzu)	220 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	0.065 M sodium dihydrogenphosphate/ acetonitrile/10% sodium dodecyl sulfate in water (59/40/1 by volume)	1.0
TZH						
NSM						
PPB						
MPB						
CPM	HPLC	Spectrophotometric detector (UV-975, JASCO)	220 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	0.065 M sodium dihydrogenphosphate controlled at pH 2.5 by using phosphoric acid/acetonitrile/10% sodium dodecyl sulfate in water (61/38/1 by volume)	1.1
GK2						
Arg	HPLC	Spectrophotometric detector (SPD-M20A, Shimadzu)	Measurement: 455 nm Exciting: 365 nm	Amino acid analysis column (7 μ m, 150 $\times$ 4.0 mm, Shimadzu)	0.075 M sodium citrate controlled at pH 10.0 by sodium hydrate	0.4
Lys						
His						
AZS	HPLC	Spectrophotometric detector (UV-975, JASCO)	246 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	Water/acetonitrile/ triethylamine (970/460/1 by volume) controlled at pH 8.0 by phosphoric acid	1.0
PPF	HPLC	Spectrophotometric detector (UV-975, JASCO)	254 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	0.1 M ammonium acetate controlled at pH 4.5 by acetic acid/acetonitrile (57/43 by volume)	0.6
CG	HPLC	Spectrophotometric detector (UV-975, JASCO)	238 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	1 % triethyl amine in water controlled at pH3.0 by phosphoric acid/methanol (73/27 by volume)	1.0
SK	HPLC	Spectrophotometric detector (UV-975, JASCO)	235 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	0.5 mM tetra- <i>n</i> -butylammonium bromide/methanol (60/40 by volume)	0.7
VA	HPLC	Spectrophotometric detector (SPD-M20A, Shimadzu)	280 nm	ODS column (5 μ m, 150 $\times$ 4.6 mm, GL Sciences)	Methanol	1.0
Glc	HPLC	Differential refractometer (Shodex RI-71S, Showa Denko)	—	Sugar analysis column (6 μ m, 300 $\times$ 8.0 mm, Showa Denko)	0.005 M sulphuric acid	0.6

grade) and propylene glycol (PG) (Azuma Co., Ltd., Japanese Pharmaceutical Codex). All the sample solutions were prepared using the Palitzsch's buffer solution¹¹⁾ with no preservative chemicals. The typical content of the mother solution is as follows (in g / 100 mL): boric acid 1.1656, borax 0.1147, sodium chloride 0.31 and moderate amount of purified water.

2.2 Procedures

The actives were dissolved in the Palitzsch's buffer solution (see above) at the concentration shown in **Table 2**: the active concentration is set at the largest dose of either (i) the standard of approval for the manufacture of drugs for over-the-counter or (ii) the blending precedent of ophthalmological drugs, unless otherwise stated. In the case of very hydrophobic actives (retinol palmitate (VA) and 1-menthol (Men)), the two surfactants were used as a solubilizer in the initial dissolution step at the concentration of 0.2 g / 100 mL for HCO60 and of 1.0 g / 100 mL for PG, respectively.

A sheet of SCL was immersed in sample solution using a 10 mL glass vial and the adsorption was equilibrated with a fixed shaking rate of 30 swings per minute. The equilibrium concentrations of the actives were basically measured using high-performance liquid chromatography (HPLC), except 1-menthol (Men, gas chromatography) and lysozyme hydrochloride (RZH, UV-Vis spectrophotometry). The analytical conditions are summarized in **Table 3**. Then, the adsorption rate was calculated according to the following equation:

$$\text{Adsorption rate (\%)} = (C_0 - C) / C_0 \times 100$$

where C is the concentration of the actives measured after a fixed shaking period and C_0 is the active concentration determined from the blank test (i.e. sample solutions prepared at the same active concentrations were shaken for a fixed period without SCL). We note that the variation of the resultant data ($3 \text{ CV} = \text{relative standard deviation} \times 3$) was estimated from repeated (6 times) experiments with the standard solution: 'a significant adsorption' is evidenced only when the adsorption rate is greater than the estimated 3 CV value.

3 RESULTS AND DISCUSSION

Before characterizing the adsorption of hydrophilic/hydrophobic actives on various kinds of SCL surfaces, it is important to study effects of experimental conditions (such as equilibration time, temperature, solution volume, and active concentration in the solution) on the adsorption behavior. **Figure 1** shows the adsorption kinetics of a cationic active, chlorpheniramine maleate (CPM), on the typical four types of SCL surfaces. For all the cases the adsorption rate is dramatically increased within 1 hour, followed by a gradual increase with time. The adsorption equilibration is attained within 6 hours and no significant changes in the adsorption rate are observed after this equilibration period. On the basis of the experimental results shown here, the adsorption rates in the following experiments were measured after equilibration for 7 days.

Figure 2 shows the adsorption rate of CPM as functions of (a) temperature, (b) solution volume, and (c) CPM concentration in the solution. It seems likely that the mean

Fig. 1 Adsorption Kinetics of CPM on SCL.

The experiments were performed under the following conditions: temperature = 37°C, solution volume = 5 mL, and CPM concentration = 0.03 g / 100 mL (0.03%). The 3 CV value was estimated to be 0.87 %.

Fig. 2 Adsorption Rate of CPM as Functions of (a) Temperature, (b) Solution Volume and (c) CPM Concentration in the Solution.

The experiments were performed under the following conditions (equilibration time = 7 days): (a) temperature = 25, 37 and 45°C, solution volume = 5 mL, and CPM concentration = 0.03 g / 100 mL (0.03 %); (b) temperature = 37°C, solution volume = 3, 5 and 10 mL, and CPM concentration = 0.03 g / 100 mL (0.03 %); and (c) temperature = 37°C, solution volume = 5 mL, and CPM concentration = 0.03 and 0.006 g / 100 mL (0.03 and 0.006 %). The 3 CV value was estimated to be 0.87 %.

adsorption rate is increased with increasing temperature, although the difference in the adsorption rate observed for a given SCL is in the range of experimental errors within the resolution (see Fig. 2a). It is generally accepted that adsorbed amount (based on physical adsorption) is increased with decreasing temperature. One reasonable interpretation for this general trend lies in the fact that physical adsorption is an exothermic reaction, and the other interpretation may arise from inactive molecular motion at lower temperatures. The trend observed in Fig. 2a suggests, therefore, that the increased temperature may result in an increase in the effective surface area on SCL even though this is not supported by any experimental data at present. Additional information is given in Fig. 2b and 2c: the adsorption rate depends significantly on the solution volume (note that the number of sheets of SCL is always fixed at 1), but the concentration of CPM (at least within the concentration region investigated in this study) makes a negligible impact on the adsorption rate for a given solution volume. Hereafter the adsorption studies were carried out under the following conditions: equilibra-

tion time = 7 days, temperature = 37°C (body temperature) and solution volume = 5 mL.

It has been reported that the adsorption of actives in tear on SCL is driven not only by the electrostatic interaction but also by the hydrophobic interaction^{5,6}. In the current study, these two factors have been considered separately in order to elucidate the complex adsorption behavior. Figure 3 presents the adsorption rates of a cationic active CPM, an anionic active PPF (pranoprofen) and a nonionic active Men on the typical four types of SCL. One can see in this figure that the cationic active CPM is able to adsorb more effectively for the ionic lenses III and IV (i.e. more than 1 mol% ionic polymers) than for the nonionic lenses I and II (i.e. less than 1 mol% ionic polymers), suggesting that the electrostatic interaction is a key factor for driving the adsorption, as expected. This is also supported by the fact that the adsorption rate of the anionic active on the anionic lens IV is remarkably lower than that on the neutral lenses I and II. Interestingly, however, a significant adsorption is observed for the anionic active on the anionic lens III. On the basis of the adsorption result, it is possible

Fig. 3 Adsorption Rates of a Cationic Active CPM, an Anionic Active PPF and a Nonionic Active Men on SCL.

The experiments were performed under the following conditions: equilibration time = 7 days, temperature = 37°C and solution volume = 5 mL.

to assume that the hydrophobic interaction also plays an important role for the adsorption. For the nonionic active the most effective adsorption occurs on the lens III presumably due to the strong attractive interaction with hydrophobic silicone monomers in/on the lens III. Clearly, all the experimental results shown here suggest that the adsorption is driven by the combined two interactions (i.e. electrostatic and hydrophobic forces), in a manner similar to the adsorption from natural tear.

Figure 4 shows the adsorption rate of ionic/nonionic actives on the selected SCL surfaces as a function of hydrophobicity of the actives (i.e. AC_log P, note that the greater hydrophobicity gives the larger AC_log P value). The active-lens combinations employed here are (a) cationic actives – the anionic lens IV, (b) anionic actives – the nonionic lens II and (c) nonionic actives – the anionic lens III, respectively, in which the most effective adsorption is observed in Fig. 3. Apparently, for all the active-lens combinations (i) the adsorption rate is observed to be increased with increasing hydrophobicity of the actives and (ii) the adsorption is negligible for the greater hydrophilic actives. This is a piece of strong evidence that the hydrophobic interaction is a key factor for determining the adsorption, as mentioned above. One may notice, however, that the adsorption rate is remarkably low (or almost negligible) in the case of the very hydrophobic active (AC_log P = 12.82, VA) as Fig. 4c. This is presumably due to solubilization of the active into the HCO60 micelle interiors. We have confirmed that no significant adsorption takes place for the solubilizers (HCO60 and PG) themselves to the lens III (data not shown).

We have also studied the adsorption of a cationic protein RZH on the anionic lens IV (data not shown). This protein

contains three cationic amino acids (Arg, His and Lys) in the AC_log P range of $-2.41 - -1.16$, and these amino acids are not able to adsorb to the lens IV significantly (see Fig. 4a). Nevertheless, the adsorption rate of the cationic protein is measured to be 18.5%. Although it is not possible to calculate the AC_log P value of this particular protein, the hydrophobicity of the protein is expected to be greater than that of each amino acid component because of (i) the larger molecular weight (and hence the less water solubility), (ii) the presence of hydrophobic amino acid components in the protein and (iii) the greater inter/intra molecular hydrophobic interaction for stabilizing the protein 3-dimensional structures in solution¹². The adsorption results suggest, therefore, that the hydrophobic interaction drives the adsorption predominantly (at least for this particular case), rather than the electrostatic attraction between the cationic actives and the anionic lenses.

On the basis of the adsorption results shown in Fig. 4, an adsorption mechanism is proposed as follows (see also schematic figures given in Fig. 5). First of all, the adsorption is predominantly governed by the hydrophobic interaction between actives and SCL surfaces, and hence, is strongly dependent on the hydrophobicity of the actives. No significant adsorption occurs in the case of relatively hydrophilic actives as a result of their hydration. With an increase in the hydrophobicity of the actives, the adsorption rate is gradually increased, overcoming the repulsive hydration forces. As is seen in Fig. 4c, however, the adsorption rate is now decreased when employing very hydrophobic water-insoluble actives (e.g. VA), presumably due to solubilization into solution micelles. Apparently, this adsorption model is applicable not only to nonionic actives but also to ionic ones, and in the latter case the electrostatic interaction assists the adsorption.

4 CONCLUSIONS

The adsorption of ionic/nonionic actives in ophthalmological drugs for over-the-counter on various types of SCL surfaces has been characterized as a function of hydrophobicity of the actives (AC_log P). The adsorption rate of the actives is measured to be generally increased with an increase in the hydrophobicity of the actives, meaning that the hydrophobic interaction drives the adsorption predominantly rather than the electrostatic interaction between the actives and the lens surfaces. When the hydrophobicity becomes too strong, however, solubilization into solution micelles takes place, and hence, the adsorption rate is dramatically decreased. The most effective adsorption occurs in the following active-lens combinations: cationic actives – the anionic and hydrated lens IV; anionic actives – the nonionic and hydrated lens II; and nonionic actives – the anionic and less-hydrated lens III (contain-

Fig. 4 Adsorption Rate of Ionic/Nonionic Actives on the Selected SCL Surfaces as a Function of AC_log P of the Actives.

The active-lens combinations employed here are (a) cationic actives — the anionic lens IV, (b) anionic actives — the nonionic lens II and (c) nonionic actives — the anionic lens III. The experiments were performed under the following conditions: equilibration time = 7 days, temperature = 37°C and solution volume = 5 mL.

Fig. 5 Schematic Representation of Adsorption of (a) Nonionic Actives on the Nonionic Lens III (corresponding to the results given in **Fig. 4c**) and (b) the Cationic Active CPM on Various Kinds of SCL Surfaces (corresponding to the results given in **Fig. 3**).

ing hydrophobic silicone monomers). It is expected that medical ionic/nonionic actives are added in ophthalmological medicines even for over-the-counter in future. Based on the experimental finding in the current study, it is now possible to expect the adsorption behavior of various types of (novel) actives on SCL surfaces.

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