Rejection of hydrophilic pharmaceutical substances by NF/RO membrane considering ground water recharge with treated waste water

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地下水への下水処理水の注入を念頭においたナノろ過膜による親水性医薬品の阻止

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本研究では，ナノろ過膜による医薬品の阻止性能を実験室タイプのテストセルを用いて調べ，医薬品の阻止特性に影響を与える因子を特定した．また，薬液洗浄による膜の劣化に着目し，ナノろ過膜の塩素劣化が阻止性能に及ぼす影響を明らかにした．ろ過実験結果から阻止シミュレーションモデルを構築し，pH が阻止性能に及ぼす影響と膜の塩素劣化機構を説明することを目指した．

1. Introduction

Since the 1990s, pharmaceutical substances have been detected in aquatic environments and they have been recognized as new unregulated contaminants [1-3]. Pharmaceutical compounds are relatively hydrophilic because they are designed to have biochemical effects on human beings and aquatic ecosystems. These human origin compounds are continually discharged to aquatic environments via a number of routes but primarily via treated wastewater.

The pharmaceuticals are considered to move easily in soil because they are hydrophilic. That is why the treatment of pharmaceuticals is important when we consider a wastewater system combined with ground water recharge. There are a few studies measuring both influent and effluent concentrations of pharmaceuticals [3,17]. According to survey in German wastewater treatment plants, clofibric acid(CA) and carbamazepine(CBZ) were removed poorly; the ratio of CA was 51% and that of CBZ was 7% [3]. It is also reported that CA and CBZ are persistent in the aquatic environment [3,18]. It is difficult to eliminate these persistent compounds efficiently by conventional activated process. So, nanofiltration is an attractive process for the removal of pharmaceuticals. Nanofiltration have been widely used water softening [4], desulfatation, rejection of heavy metal complexes [5], removal of colours [6], natural organic matter [7], and some organic pollutants such as plastic additives, endocrine disrupting chemicals and pesticides [8-9,16], however the rejection performance for the compounds which charge state is dependent on pH of solution like pharmaceuticals is not clarified.

In this study, the rejections of pharmaceuticals by various nanofiltration membranes and reverse osmosis membranes, which were in the market and in a development stage, were examined by laboratory scale experiment. It is difficult to estimate the rejection of pharmaceuticals quantitatively by full scale experiment. That is why it is important to estimate the rejection performance by laboratory scale experiment.

In addition, membrane fouling was occurred for long term operation by the adhesion of contaminants to the membrane. To recover from fouling, the chemical cleaning was needed where the sodium hypochlorite was used as the chemical cleaning solution. The nanofiltraiton membrane and reverse osmosis membrane are generally made of polyamide-polymer but the polyamide has low resistance to chlorine. The focus of this study was the deterioration of membrane by immersion in the sodium hypochlorite and the effect of the chlorine deterioration of membranes on the rejection performance was examined by the change of rejection of pharmaceuticals before and after deterioration.

The model was introduced to determine the effect of pH on the rejection of pharmaceuticals. Then the chlorine deterioration mechanism of membranes was analysed by a numerical simulation.

2. Experiment and method

2.1 Target compounds

The target compounds in this study were clofibric acid (CA), gemfibrozil (GFZ), ibuprofen (IBP), fenoprofen (FEP), ketoprofen (KEP), naproxen (NPX), diclofenac (DCF), indomethacin (IDM), propyphenazone (PPZ) and carbamazepine (CBZ). CA is a metabolite of a certain type of lipid regulators like clofibrate, etofibrate and etofyllinclofibrate. GFZ is a lipid regulator. IBP, FEP, KEP, NPX, DCF, IDM, PPZ are commonly used non-steroidal anti-inflammatory drugs. CBZ is an antiepileptic agent. Table 1 shows the physical and chemical properties of these compounds. The size parameters, which were the molecular width and the molecular radius, were calculated by a method proposed by Kiso et al. [10], with the use of Chem-Office. And the dipole moment of target compounds was calculated with this software.

2.2 Nanofiltration experiments

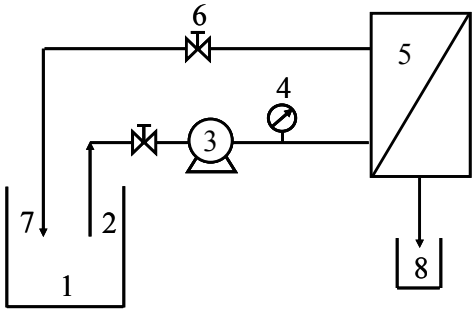
Membrane rejection and flux measurements were obtained using a Nitto Denko bench-top laboratory test cell C-10T nanofiltration unit showing in figure 1.

Table 1 Physical and Chemical properties of target compounds

S/N	Chemical Name	Abbrev.	Mol. Formula	Mol. Weight	$LogK_{ow}$	Dipole [Debye]	pKa	Mol.Width [nm]	Mol.Radius [nm]
1	Clofibric acid	CA	$C_{10}H_{11}ClO_3$	214.65	2.57	1.862	3.00	0.262	0.274
2	Gemfibrozil	GFZ	$C_{15}H_{22}O_3$	250.34	4.77	0.833		0.315	0.379
3	Ibuprofen	IBP	$C_{13}H_{18}O_2$	206.29	3.97	2.089	4.91	0.276	0.295
4	Fenoprofen	FEP	$C_{15}H_{14}O_3$	242.28	3.9	1.991	7.3	0.293	0.299
5	Ketoprofen	KEP	$C_{16}H_{14}O_3$	254.29	3.12	3.604	4.45	0.295	0.337
6	Naproxen	NPX	$C_{14}H_{14}O_3$	230.27	3.18	3.168	4.15	0.284	0.297
7	Diclofenac	DCF	$C_{14}H_{11}Cl_2NO_2$	296.16	4.51	0.966	4.15	0.293	0.414
8	Indomethacin	IDM	$C_{19}H_{16}ClNO_4$	357.8	4.27	1.432	4.5	0.348	0.473
9	Propyphenazone	PPZ	$C_{14}H_{18}N_2O$	230.31	1.94	4.100		0.286	0.341
10	Carbamazepine	CBZ	$C_{15}H_{12}N_2O$	236.28	2.45	3.943		0.315	0.319

The process pumps the feed solution to the module where it flows over a flat sheet membrane, with a total effective surface area of 60 cm^2. The filtrate was collected as permeate. The retentate flow which is not passed through the membrane was recycled to the feed and then circulated through the system. The membranes used in this study were UTC60, B-membrane, C-membrane, D-membrane and ES20 membrane. B-, C- and D-membrane are in a development stage.

The feed solution was prepared by adding the target compounds dissolved in methanol and 5% leachate from a solid waste disposal site to pure water in order to simulate artificial wastewater where the concentrations of target compounds were 100μg/L. The applied pressure was 0.3Mpa. pH of the solution was adjusted at 3, 5, 7 and 9. The retention was measured at 2 hours and 4 hours after starting of the experiment and the steady state condition was confirmed by the comparison of the two samples.



1.Feed 2.Feed flow 3.Pump 4.Gauge 5.Module

6.Valve 7.Retentate flow 8.Permeate

Figure 1 The experimental set-up of the nanofiltration

2.3 Deterioration of membrane

The chemical cleaning solution was prepared by adding the sodium hypochlorite to pure water where the concentration of the sodium hypochlorite was 1250mg/L. And the membrane was deteriorated by immersion in the cleaning solution for several hours at 25°C. When the membrane type is same but the serial number is different, the flux and the chloride rejection by individual membrane are slightly different. In this study to prevent the deviation of the results caused by the difference in membrane piece, the membrane, which was tested as the virgin membrane, was deteriorated and tested as the deteriorated membrane. Following this procedure, the change in rejection of pharmaceuticals before and after deterioration can be comprehended.

2.4 Chemical Analysis

Target pharmaceutical substances like CA, GFZ, IBP, FEP, KEP, NPX, DCF, and IDM were analyzed by the method using GC/MS (Column: DB-5 MS, Temperature: 100 Celsius degree to 260 Celsius degree) after solid phase extraction by C18 disks followed by the pentafluorobenzyl derivatization [11-12]. The water sample was mixed with internal standards, 2,3-dichlorophenoxyacetic acid and chrysene-d12 , and pH was adjusted at 2 by adding hydrochloric acid. 10 mL of methanol and 10 mL of acidic pure water was used in the conditioning step of the extraction filter and 5 mL of methanol was used in the elution step of the solid phase extraction. PPZ and CBZ, which require no derivatization in the analysis, were quantified in the same chromatogram. 2, 4-dichlorobenzoic acid was added to check the recovery in the derivatization step.

3. Theoretical development

3.1 Basic theory

The following steps can explain the transport phenomena of solutes through the electrically charged membranes. Donnan equilibrium caused by the agreement with the electrochemical potential is occurred between bulk solution and membrane phase. The transport of solutes inside membrane phase can be expressed by Extended Nernst-Planck equation, where the solute flux is related to concentration gradient, electric potential gradient, and convection. Finally, Donnan equilibrium and electric neutrality condition also can be applied to the concentration change of a solute between membrane side and permeate solution. The concentration change by Donnan equilibrium can be described by

Eq.(1).

$$\left(\frac{c_i}{C_i}\right)^{\frac{1}{z_i}} = \exp\left(\frac{-F\Delta\psi_D}{RT}\right) \quad (1)$$

where C_i is concentration of i solute in bulk side[mol/m^3], c_i is concentration of i solute inside membrane[mol/m^3], z_i is charge valence of i solute, F is faraday constant[C/mol], ψ_D is Donnan potential at the membrane interface[V], R is gas constant[J/mol K], T is temperature[K].

The electric neutrality conditions inside membrane and in external solution are expressed as follows

In external solution:

$$\sum_i z_i C_i = 0 \quad (2)$$

In membrane:

$$\sum_i z_i c_i + \phi X = 0 \quad (3)$$

where ΦX is effective charge density of membrane[mol/m^3].

The extended Nernst-Planck equation, often applied to describe transport phenomena of solution in electrically charged membranes, can be written as following Eq.(4).

$$j_i = -u_i RT\frac{dc_i}{dx} - z_i c_i u_i F\frac{d\psi}{dx} + c_i j_v \quad (4)$$

where j_i is the flux of the i solute through the membrane based on membrane pore area[mol/m^2/s], u_i is mobility of the i solute[mol m^2/J/s], ψ is electric potential[V], j_v is volume flux based on pore area[m/s].

In the case of conventional steric hindrance model, transport equation through nanodfiltration is modified as shown in Eq.(5). It is extended Nernst-Planck equation coupled with steric hindrance factors.

$$j_i = -K_D\left(u_i RT\frac{dc_i}{dx} + z_i c_i u_i F\frac{d\psi}{dx}\right) + K_F c_i j_v \quad (5)$$

where K_D is the steric hindrance factor under the diffusion condition, K_F is the steric hindrance factor under the convection condition.

Steric hindrance factors depend on the ratio of permeable solute radius to pore radius of the membrane. In this study, the following factors are used [13-14].

$$K_D = (1-q)^2 \quad (6)$$

$$K_F = \left(1+\frac{16}{9}q^2\right)(1-q)^2\left\{2-(1-q)^2\right\} \quad (7)$$

$$q = \frac{r_s}{r_p} \quad (8)$$

where q is ratio of permeable solute radius to pore radius[-], r_s is solute radius[nm], r_p is pore radius of membrane[nm].

3.2 Model structure

In this study, the model for acidic pharmaceuticals was introduced with the assumption of the membrane parameters showing in table 2 where ΔX is membrane thickness[m], Ak is surface porosity[-].

Table 2 Membrane parameters assumed

Membrane	ΔX [nm]	Ak [-]	Ak/ΔX [m-1]	r_p [nm]
C-membrane	10	0.1	10000	0.45
ES20	10	0.002	2000	0.31

First, the effective charge density of membrane was determined by using Eq.(1)-(4) and the chloride rejection and the flux obtained from the nanofiltration experiment. In addition, the dissociative state of acidic pharmaceuticals can be expressed as follows.

$$-\log_{10}\frac{[\text{Pharm}^-]\cdot[\text{H}^+]}{[\text{Pharm}]} = \text{pKa} - 3 \quad (9)$$

where [Pharm$^-$] is concentration of dissociated acidic pharmaceuticals [mol/m^3], [Pharm] is concentration of non-dissociated acidic pharmaceuticals [mol/m^3]. Then concentration for the permeate was calculated by using Eq.(1) and (5). There after the rejection was calculated by using Eq.(10).

$$R_i = \left(1-\frac{C_{i,p}}{C_{i,b}}\right)\times 100[\%] \quad (10)$$

where R_i is rejection[%], $C_{i,p}$ is concentration of i solute for the permeate, $C_{i,b}$ is concentration of i solute for the retentate.

4. Results and discussion

4.1 Classification of membranes by chloride rejection and flux

The experimental rejections of the chloride ion and colour and the fluxes by the different membranes at pH 7 are given in Table3. This enabled the classification of membranes with high salt rejection as tight for nanofiltration membranes B-membrane and D-membrane and with low salt rejection as loose for nanofiltration membranes UTC60 and C-membrane. And ES20 was classified into reverse osmosis membrane. The colour rejections measured by E_{390} were more than 98% for all membranes.

Table 3 Flux and Chloride and Colour rejection by different membrane at pH 7

	UTC60	B-membrane	C-membrane	D-membrane	ES20
Water flux [×10^{-6}m/s]	11.989	5.143	15.761	11.554	3.111
Water flux with solute[×10^{-6}m/s]	11.055	4.317	13.082	10.118	2.747
Chloride rejection [%]	39.995	96.436	75.015	90.648	99.226
Colour rejection [%]	>98	>98	>98	>98	>98

4.2 Effect of pH on the rejection of pharmaceuticals

Figure 2 shows the rejection of pharmaceuticals at different pH. The rejections of acidic pharmaceuticals with carboxyl functional group like CA, GFZ, IBP, FEP, KEP, NPX and DCF by nanofiltration membranes, which were UTC60, B-membrane, C-membrane and D-membrane, were over 95% at pH 7 and 9, while their rejections were lowered at pH 3 and 5. Most of the pharmaceuticals in this group are neutral solutes at acidic pH because their pKa is around 4. These acidic pharmaceuticals cannot be retained by the electric charge repulsion effect in the case of low pH operation and retained only by the sieving effect, because the mechanism of solute rejection in nanofiltration includes both the electric charge repulsion effect and the sieving effect. The rejection of IDM, which has the largest molecular size in this study, was always high and was not affected by pH probably because IDM is large enough to be retained only by the sieving effect. The rejection of PPZ and CBZ, which have no acidic functional group, gave the constant rejection as high as 90% regardless of pH. The rejection of all pharmaceuticals by reverse osmosis membrane, which was ES20, was over 99% at different pH and was not effected by pH probably because ES20 is tight enough to retain all pharmaceuticals only by the sieving effect in the case of low pH operation.

4.3 Suitable parameter for describing the sieving effect of pharmaceuticals

Molecular weight has most often been used to reflect molecular size of solutes. In the consideration of sieving effect on rejection, comparison has been made for the rejections of pharmaceuticals by the loose nanofiltration membranes at pH 3 with the molecular weight and the size parameters, which were the molecular width and the molecular radius, of solutes because the acidic pharmaceuticals with carboxyl functional groups were thought not to be ionized at pH 3. Figure 3 shows the correlation of the rejection with the molecular weight, the molecular width and the molecular radius. The rejection of pharmaceuticals except for CA, PPZ and CBZ was correlated with the molecular weight, the molecular width and the molecular radius of the solutes. The correlation of the rejection with the molecular width was not clear because the molecular width of target compounds was within the narrow range, but the molecular radius gave a better prediction for the rejection of pharmaceuticals by sieving effect. The rejection of CA, PPZ and CBZ was relatively high but these molecular sizes, which included the molecular weight, the molecular width and the molecular radius, are not especially large. The pKa of CA is 3 and CA was not fully ionized at pH around 3.2. And the rejection of CA was relatively high probably because the electric repulsion effect was thought to interact with CA at pH around 3. On the other hand, the high rejection of PPZ and CBZ was explained by considering the dipole moment. The dipole moment of PPZ and CBZ is relatively high compared to acidic pharmaceuticals. The high dipole moment means high polarity in a molecule. This is why the electric repulsion effect due to high polarity may increase the rejection of PPA and CBZ regardless of pH. Kimura et al. [15] examined the performance of RO membranes made of cellulose acetate to retain neutral pharmaceutically active compounds and showed that molecules with a higher dipole moment showed a higher rejection than molecules with a lower dipole moment. Our result is consistent with their result.

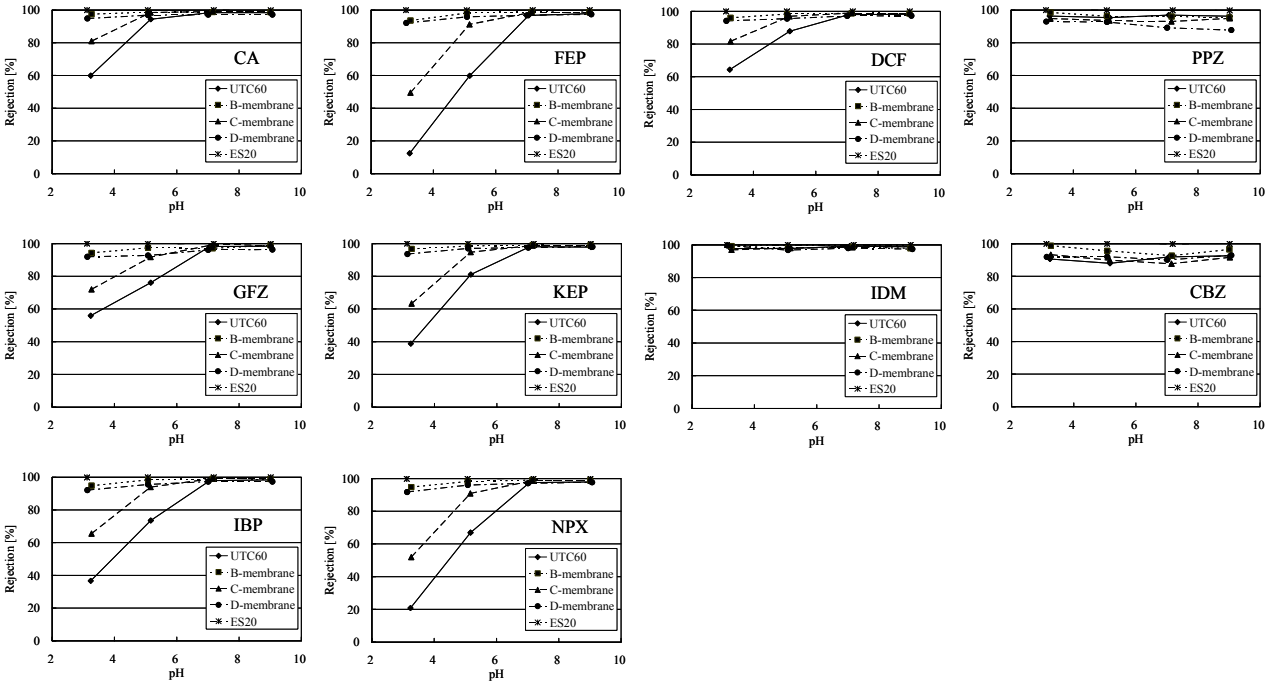


Figure 2 Effect of pH on the rejection of pharmaceuticals by different pH

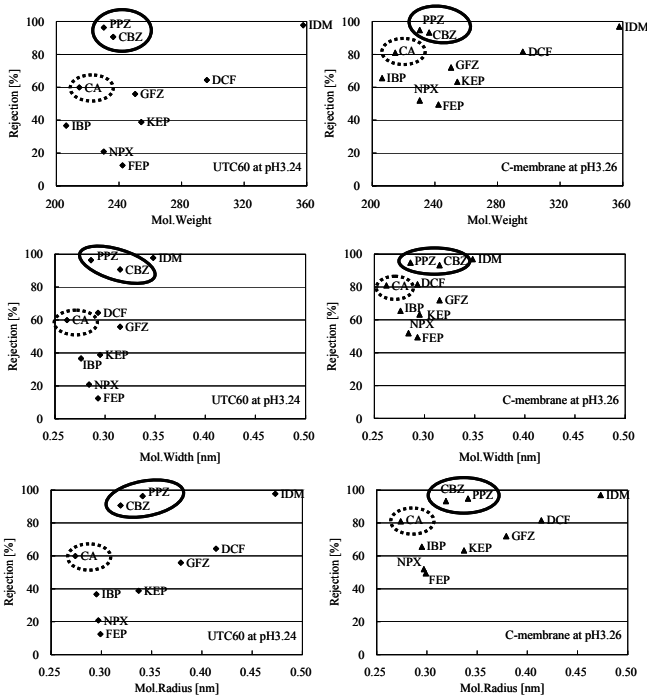


Figure 3 The relationship between rejection and molecular weight, molecular width and molecular radius

4.4 Change of water flux with solute and chloride rejection before and after deterioration

Figure 4 shows the water flux and the chloride rejection by C-membrane and ES20 before and after deteriorated by immersion in sodium hypochlorite. C-membrane was immersed in sodium hypochlorite for 6 hours and ES20 was immersed in sodium hypochlorite for 12 hours, respectively. The chloride rejection was decreased at different pH except for pH 3. On the other hand, the water flux with solute was increased at different pH. This was thought to attribute to the fact that the pore size of membrane was expanded or the surface layer of membrane, which was contributed to

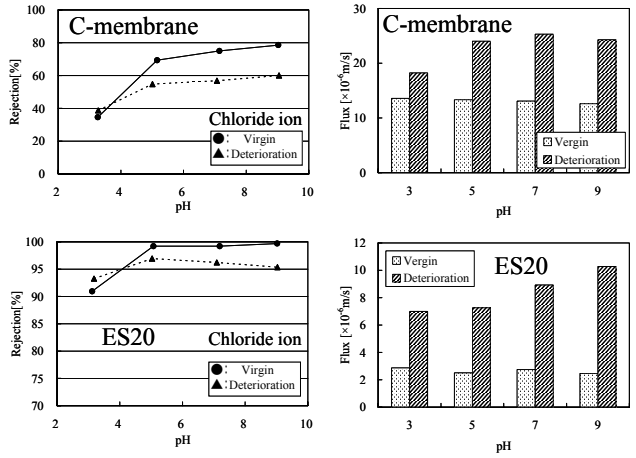


Figure 4 Change of flux and chloride rejection before and after deterioration

hydraulic resistance, was become thinner by immersion in the sodium hypochlorite. In addition, the water flux with solute after deteriorated was high at pH 7 and 9 compared to at pH 3 and 5. Effect of pH on the water flux with solute was observed. The effect was different before deterioration of membrane. This is because the chlorine deterioration of membrane affected the dependence of pH on water permeation.

4.5 Change of rejection of pharmaceuticals before and after deterioration

Figure 5 shows the rejection of pharmaceuticals by C-membrane before and after deteriorated by immersion in sodium hypochlorite. The rejection of pharmaceuticals by C-membrane after chlorine deterioration was decreased at different pH. The rejection decrease of acidic pharmaceuticals at pH 7 and 9 was low compared to those at pH 3 and 5. The rejection decrease at lower pH was especially observed for DCF and IDM which molecular weight and size parameter were relatively large in this study. These acidic pharmaceuticals were retained by the sieving effect in the case of low pH operation. This is because the sieving effect was considerably deteriorated by immersion in sodium hypochlorite compared to the electric charge repulsion effect. The rejection decrease of PPZ and CBZ, which were practically retained by the sieving effect at different pH, was constant regardless of pH.

Figure 6 shows the rejection of pharmaceuticals by ES20 before and after deteriorated by immersion in sodium hypochlorite. The rejection decrease of acidic pharmaceuticals by ES20 after chlorine deterioration was not observed at pH 7 and 9 but that was clearly observed at pH 3 and 5. The rejection decrease of IDM was hardly observed at different pH. The rejection decrease of PPZ and CBZ was constant regardless of pH. These results indicated that the sieving effect was deteriorated by immersion in the sodium hypochlorite in the earlier stage than the electric charge repulsion effect was deteriorated.

4.6 Comparison of the calculated results with the experimental results

In this study, the theoretical rejection by C-membrane and ES20 were calculated with the assumption of acidic pharmaceuticals showing in table 4.

Table 4 Physical and Chemical properties of acidic pharmaceuticals assumed

	Mol.Weight	Mol.Size [nm]	pKa
Acidic Pharmaceuticals	250	0.3	4

Figure 7 shows the comparison of the calculated results with the experimental results by the respective membranes where the experimental results mean the averaged rejections of acidic pharmaceuticals except for IDM obtained from nanofiltration experiment. The

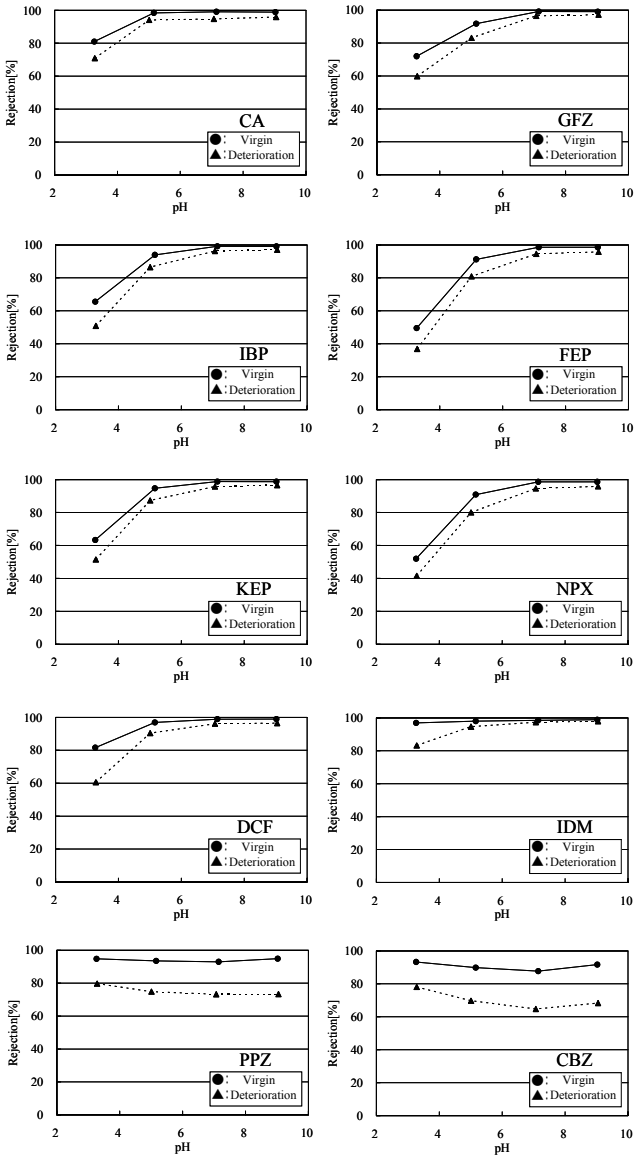


Figure 5 Change of the rejection of pharmaceuticals before and after deteriorated C-membrane

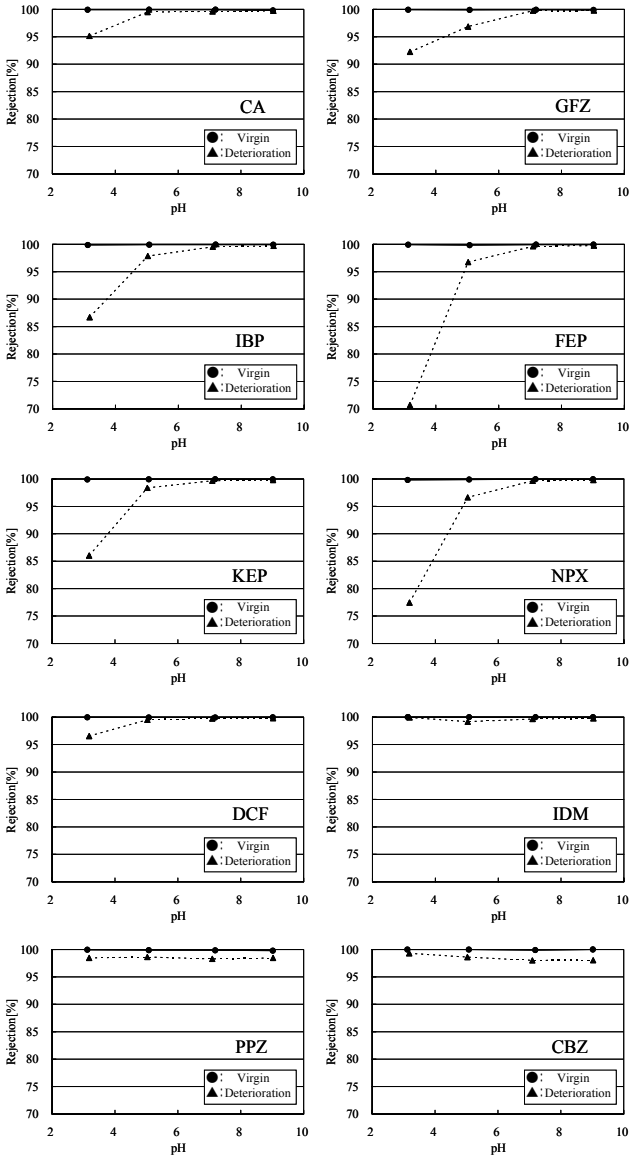


Figure 6 Change of the rejection of pharmaceuticals before and after deteriorated ES20

calculated results were accorded with the experimental results for the respective membranes. From these comparisons, the model structured for acidic pharmaceuticals could express the dependence of pH on the experimental rejection of acidic pharmaceuticals and practically simulate the transport phenomenon in membrane. In addition, the assumption of membrane parameters shown in table 2 was identified to be correct approximately.

4.7 Analysis of deterioration mechanism by using numerical simulation

Figure 8 shows the comparison of the calculated results with the experimental results for the deteriorated C-membrane. The theoretical rejection by the deteriorated C-membrane was calculated with the assumption of membrane parameters showing in table.2. At pH 3 and 5, the calculated rejection was high compared to the experimental rejection. In this calculation, the effective charge density of membrane was determined on the basis of the chloride rejection obtained from nanofiltration experiment. The deterioration of the electric charge repulsion effect was comprehended in this step but the deterioration of the sieving effect was not done. To estimate the deterioration of the sieving effect, the calculation was repeated as increasing the pore size of membrane. By calculating with the assumption of the pore size of membrane of 0.53nm, the calculated rejection was accorded with the experimental rejection at pH 3 and 5 but the calculated rejection was lower than the experimental rejection at pH 7 and 9.

Figure 9 shows the comparison of the calculated results with the experimental results for the deteriorated ES20. The theoretical rejection by the deteriorated ES20 was calculated with the assumption of membrane parameters showing in table 2. At pH 3 and 5, the calculated rejection was high compared to the experimental rejection. The deterioration of sieving effect was not comprehended as mentioned before because the effec-

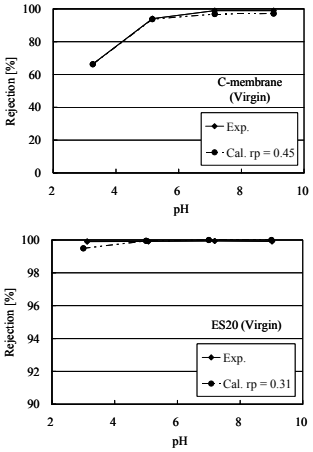


Figure 7 Comparison of calculated rejection and experimental rejection for C-membrane and ES20

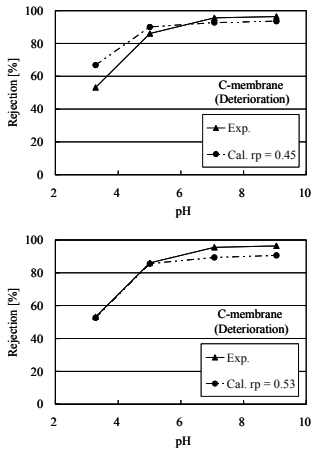


Figure 8 Comparison of calculated rejection and experimental rejection by deteriorated C-membrane

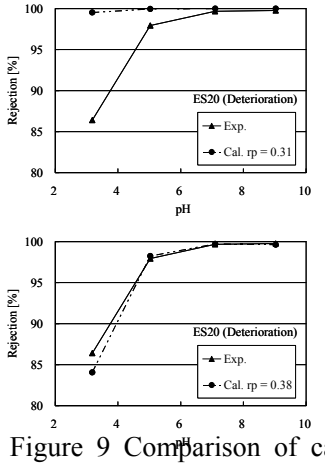


Figure 9 Comparison of calculated rejection and experimental rejection by deteriorated ES20

tive charge density of membrane was determined on the basis of the chloride rejection obtained from nanofiltration experiment. Then to estimate the deterioration of the sieving effect, the calculation was repeated as increasing the pore size of membrane. By calculating with the assumption of pore size of membrane of 0.38nm, the rejection was accorded with the experimental rejection. These simulated results indicated that the pore size of ES20 was expanded from 0.31nm to 0.38nm by immersion in the sodium hypochlorite. In the same way, the pore size of C-membrane was thought to be expanded from 0.45nm to 0.53nm by immersion in the sodium hypochlorite but another factor which was not taken into account in this study may affect the results.

5. Conclusions

The rejection of clofibric acid (CA), gemfibrozil (GFZ), ibuprofen (IBP), fenoprofen (FEP), ketoprofen (KEP), naproxen (NPX), diclofenac (DCF), indomethacin (IDM), propyphenazone (PPZ) and carbamazepine (CBZ) by NF and RO membranes and the change of rejection before and after deterioration of the membrane by immersion in the sodium hypochlorite was examined. The numerical simulation clarified whether the deterioration was caused by pore radius increase or by electric charge decrease. The conclusions were summarized as follows:

1. The rejections of acidic pharmaceuticals with carboxyl functional group like CA, GFZ, IBP, FEP, KEP and DCF by nanofiltration membrane were over 95% at pH 7 and 9, while their rejections were lowered at pH 3 and 5. The numerical simulation model successfully expressed the dependence of pH on the experimental rejection of acidic pharmaceuticals and practically simulated the transport phenomenon in membrane.
2. The rejection of IDM, which was the largest molecular size in this study, by nanofiltration membrane was always high and was not affected by pH.
3. The rejection of PPZ and CBZ, which have no acidic functional group, by nanofiltration membrane gave the constant rejection as high as 90% regardless of pH. The high rejection of PPZ and CBZ could be explained by considering the dipole moment.
4. The rejection of all pharmaceuticals by reverse osmosis membrane was over 99% at different pH and was not affected by pH.
5. The rejection of pharmaceuticals at pH around 3 was correlated with the molecular weight, the molecular width and the molecular radius of the solutes. The molecular radius gave a better prediction for the rejection of pharmaceuticals by sieving effect.
6. After chlorine deterioration of membrane, the chloride rejection was decreased at different pH except for pH 3 and the water flux with solute was increased at different pH.
7. The rejection of acidic pharmaceuticals by deteriorated membranes was decreased at pH 3 and 5 especially. The sieving effect was deteriorated by immersion in the sodium hypochlorite in the earlier stage than the electric repulsion effect was deteriorated. The numerical simulation indicated that the pore size of membrane was expanded by chlorine deterioration while the effect of chlorine deterioration on the decrease of the electric repulsion was small.

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