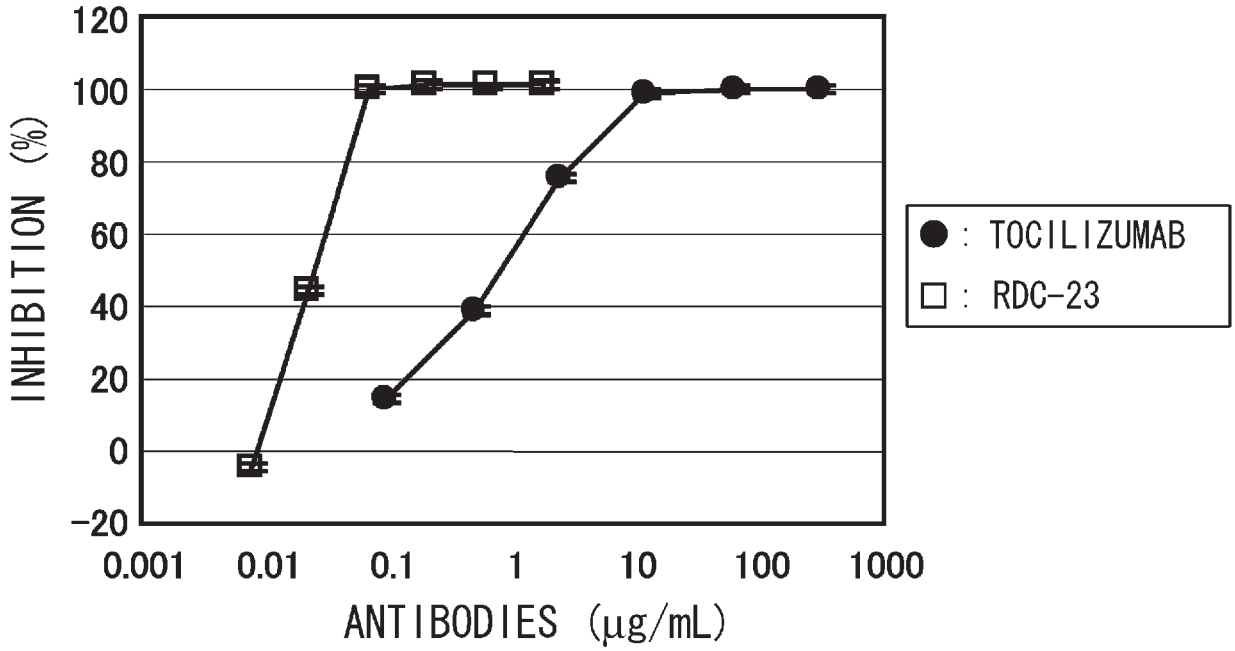
[Fig. 1]

CDR CLASSIFICATION	TOCILIZUMAB CDR SEQUENCE	MUTATION SITE (Kabat No.)	AMINO ACID OF TOCILIZUMAB	AMINO ACID AFTER MUTATION	CDR SEQUENCE AFTER MUTATION
HCDR2	YISYSGITTYNPSLKS (SEQ ID NO: 81)	50	Y	F	FISYSGITTYNPSLKS (SEQ ID NO: 82)
HCDR2	YISYSGITTYNPSLKS (SEQ ID NO: 81)	58	T	N	YISYSGITNYNPSLKS (SEQ ID NO: 83)
HCDR3	SLARTTAMDY	95	S	L	LLARTTAMDY (SEQ ID NO: 85)
HCDR3	SLARTTAMDY (SEQ ID NO: 84)	99	T	A	SLARATAMDY (SEQ ID NO: 86)
LCDR1	RASQDISSYLN	27	Q	T	RASTDISSYLN (SEQ ID NO: 88)
LCDR1	RASQDISSYLN (SEQ ID NO: 87)	27	Q	R	RASRDISSYLN (SEQ ID NO: 89)
LCDR3	QQGNTLPYT	89	Q	G	GQGNTLPYT (SEQ ID NO: 91)
LCDR3	QQGNTLPYT (SEQ ID NO: 90)	93	T	R	QQGNRLPYT (SEQ ID NO: 92)

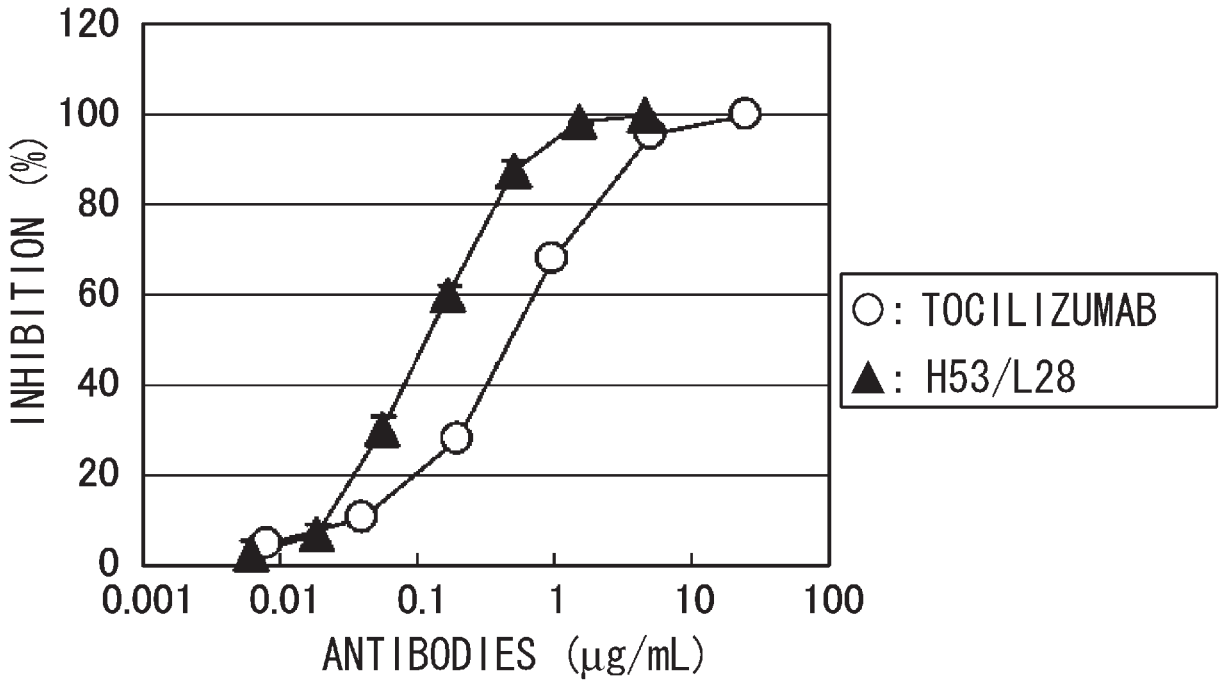
[Fig. 2]



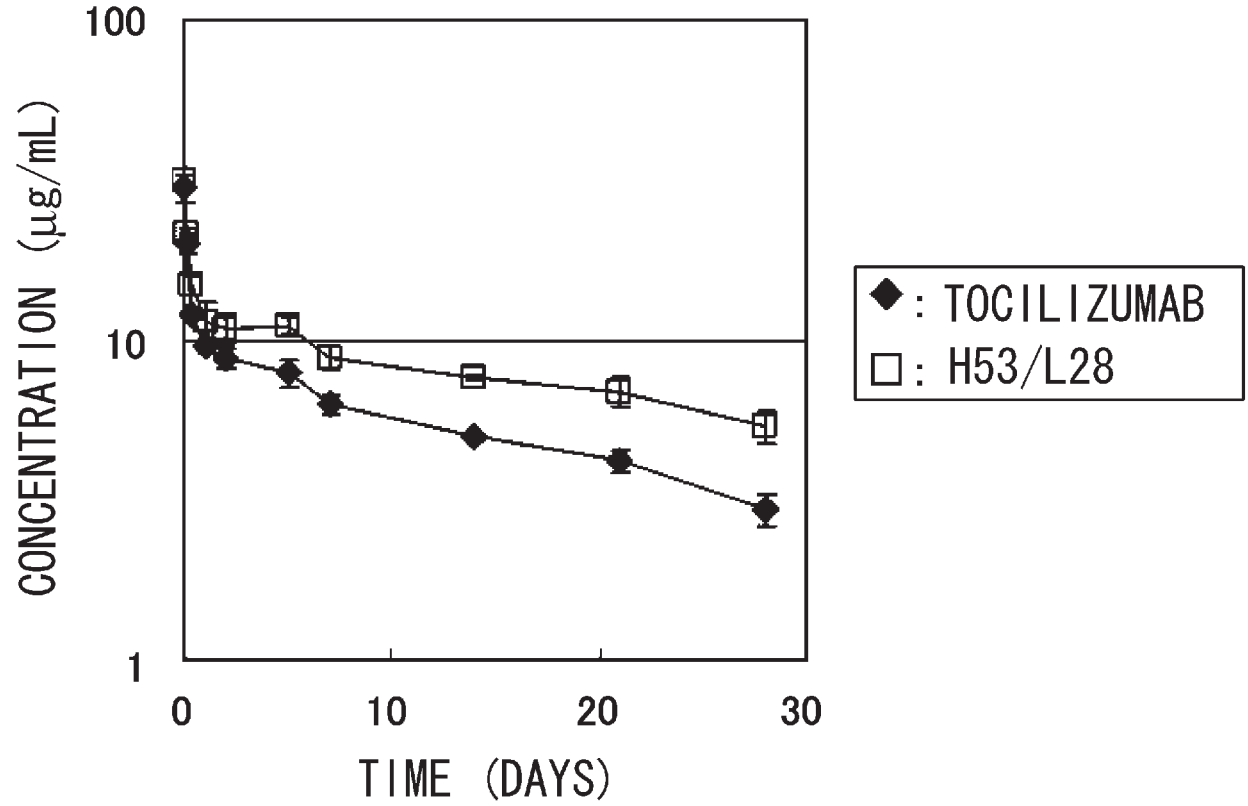
[Fig. 3]

CLASSIFICATION	TOCILIZUMAB SEQUENCE	MUTATION SITE (Kabat No.)	AMINO ACID OF TOCILIZUMAB	AMINO ACID AFTER MUTATION	SEQUENCE AFTER MUTATION
HFR1	QVQLQESGPGLVRPSQTLSLTC TVSGYSIT (SEQ ID NO: 93)	13	R	K	QVQLQESGPGLVKPSETLSLTC AVSGYSIS (SEQ ID NO: 94)
		16	Q	E	
		23*	T	A	
		30*	T	S	
HCDR1	SDHAWS (SEQ ID NO: 95)	31	S	D	DDHAWS (SEQ ID NO: 96)
HFR2	WVRQPPGRGLEWIG (SEQ ID NO: 97)	43	R	E	WVRQPPGEGLEWIG (SEQ ID NO: 98)
HCDR2	YISYSGITTYNPSLKS (SEQ ID NO: 81)	64	K	Q	YISYSGITTYNPSLQD (SEQ ID NO: 99)
		65	S	D	
HFR4	WGQGSLVTVSS (SEQ ID NO: 100)	105	Q	E	WGEGTLVTVSS (SEQ ID NO: 101)
		107*	S	T	
LFR1	DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 102)	18	R	S	DIQMTQSPSSLSASVGDSVTITC (SEQ ID NO: 103)
LCDR1	RASQDISSYLN (SEQ ID NO: 87)	24	R	Q	QASQDISSYLN (SEQ ID NO: 104)
LFR2	WYQQKPGKAPKLLIY (SEQ ID NO: 105)	45	K	E	WYQQKPGKAPELLIY (SEQ ID NO: 106)
LCDR2	YTSRLHS (SEQ ID NO: 107)	53	R	E	YTSELES (SEQ ID NO: 108)
		55	H	E	
		55	H	L	YTSRLLS (SEQ ID NO: 109)
LFR3	GVPSRFSGSGSGTDFTFTISSLQPE DIATYYC (SEQ ID NO: 110)	80	Q	E	GVPSRFSGSGSGTDFTFTISSLEAE DAATYYC (SEQ ID NO: 111)
		81*	P	A	
		83*	I	A	
LFR4	FGQGTKVEIK (SEQ ID NO: 112)	107	K	E	FGQGTKVEIE (SEQ ID NO: 113)

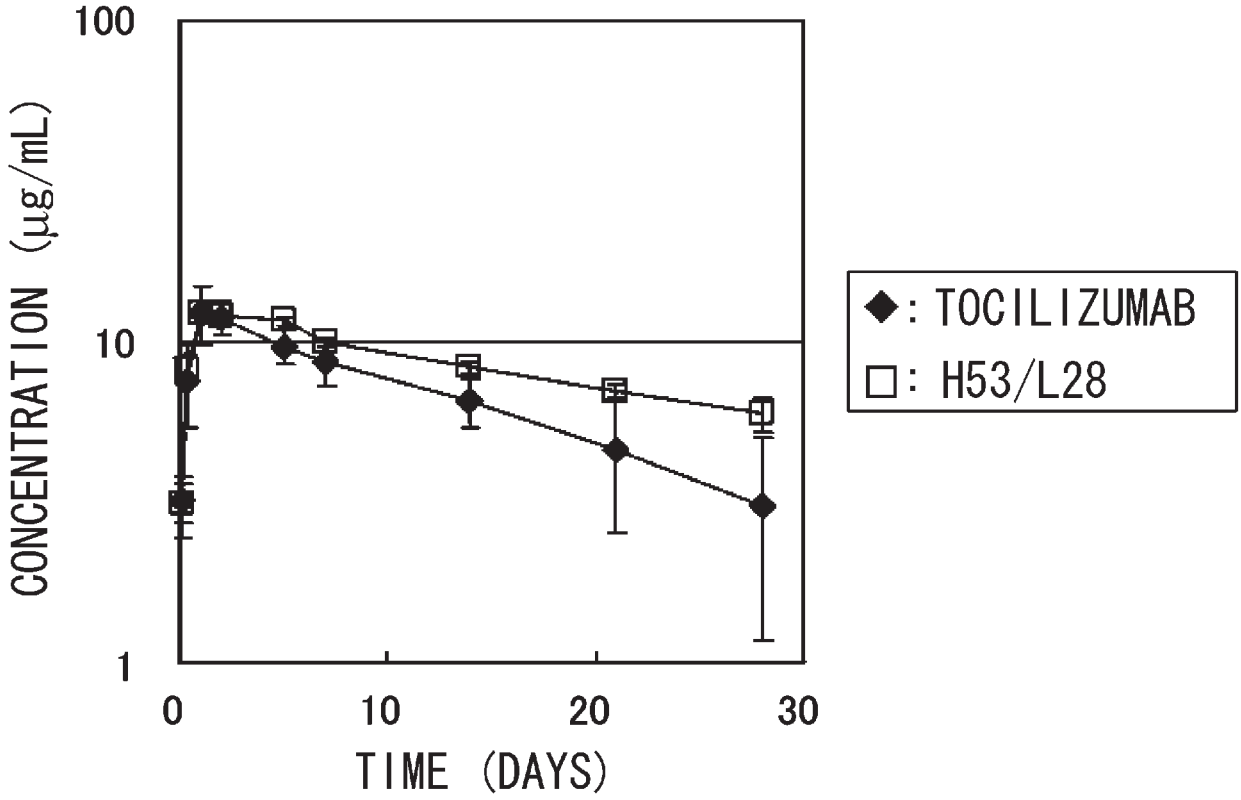
[Fig. 4]


120
100
80
60
40
20
0
INHIBITION (%)
0.001
0.01
0.1
1
10
100
ANTIBODIES (μg/mL)
○: TOCILIZUMAB
▲: H53/L28

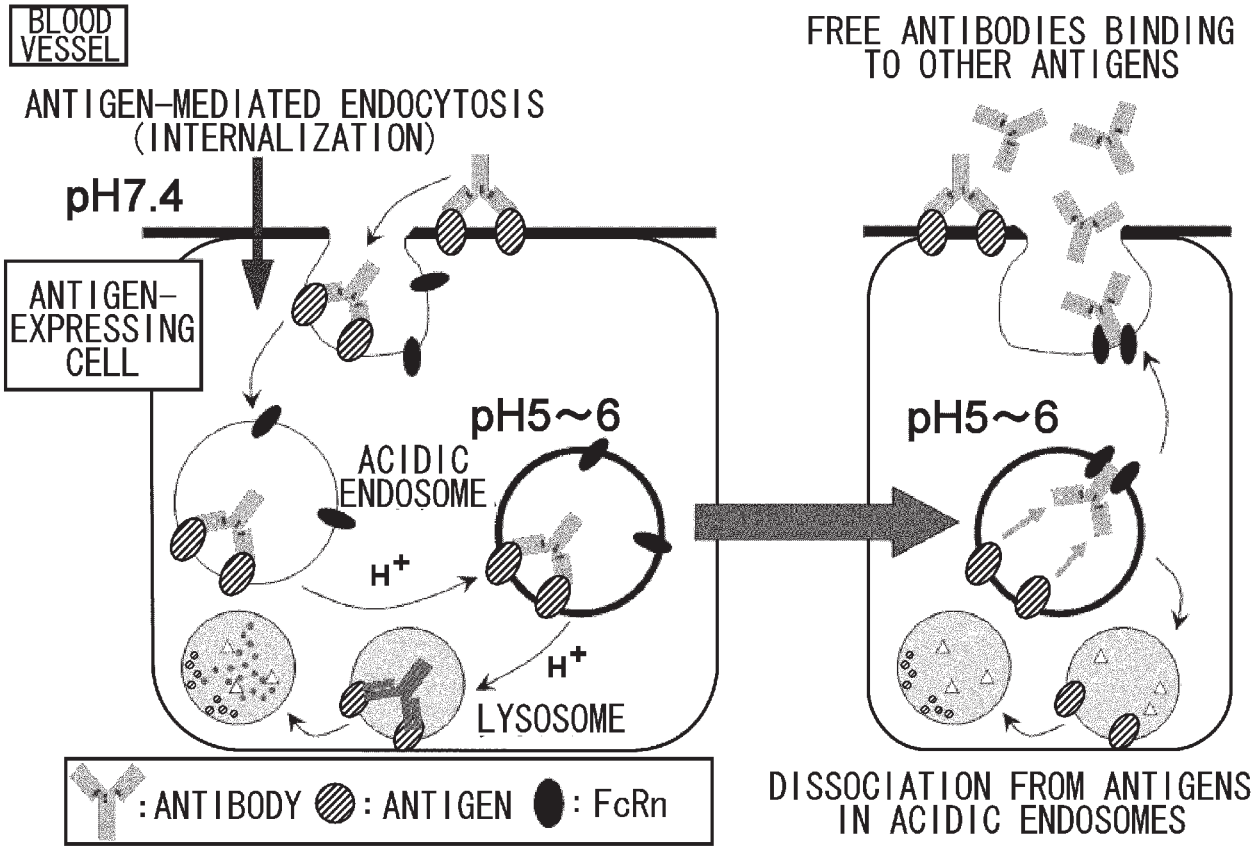
[Fig. 5]


100
10
1
CONCENTRATION (μg/mL)
0
10
20
30
TIME (DAYS)
◆: TOCILIZUMAB
□: H53/L28

[Fig. 6]


100
10
1
CONCENTRATION (μg/mL)
0
10
20
30
TIME (DAYS)
◆: TOCILIZUMAB
□: H53/L28

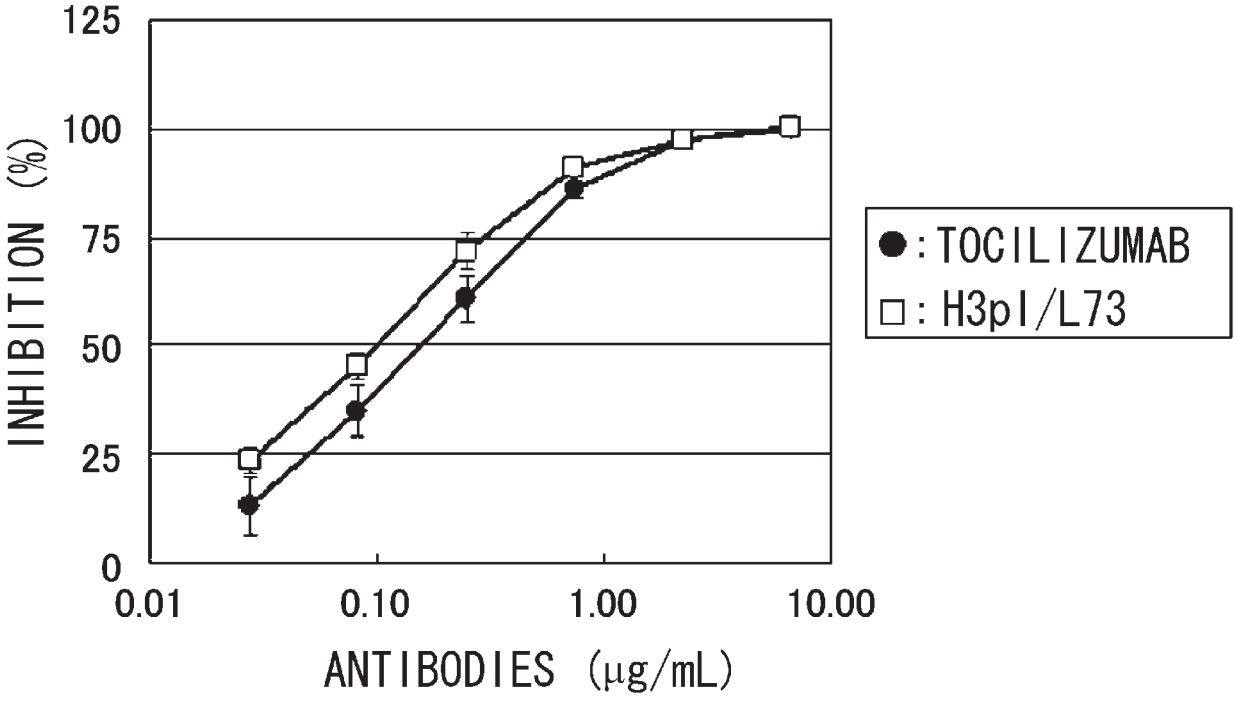
[Fig. 7]


BLOOD VESSEL
ANTIGEN-MEDIATED ENDOCYTOSIS (INTERNALIZATION)
pH7.4
ANTIGEN-EXPRESSING CELL
pH5~6
ACIDIC ENDOSOME
H+
H+
LYSOSOME
FREE ANTIBODIES BINDING TO OTHER ANTIGENS
pH5~6
DISSOCIATION FROM ANTIGENS IN ACIDIC ENDOSOMES
:ANTIBODY :ANTIGEN :FcRn

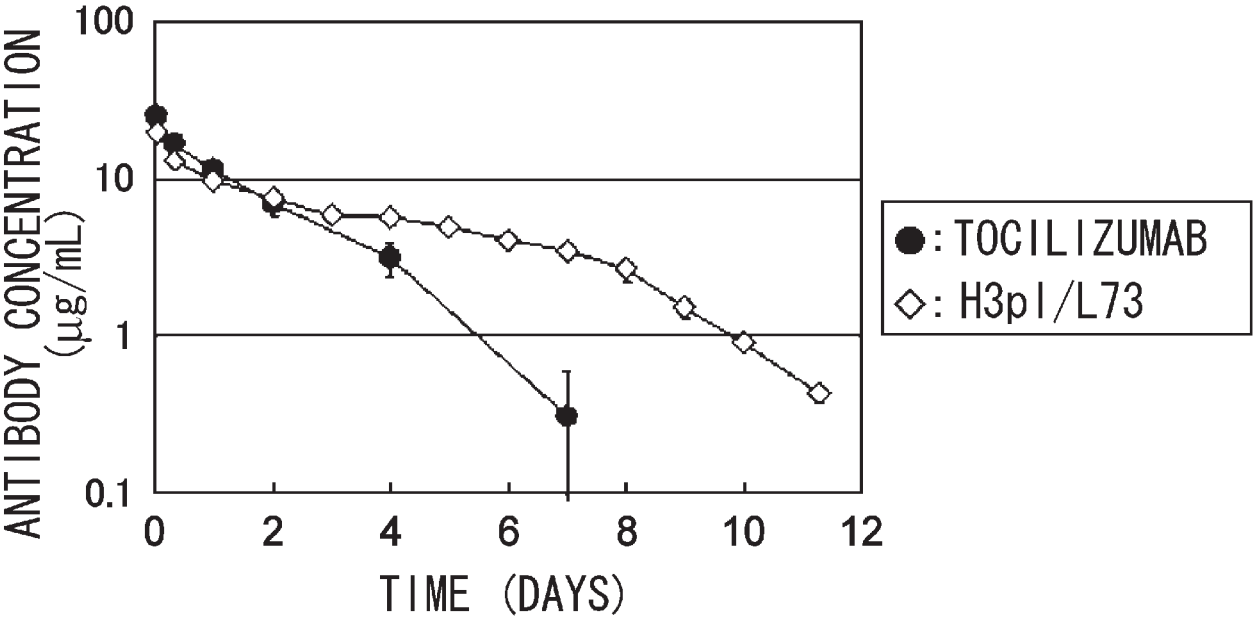
[Fig. 8]

CLASSIFICATION	TOCILIZUMAB SEQUENCE	MUTATION SITE (Kabat No.)	AMINO ACID OF TOCILIZUMAB	AMINO ACID AFTER MUTATION	SEQUENCE AFTER MUTATION
HFR1	QVQLQESGPGLVRPSQTLS LTCTVSGYSIT (SEQ ID NO: 93)	27	Y	H	QVQLQESGPGLVRPSQTLS LTCTVSGHSIT (SEQ ID NO: 114)
HCDR1	SDHAWS (SEQ ID NO: 95)	31	S	H	HDHAWS (SEQ ID NO: 115)
LCDR1	RASQDISSYLN (SEQ ID NO: 87)	32	Y	H	RASQDISSHLN (SEQ ID NO: 116)
LCDR2	YTSRLHS (SEQ ID NO: 107)	53	R	H	YTSHLHS (SEQ ID NO: 117)

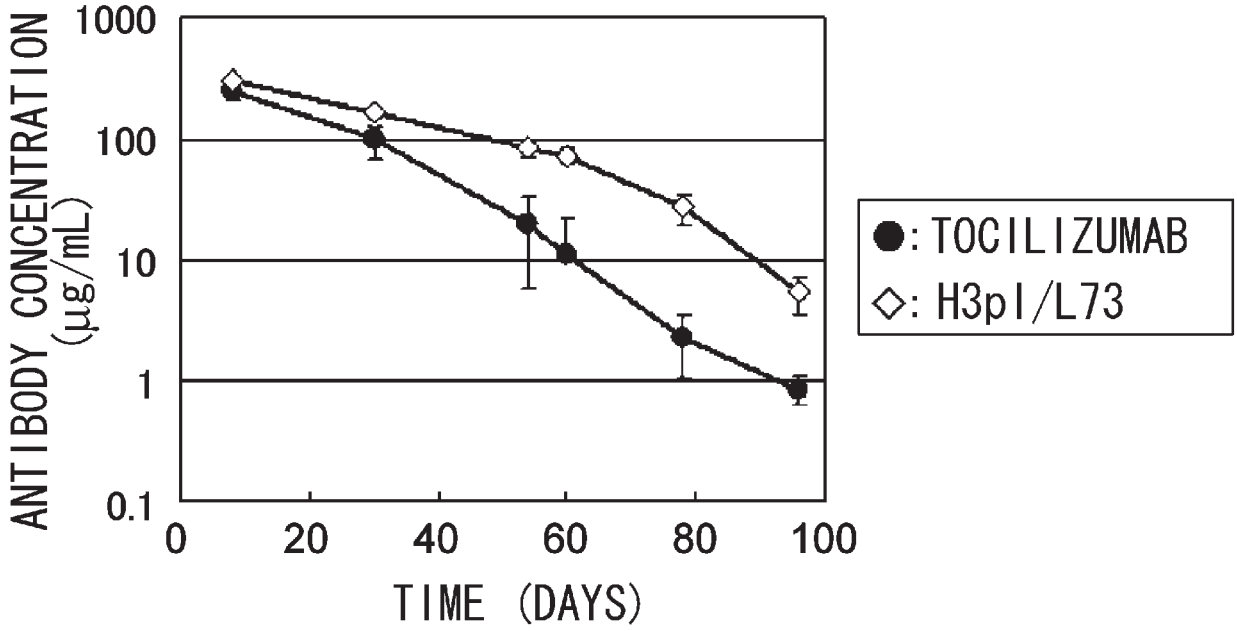
[Fig. 9]



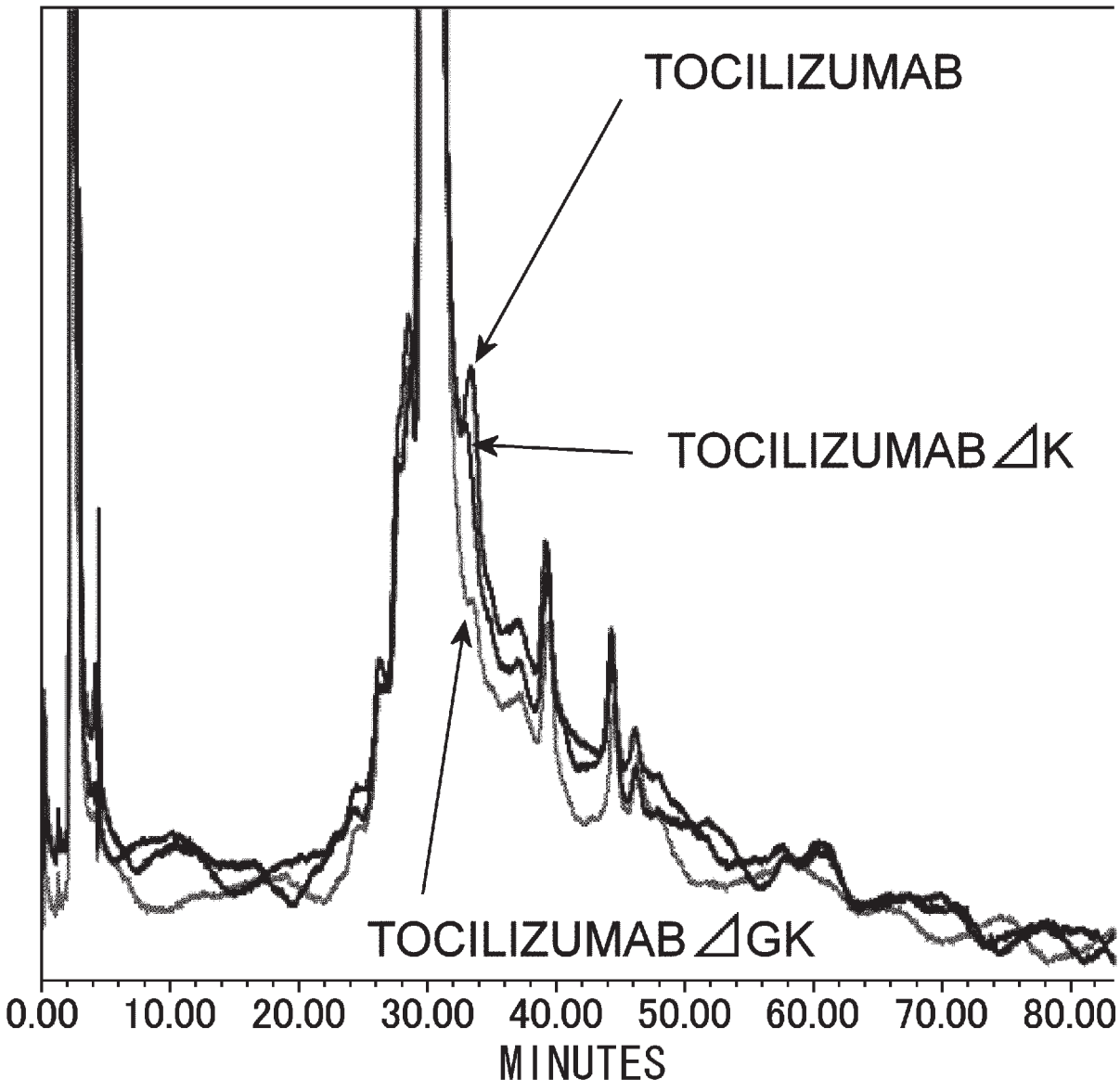
[Fig. 10]



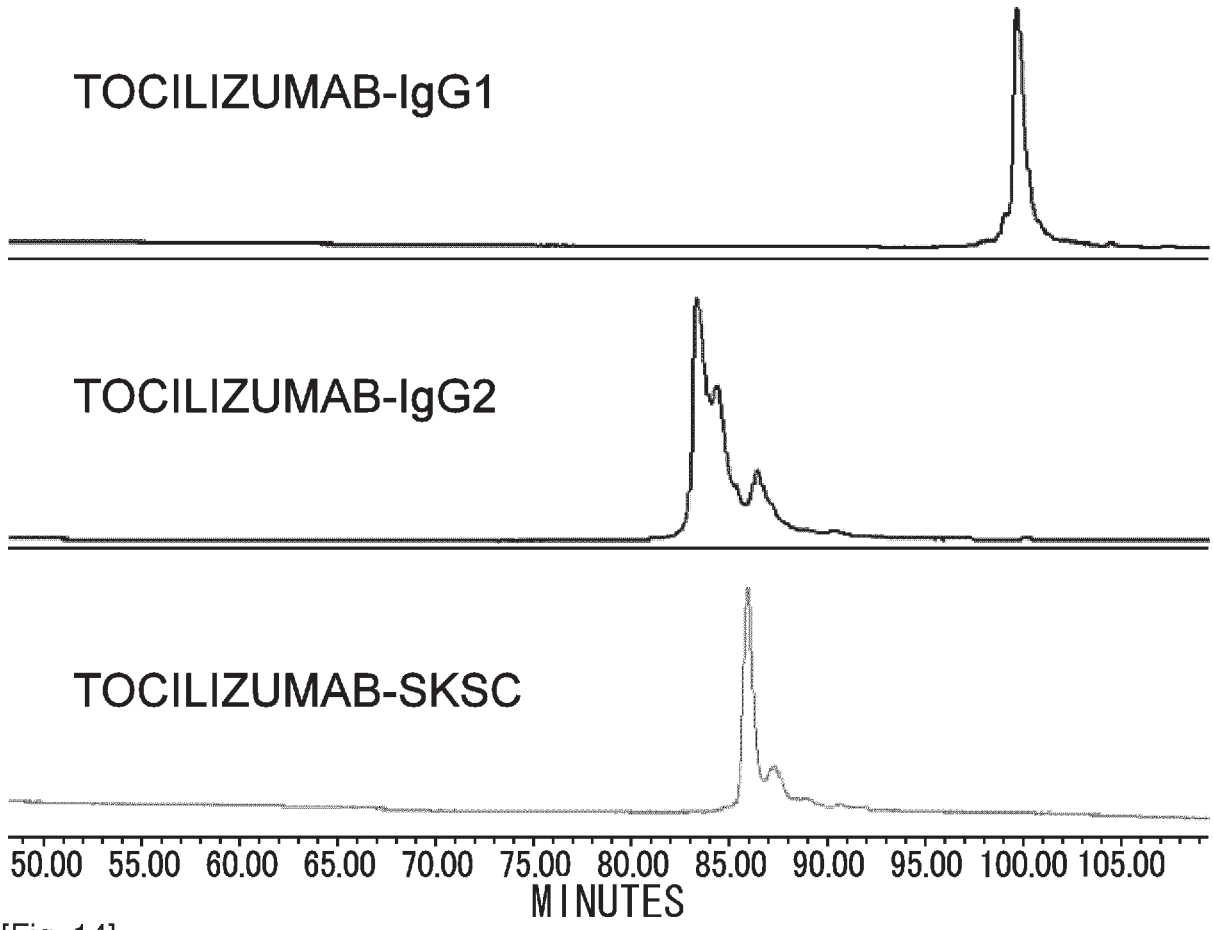
[Fig. 11]


ANTIBODY CONCENTRATION (μg/mL)
1000
100
10
1
0.1
0
20
40
60
80
100
TIME (DAYS)
●: TOCILIZUMAB
◇: H3pI/L73

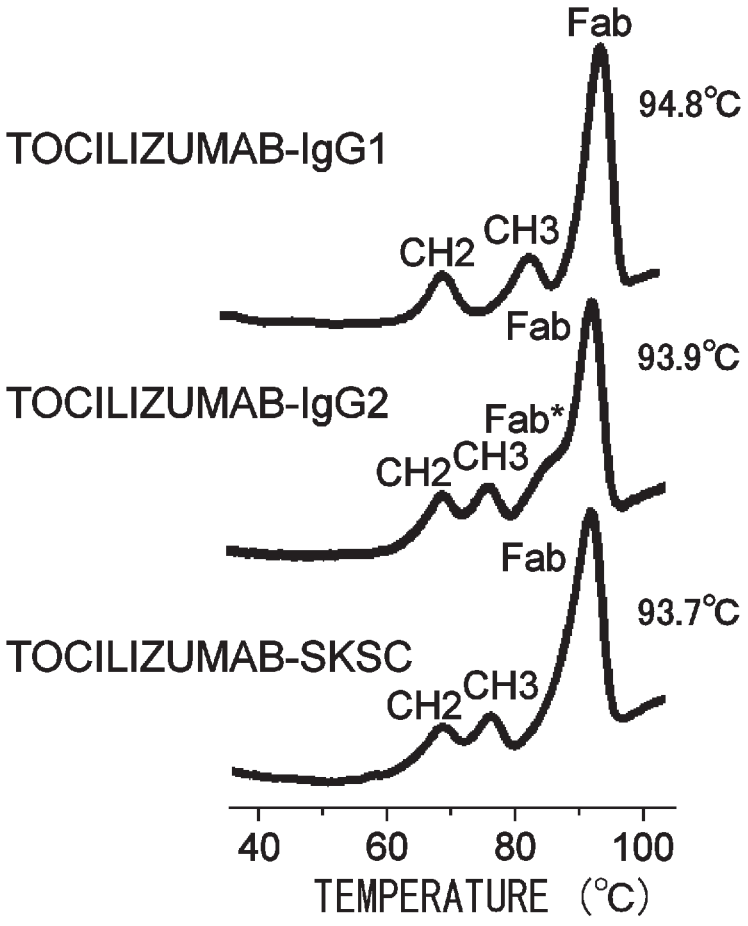
[Fig. 12]


TOCILIZUMAB
TOCILIZUMAB⊿K
TOCILIZUMAB⊿GK
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
MINUTES

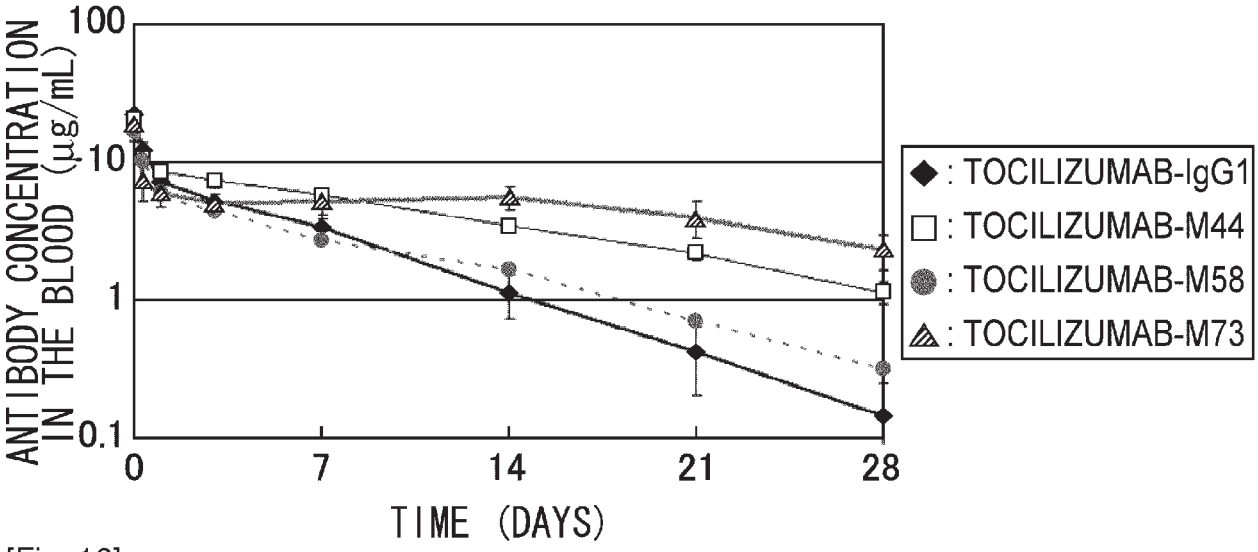
[Fig. 13]


TOCILIZUMAB-IgG1
TOCILIZUMAB-IgG2
TOCILIZUMAB-SKSC
50.00 55.00 60.00 65.00 70.00 75.00 80.00 85.00 90.00 95.00 100.00 105.00
MINUTES

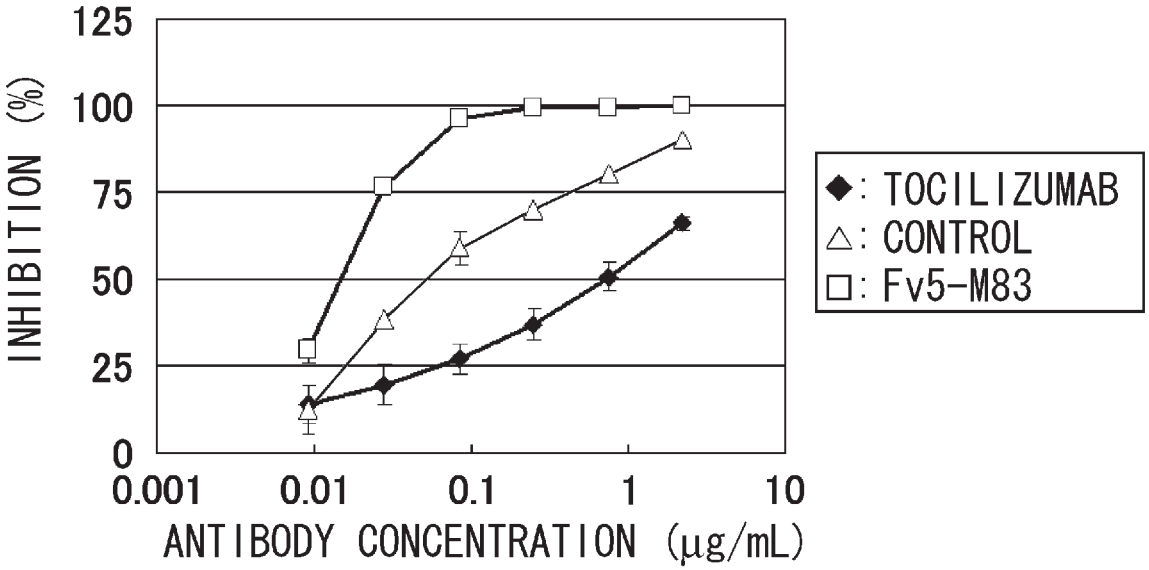
[Fig. 14]


Fab
94.8℃
TOCILIZUMAB-IgG1
CH2
CH3
Fab
93.9℃
TOCILIZUMAB-IgG2
Fab*
CH2
CH3
Fab
93.7℃
TOCILIZUMAB-SKSC
CH2
CH3
40 60 80 100
TEMPERATURE (℃)

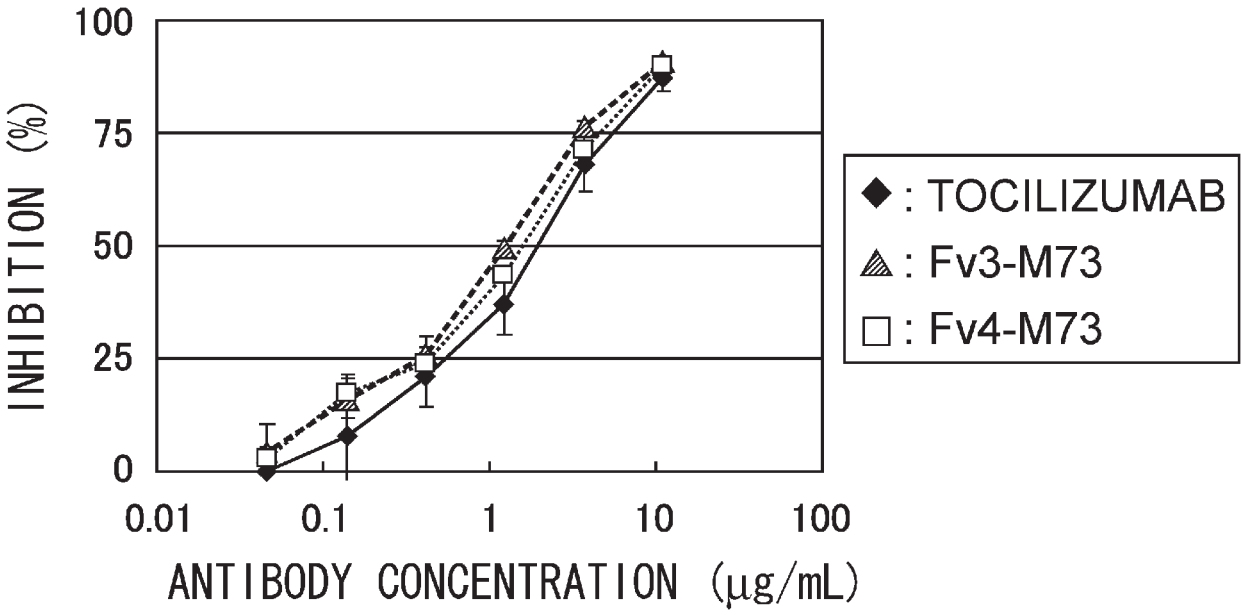
[Fig. 15]



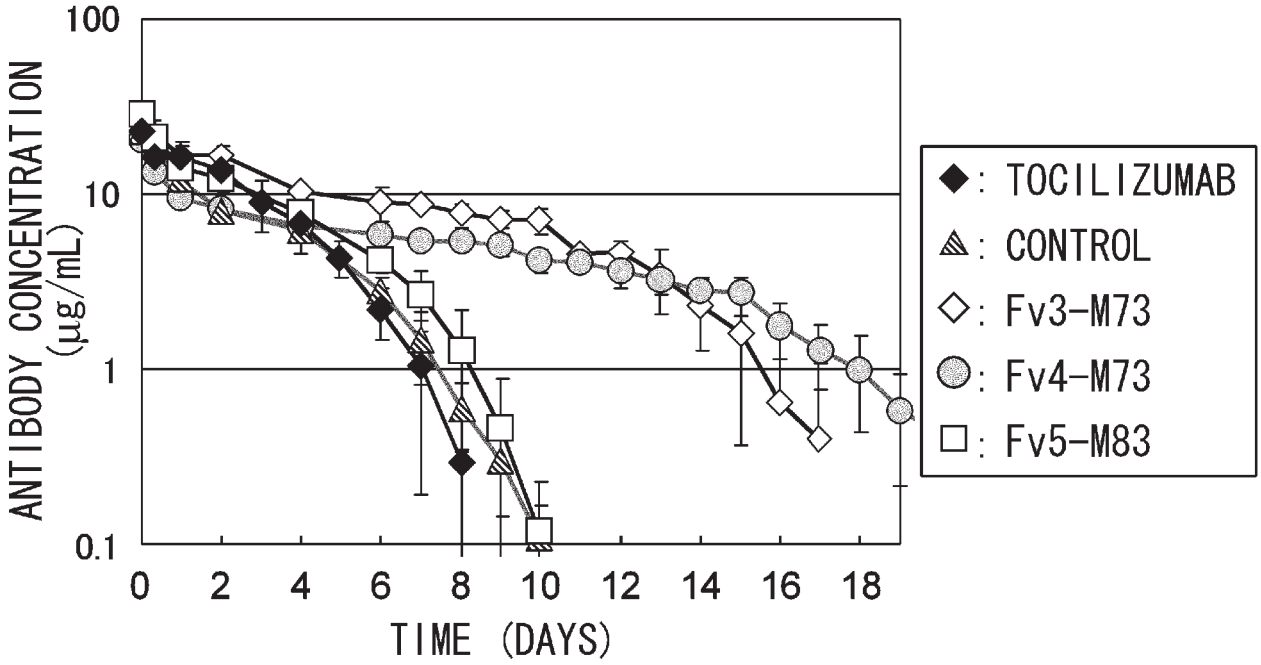
[Fig. 16]



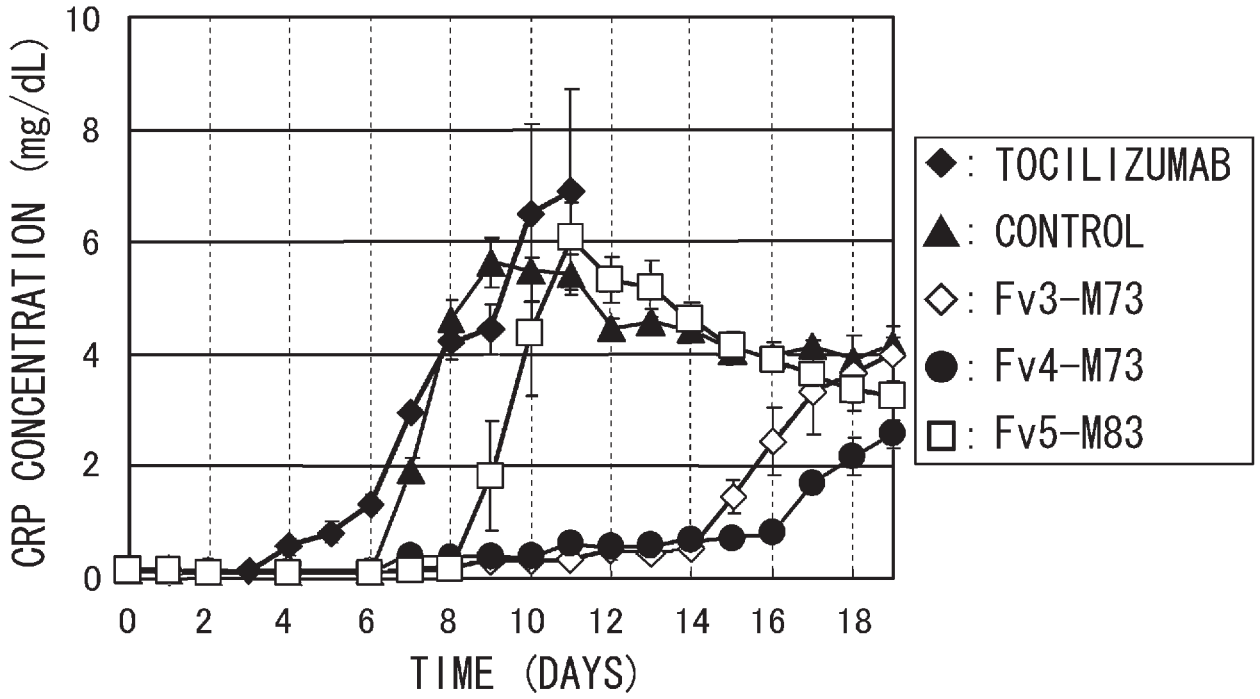
[Fig. 17]



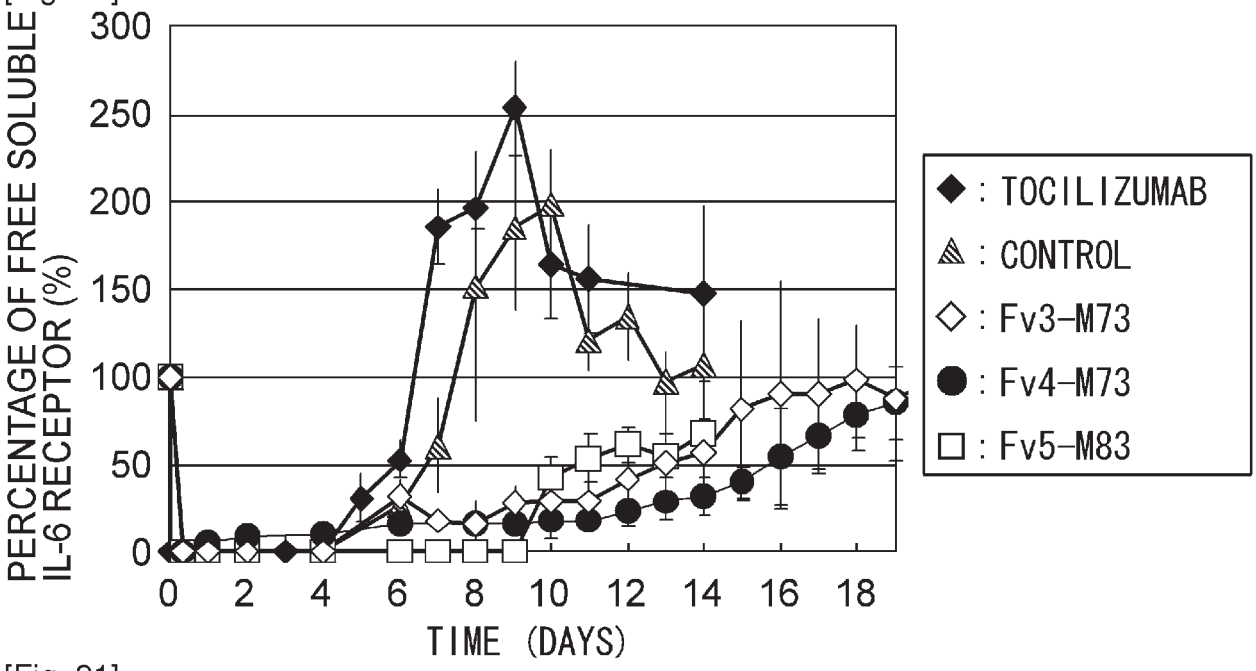
[Fig. 18]


ANTIBODY CONCENTRATION (μg/mL)
100
10
1
0.1
0 2 4 6 8 10 12 14 16 18
TIME (DAYS)
◆: TOCILIZUMAB
△: CONTROL
◇: Fv3-M73
●: Fv4-M73
□: Fv5-M83

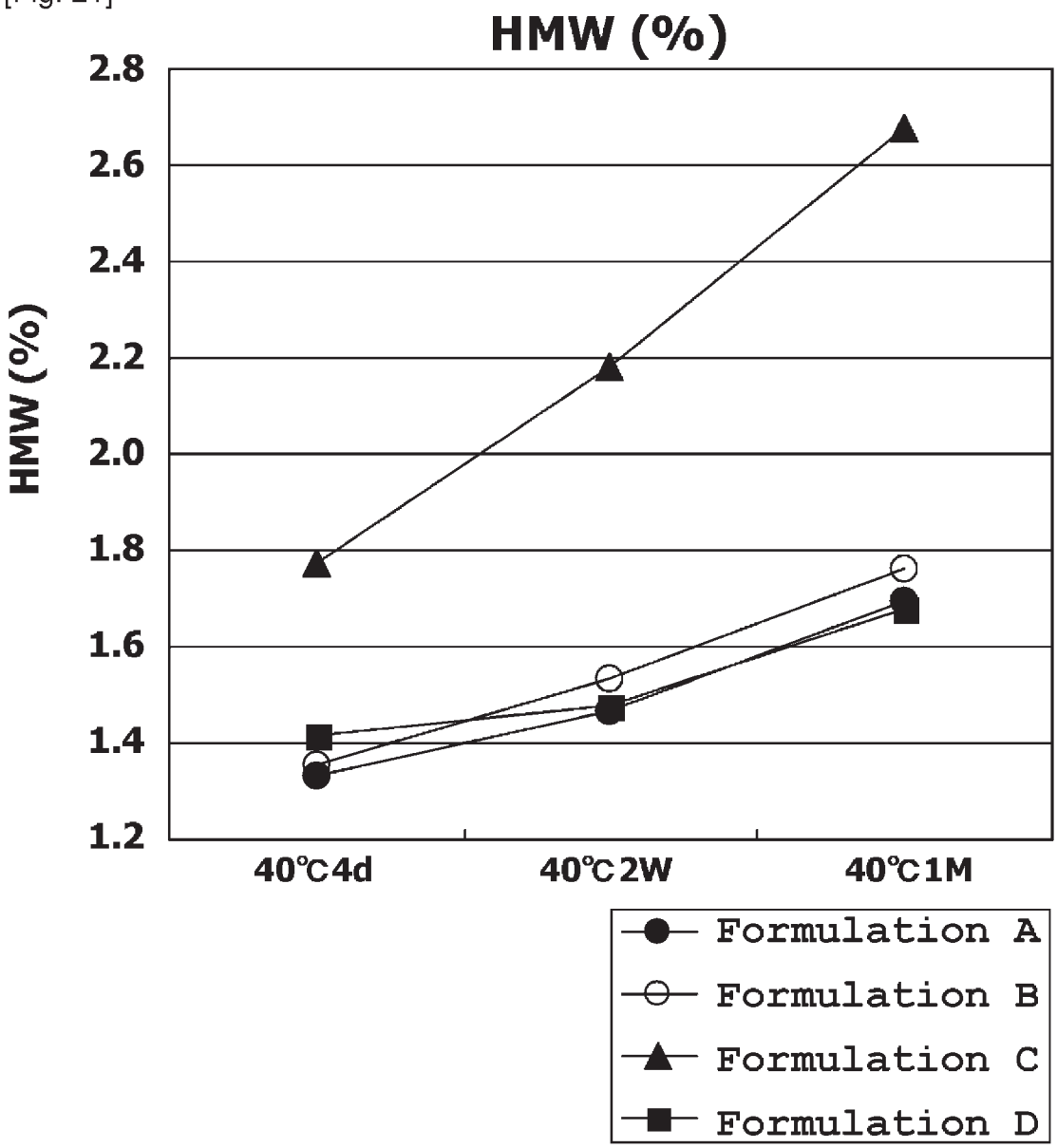
[Fig. 19]


CRP CONCENTRATION (mg/dL)
10
8
6
4
2
0
0 2 4 6 8 10 12 14 16 18
TIME (DAYS)
◆: TOCILIZUMAB
▲: CONTROL
◇: Fv3-M73
●: Fv4-M73
□: Fv5-M83

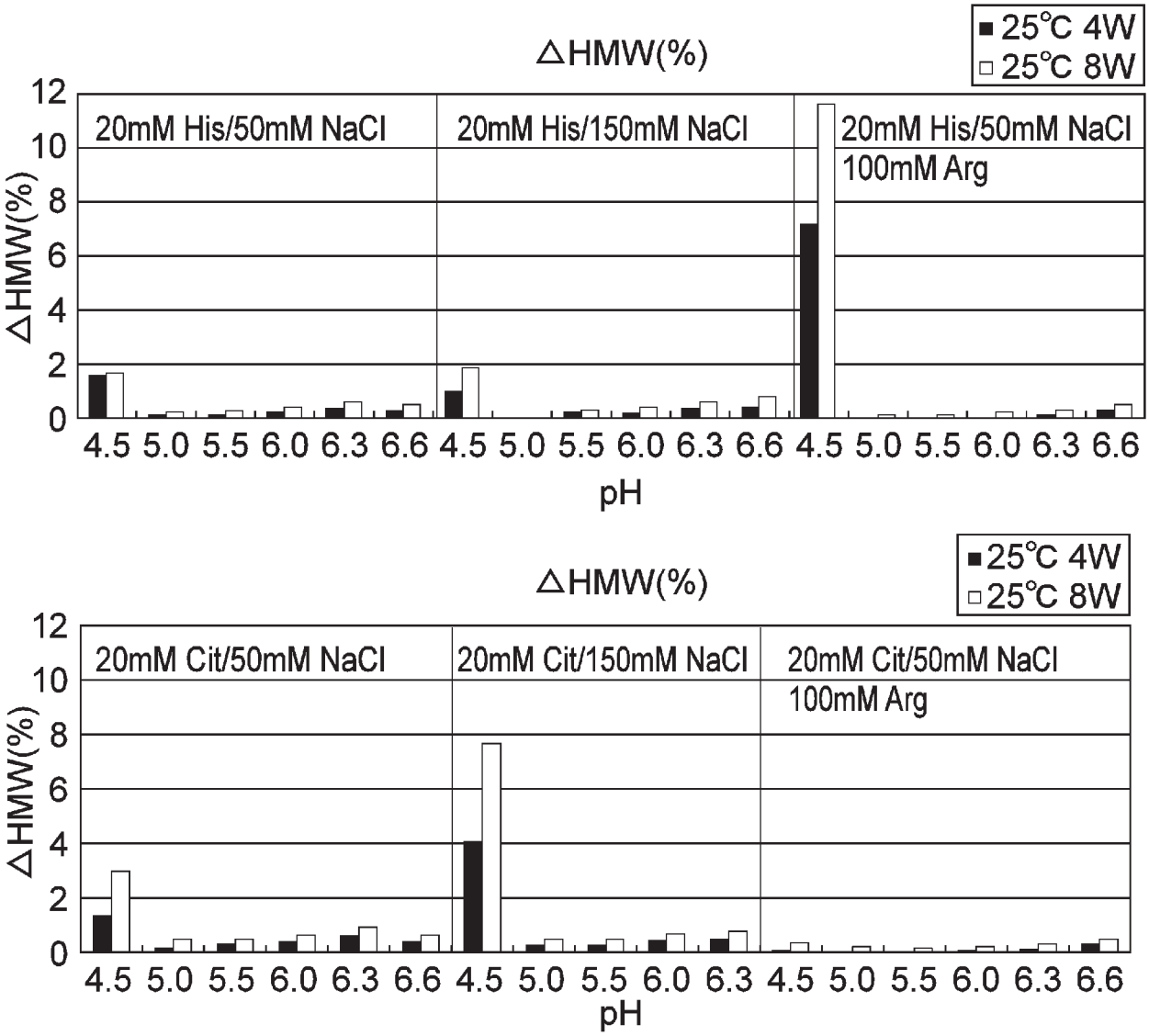
[Fig. 20]


PERCENTAGE OF FREE SOLUBLE IL-6 RECEPTOR (%)
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18
TIME (DAYS)
◆ : TOCILIZUMAB
△ : CONTROL
◇ : Fv3-M73
● : Fv4-M73
□ : Fv5-M83

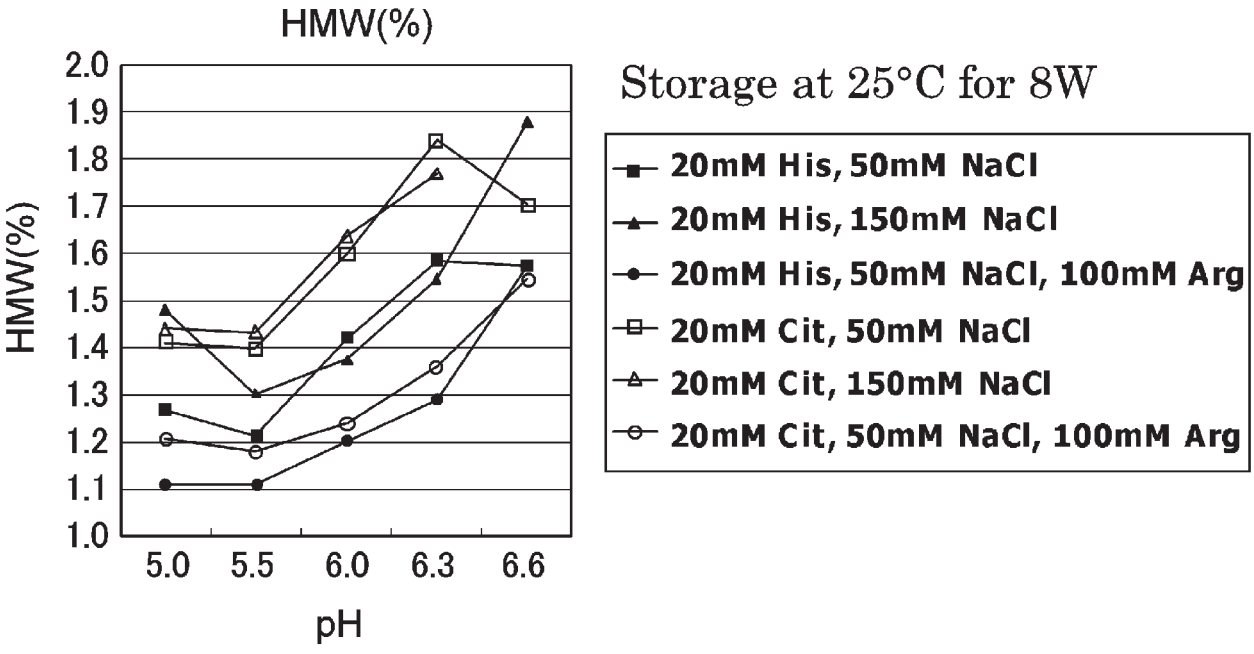
[Fig. 21]


HMW (%)
HMW (%)
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
40℃4d
40℃2W
40℃1M
Formulation A
Formulation B
Formulation C
Formulation D

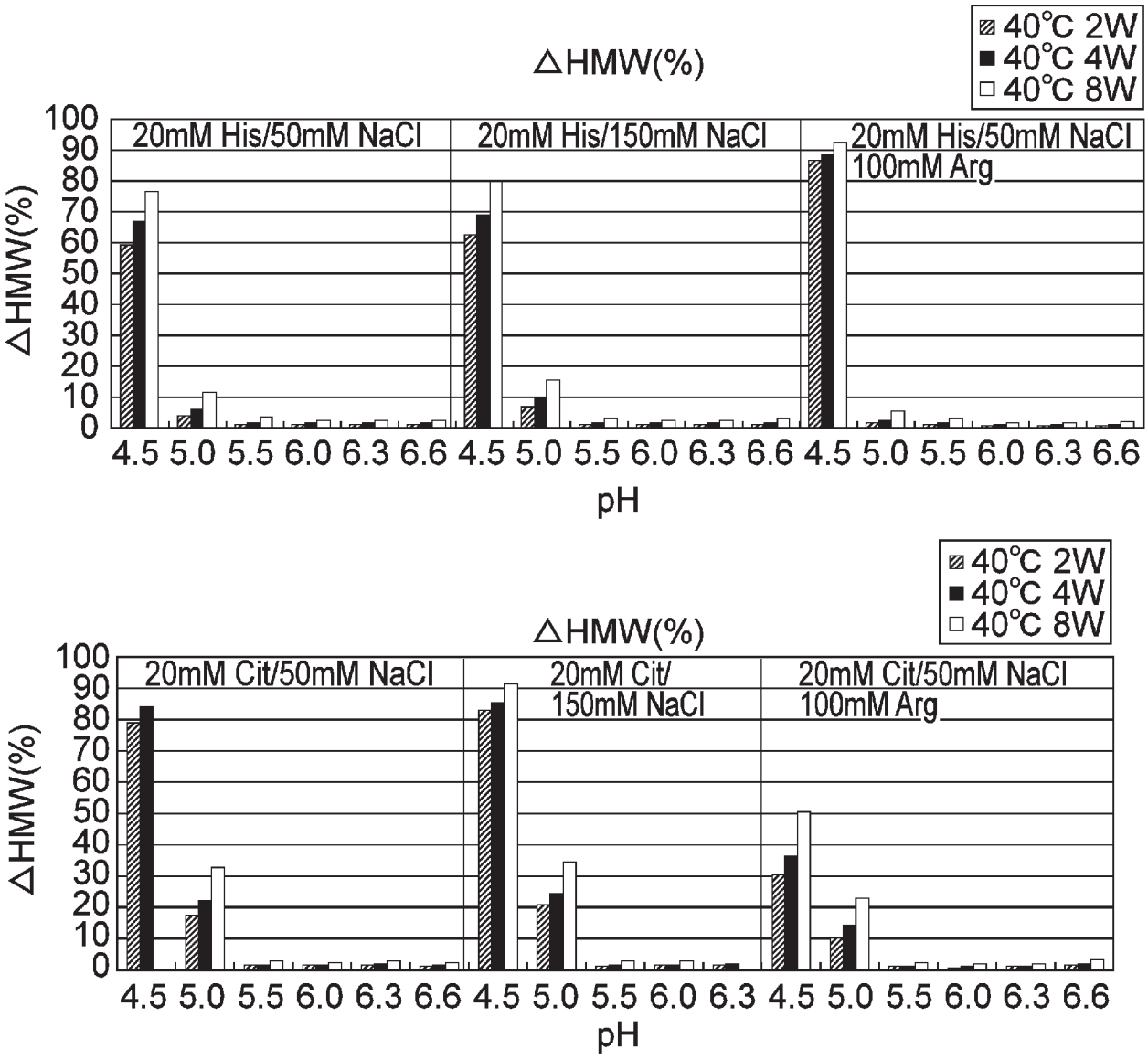
[Fig. 22]


△HMW(%)
25℃ 4W
25℃ 8W
20mM His/50mM NaCl
20mM His/150mM NaCl
20mM His/50mM NaCl
100mM Arg
△HMW(%)
0
2
4
6
8
10
12
4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 6.6
pH
△HMW(%)
25℃ 4W
25℃ 8W
20mM Cit/50mM NaCl
20mM Cit/150mM NaCl
20mM Cit/50mM NaCl
100mM Arg
△HMW(%)
0
2
4
6
8
10
12
4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 4.5 5.0 5.5 6.0 6.3 6.6
pH

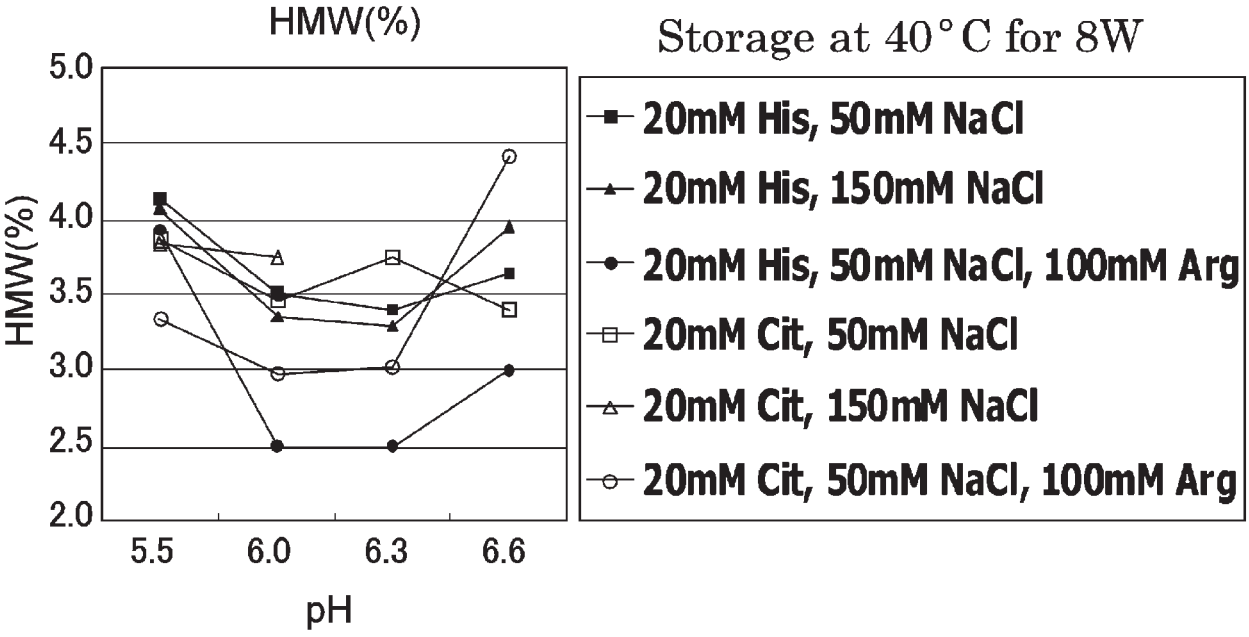
[Fig. 23]


HMW(%)
HMW(%)
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
5.0 5.5 6.0 6.3 6.6
pH
Storage at 25°C for 8W
20mM His, 50mM NaCl
20mM His, 150mM NaCl
20mM His, 50mM NaCl, 100mM Arg
20mM Cit, 50mM NaCl
20mM Cit, 150mM NaCl
20mM Cit, 50mM NaCl, 100mM Arg

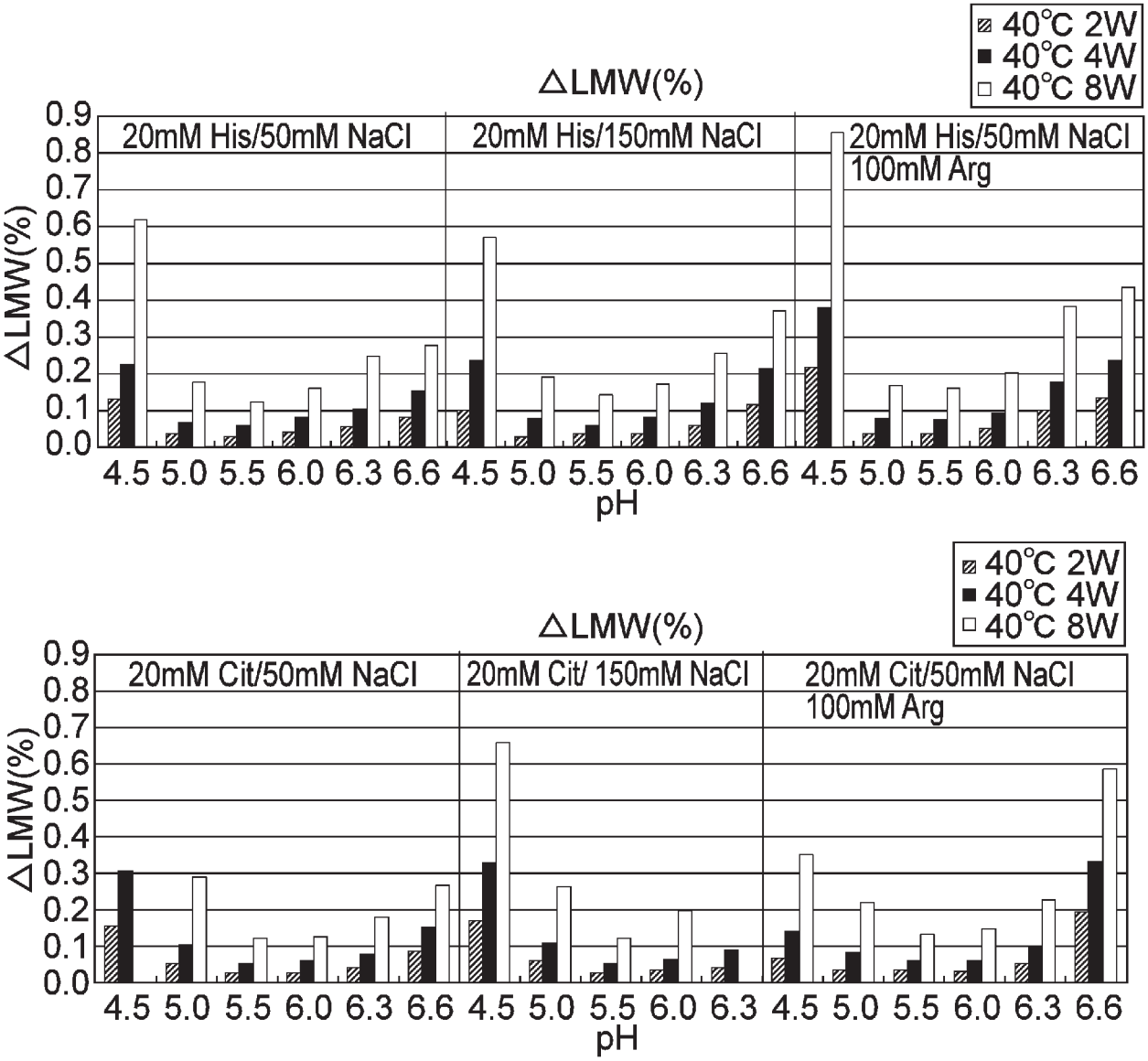
[Fig. 24]


△HMW(%)
40℃ 2W
40℃ 4W
40℃ 8W
△HMW(%)
20mM His/50mM NaCl
20mM His/150mM NaCl
20mM His/50mM NaCl
100mM Arg
4.5 5.0 5.5 6.0 6.3 6.6
pH
△HMW(%)
20mM Cit/50mM NaCl
20mM Cit/
150mM NaCl
20mM Cit/50mM NaCl
100mM Arg
pH

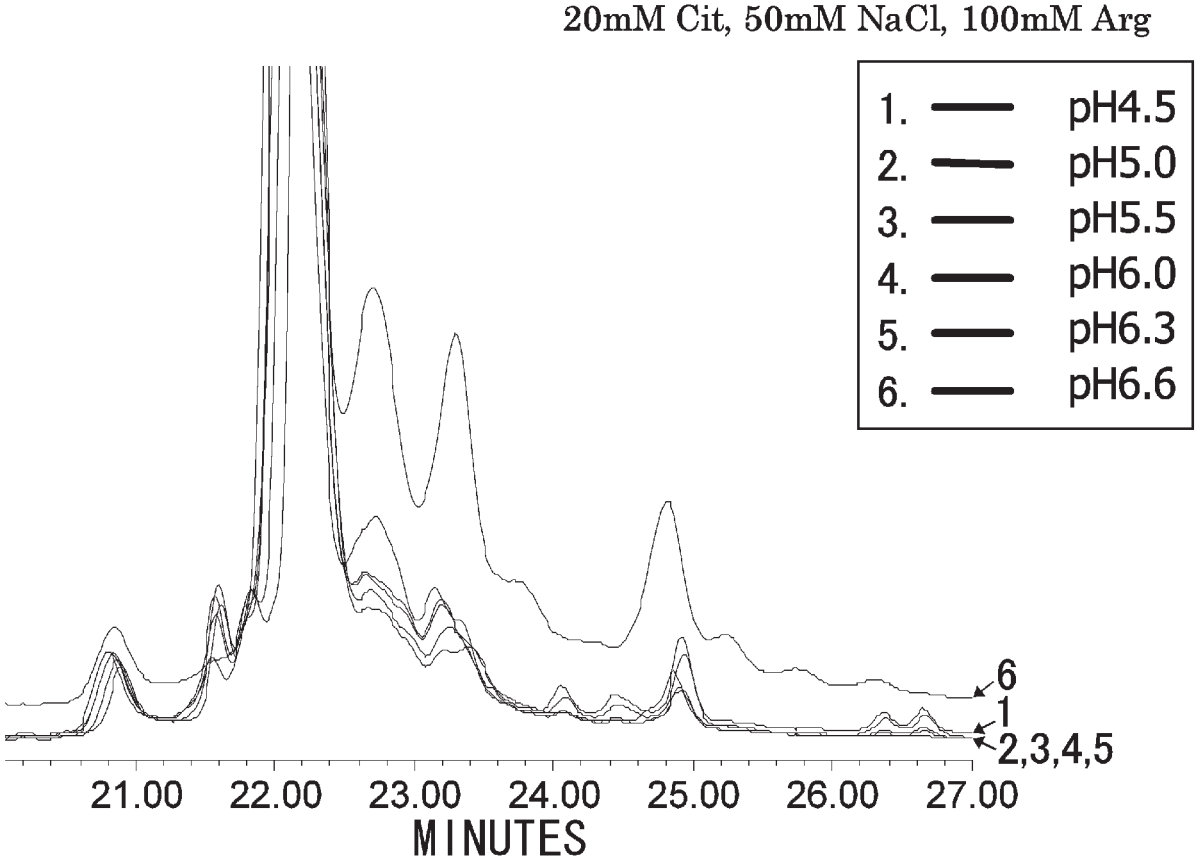
[Fig. 25]


HMW(%)
HMW(%)
pH
Storage at 40°C for 8W
20mM His, 50mM NaCl
20mM His, 150mM NaCl
20mM His, 50mM NaCl, 100mM Arg
20mM Cit, 50mM NaCl
20mM Cit, 150mM NaCl
20mM Cit, 50mM NaCl, 100mM Arg

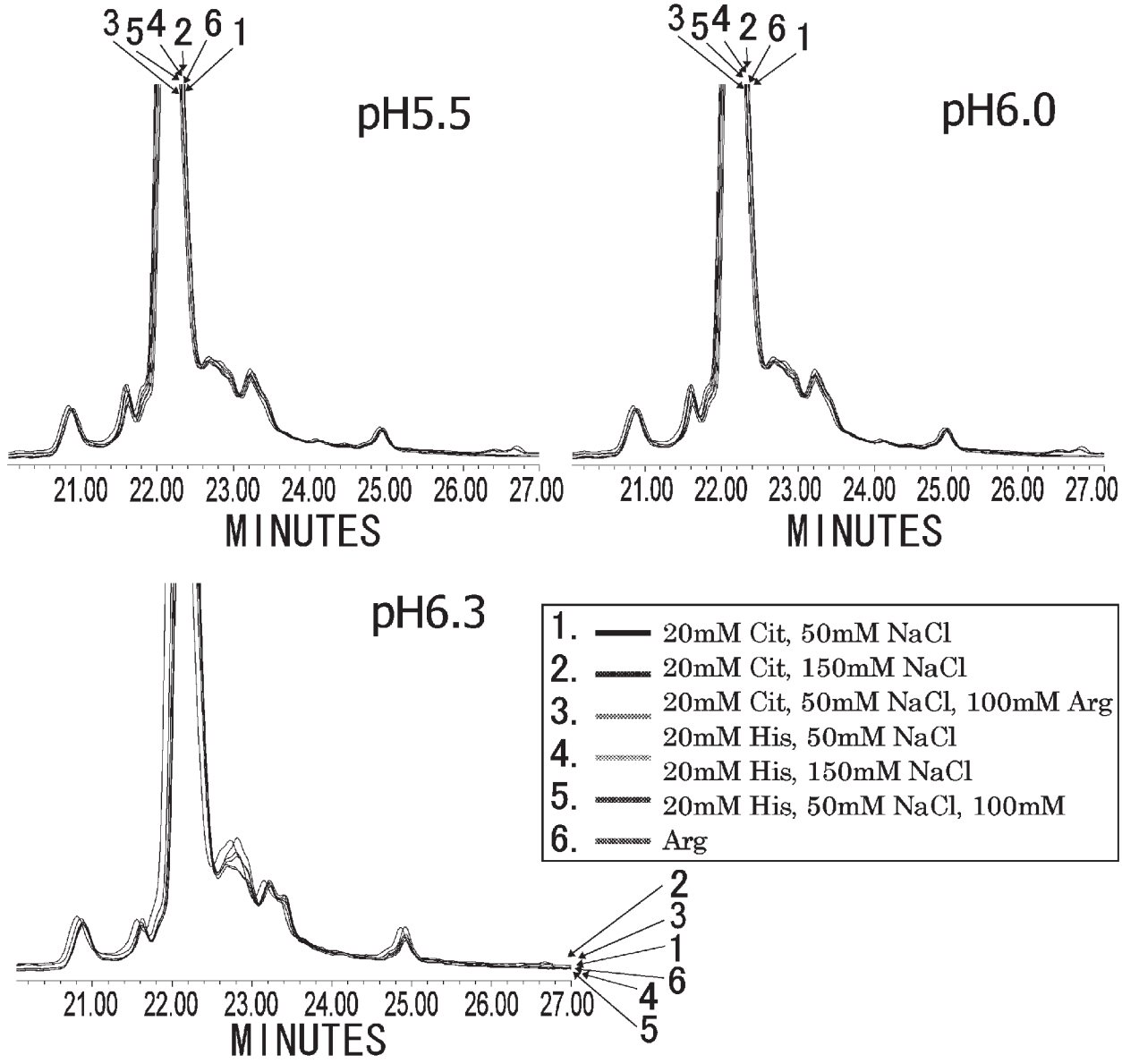
[Fig. 26]


40℃ 2W
40℃ 4W
40℃ 8W
△LMW(%)
20mM His/50mM NaCl
20mM His/150mM NaCl
20mM His/50mM NaCl
100mM Arg
△LMW(%)
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 6.6
pH
40℃ 2W
40℃ 4W
40℃ 8W
△LMW(%)
20mM Cit/50mM NaCl
20mM Cit/ 150mM NaCl
20mM Cit/50mM NaCl
100mM Arg
△LMW(%)
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 4.5 5.0 5.5 6.0 6.3 6.6
pH

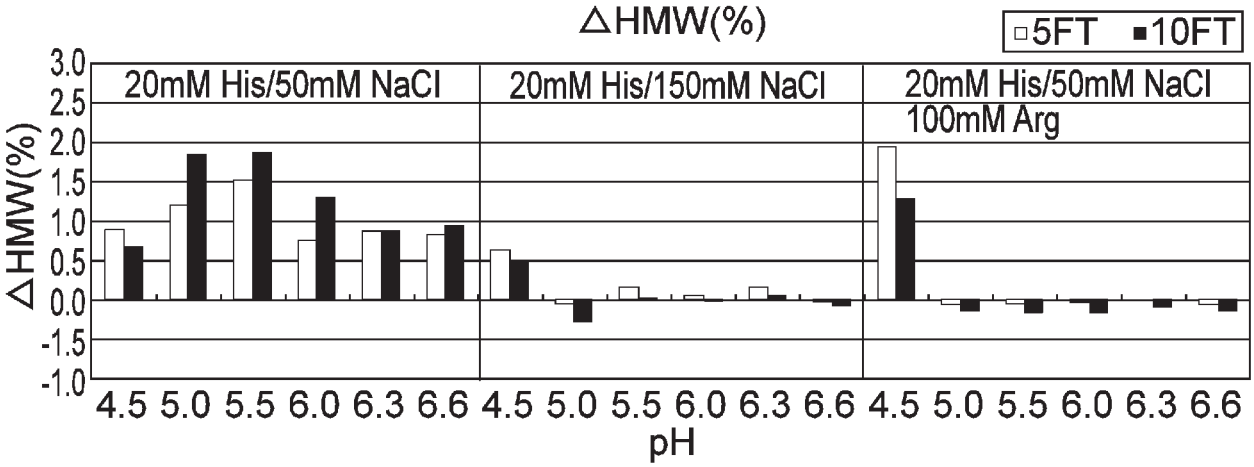
[Fig. 27]

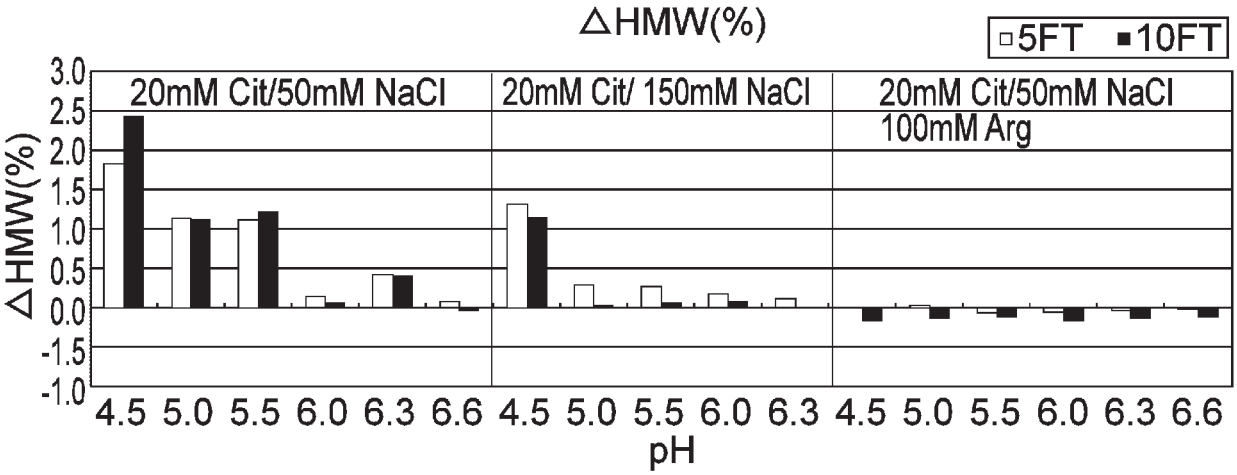

20mM Cit, 50mM NaCl, 100mM Arg
1. pH4.5
2. pH5.0
3. pH5.5
4. pH6.0
5. pH6.3
6. pH6.6
6
1
2,3,4,5
21.00
22.00
23.00
24.00
25.00
26.00
27.00
MINUTES

[Fig. 28]

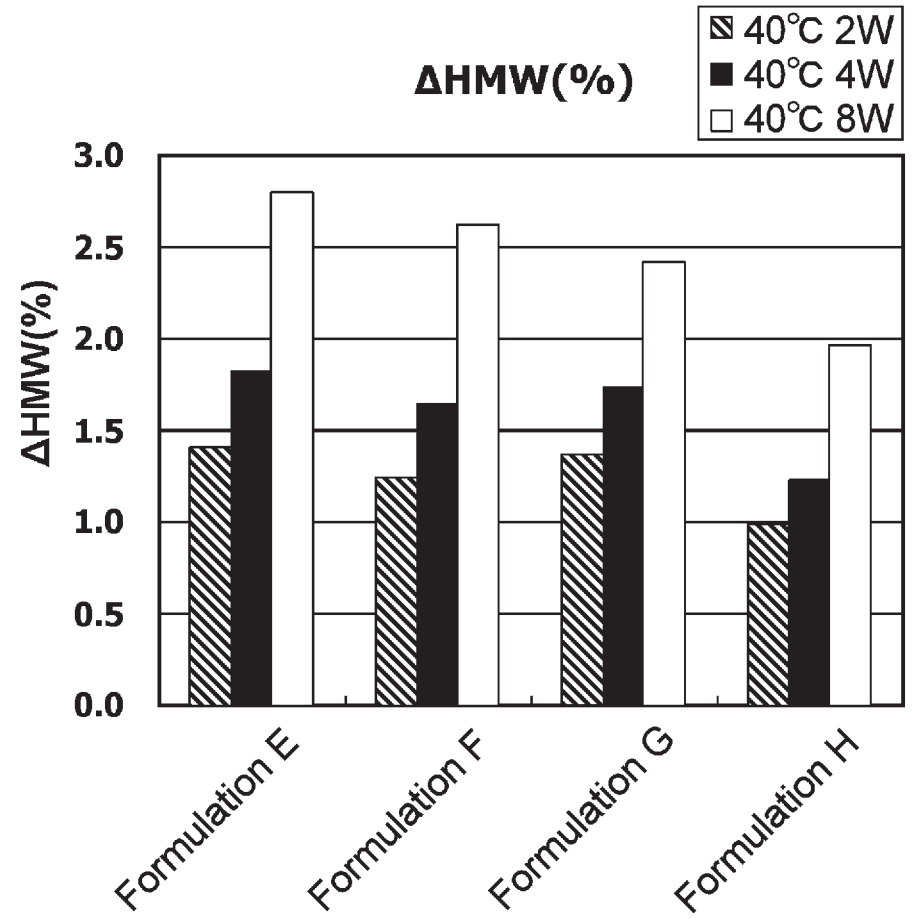

3 5 4 2 6 1
pH5.5
21.00 22.00 23.00 24.00 25.00 26.00 27.00
MINUTES
3 5 4 2 6 1
pH6.0
21.00 22.00 23.00 24.00 25.00 26.00 27.00
MINUTES
pH6.3
21.00 22.00 23.00 24.00 25.00 26.00 27.00
MINUTES
2
3
1
6
4
5
1. 20mM Cit, 50mM NaCl
2. 20mM Cit, 150mM NaCl
3. 20mM Cit, 50mM NaCl, 100mM Arg
4. 20mM His, 50mM NaCl
5. 20mM His, 150mM NaCl
6. 20mM His, 50mM NaCl, 100mM Arg

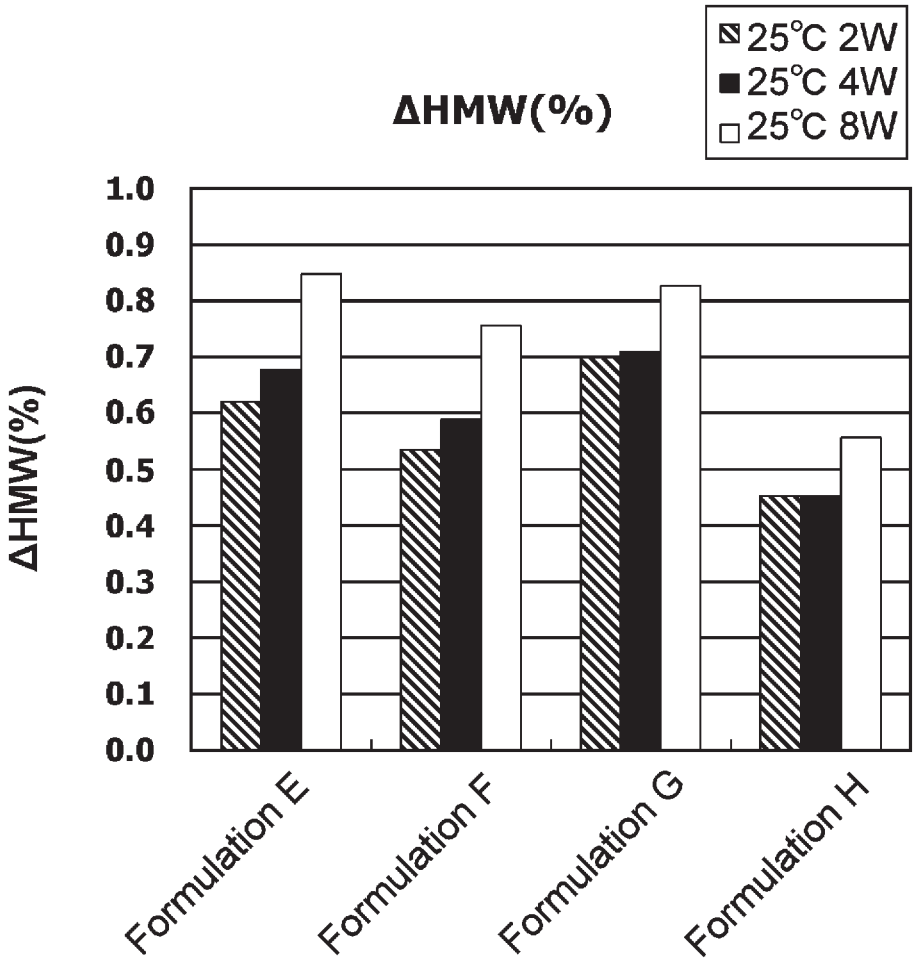
[Fig. 29]


△HMW(%)
□5FT ■10FT
20mM His/50mM NaCl
20mM His/150mM NaCl
20mM His/50mM NaCl
100mM Arg
△HMW(%)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.5
-1.0
4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 6.6
pH

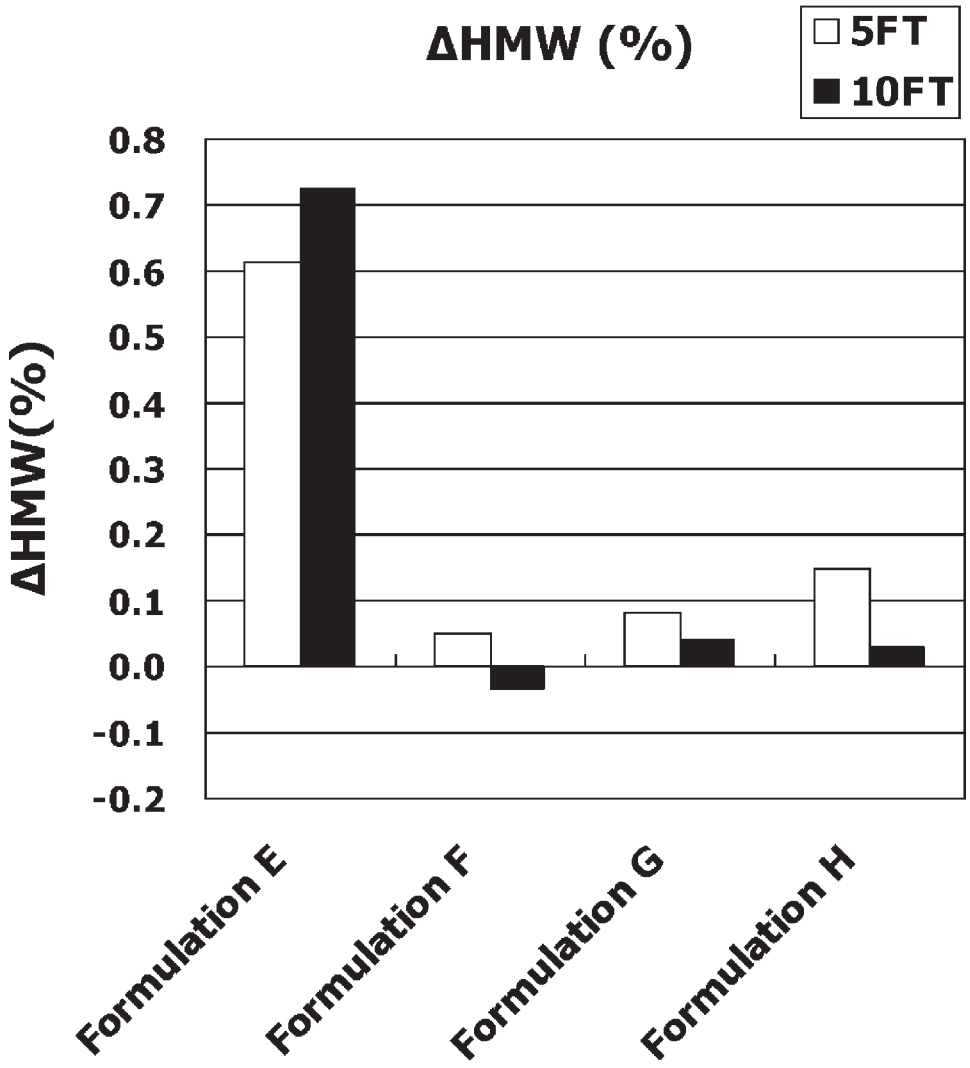

△HMW(%)
□5FT ■10FT
20mM Cit/50mM NaCl
20mM Cit/ 150mM NaCl
20mM Cit/50mM NaCl
100mM Arg
△HMW(%)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-1.5
-1.0
4.5 5.0 5.5 6.0 6.3 6.6 4.5 5.0 5.5 6.0 6.3 4.5 5.0 5.5 6.0 6.3 6.6
pH

[Fig. 30]

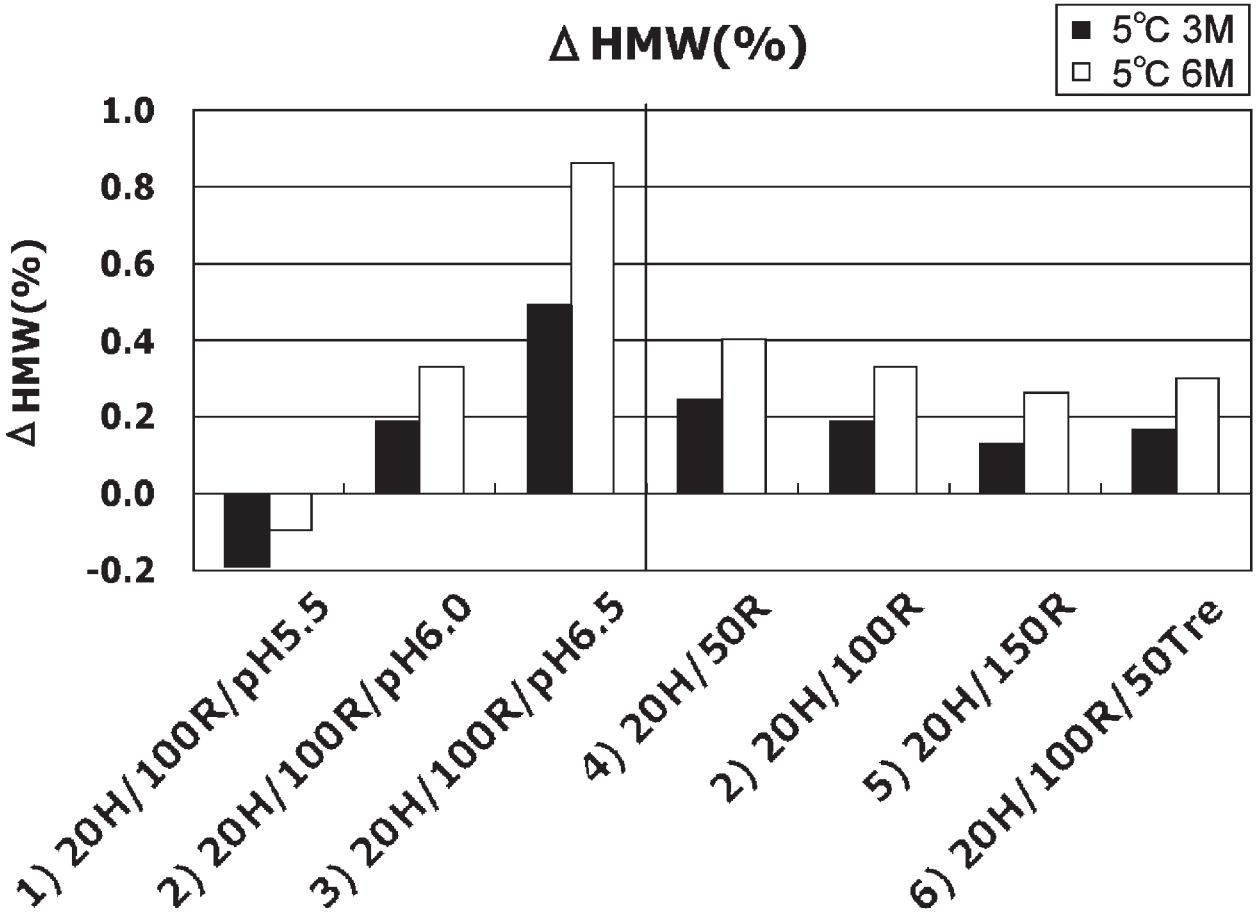

ΔHMW(%)
40℃ 2W
40℃ 4W
40℃ 8W
ΔHMW(%)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Formulation E
Formulation F
Formulation G
Formulation H


ΔHMW(%)
25℃ 2W
25℃ 4W
25℃ 8W
ΔHMW(%)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Formulation E
Formulation F
Formulation G
Formulation H

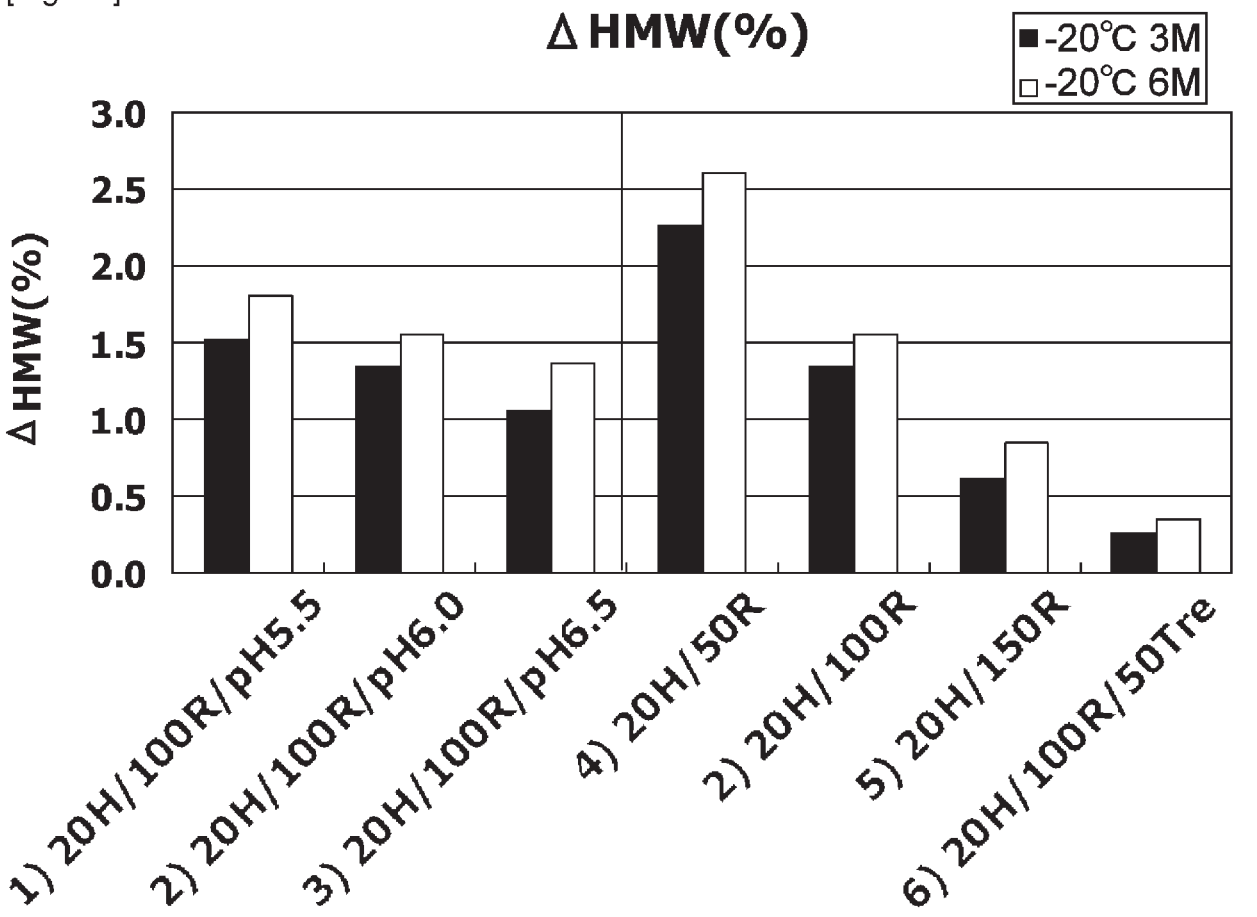
[Fig. 31]


ΔHMW (%)
5FT
10FT
ΔHMW(%)
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
Formulation E
Formulation F
Formulation G
Formulation H

[Fig. 32]


Δ HMW(%)
5℃ 3M
5℃ 6M
Δ HMW(%)
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
1) 20H/100R/pH5.5
2) 20H/100R/pH6.0
3) 20H/100R/pH6.5
4) 20H/50R
2) 20H/100R
5) 20H/150R
6) 20H/100R/50Tre

[Fig. 33]


Δ HMW(%)
-20℃ 3M
-20℃ 6M
Δ HMW(%)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1) 20H/100R/pH5.5
2) 20H/100R/pH6.0
3) 20H/100R/pH6.5
4) 20H/50R
2) 20H/100R
5) 20H/150R
6) 20H/100R/50Tre