Figure 1

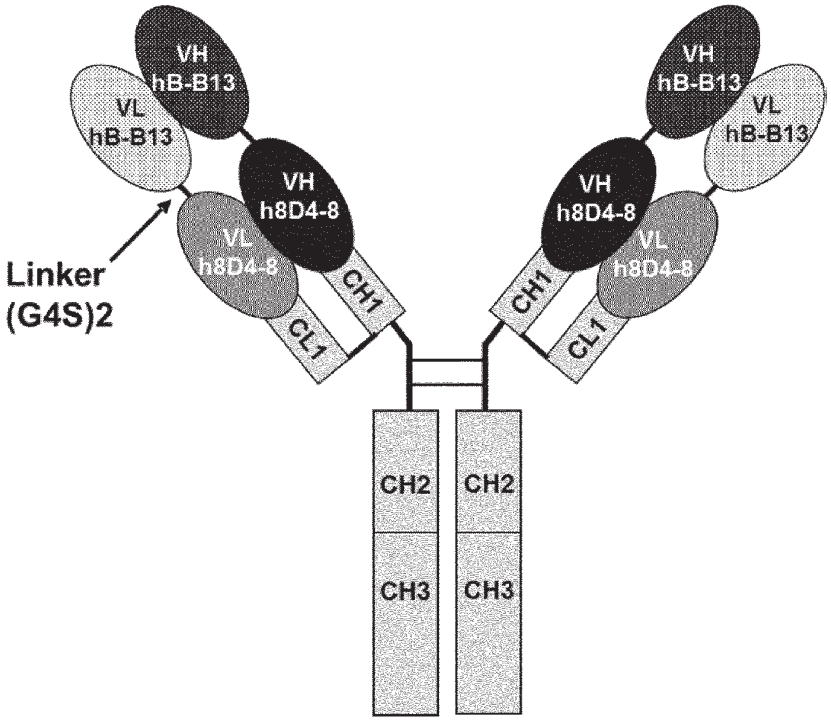

VH
hB-B13
VL
hB-B13
VH
h8D4-8
VL
h8D4-8
Linker
(G4S)2
CH1
CL1
CH2
CH3
VH
hB-B13
VL
hB-B13
VH
h8D4-8
VL
h8D4-8
CH1
CL1
CH2
CH3

Figure 2

Anti-IL13 hB-B13 VL3 (SEQ ID NO: 1):
DIVLTQSPAS LAVSLGQRAT ISC**RASESVD SYGQSYMH**WY QQKAGQPPKL LIY**LASNLES** GVPARFSGSG SRTDFTLTID PVQAEDAATY YC**QQNAEDSR T**FGGGTKLEI K

Anti-IL13 hB-B13 VH2 (SEQ ID NO: 2):
EVQLKESGPG LVAPGGSLSI TCTVS**GFSLT DSSIN**WVRQP PGKGLEWLGM IWG**DGRID**YA DALKSRLSIS KDSSKSQVFL EMTSLRTDDT ATYYCAR**DGY FPYAMDF**WGQ GTSVTVSS

Anti-IL4 h8D4-8 VL1 (SEQ ID NO: 3):
DIQMTQSPAS LSVSVGDTIT LTC**HASQNID VWLS**WFQQKP GNIPKLLIY**K ASNLHTG**VPS RFSGSGSGTG FTLTISSLQP EDIATYYC**QQ AHSYPFT**FGG GTKLEIKR

Anti-IL4 h8D4-8 VH1 (SEQ ID NO: 4):
QVQLQQSGPE LVKPGASVKI SCKAS**GYSFT SYWIH**WIKQR PGQGLEWIGM **IDPSDGETR**L NQRFQGRATL TVDESTSTAY MQLRSPTSED SAVYYCTR**LK EYGNYDSFYF DV**WGAGTLVT VSSA

Anti-IL4 h8D4-8 VH2 (SEQ ID NO: 5):
QVQLQQSGPE LVKPGASVKI SCKAS**GYSFT SYWIH**WIKQR PGQGLEWIGM **IDASDGETR**L NQRFQGRATL TVDESTSTAY MQLRSPTSED SAVYYCTR**LK EYGNYDSFYF DV**WGAGTLVT VSSA

Figure 3

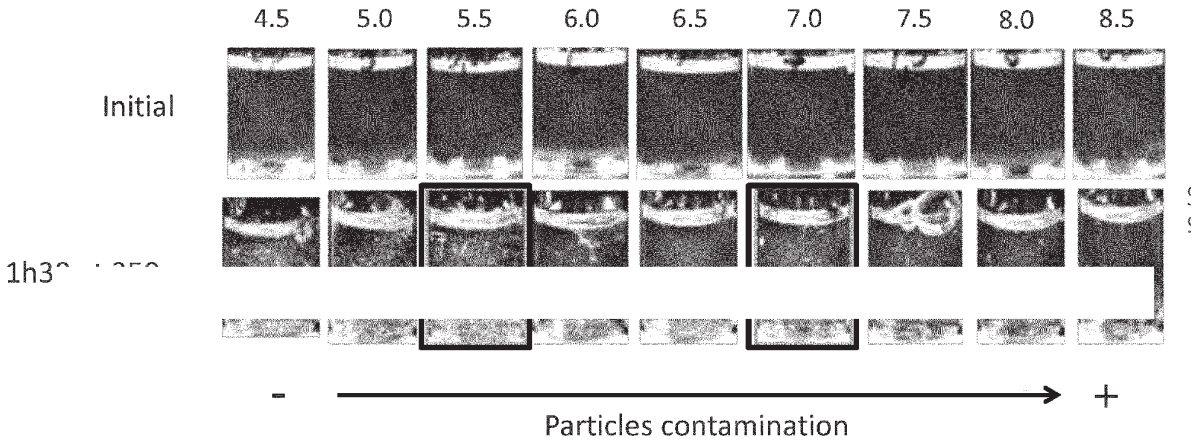


Figure 4

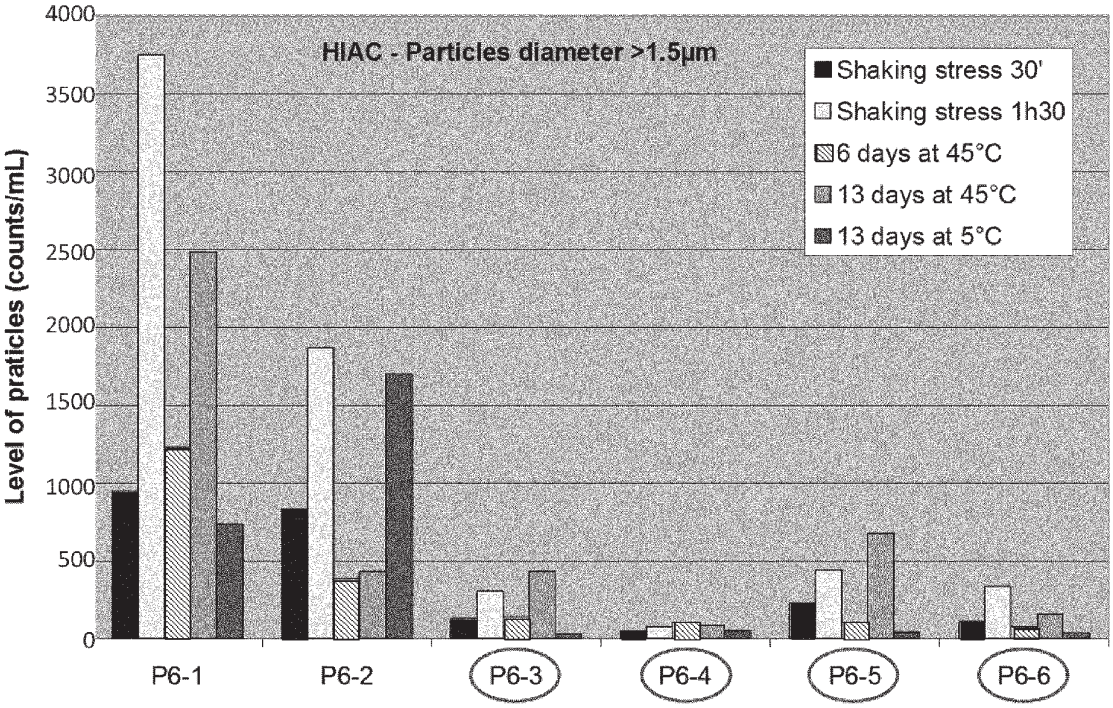

HIAC - Particles diameter >1.5µm
Shaking stress 30'
Shaking stress 1h30
6 days at 45°C
13 days at 45°C
13 days at 5°C
Level of praticles (counts/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
P6-1
P6-2
P6-3
P6-4
P6-5
P6-6

Figure 5

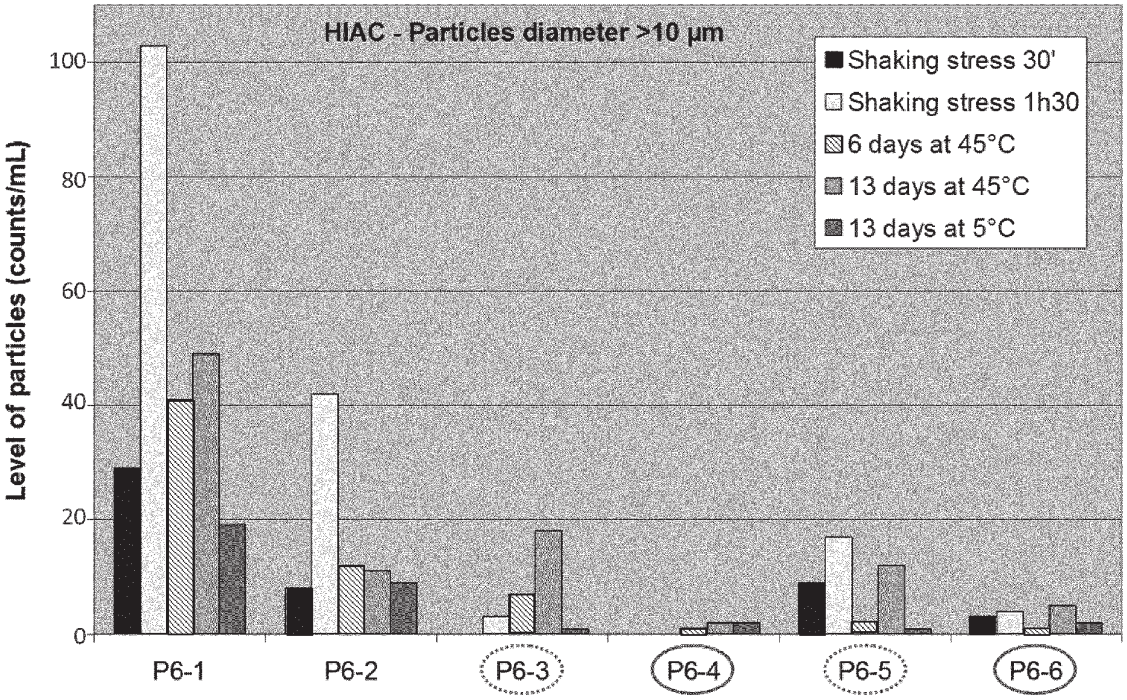

HIAC - Particles diameter >10 µm
Level of particles (counts/mL)
100
80
60
40
20
0
Shaking stress 30'
Shaking stress 1h30
6 days at 45°C
13 days at 45°C
13 days at 5°C
P6-1
P6-2
P6-3
P6-4
P6-5
P6-6

Figure 6

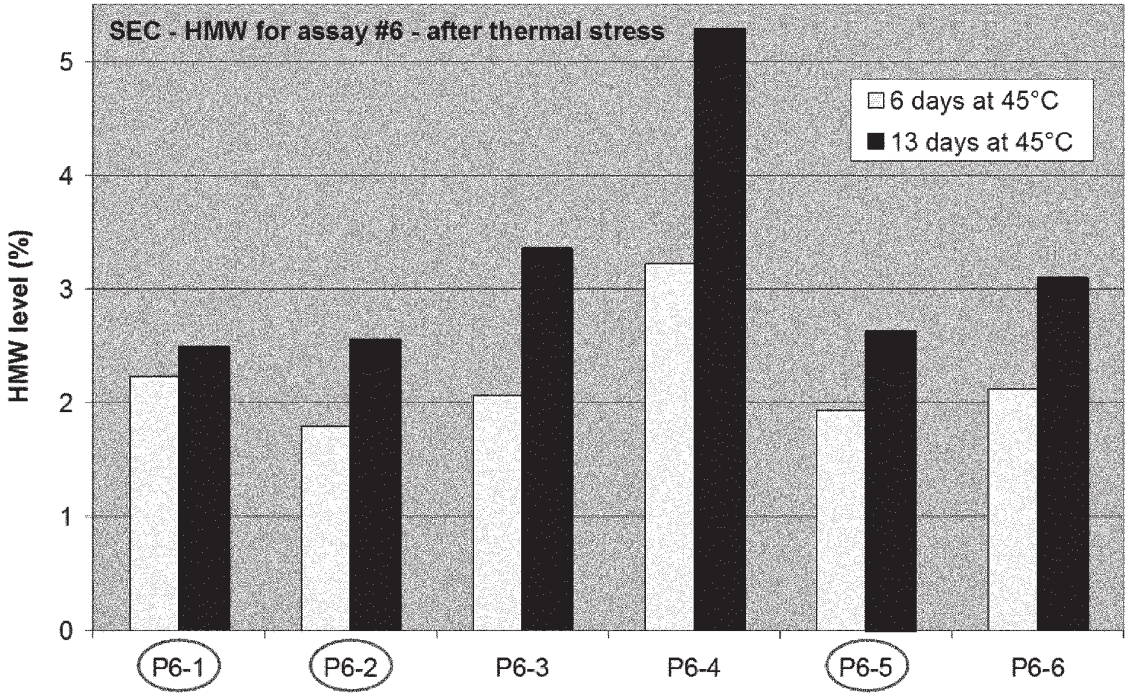

SEC - HMW for assay #6 - after thermal stress
6 days at 45°C
13 days at 45°C
HMW level (%)
0
1
2
3
4
5
P6-1
P6-2
P6-3
P6-4
P6-5
P6-6

Figure 7

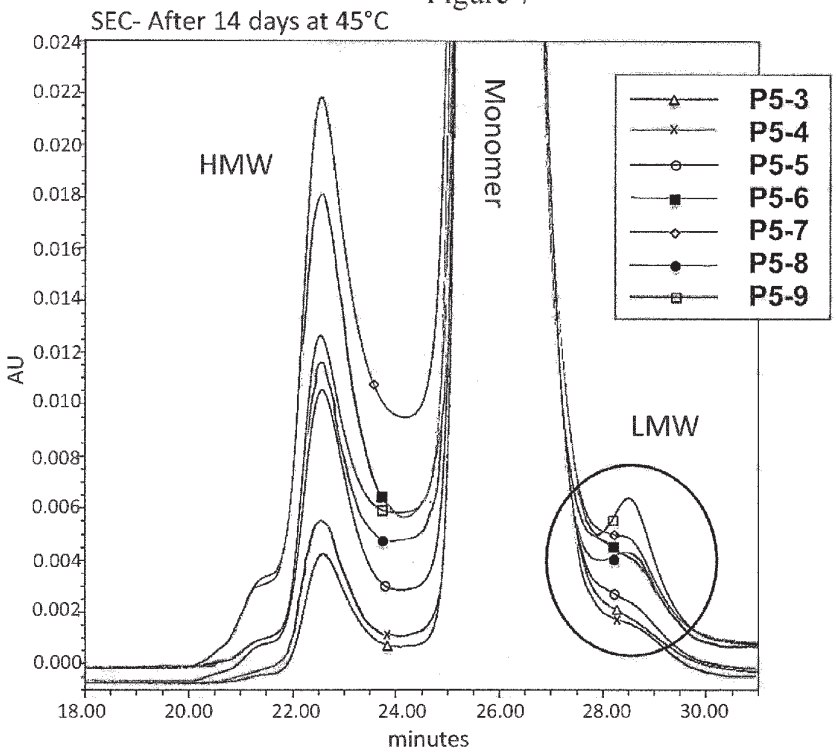
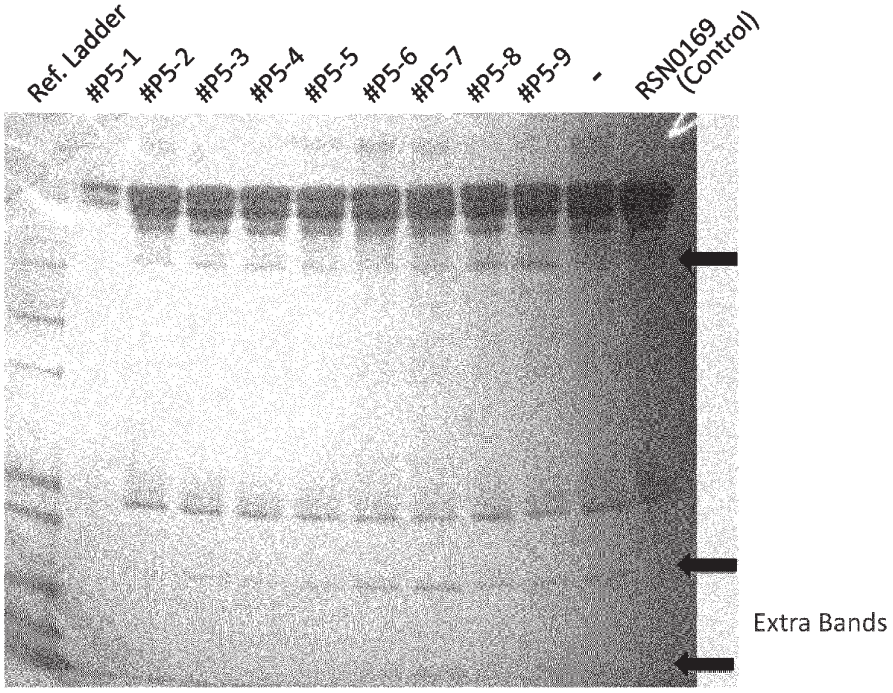

SEC- After 14 days at 45°C
HMW
Monomer
LMW
P5-3
P5-4
P5-5
P5-6
P5-7
P5-8
P5-9
AU
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
18.00
20.00
22.00
24.00
26.00
28.00
30.00
minutes

Figure 8



SDS-PAGE: 2 weeks at 45°C

Figure 9

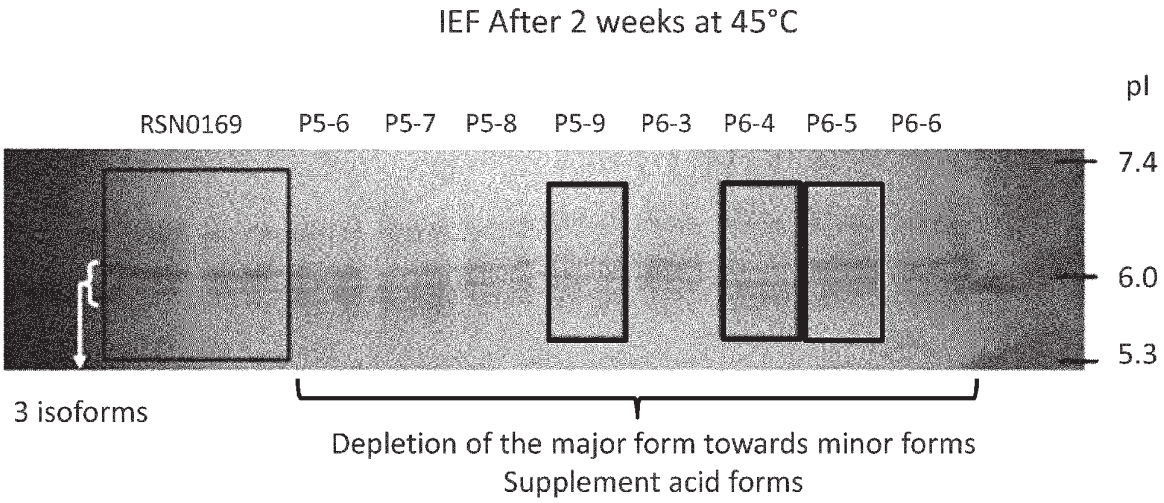

IEF After 2 weeks at 45°C
pI
RSN0169
P5-6
P5-7
P5-8
P5-9
P6-3
P6-4
P6-5
P6-6
7.4
6.0
5.3
3 isoforms
Depletion of the major form towards minor forms
Supplement acid forms

Figure 10

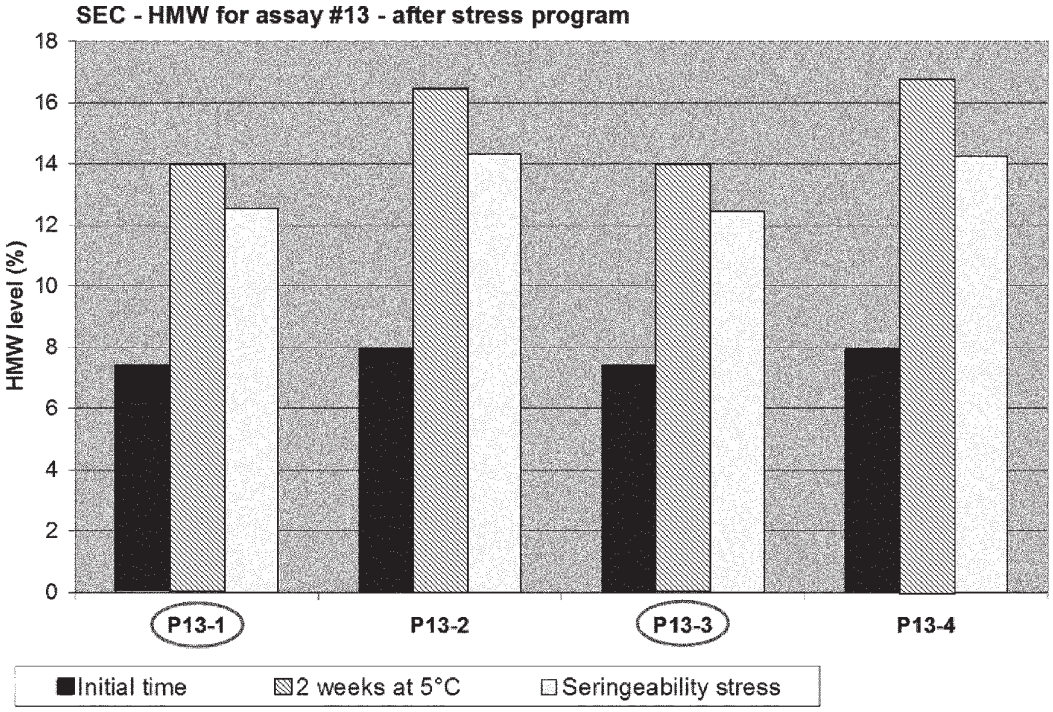

SEC - HMW for assay #13 - after stress program
HMW level (%)
18
16
14
12
10
8
6
4
2
0
P13-1
P13-2
P13-3
P13-4
Initial time
2 weeks at 5°C
Seringeability stress

Figure 11

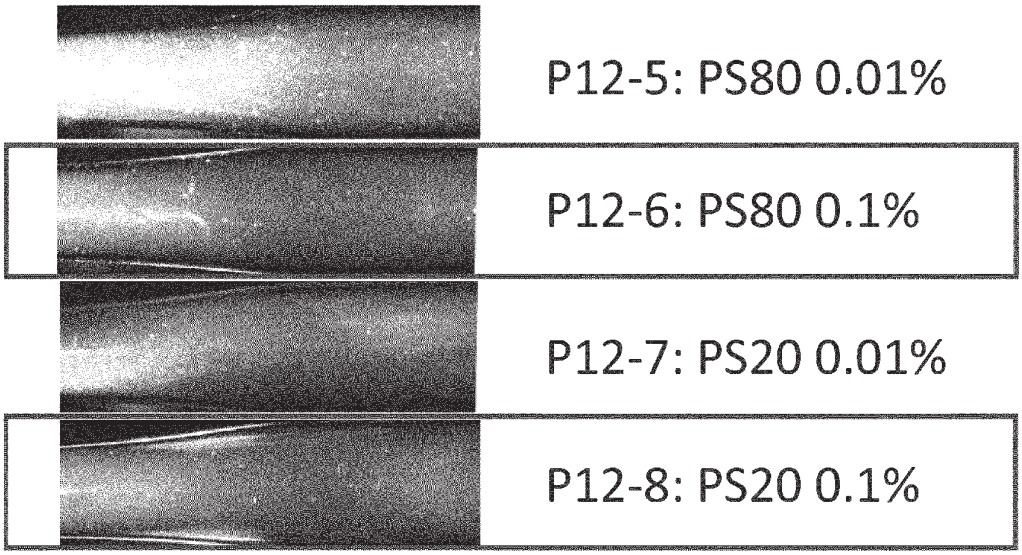


Figure 12

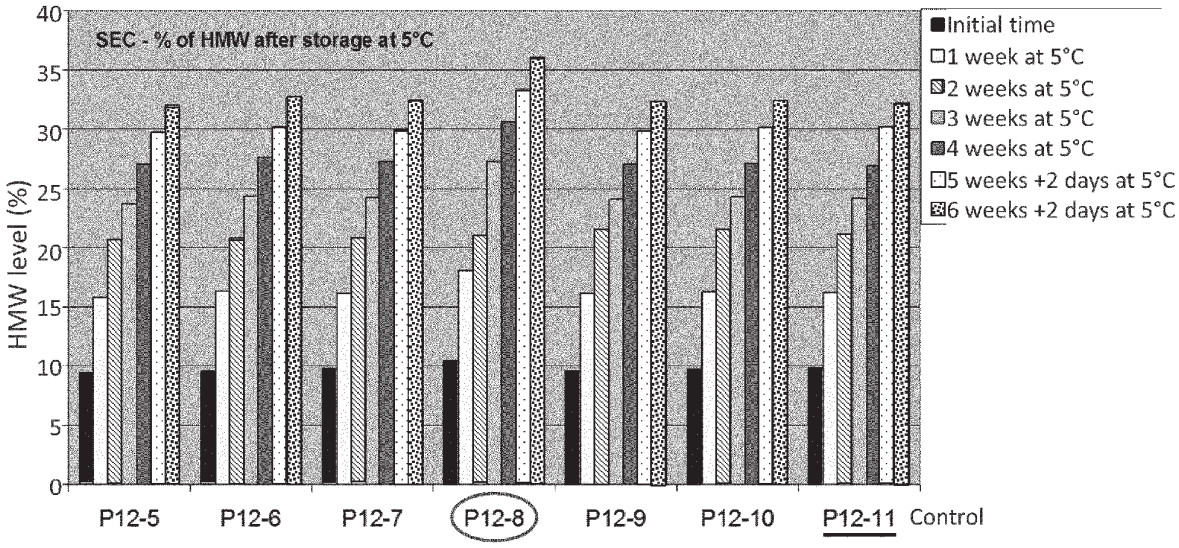

SEC - % of HMW after storage at 5°C
HMW level (%)
40
35
30
25
20
15
10
5
0
P12-5
P12-6
P12-7
P12-8
P12-9
P12-10
P12-11
Control
Initial time
1 week at 5°C
2 weeks at 5°C
3 weeks at 5°C
4 weeks at 5°C
5 weeks +2 days at 5°C
6 weeks +2 days at 5°C

Figure 13

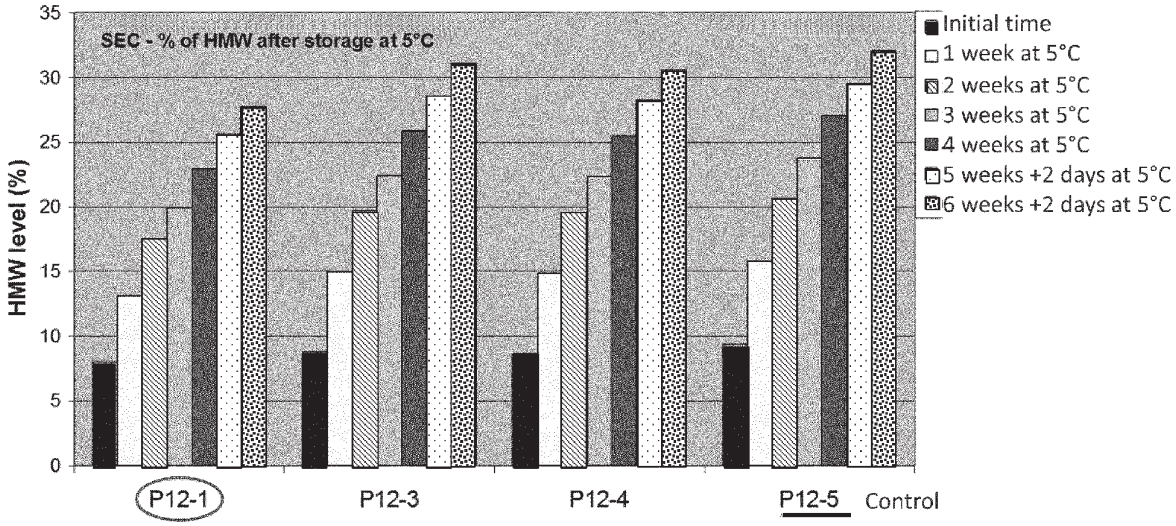

SEC - % of HMW after storage at 5°C
HMW level (%)
35
30
25
20
15
10
5
0
P12-1
P12-3
P12-4
P12-5
Control
Initial time
1 week at 5°C
2 weeks at 5°C
3 weeks at 5°C
4 weeks at 5°C
5 weeks +2 days at 5°C
6 weeks +2 days at 5°C

Figure 14

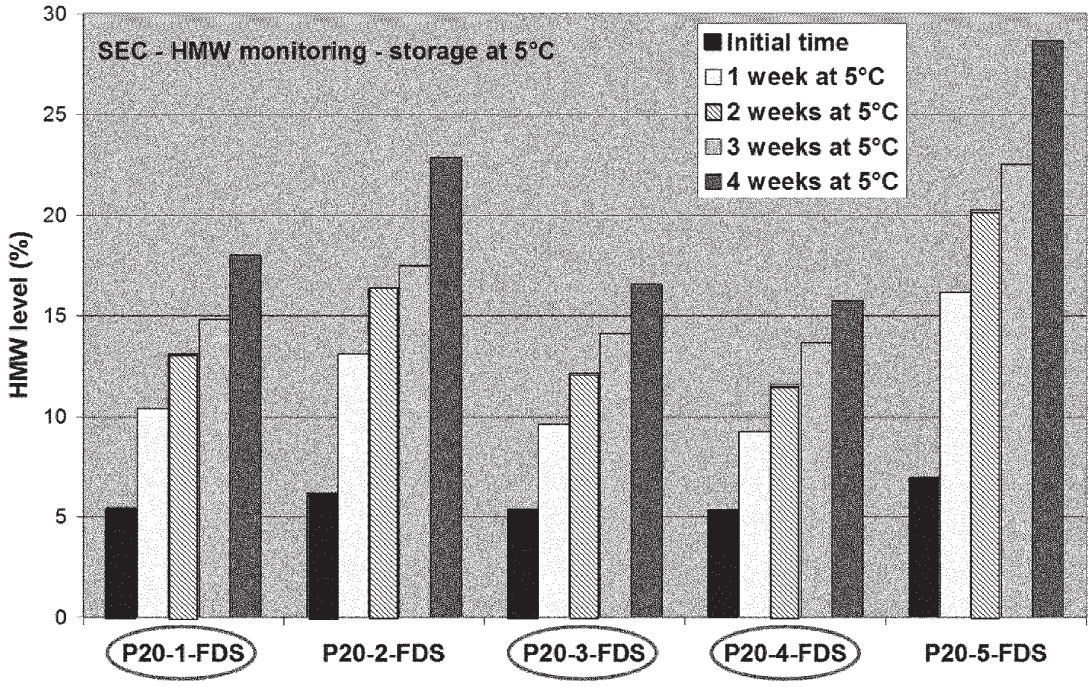

SEC - HMW monitoring - storage at 5°C
Initial time
1 week at 5°C
2 weeks at 5°C
3 weeks at 5°C
4 weeks at 5°C
HMW level (%)
30
25
20
15
10
5
0
P20-1-FDS
P20-2-FDS
P20-3-FDS
P20-4-FDS
P20-5-FDS

Figure 15

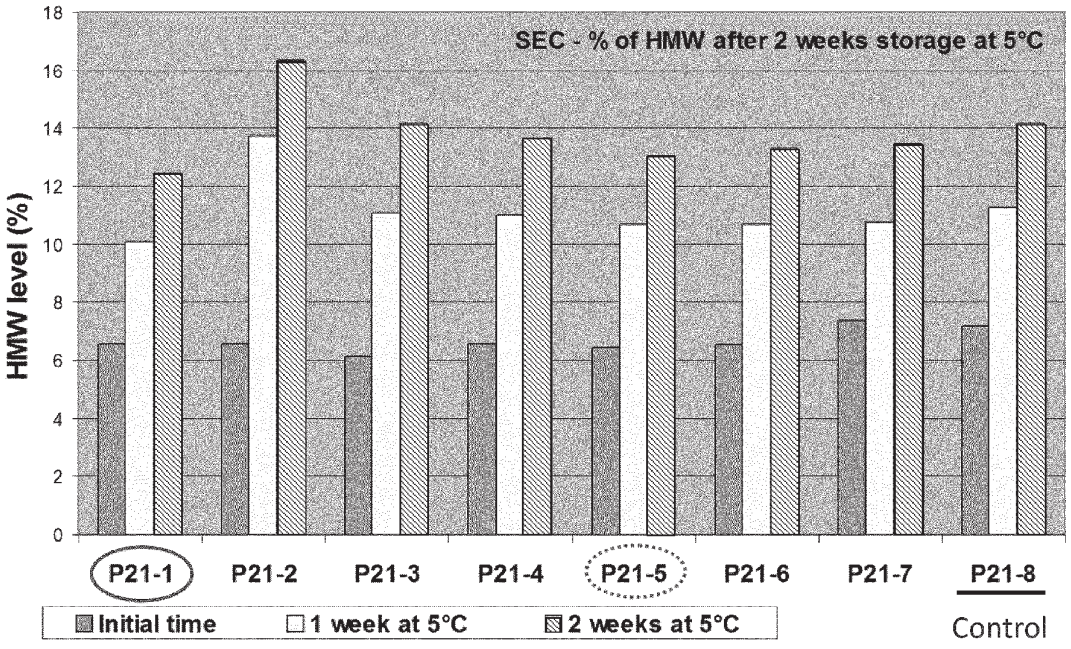

SEC - % of HMW after 2 weeks storage at 5°C
HMW level (%)
18
16
14
12
10
8
6
4
2
0
P21-1
P21-2
P21-3
P21-4
P21-5
P21-6
P21-7
P21-8
Initial time
1 week at 5°C
2 weeks at 5°C
Control

Figure 16

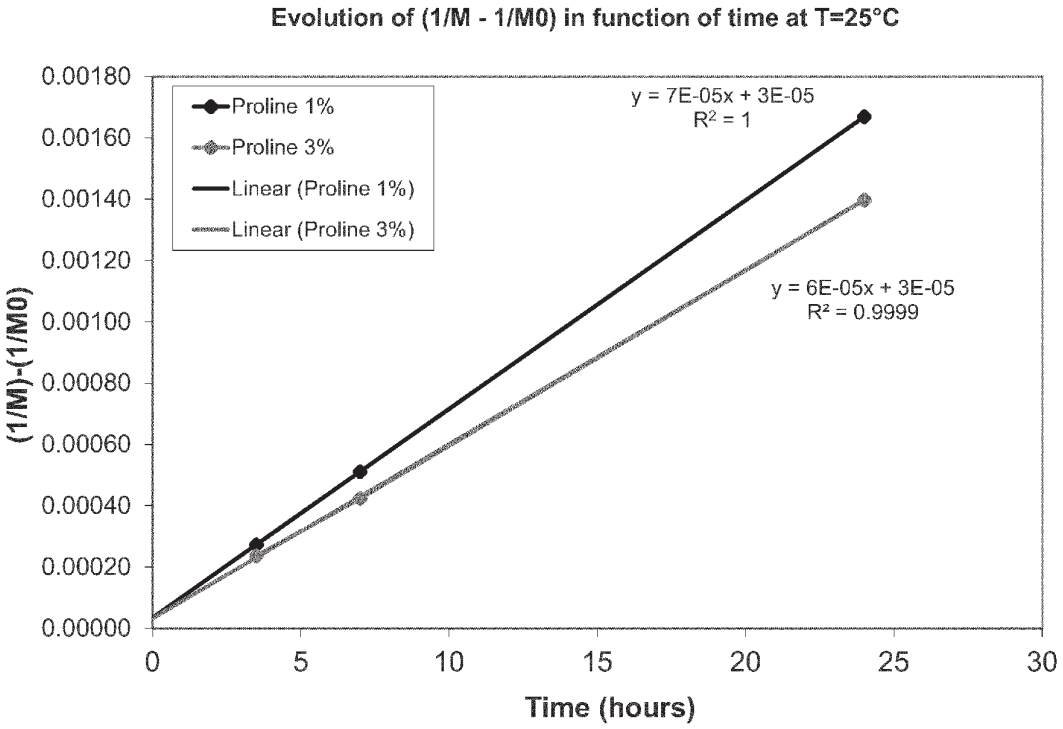

Evolution of (1/M - 1/M0) in function of time at T=25°C
Proline 1%
Proline 3%
Linear (Proline 1%)
Linear (Proline 3%)
y = 7E-05x + 3E-05
R² = 1
y = 6E-05x + 3E-05
R² = 0.9999
(1/M)-(1/M0)
0.00180
0.00160
0.00140
0.00120
0.00100
0.00080
0.00060
0.00040
0.00020
0.00000
0
5
10
15
20
25
30
Time (hours)

Figure 17

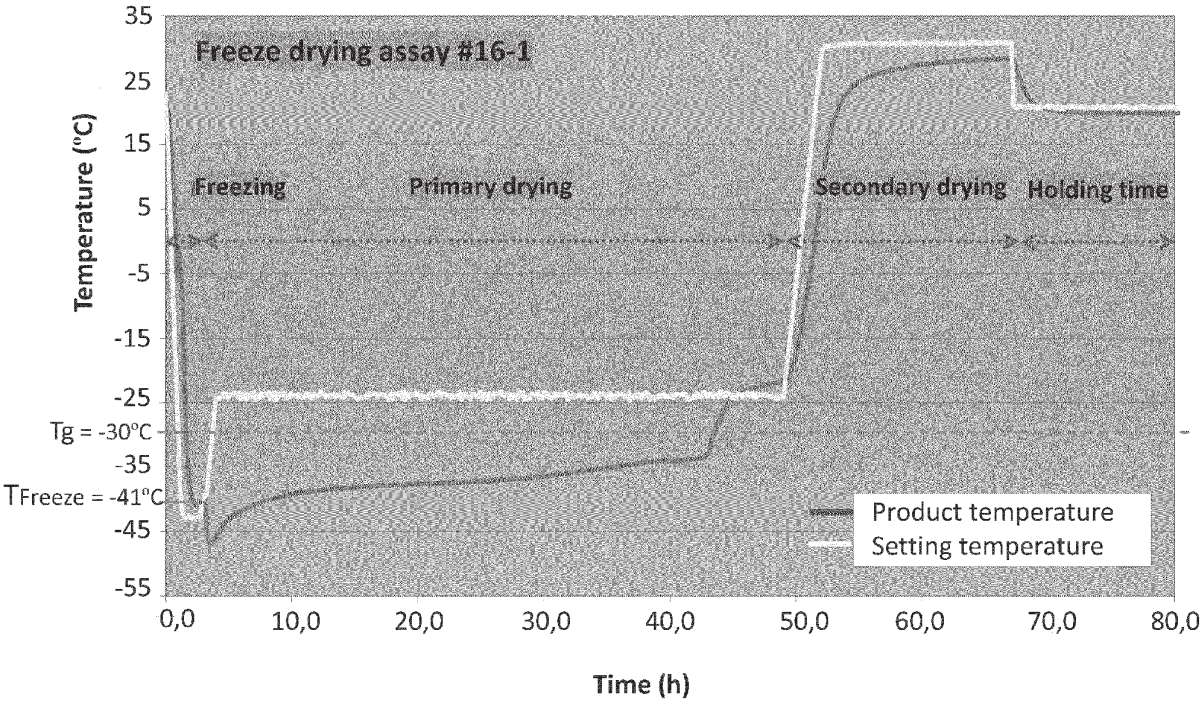

Freeze drying assay #16-1
Temperature (°C)
35
25
15
5
-5
-15
-25
-35
-45
-55
Tg = -30°C
TFreeze = -41°C
Freezing
Primary drying
Secondary drying
Holding time
Product temperature
Setting temperature
0,0
10,0
20,0
30,0
40,0
50,0
60,0
70,0
80,0
Time (h)

Figure 18

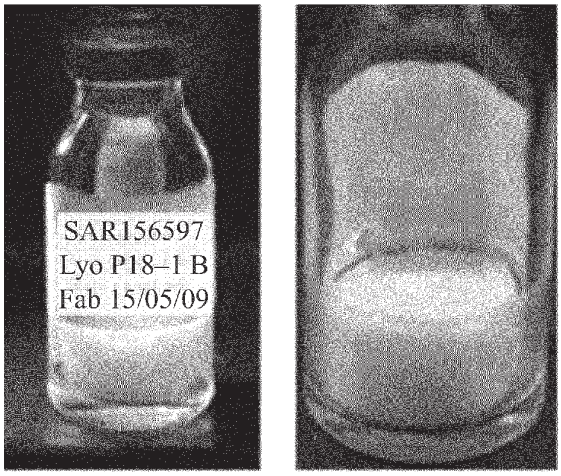


Figure 19

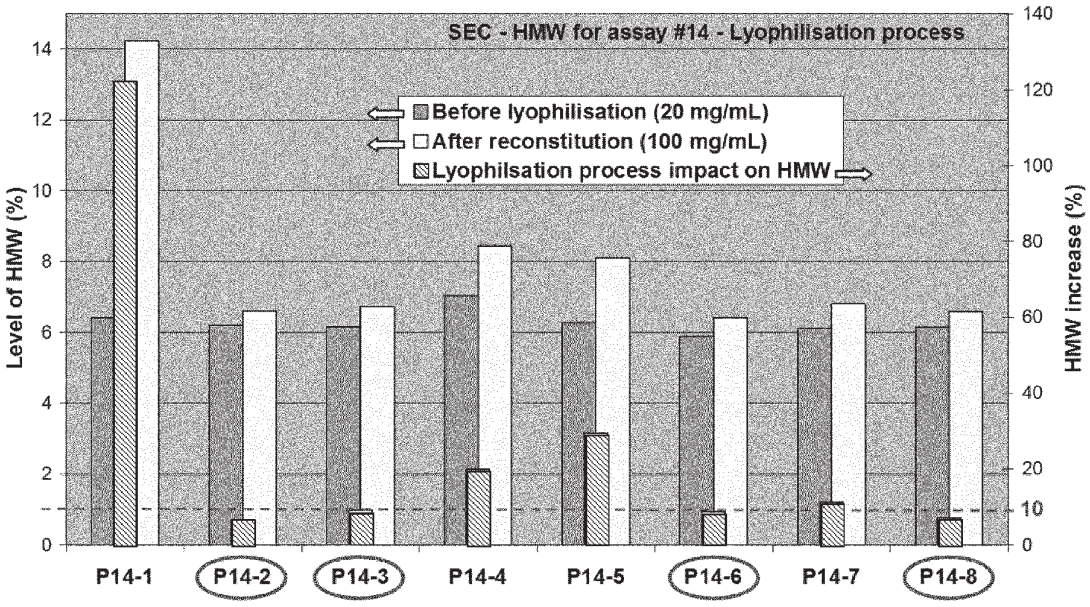

SEC - HMW for assay #14 - Lyophilisation process
Before lyophilisation (20 mg/mL)
After reconstitution (100 mg/mL)
Lyophilsation process impact on HMW
Level of HMW (%)
HMW increase (%)
0
2
4
6
8
10
12
14
0
20
40
60
80
100
120
140
P14-1
P14-2
P14-3
P14-4
P14-5
P14-6
P14-7
P14-8

Figure 20

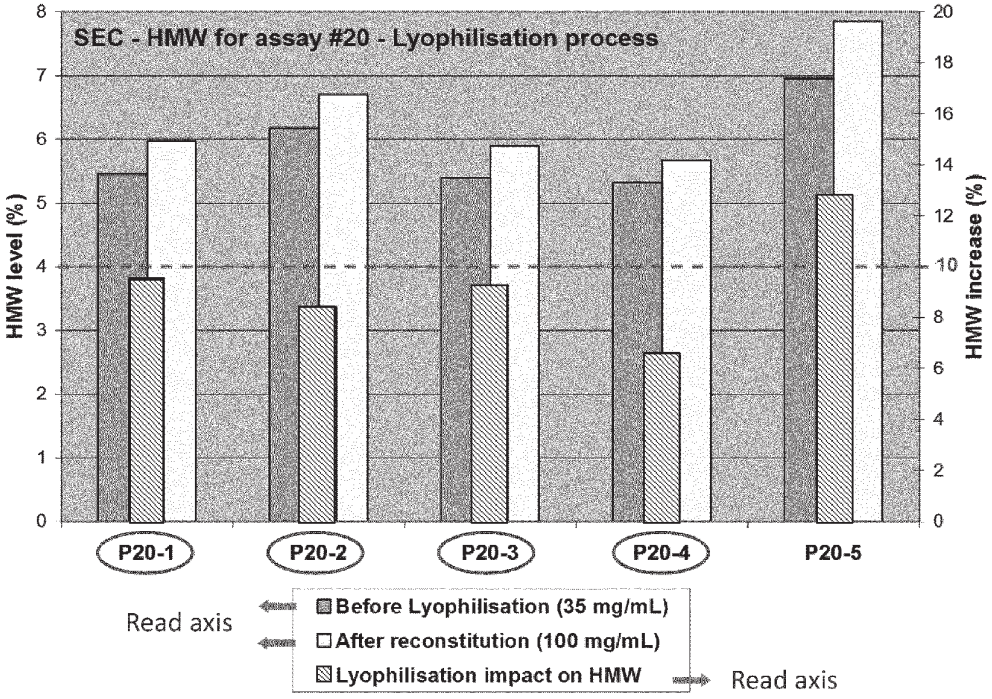

SEC - HMW for assay #20 - Lyophilisation process
HMW level (%)
HMW increase (%)
0
1
2
3
4
5
6
7
8
0
2
4
6
8
10
12
14
16
18
20
P20-1
P20-2
P20-3
P20-4
P20-5
Read axis
Before Lyophilisation (35 mg/mL)
After reconstitution (100 mg/mL)
Lyophilisation impact on HMW
Read axis

Figure 21

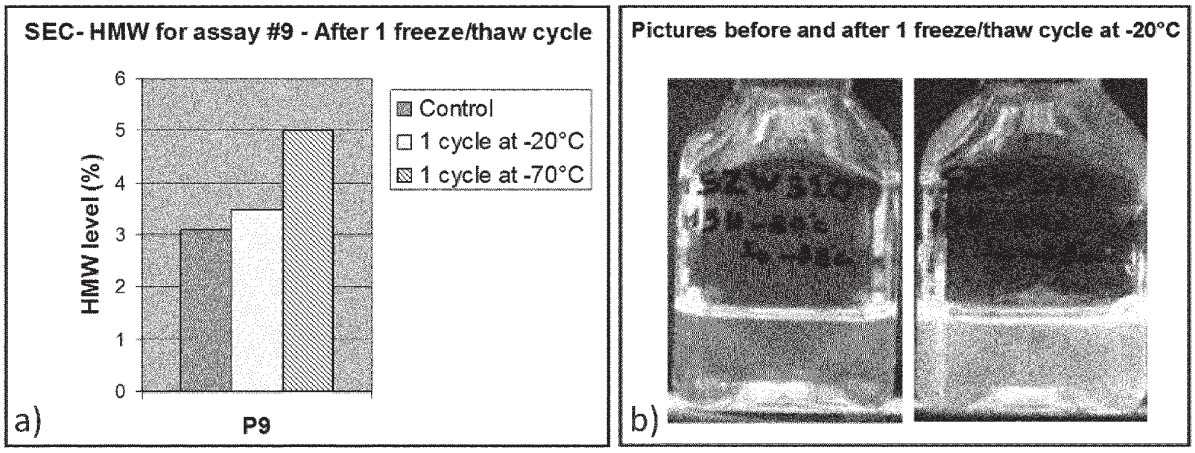

SEC- HMW for assay #9 - After 1 freeze/thaw cycle
HMW level (%)
0
1
2
3
4
5
6
Control
1 cycle at -20°C
1 cycle at -70°C
P9
a)
Pictures before and after 1 freeze/thaw cycle at -20°C
b)

Figure 22

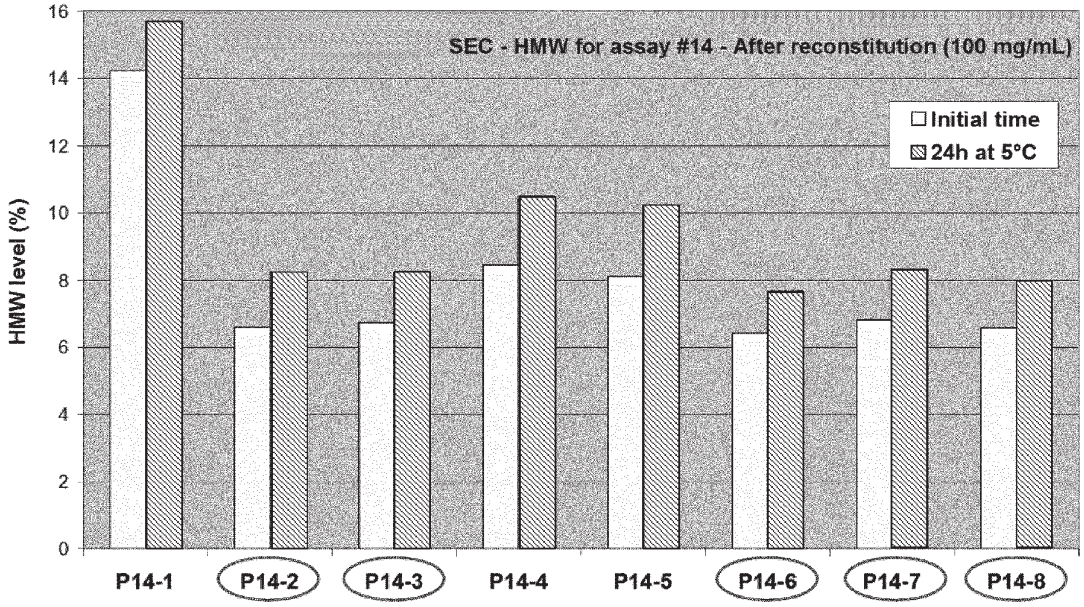

SEC - HMW for assay #14 - After reconstitution (100 mg/mL)
Initial time
24h at 5°C
HMW level (%)
16
14
12
10
8
6
4
2
0
P14-1
P14-2
P14-3
P14-4
P14-5
P14-6
P14-7
P14-8

Figure 23

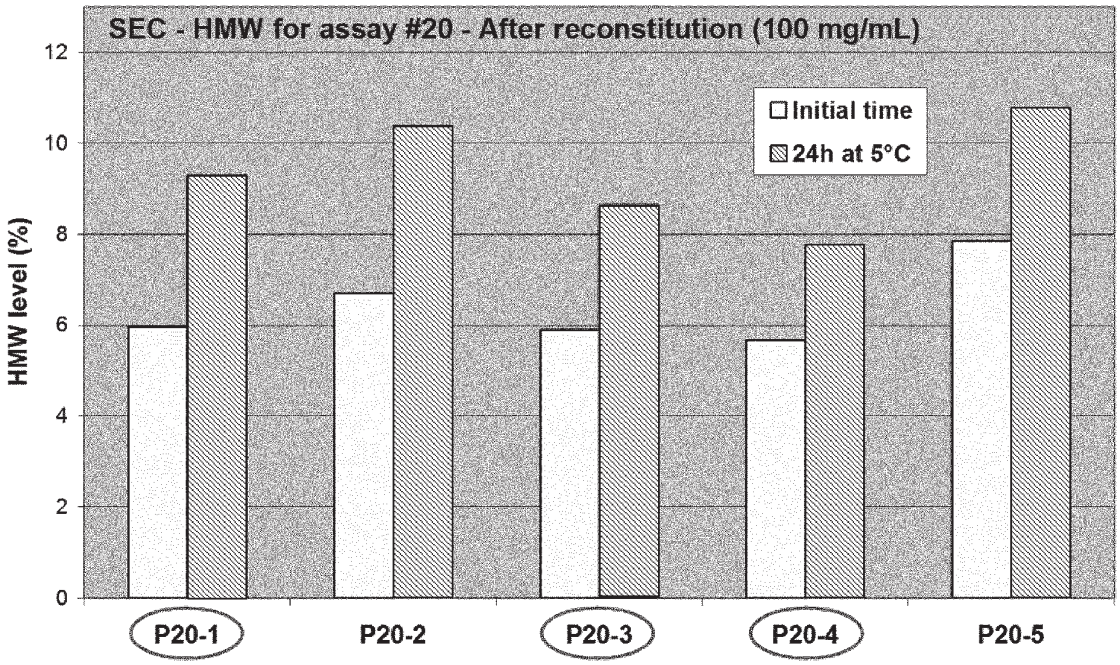

SEC - HMW for assay #20 - After reconstitution (100 mg/mL)
HMW level (%)
0
2
4
6
8
10
12
Initial time
24h at 5°C
P20-1
P20-2
P20-3
P20-4
P20-5

Figure 24

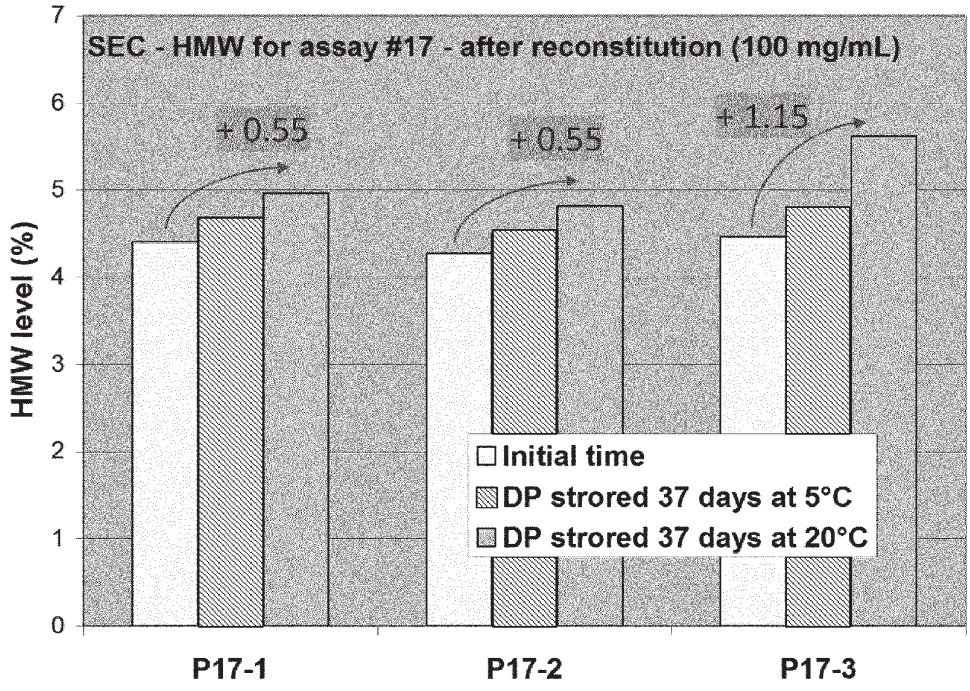

SEC - HMW for assay #17 - after reconstitution (100 mg/mL)
HMW level (%)
0
1
2
3
4
5
6
7
+ 0.55
+ 0.55
+ 1.15
Initial time
DP strored 37 days at 5°C
DP strored 37 days at 20°C
P17-1
P17-2
P17-3

Figure 25

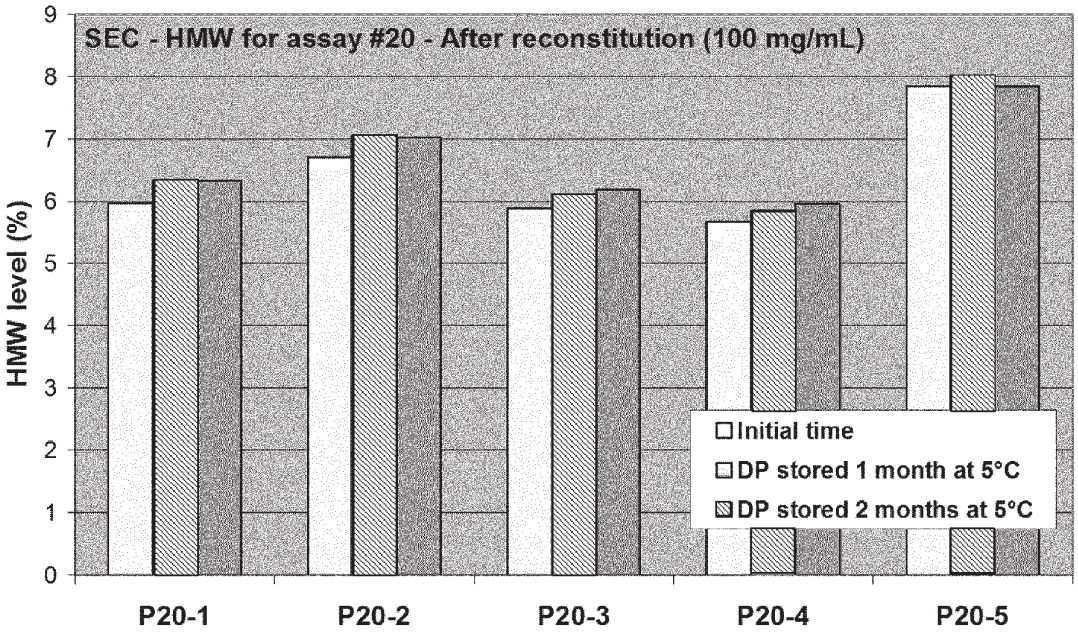

SEC - HMW for assay #20 - After reconstitution (100 mg/mL)
HMW level (%)
0
1
2
3
4
5
6
7
8
9
P20-1
P20-2
P20-3
P20-4
P20-5
Initial time
DP stored 1 month at 5°C
DP stored 2 months at 5°C

Figure 26

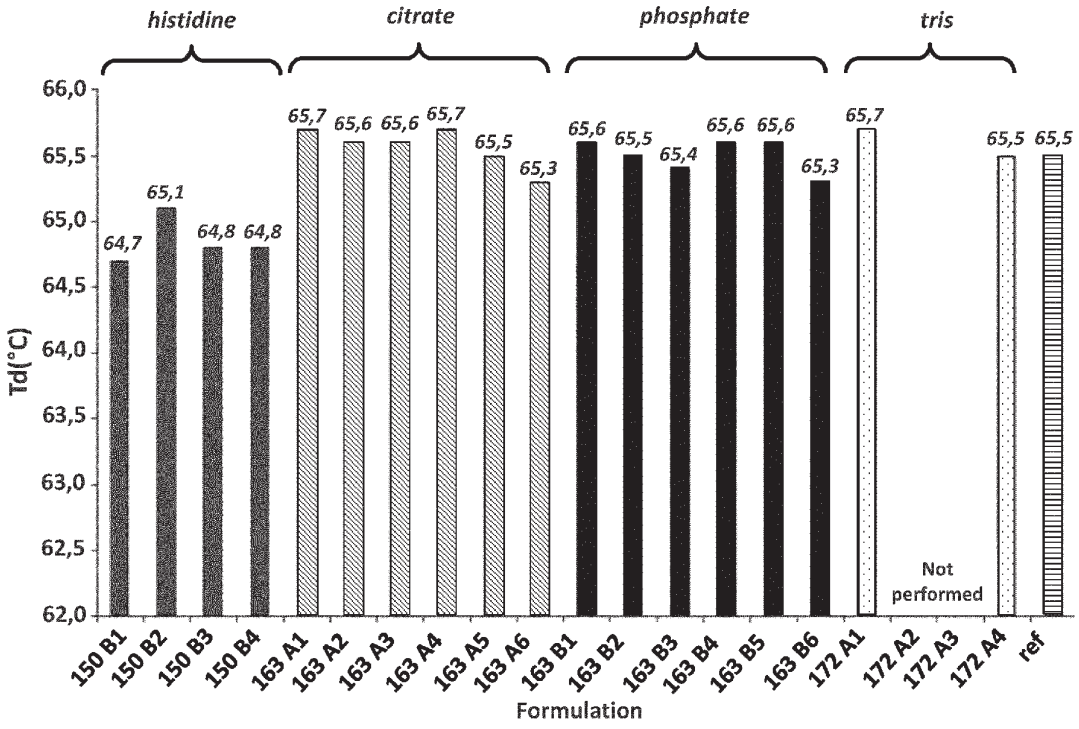

histidine
citrate
phosphate
tris
Td(°C)
66,0
65,5
65,0
64,5
64,0
63,5
63,0
62,5
62,0
64,7
65,1
64,8
64,8
65,7
65,6
65,6
65,7
65,5
65,3
65,6
65,5
65,4
65,6
65,6
65,3
65,7
Not performed
65,5
65,5
150 B1
150 B2
150 B3
150 B4
163 A1
163 A2
163 A3
163 A4
163 A5
163 A6
163 B1
163 B2
163 B3
163 B4
163 B5
163 B6
172 A1
172 A2
172 A3
172 A4
ref
Formulation

Figure 27

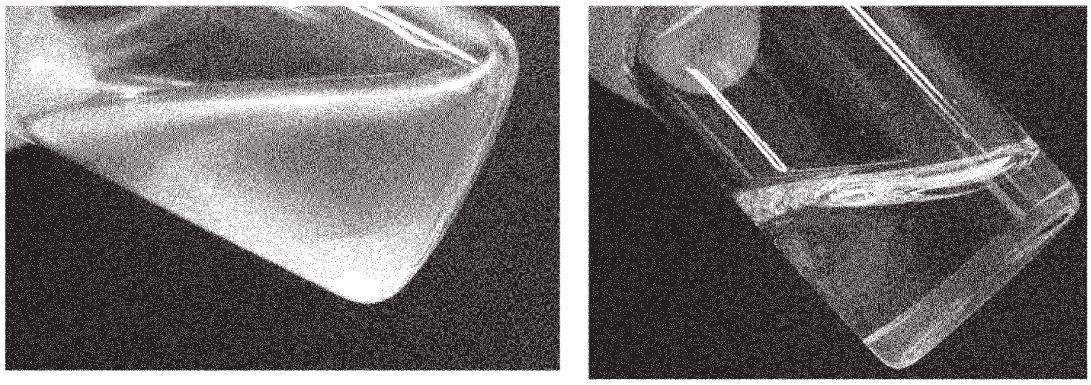


Figure 28A

	ΔHMW at 5°C	
Time (h)	150 B1 Histidine 10mM pH 6.6	Reference 156597-H04-016
0	0,0	0,0
48	0,3	0,7
72	0,6	1,0
144	2,4	3,2

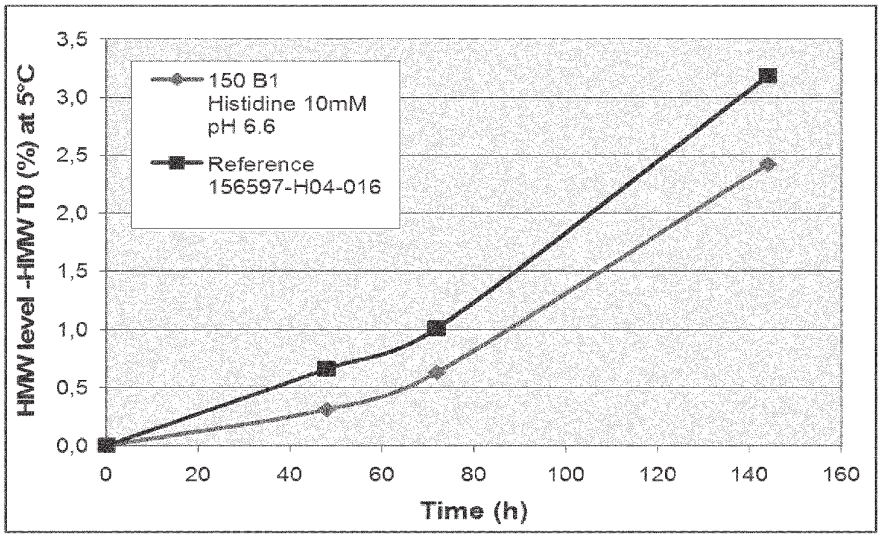


Figure 28B

	ΔHMW at RT			
Time (h)	163 A1 Citrate 10mM pH 6.6	163 B1 Phophate 10mM pH 6.6	163 B2 Phophate 10mM pH 7.0	Reference 156597-H04-016
0	0,0	0,0	0,0	0,0
24	4,6	4,8	5,3	5,2
48	8,5	8,2	8,7	9,0

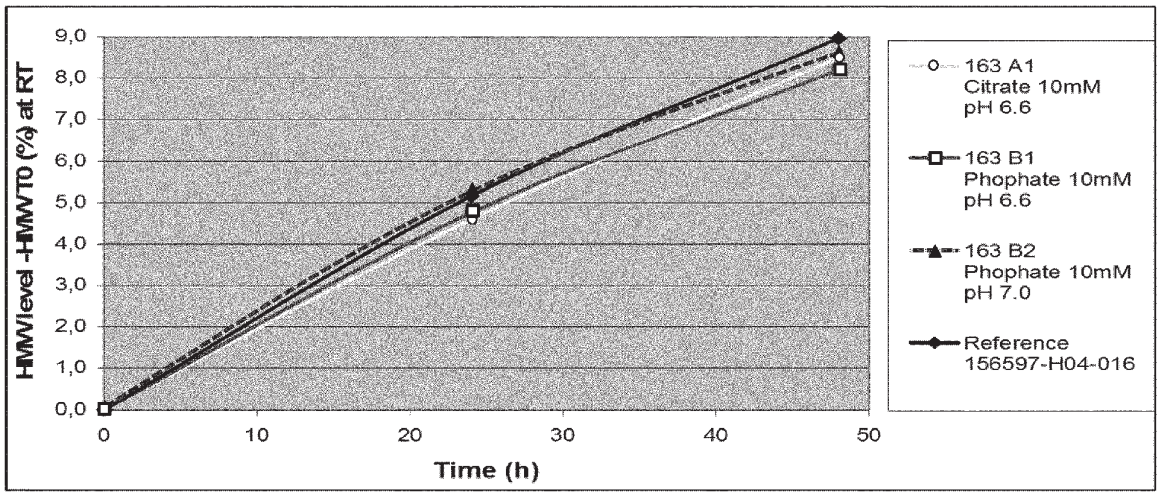


Figure 28C

	ΔHMW at RT		
Time (h)	172 A1 Tris 10mM pH 7.0	172 A2 Tris 10mM pH 7.4	Reference 156597-H04-016
0	0,0	0,0	0,0
24	4,2	3,9	3,6
48	7,8	7,2	7,0

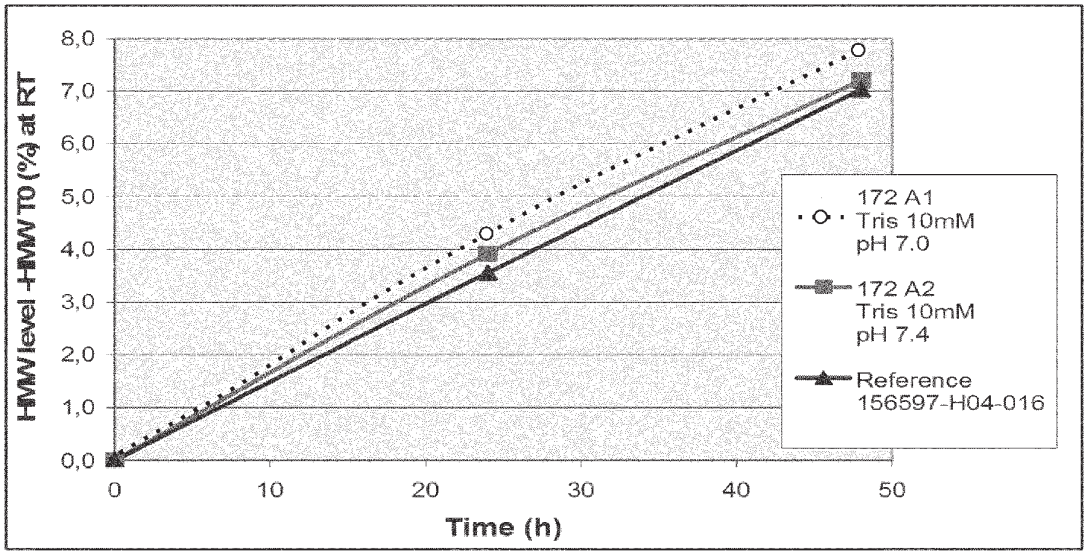


Figure 29

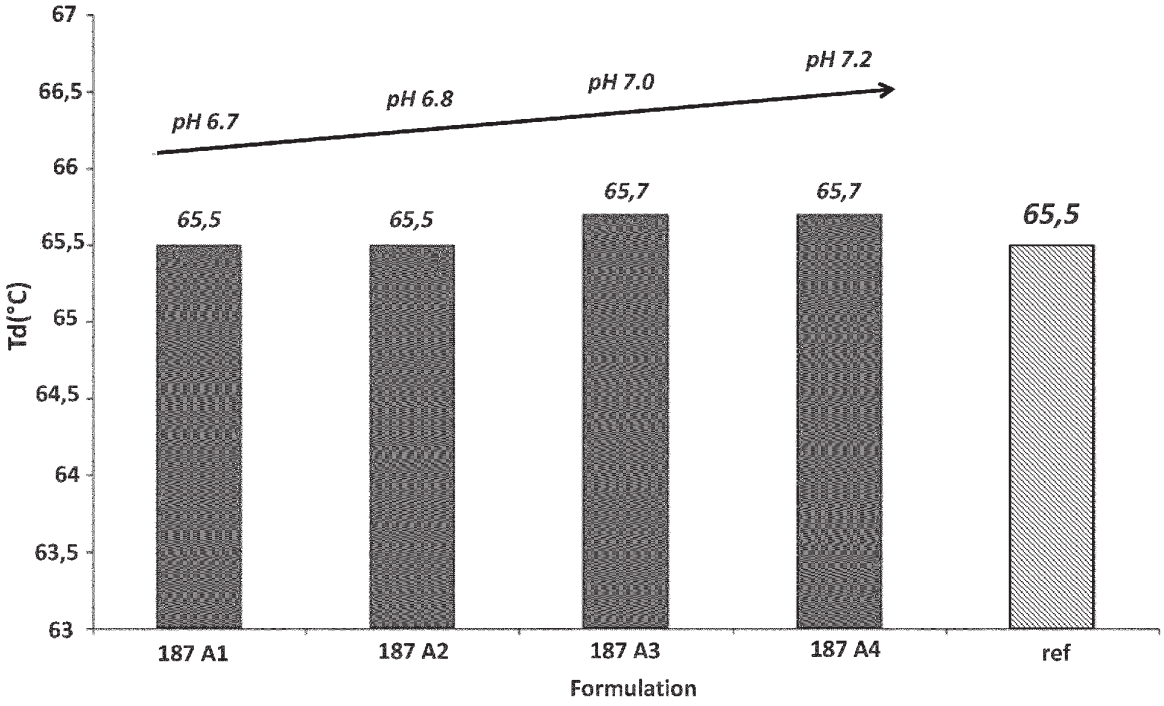

67
66,5
66
65,5
65
64,5
64
63,5
63
Td(°C)
pH 6.7
pH 6.8
pH 7.0
pH 7.2
65,5
65,5
65,7
65,7
65,5
187 A1
187 A2
187 A3
187 A4
ref
Formulation

Figure 30

	ΔHMW at RT				
Time (h)	187 A1 pH 6.7	187 A2 pH 6.8	187 A3 pH 7.0	187 A4 pH 7.2	Reference LT-10006-DS
0	0,0	0,0	0,0	0,0	0,0
16	2,8	2,7	2,4	2,2	2,8
24	4,1	4,0	3,6	3,4	4,0
40	5,8	5,7	5,2	4,9	5,6

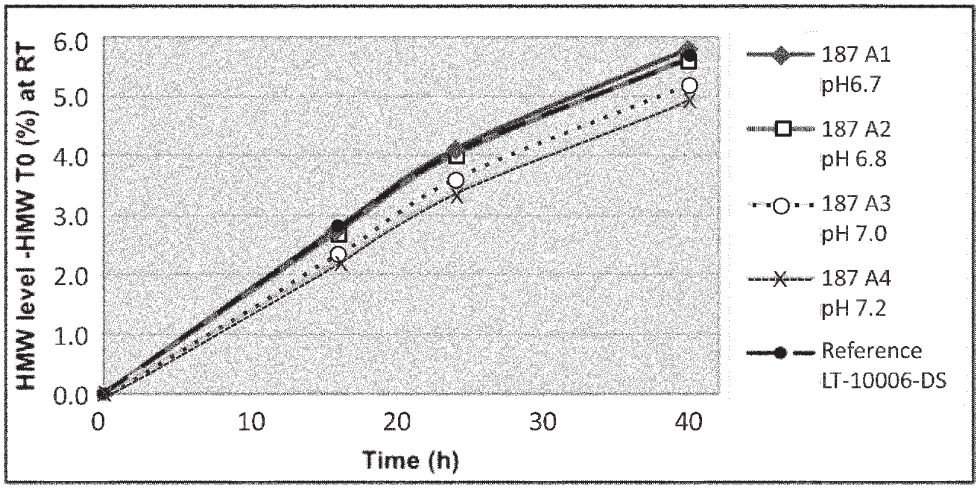


Figure 31

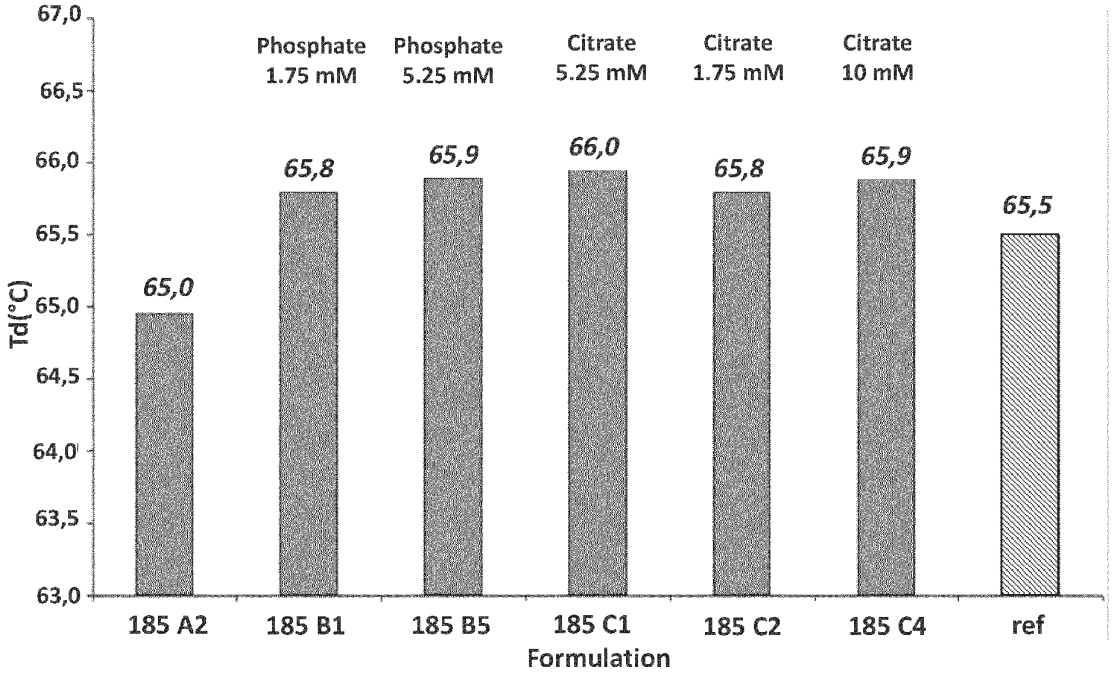

67,0
66,5
66,0
65,5
65,0
64,5
64,0
63,5
63,0
Td(°C)
Phosphate 1.75 mM
Phosphate 5.25 mM
Citrate 5.25 mM
Citrate 1.75 mM
Citrate 10 mM
65,0
65,8
65,9
66,0
65,8
65,9
65,5
185 A2
185 B1
185 B5
185 C1
185 C2
185 C4
ref
Formulation

Figure 32A

	ΔHMW at RT				
Time (h)	185 A2 -	185 C2 Citrate 1.75mM	185 C1 Citrate 5.25mM	185 C4 Citrate 10mM	Reference 185 D
0	0,0	0,0	0,0	0,0	0,0
24	3,9	3,2	3,8	3,7	3,2
48	7,0	7,1	7,7	7,8	6,8
72	9,8	10,1	10,8	11,0	9,8

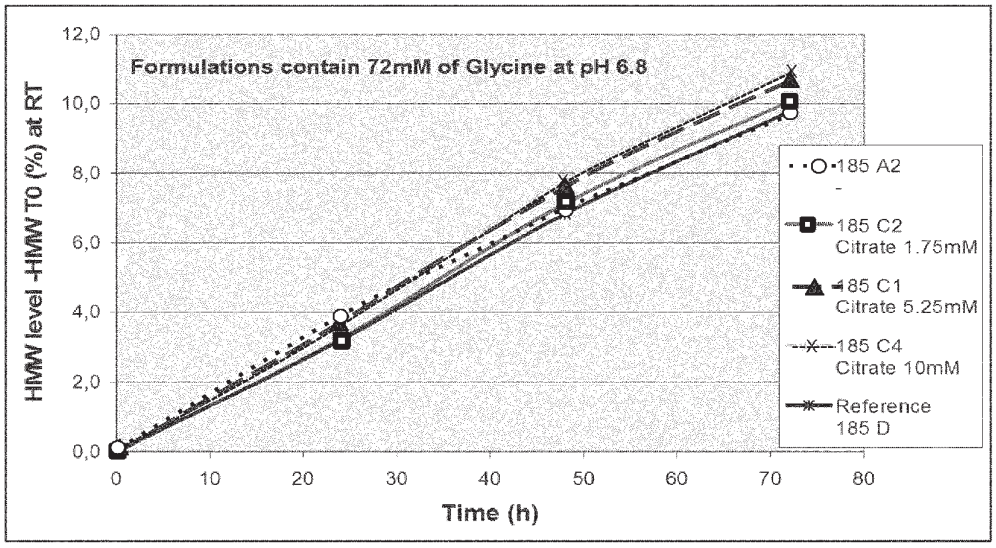


Figure 32B

	ΔHMW at RT			
Time (h)	185 A2 -	185 B1 Phosphate 1.75mM	187 B5 Phosphate 5.25mM	Reference 185 D
0	0,0	0,0	0,0	0,0
24	3,9	4,0	3,9	3,2
48	7,0	7,5	8,0	6,8
72	9,8	10,4	11,2	9,8

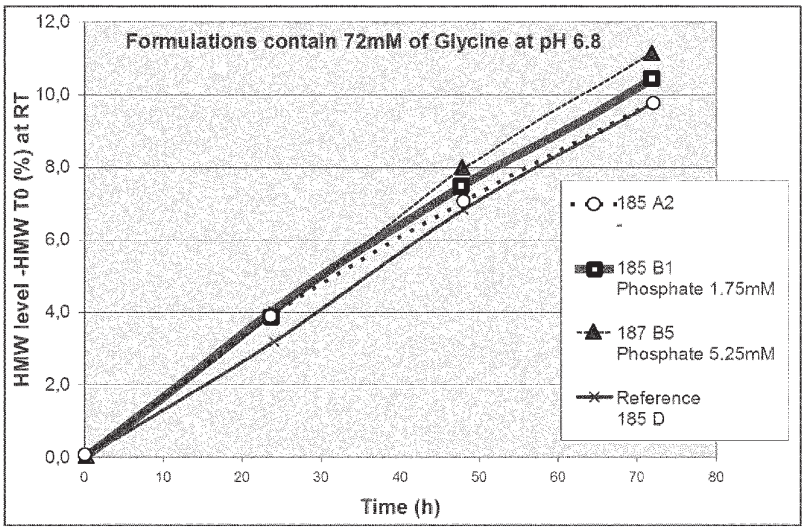


Figure 33

	ΔHMW at RT		
Time (h)	185 B1 Phosphate 1.75mM Glycine 72mM	185 B4 Phosphate 1.75mM NaCl 38.5mM	Reference 185 D
0	0,0	0,0	0,0
24	4,0	5,2	3,2
48	7,5	9,4	6,8
72	10,4	12,5	9,8

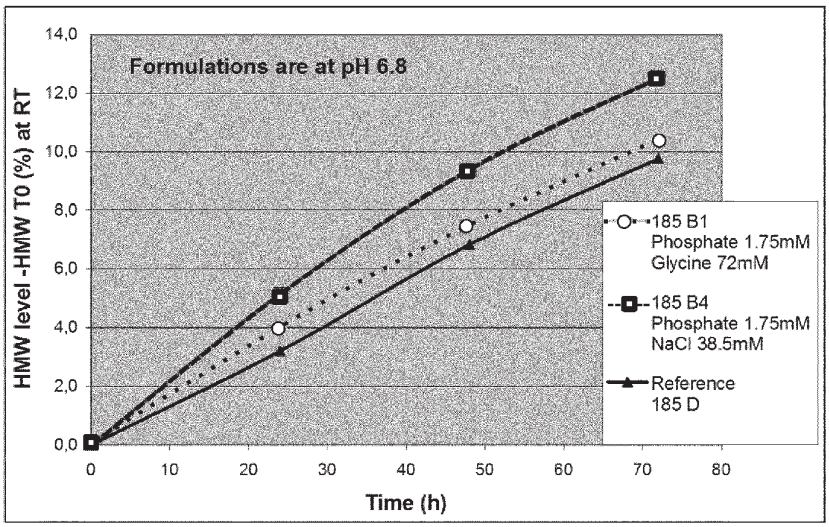


Figure 34

	ΔHMW at RT						
Time (h)	185 A2 - Glycine 72mM	185 A1 - Sucrose 2.4%	185 B1 Phos 1.75mM Glycine 72mM	185 B2 Phos 1.75mM Sucrose 2.4%	185 C2 Citrate 1.75mM Glycine 72mM	185 C3 Citrate 1.75mM Sucrose 2.4%	Reference 185 D
0	0,0	0,0	0,0	0,0	0,0	0,0	0,0
24	3,9	4,1	4,0	4,2	3,2	4,1	3,2
48	7,0	7,5	7,5	7,5	7,1	7,9	6,8
72	9,8	10,1	10,4	10,4	10,1	10,9	9,8

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<151> 2013-04-29

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35 40 45

Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60

Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Asp
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35 40 45

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35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Gly Met Ile Asp Pro Ser Asp Gly Glu Thr Arg Leu Asn Gln Arg Phe
50 55 60

Gln Gly Arg Ala Thr Leu Thr Val Asp Glu Ser Thr Ser Thr Ala Tyr
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Met Gln Leu Arg Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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Thr Arg Leu Lys Glu Tyr Gly Asn Tyr Asp Ser Phe Tyr Phe Asp Val
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Gln Gly Arg Ala Thr Leu Thr Val Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Arg Ser Pro Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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