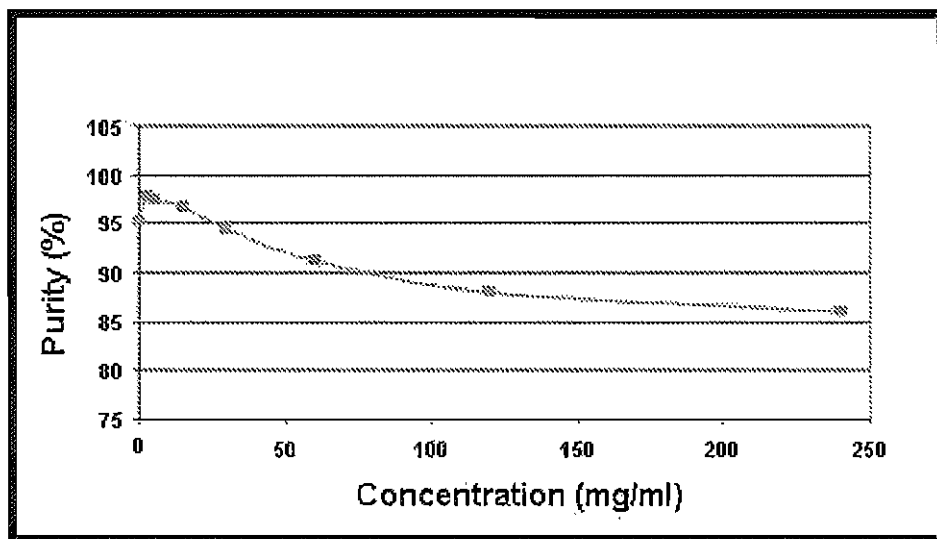


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FIGURE 1

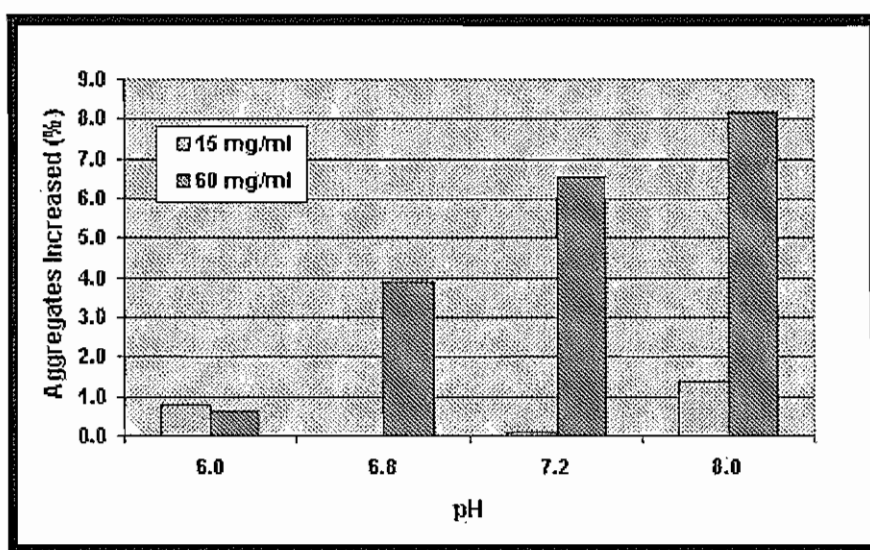
Effects of Concentrations on rHSA-G-CSF



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FIGURE 2

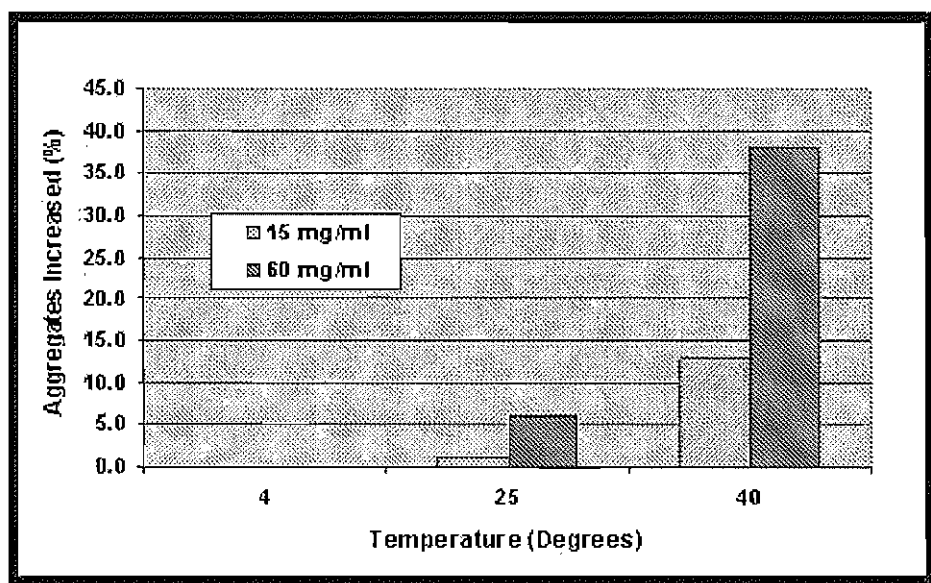
pH Effects (7 Day, 25°)



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FIGURE 3

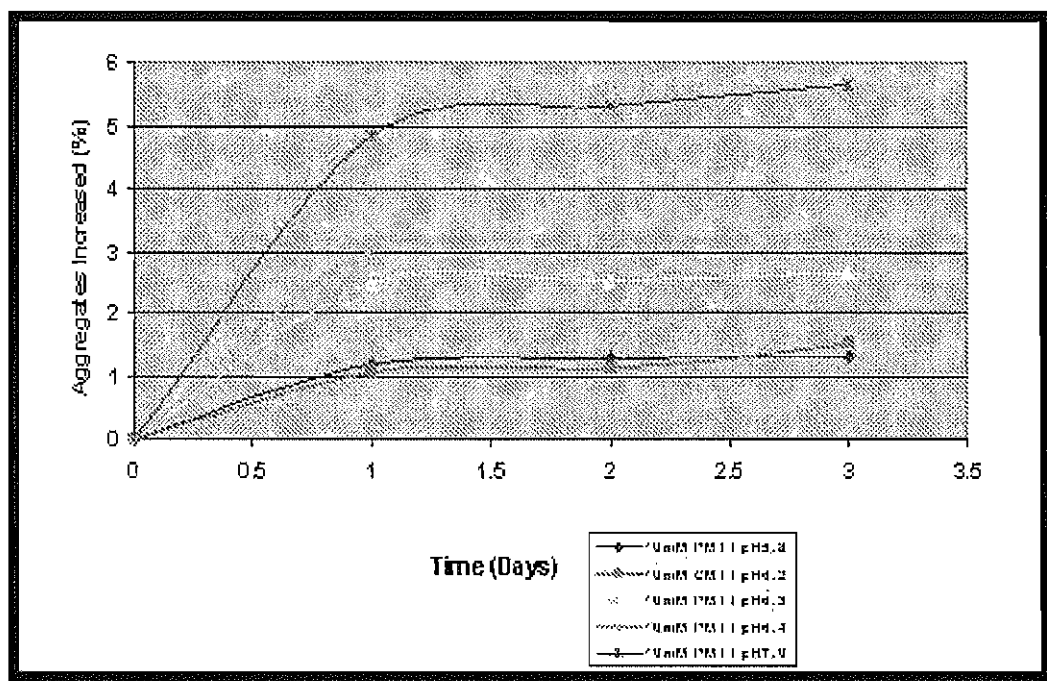
Temperature Effects (1 Day, pH 7.2)



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FIGURE 4

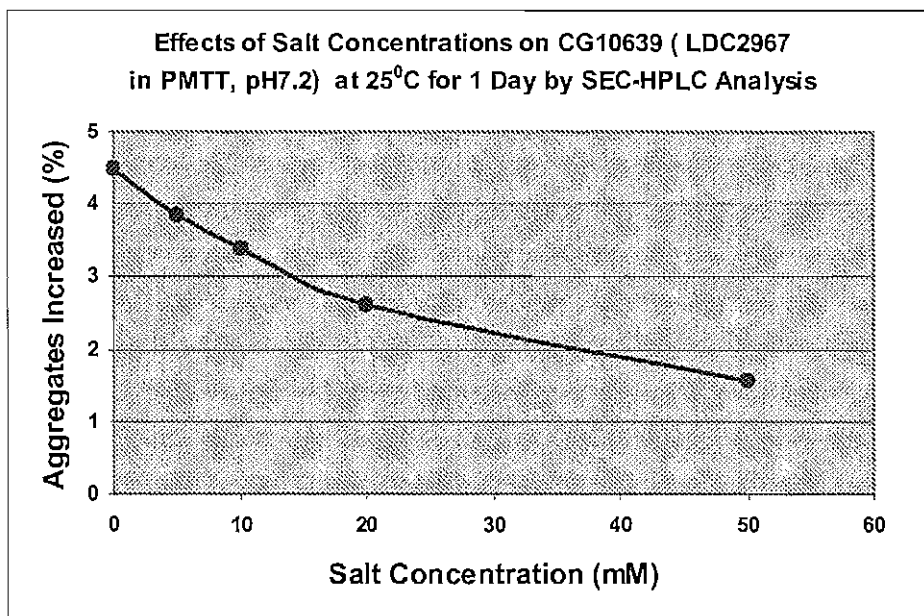
pH Effects (up to 3 days, 25°)



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FIGURE 5

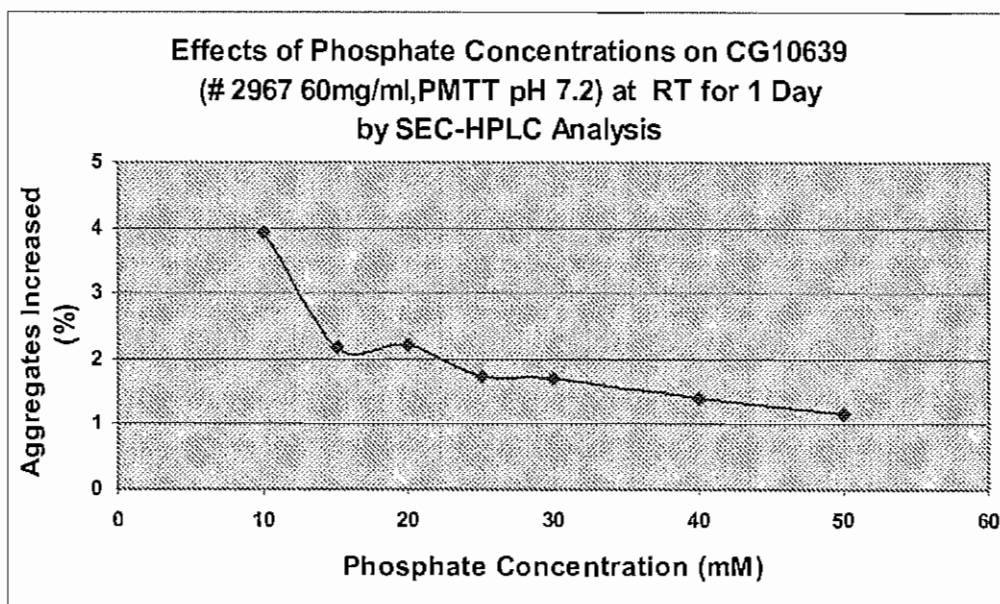
Effects of NaCl on rHSA-G-CSF (7 Day, 25°)



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FIGURE 6

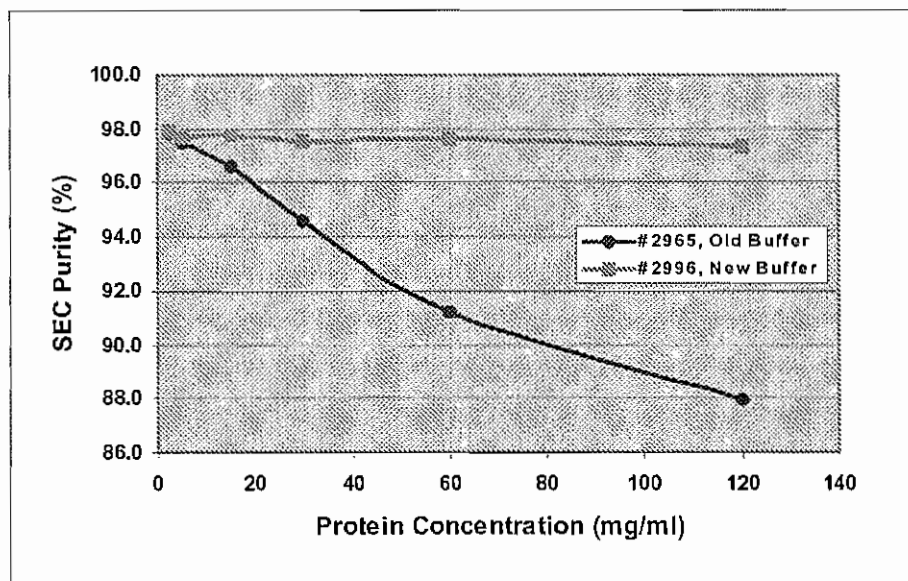
Effects of Phosphate on rHSA-G-CSF (1 Day, 25°)



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FIGURE 7

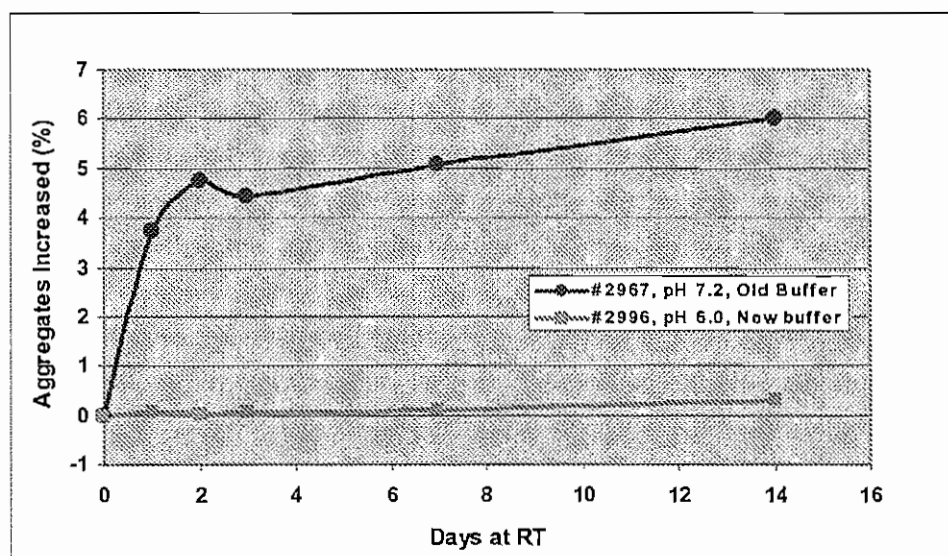
Comparison of Protein Concentration Effects in
PMTT20/6.0 and PMTT10/7.2 Formulation Buffers



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FIGURE 8

Comparison of Stability in PMTT20/6.0
and PMTT10/7.2 Formulation Buffers



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FIGURE 9A

1 GATGCACACAAGAGTGAGGTGCTCATCGGTTTAAAGATTGGGAGAAGAAAATTTCAA 60
1 D A H K S E V A H R F K D L G E E N F K 20

61 GCCTTGGTGTGATTGCCTTTGCTCAGTATCTTCAGCAGTGCCATTTGAAGATCATGTA 120
21 A L V L I A F A Q Y L Q Q C P F E D H V 40

121 AAATTAGTGAATGAAGTAACTGAATTTGCAAAAACATGTGTGCTGATGAGTCAGCTGAA 180
41 K L V N E V T E F A K T C V A D E S A E 60

181 AATGTGTACAAATCACTTCATACCCTTTGGAGACAAATTATGCACAGTTGCAACTCTT 240
61 N C D K S L H T L F G D K L C T V A T L 80

241 CGTGAAACCTATGGTGAAATGGCTGACTGCTGTGCAAAACAAGAACCTGAGAGAAATGAA 300
81 R E T Y G E M A D C C A K Q E P E R N E 100

301 TGCTTCTTGCAACACAAAGATGACAACCCAAACCTCCCCGATTGGTGAGACCAGAGGTT 360
101 C F L Q H K D D N P N L P R L V R P E V 120

361 GATGTGATGTGCACTGCTTTTCATGACAATGAAGAGACATTTTGAAAAAATACTTATAT 420
121 D V M C T A F H D N E E T F L K K Y L Y 140

421 GAAATTGCCAGAAGACATCCTTACTTTTATGCCCCGGAACCTCTTTCTTTGCTAAAAGG 480
141 E I A R R H P Y F Y A P E L L F F A K R 160

481 TATAAAGCTGCTTTTACAGAATGTTGCCAAGCTGCTGATAAAGCTGCCTGCCTGTTGCCA 540
161 Y K A A F T E C C Q A A D K A A C L L P 180

541 AAGCTCGATGAACCTTCGGGATGAAGGGAAGGCTTCGCTGCCAAACAGAGACTCAAGTGT 600
181 K L D E L R D E G K A S S A K Q R L K C 200

601 GCCAGTCTCCAAAATTTGGAGAAAGAGCTTTCAAAGCATGGGCAGTAGCTCGCCTGAGC 660
201 A S L Q K F G E R A F K A W A V A R L S 220

661 CAGAGATTTCCAAAGCTGAGTTTGCAGAAGTTTCCAAGTTAGTGACAGATCTTACCAA 720
221 Q R F P K A E F A E V S K L V T D L T K 240

721 GTCCACACGGAATGCTGCCATGGAGATCTGCTTGAATCTGCTGATGACAGGGCGGACCTT 780
241 V H T E C C H G D L L E C A D D R A D L 260

781 GCCAAGTATATCTGTGAAAATCAAGATTCGATCTCCAGTAACTGAAGGAATGCTGTGAA 840
261 A K Y I C E N Q D S I S S K L K E C C E 280

841 AAACCTCTGTTGAAAAATCCCACTGCATGCGAAGTGGAATGATGAGATGCCTGCT 900
281 K P L L E K S H C I A E V E N D E M P A 300

901 GACTTGCTTCATTAGCTGCTGATTTTGTGAAAGTAAGGATGTTTGCAAAAATATGCT 960
301 D L P S L A A D F V E S K D V C K N Y A 320

961 GAGGCAAGGATGTCTTCCCTGGGCATGTTTGTATGAATATGCAAGAAGGCATCCTGAT 1020
321 E A K D V F L G M F L Y E Y A R R H P D 340

1021 TACTCTGTCTGCTGCTGCTGCTGAGACTTGCCAAGACATATGAAACCACTCTAGAGAAGTGC 1080
341 Y S V V L L L R L A K T Y E T T L E K C 360

1081 TGTGCCGCTGCAGATCCTCATGAATGCTATGCCAAAGTGTTGATGAATTTAAACCTCTT 1140
361 C A A A D P H E C Y A K V F D E F K P L 380

1141 GTGGAAGAGCCTCAGAATTTAATCAAACAAAATTTGTGAGCTTTTGTGAGCAGCTTGAGAG 1200
381 V E E P Q N L I K Q N C E L F E Q L G E 400

1201 TACAAATTCAGAATGCGCTATTAGTTCGTTACACCAAGAAAGTACCCCAAGTGCAACT 1260
401 Y K F Q N A L L V R Y T K K V P Q V S T 420

1261 CCAACTCTTGTAGAGGTCTCAAGAAACCTAGGAAAAGTGCGCAGCAAATGTTGTAAACAT 1320
421 P T L V E V S R N L G K V G S K C C K H 440

1321 CCTGAAGCAAAAAGAATGCCCTGTGCAGAAGACTATCTATCCGTGGTCTGAACCAAGTTA 1380
441 P E A K R M P C A E D Y L S V V L N Q L 460

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1381 TGTGTGTTGCATGAGAAAACGCCAGTAAGTGACAGAGTCACCAAATGCTGCACAGAATCC 1440
461 C V L H E K T P V S D R V T K C C T E S 480

1441 TTGGTGAACAGGCGACCATGCTTTTCAGCTCTGGAAGTCGATGAAACATACGTTCCCAA 1500
481 L V N R R P C F S A L E V D E T Y V P K 500

1501 GAGTTTAATGCTGAAACATTACCTTCCATGCAGATATATGCACACTTTCTGAGAAGGAG 1560
501 E F N A E T F T F H A D I C T L S E K E 520

1561 AGACAAATCAAGAAACAACTGCACCTGTTGAGCTCGTGAAACACAAGCCCAAGGCAACA 1620
521 R Q I K K Q T A L V E L V K H K P K A T 540

1621 AAAGAGCAACTGAAAGCTGTTATGGATGATTTTCGCAGCTTTTGTAGAGAAGTGCTGCAAG 1680
541 K E Q L K A V M D D F A A F V E K C C K 560

1681 GCTGACGATAAGGAGACCTGCTTTGCCGAGGAGGGTAAAAAACTTGTTGCTGCAAGTCAA 1740
561 A D D K E T C F A E E G K K L V A A S Q 580

1741 GCTGCCTTAGGCTTAACCCCTGCGGCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTC 1800
581 A A L G L T P L G P A S S L P Q S F L L 600

1801 AAGTGCTTAGAGCAAGTGAGGAAGATCCAGGCGATGGCGCAGCGCTCCAGGAGAAGCTG 1860
601 K C L E Q V R K I Q G D G A A L Q E K L 620

1861 TGTGCCACCTACAAGCTGTGCCACCCGAGGAGCTGGTGCTGCTCGGACACTCTCTGGGC 1920
621 C A T Y K L C H P E E L V L L G H S L G 640

1921 ATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGGCTGCTTG 1980
641 I P W A P L S S C P S Q A L Q L A G C L 660

1981 AGCCAACTCCATAGCGGCCTTTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATC 2040
661 S Q L H S G L F L Y O G L L O A L E G I 680

2041 TCCCCGAGTTGGGTCCCACCTTGGACACACTGCAGCTGGACGTCGCCGACTTTGCCACC 2100
681 S P E L G P T L D T L Q L D V A D F A T 700

2101 ACCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCTGCCCTGCAGCCCACCCAGGGT 2160
701 T I W Q Q M E E L G M A P A L O P T O G 720

2161 GCCATGCCGGCCTTCGCCTCTGCTTTCCAGCGCCGGCAGGAGGGTCTGTTGCCTCC 2220
721 A M P A F A S A F Q R R A G G V L V A S 740

2221 CATCTGCAGAGCTTCCTGGAGGTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCC 2280
741 H L Q S F L E V S Y R V L R H L A O P 759

```

The amino acid sequence of G-CSF is underlined.

cDNA sequence: A = adenine, C = cytosine, G = guanine, T = thymidine

Amino acid sequence: A = Ala, C = Cys, D = Asp, E = Glu, F = Phe, G =

Gly, H = His, I = Ile, K = Lys, L = Leu, M = Met, N = Asn, P = Pro, Q = Gln,

R = Arg, S = Ser, T = Thr, V = Val, W = Trp, Y = Tyr

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FIGURE 9B

1 MAGPATQSPM KLMAQLLLW HSALWTVQEA TPLGPASSLP QSFLKLCLEQ
VRKIQGDGAA

61 LQEKLCATYK LCHPEELVLL GHSLGIPWAP LSSCPSQALQ LAGCLS QLHS
GLFLYQGLLQ

121 ALEGISPELG PTLDTLQLDV ADFATTIWQQ MEELGMAPAL QPTQGAMPAF
ASAFQRRAGG

181 VLVASHLQSF LEVSYRVLRH LAQP

FIGURE 9C

1 MKWVTFISLL FLFSSAYSRG VFRDAHKSE VAHRFKDLGE ENFKALVLIA
FAQYLQQCPF

61 EDHVKL VNEV TEFAKTCVAD ESAENC DKSL HTLFGDKLCT VATLRETYGE
MADCCAKQEP

121 ERNECFLQHK DDNP NL PRLV RPEVDVMCTA FHDNEETFLK KYLYEIARRH
PYFYAPELLF

181 FAKRYKAAFT ECCQAADKAA CLLPKLDEL R DEGKASSAKQ RLK CASLQKF
GERAFKAWAV

241 ARLSQRFPKA EFAEVSKLVT DLT KVHTECC HGD LLECADD RADLAKYICE
NQDSISSKLK

301 ECCEKPLLEK SHCIAEVEND EMPADLPSLA ADFVESKDVC KNYAEAKDVF
LGMFLYEYAR

361 RHPDYSVVLL LRLAKTYETT LEKCCAAADP HECYAKVFDE FKPLVEEPQN
LIKQNC ELF E

421 QLGEYKFQNA LLVRYTKKVP QVSTPTLVEV SRNLGKVGSK CCKHPEAKRM
PCAEDYLSVV

481 LNQLCVLHEK TPVSDRVTKC CTESLVNRRP CFSALEVDET YVPKEFNAET
FTFHADICTL

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541 SEKERQIKKQ TALVELVKHK PKATKEQLKA VMDDFAAFVE KCCKADDKET
CFAEEGKKLV

601 AASQAALGL

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FIGURE 10

Formulation	Osmolality mOsm/kg	SEC% Day at RT			
		0	1	2	3
10mM PMTT pH5.8	297	96.75	95.55	95.46	95.43
10mM CMTT pH6.2	299	96.55	95.47	95.42	95.01
10mM PMTT pH6.3	299	96.52	94.01	93.99	93.87
10mM PMTT pH6.4	294	96.58	93.57	93.51	93.24
10mM PMTT pH7.0	299	95.96	91.12	90.65	90.33

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FIGURE 11

Temperature °C	Time (Day)	SEC (%)			
		pHs			
		6.0	6.8	7.2	8.0
4	0	98.67	97.72	97.75	97.17
	1	98.56	98.19	97.85	96.87
	7	98.31	98.44	98.26	97.72
	10	98.48	98.35	98.22	97.67
25	0	98.43	97.02	96.74	97.03
	1	98.5	97.58	96.87	97.11
	3	98.47	97.57	96.69	96.68
	5	98.32	97.45	96.88	95.9
	7	97.65	97.28	96.62	95.64
40	0	98.67	97.72	97.75	97.17
	1	93.53	90.90	84.82	69.87
	7	80.47	77.09	64.80	40.2
	10	75.44	73.35	59.41	34.11
4	0	98.21	97.30	97.2	97.12
	1	98.52	97.51	97.26	97.07
	7	98.45	98.14	97.16	96.33
	10	98.11	97.65	97.24	96.24
25	0	97.96	95.62	95.92	96.52
	1	97.32	92.11	90.8	91.85
	3	97.48	91.76	90.32	90.38
	5	97.13	91.84	90.07	89.45
	7	97.3	91.74	89.74	88.37
40	0	98.21	97.30	97.2	97.12
	1	82.67	71.98	59.16	33.29
	7	41.23	40.54	24.71	8.69
	10	31.98	33.97	20.09	6.15

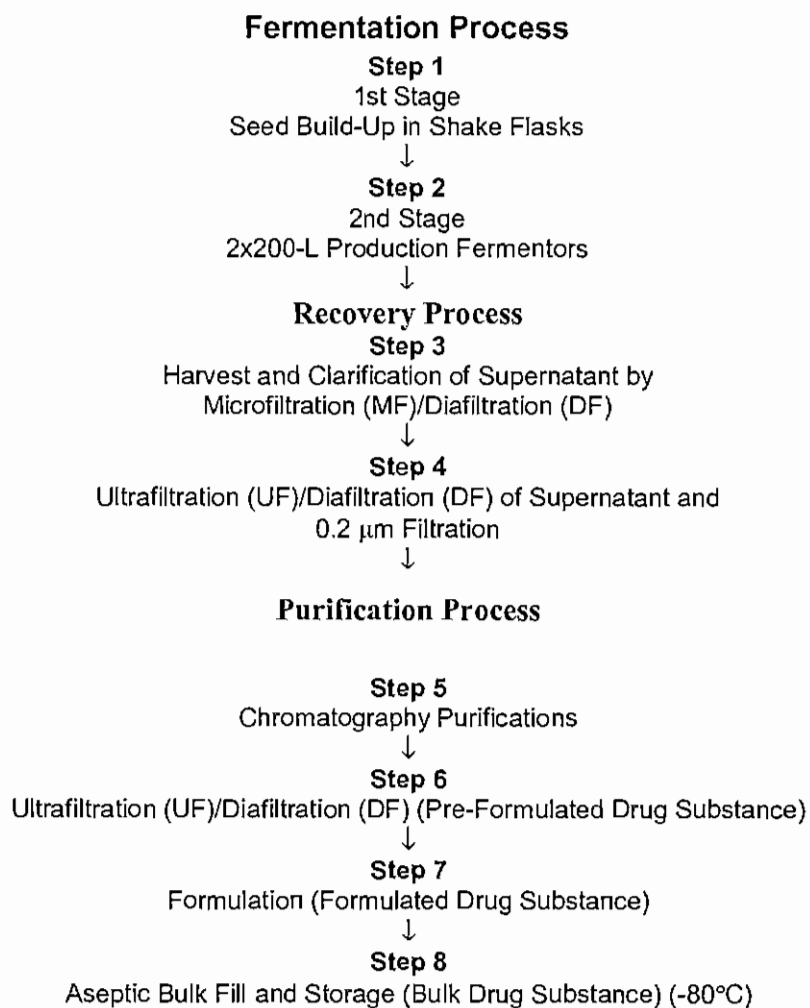
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FIGURE 12

Concentration (mg/ml)	Temperature °C	Time (Day)	Bioassay (Relative Potency %)			
			pHs			
			6.0	6.8	7.2	8.0
15	4	0	141	141	141	141
		1				
		7				
		10	161	102	132	116
	25	0	121	121	121	121
		1				
		3				
		5				
		7	128	112	124	88
	40	0				
		1				
		7				
		10				
60	4	0	138	138	138	138
		1				
		7				
		10	118	96	89	96
	25	0	104	104	104	104
		1				
		3				
		5				
		7	126	116	113	107
	40	0	130	130	130	130
		1				
		7				
		10	110	92	105	41

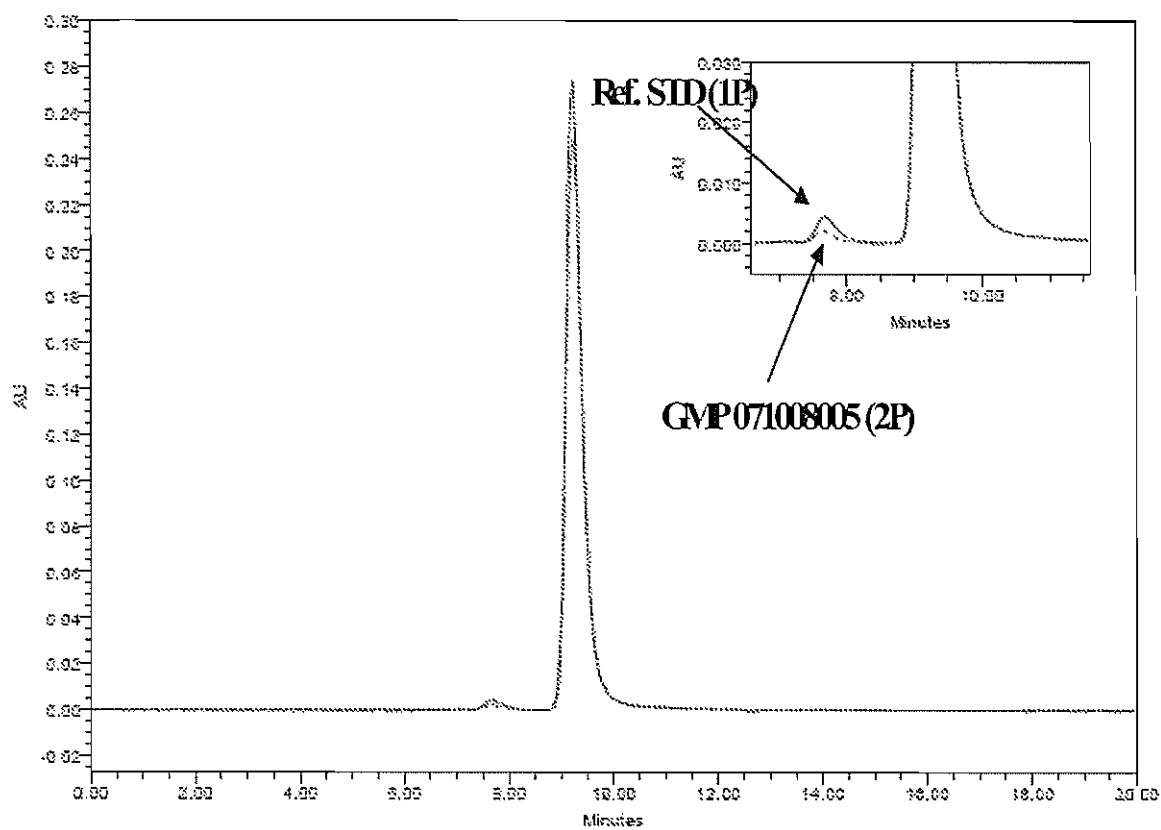
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FIGURE 13



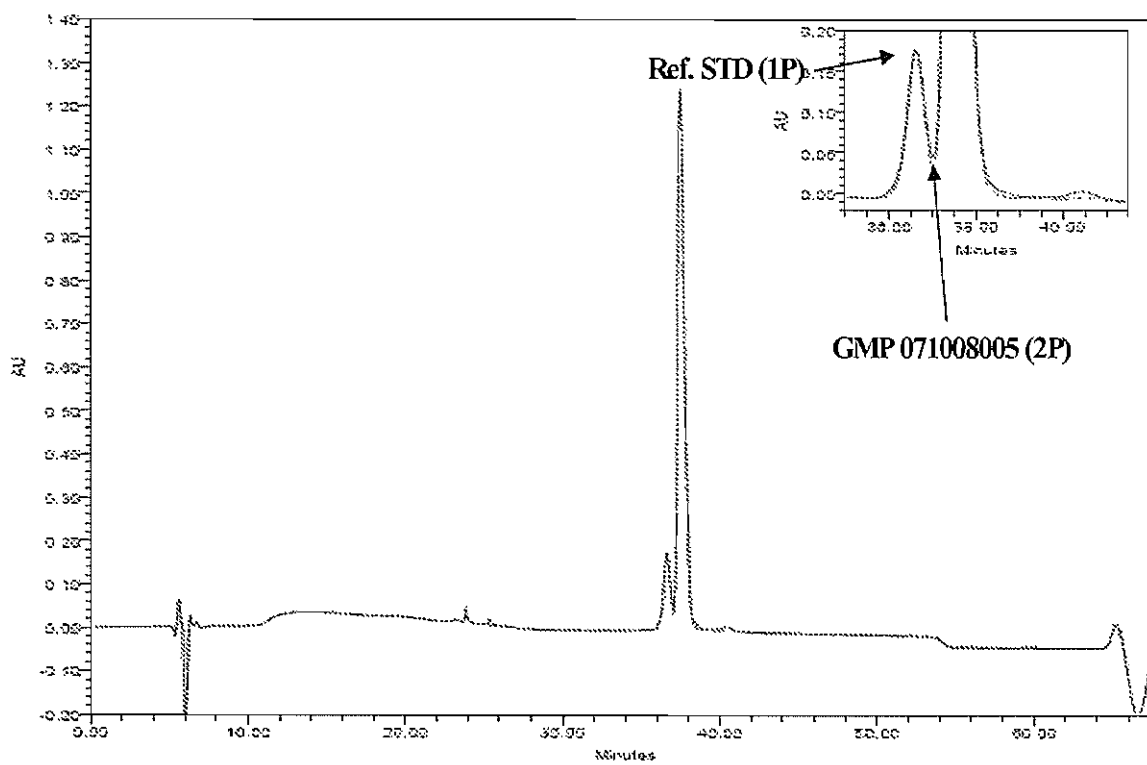
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FIGURE 14A



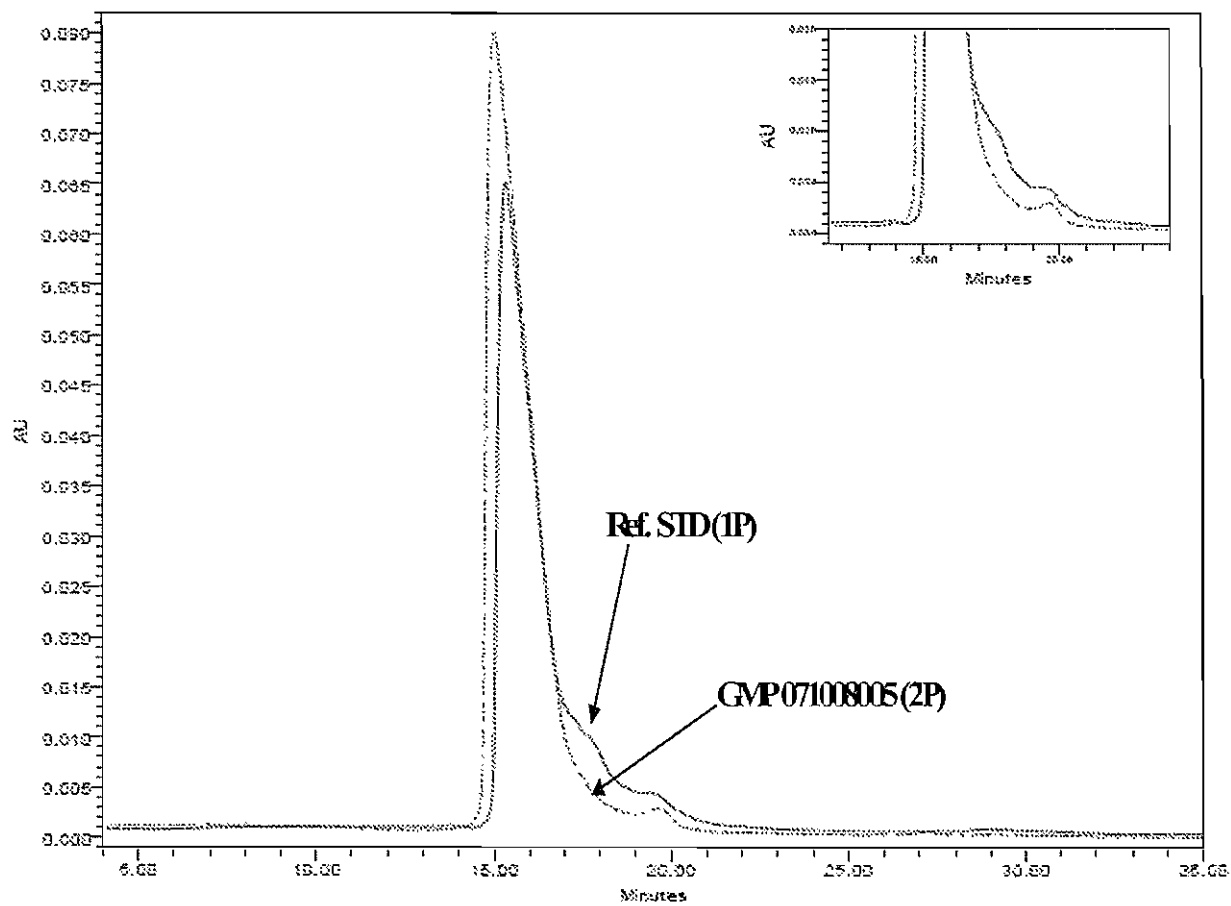
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FIGURE 14B



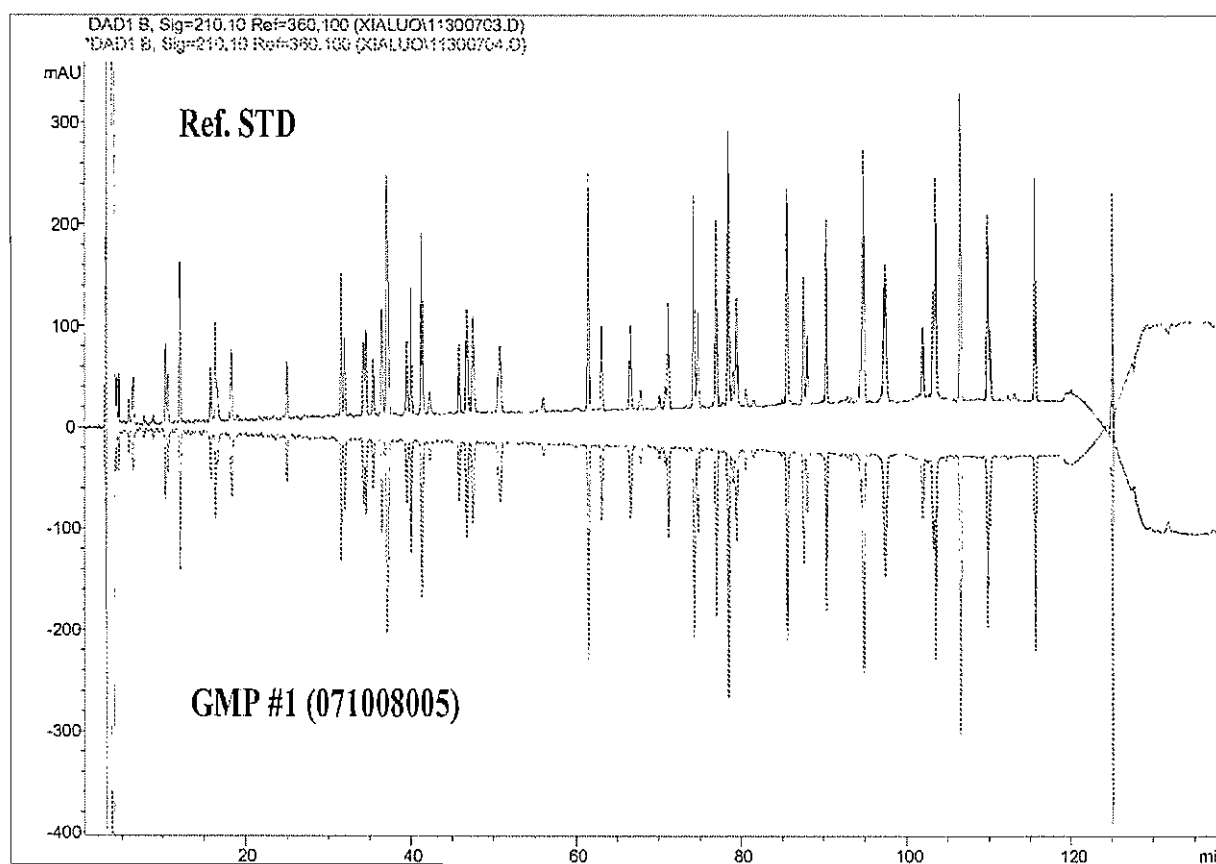
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FIGURE 15A



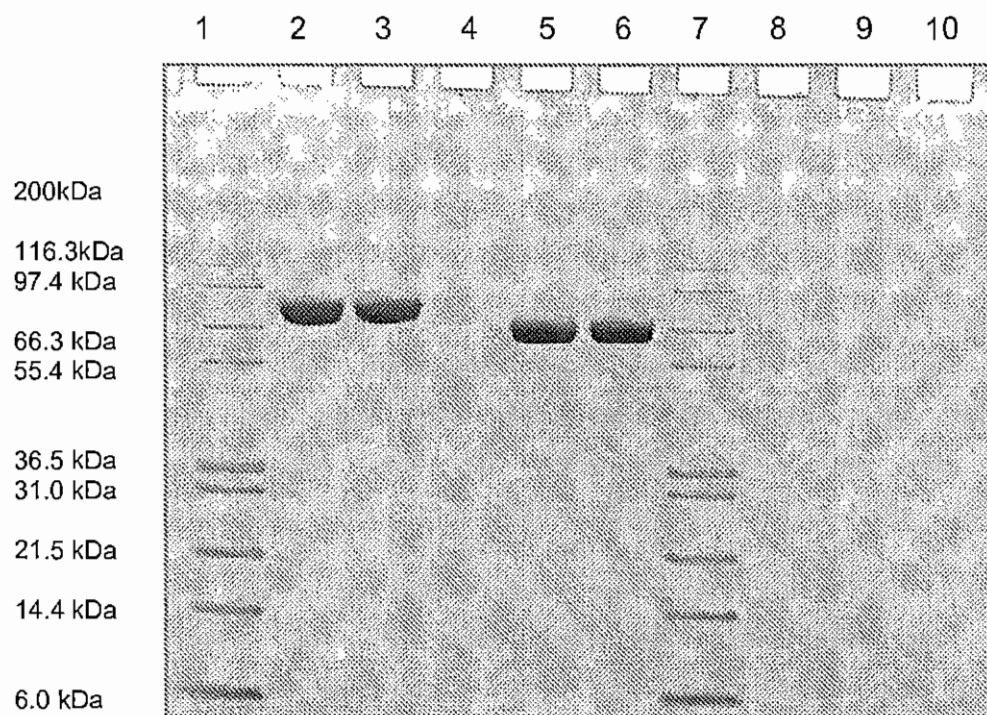
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FIGURE 15B



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FIGURE 16



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FIGURE 17A

Test	Analytical Method	Acceptance Criteria	Lot 071008005	Lot 071025001	Lot 071026004	Lot 071106001	Lot 071116001
Appearance	Visual inspection	Clear to opalescent, pale yellow to yellow solution	Clear, pale yellow solution	Clear, pale yellow solution	Clear, pale yellow solution	Clear, pale yellow solution	Clear, pale yellow solution
pH	pH Electrode	6.0 ± 0.3	6.0	6.0	6.0	6.1	6.1
Osmolality	Freezing point	300 ± 30 mOsm/kg	305 mOsm/kg	310 mOsm/kg	313 mOsm/kg	313 mOsm/kg	312 mOsm/kg
Protein concentration	Absorbance at 280 nm	Report result (X.X mg/mL)	64.5 mg/mL	61.4 mg/mL	62.0 mg/mL	64.3 mg/mL	71.3 mg/mL
Purity	SDS-PAGE: Reduced and non-reduced with Coomassie Blue Stain	$\geq 95\%$	R: 100% NR: 100%	R: 100% NR: 100%	R: 100% NR: 100%	R: 100% NR: 100%	R: 100% NR: 100%
Purity	SDS-PAGE: Reduced and non-reduced with Silver stain	Comparable to reference standard	Comparable to reference standard	Comparable to reference standard	Comparable to reference standard	Comparable to reference standard	Comparable to reference standard
Purity	SEC-HPLC	$\geq 90.0\%$	98.9%	99.4%	98.1%	98.1%	98.3%
Purity	RP-HPLC	Report result (X.X%)	86.3%	88.5%	87.5%	86.7%	87.3%
Identity	ELISA	Identity confirmed	Identity confirmed	Identity Confirmed	Identity Confirmed	Identity Confirmed	Identity Confirmed

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Potency	Cell Proliferation	50-150%	113%	79.6%	87.2%	102%	83.4%
Bacterial Endotoxin	Kinetic turbidimetric (USP <85>)	≤ 1.0 EU/mg	<0.003 EU/mg	< 0.003 EU/mg	<0.003 EU/mg	< 0.003 EU/mg	< 0.003 EU/mg
Bioburden	Membrane Filtration	≤ 10 CFU/10mL	0 CFU/10mL	0 CFU/10mL	0 CFU/10mL	0 CFU/10mL	0 CFU/10mL
Residual DNA	Threshold	≤ 100 pg/mg	ND	ND	ND	ND	ND

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FIGURE 17B

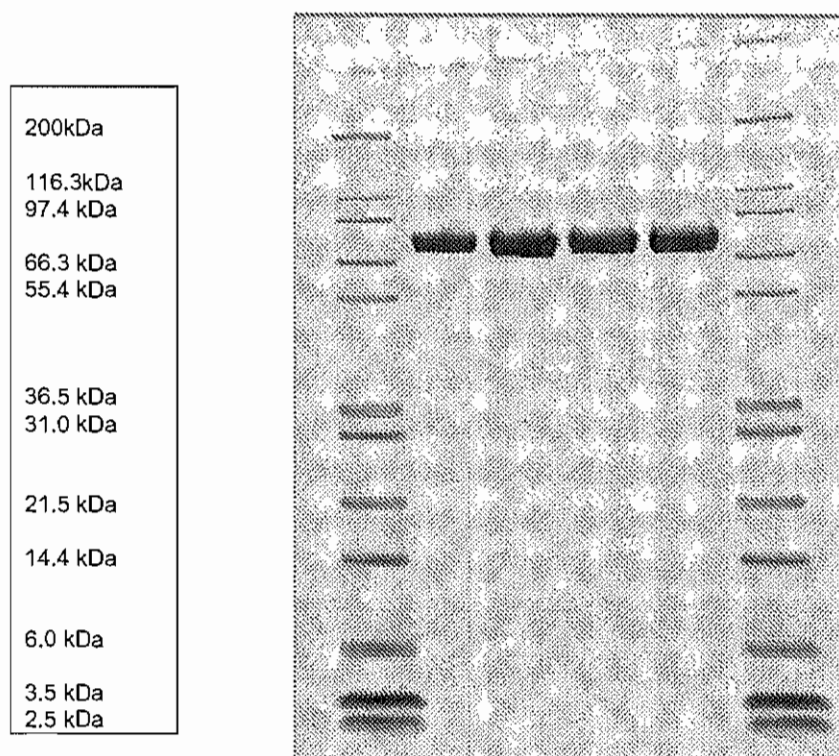
Attribute	Analytical Method	Acceptance Criteria	cGMP Lot 060615001	cGMP lot 060628001	cGMP lot 060707001
Appearance	Visual inspection	Clear to opalescent, pale yellow to yellow solution	Clear to opalescent, pale yellow to yellow solution	Clear to opalescent, pale yellow to yellow solution	Clear to opalescent, pale yellow to yellow solution
pH	pH Electrode	7.2 ± 0.3	7.3	7.4	7.2
Osmolality	Freezing point	Report result (X mOsm/kg)	310 mOsm/kg	311 mOsm/kg	310 mOsm/kg
Protein concentration	Absorbance at 280 nm	Report result (XX mg/mL)	26.6 mg/ml	24.7 mg/ml	30.1 mg/ml
Identity	ELISA	Identity confirmed	Identity confirmed	Identity confirmed	Identity confirmed
Purity	SDS-PAGE: Reduced and non-reduced with Coomassie blue stain	≥ 90%	100% Reduced 100% Non- Reduced	100% Reduced 99% Non- Reduced	100% Reduced 98% Non- Reduced
Purity	SDS-PAGE: Reduced and non-reduced with silver stain	Comparable to reference standard	Comparable to reference standard	Comparable to reference standard	Comparable to reference standard
Purity	SEC-HPLC	≥ 90.0%	97.8%	99.2%	98.7%
Purity	RP-HPLC	Report result (X.X%)	85.5%	85.2%	84.5%
Potency	Bioassay (NFS-60 cell proliferation)	Report result (X%)	125%	106%	109%

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Attribute	Analytical Method	Acceptance Criteria	cGMP Lot 060615001	cGMP lot 060628001	cGMP lot 060707001
Residual DNA	Threshold	≤ 300 pg/mg	<4 pg/mg	<4 pg/mg	<4 pg/mg
Bacterial Endotoxin	Kinetic turbidimetric (USP <85>)	≤ 10 EU/mg	<0.008 EU/mg	<0.008 EU/mg	<0.008 EU/mg
Bioburden	Membrane Filtration	≤ 10 CFU/10mL	0 CFU/10 ml	0 CFU/10ml	0 CFU/10ml

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FIGURE 18

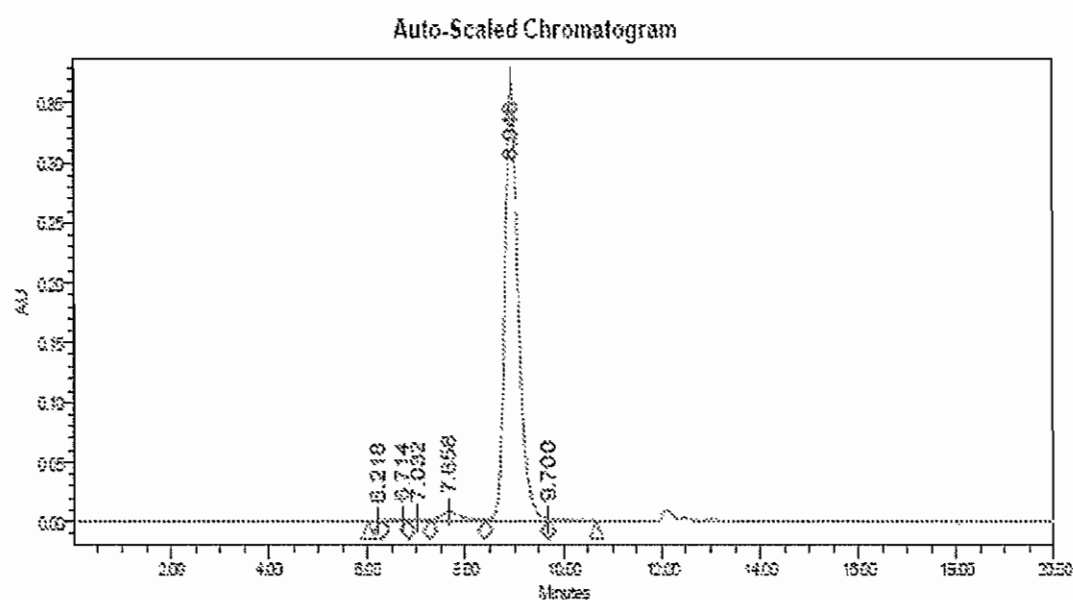


Lane #	Lot	Description	Conditions	µg Load
1	Mrk1320414	Size Marker 12	R	N/A
2	2579-092	Development BDS lot	R	4
3	LDC2378-R	Neugranin Ref. Std.	R	4
4	02A14078	Development FDP	R	4
5	2378FDP	Neugranin FDP	R	4
6	Mrk1320414	Size Marker 12	R	N/A

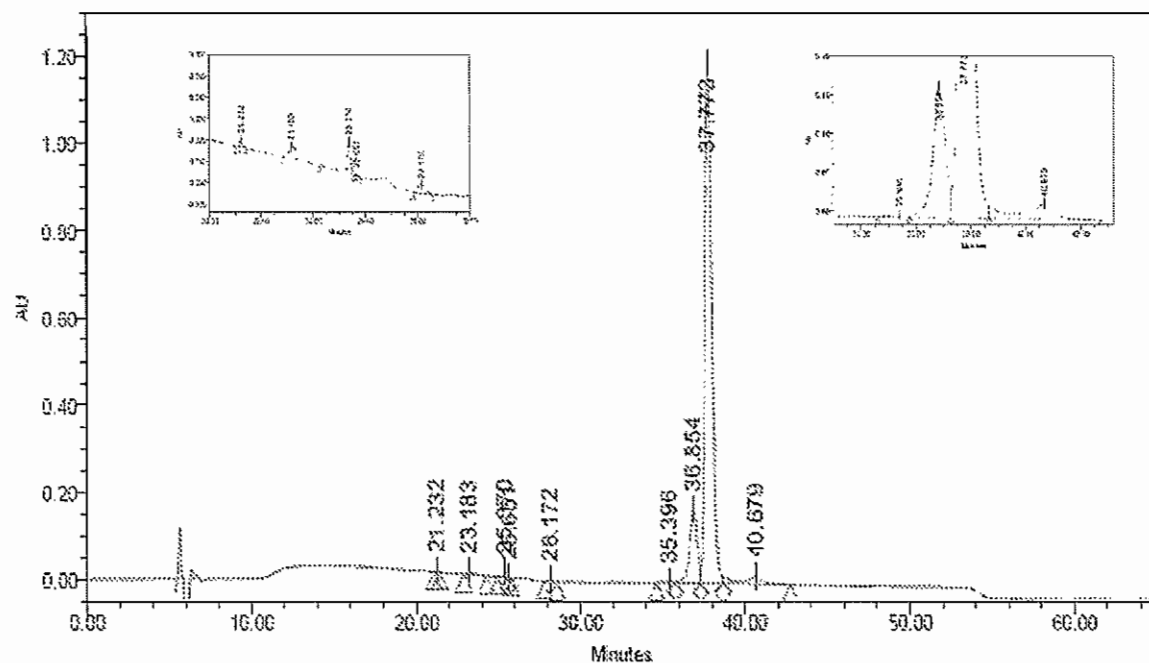
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FIGURE 19

A



B



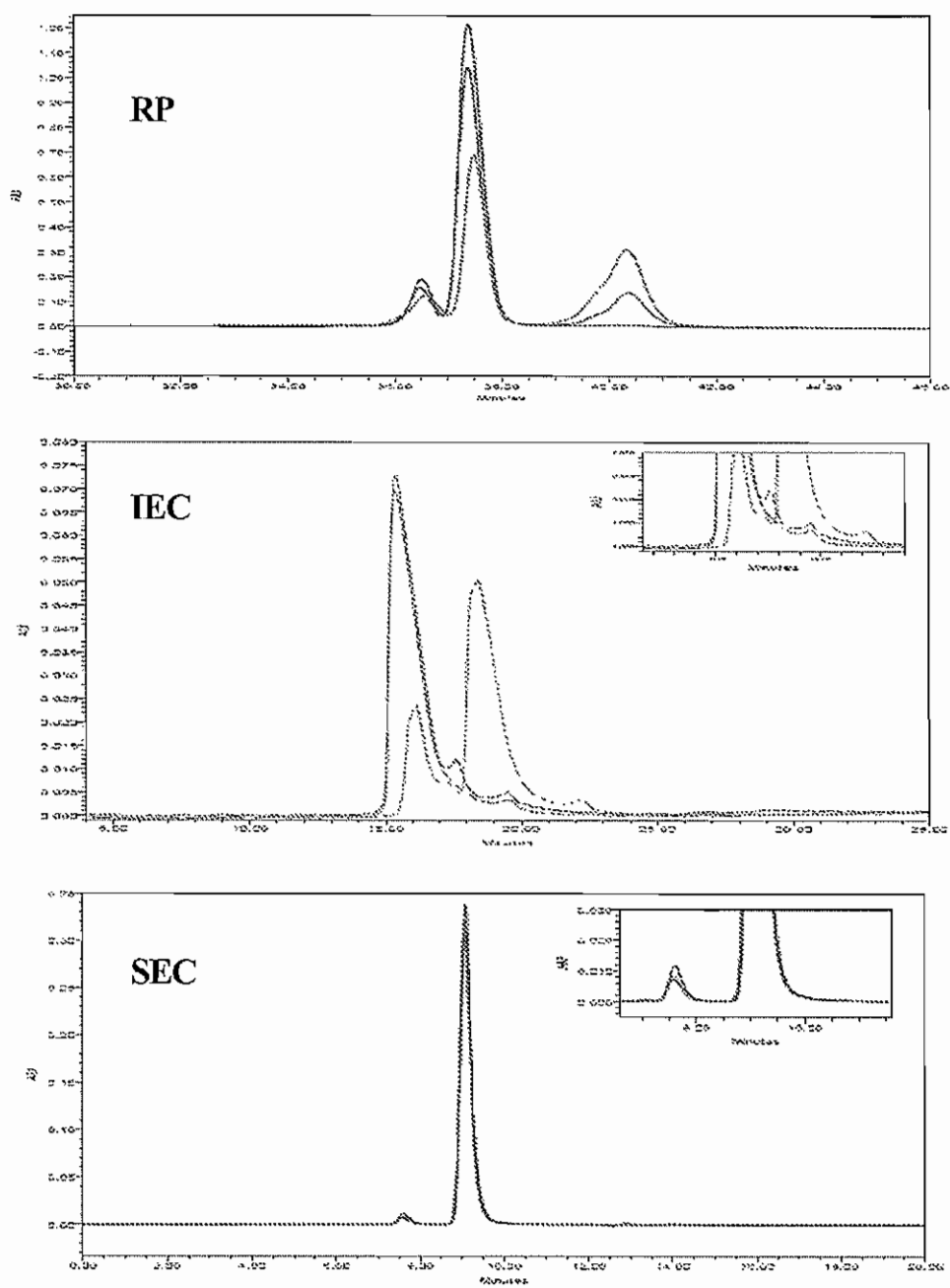
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FIGURE 20

Attribute	Analytical Method	Acceptance Criteria	Lot 3029DP
Appearance	Visual inspection	White to off-white cake	White cake
Reconstitution Time (reconstituted with WFI)	Visual inspection	Report result (X sec)	29 sec.
Appearance (post-reconstitution)	Visual inspection	Clear to opalescent, pale yellow to yellow solution, essentially free from foreign particulate matter	Clear, pale yellow, essentially free from foreign particulate matter
pH	pH Electrode	6.0 ± 0.4	6.0
Osmolality	Freezing point	300 ± 50 (X mOsm/kg)	293 mOsm/kg
Purity	SDS-PAGE: Reduced and non-reduced with Coomassie blue stain	$\geq 95\%$	Reduced: 100% Non-reduced: 100%
Purity	SDS-PAGE: Reduced and non-reduced with Silver stain	Comparable to reference standard	Comparable to reference standard
Purity	SEC-HPLC	$\geq 90.0\%$	98.8%
Purity	RP-HPLC	Report result (X.X%)	86.4%
Identity	ELISA	Identity confirmed	ND
Potency	Bioassay (NFS-60 cell proliferation)	50-150%	95.2%
Protein Concentration	Absorbance at 280 nm	50.0 ± 10.0 mg/mL	47.7 mg/mL
Sterility	USP <71>	No growth	ND
Bacterial Endotoxin	Kinetic turbidimetric (USP <85>)	≤ 1 EU/mg	ND
Subvisible Particulate Matter	USP <788> Light Obscuration	Meets USP <788>	ND
Residual Moisture	Karl-Fischer Coulometer	$\leq 3.0\%$	0.2%

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FIGURE 21



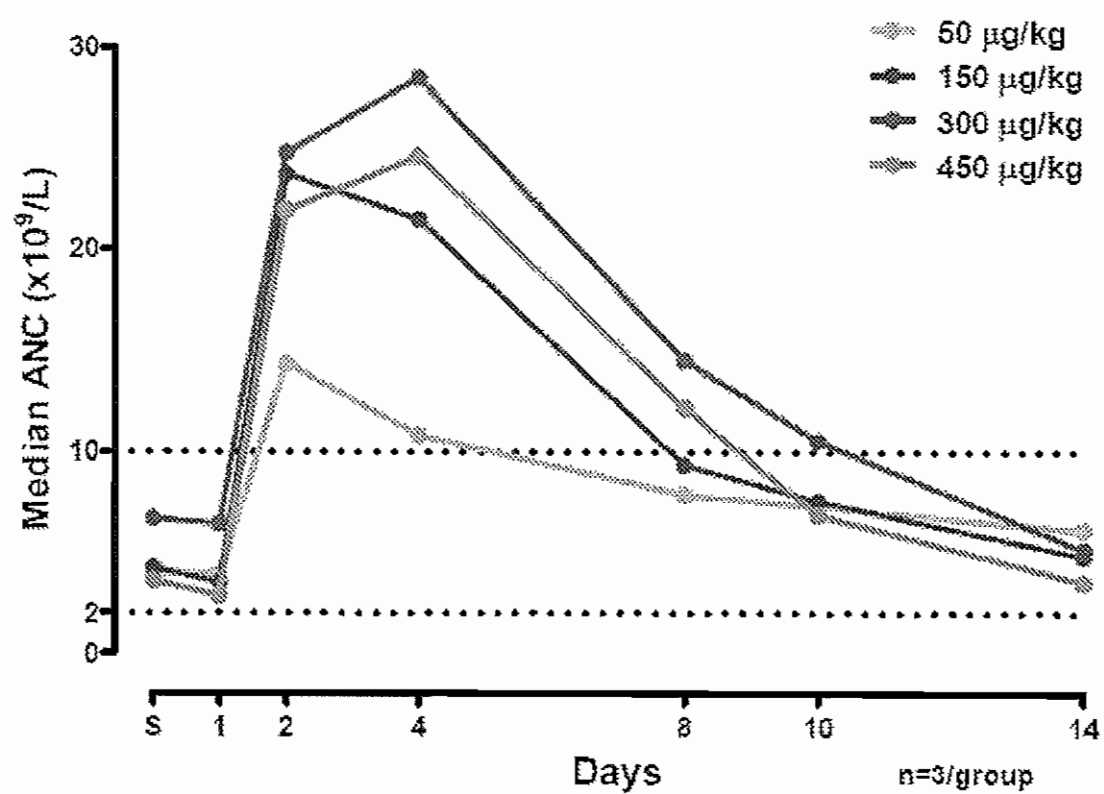
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FIGURE 22

Time (hr)	SEC%		RP%		IEC%		Relative Potency (%)	
	H ₂ O ₂	TPB	H ₂ O ₂	TPB	H ₂ O ₂	TPB	H ₂ O ₂	TPB
0	96.06	96.06	83.86	83.86	87.53	87.53	103	108
1	96.01	96.17	44.49	70.2	21.04	82.98		
3	96.22	97.14	41.19	55.72	18.78	82.69	90.2	113
5	96.31	97.18	37.08	47.52	14.85	81.89		
8	96.05	97.09	31.86	40.23	11.8	80.87	91.8	127
20	95.17	97.23	17.29	32.36	13.68	79.5		
24	95.01	97.2	14.54	31.91	12.89	77.2	72.8	112

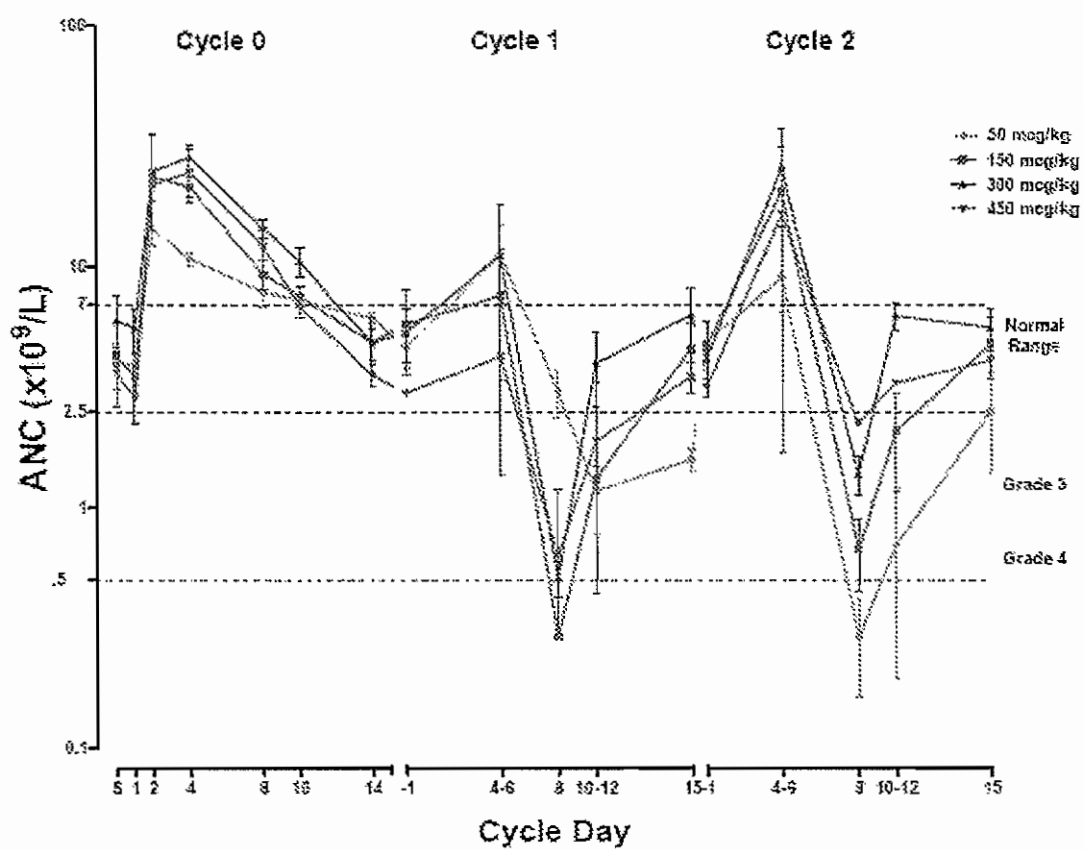
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FIGURE 23



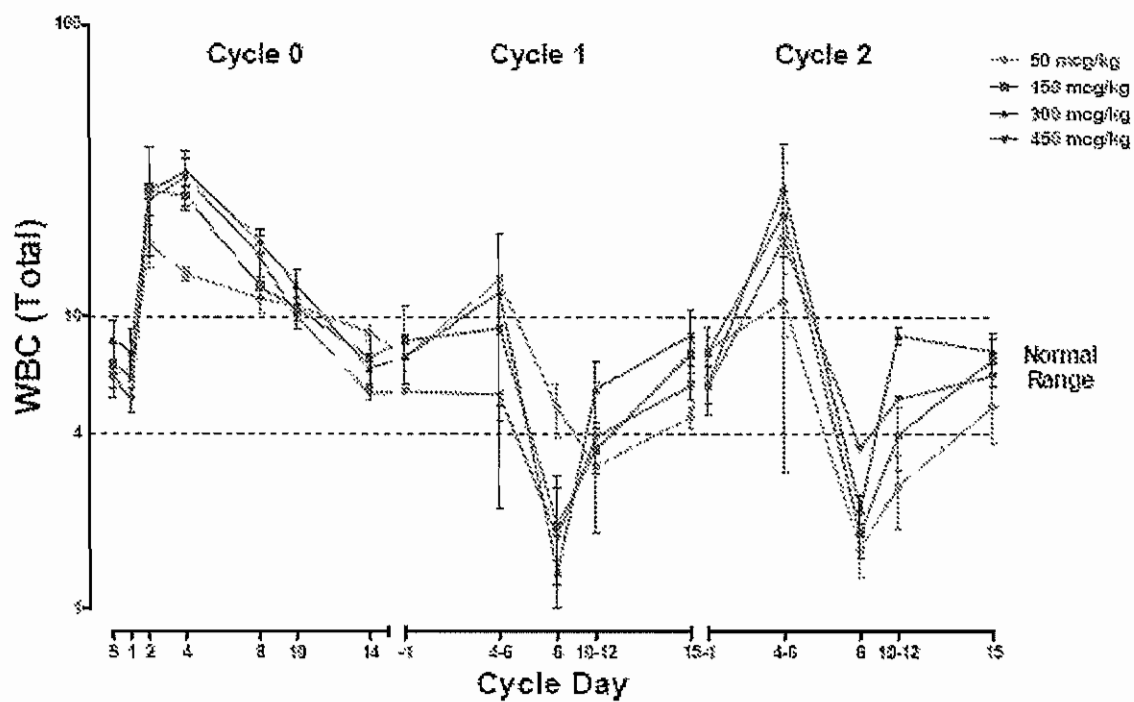
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FIGURE 24A



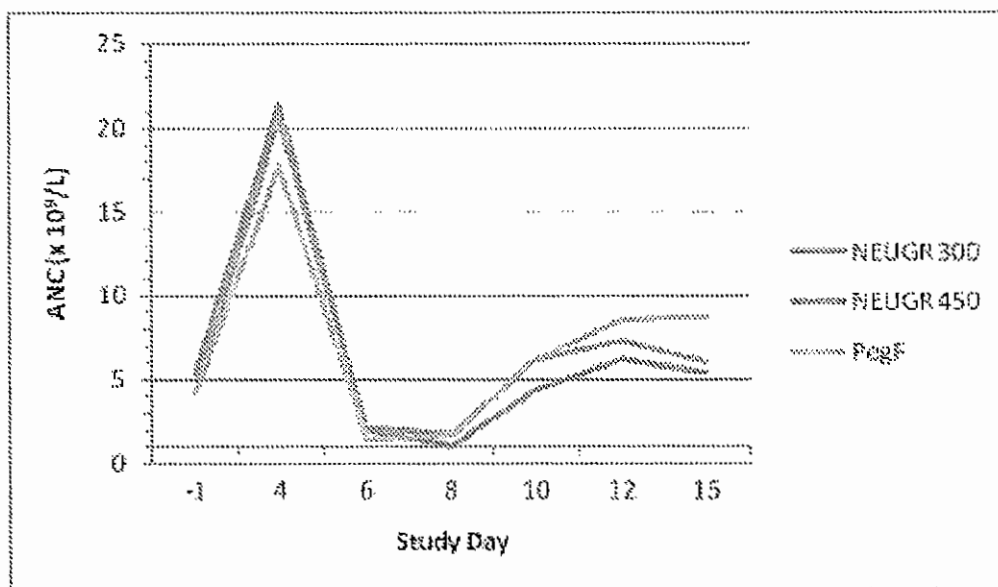
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FIGURE 24B



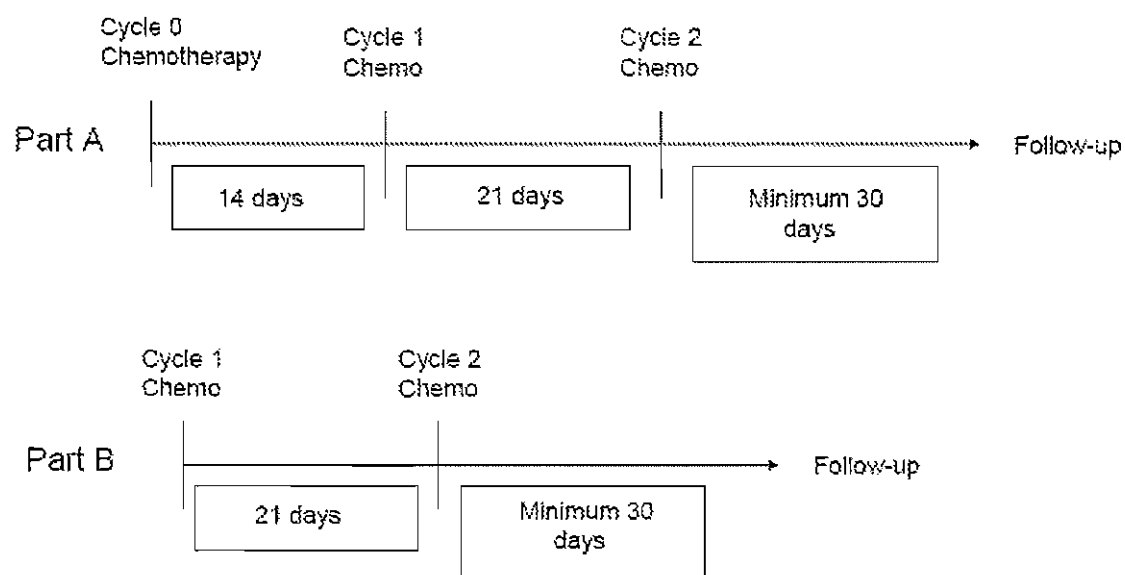
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FIGURE 25



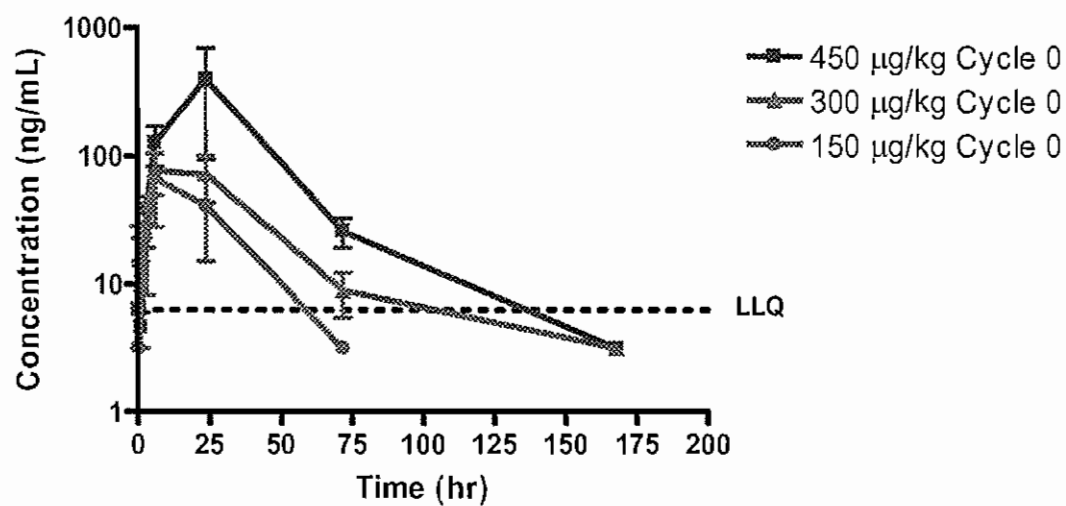
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FIGURE 26



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FIGURE 27

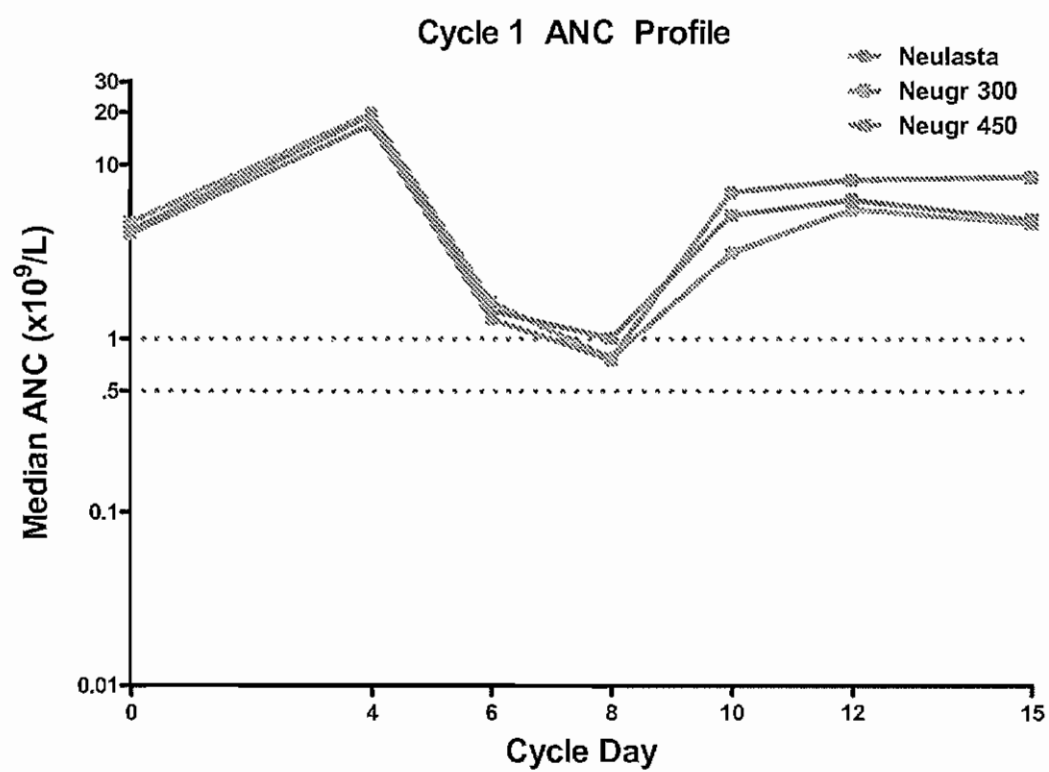


Pharmacokinetics of Neugranin in Phase 1 Human Subjects (Cycle 0)

The serum concentration of NEUG administered subcutaneously at the indicated doses was measured in subjects with breast cancer in the absence of chemotherapy.

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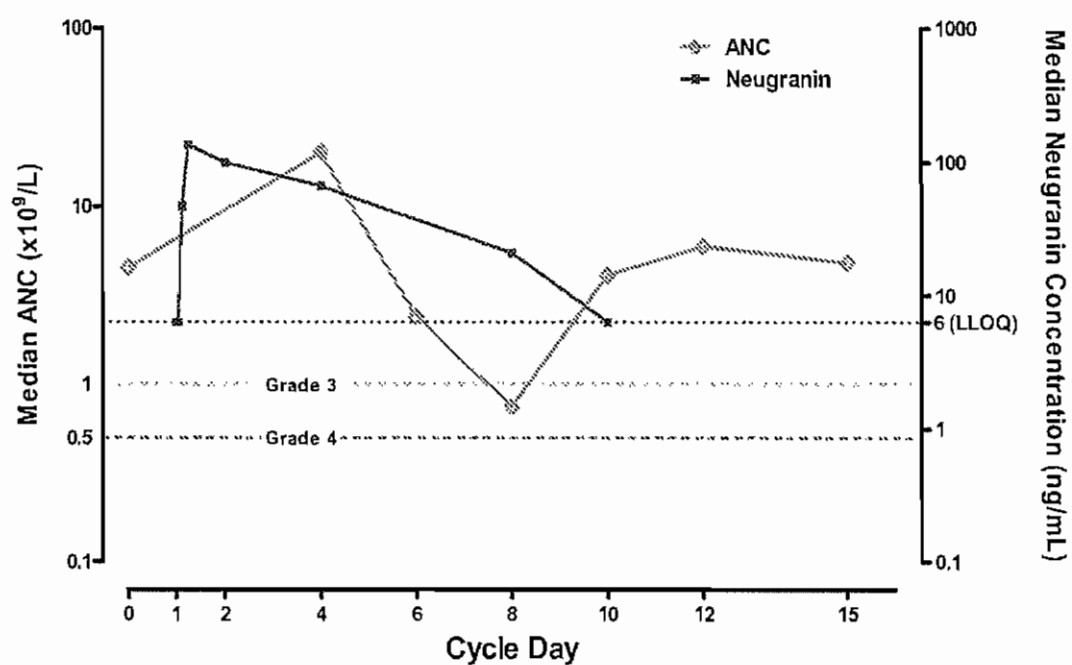
FIGURE 28



ANC for Subjects in part B, Phase I

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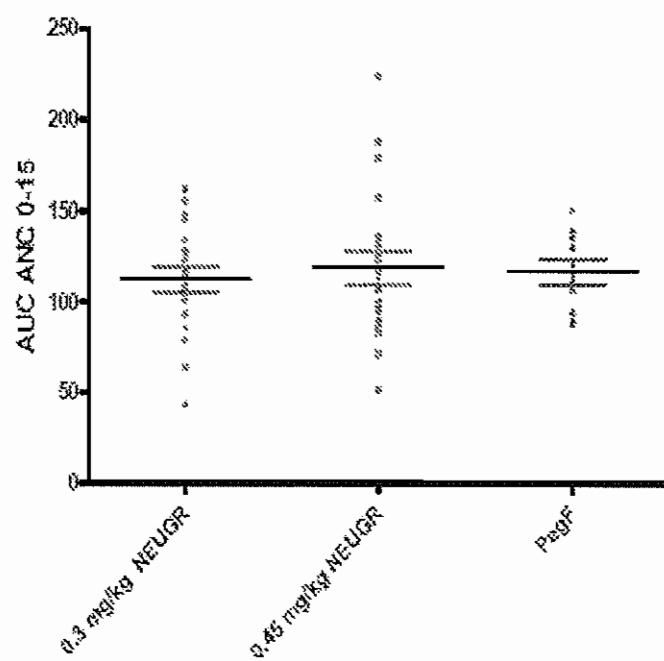
FIGURE 29



PK/PD of Neugranin in cycle 1 of chemotherapy
Phase I, Part B (450µg/kg Neugranin)

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FIGURE 30



Treatment Group	Mean	SEM	N
0.3 mg/kg NEUGR	112.3	6.7	20
0.45 mg/kg NEUGR	119.0	9.0	21
PegF	116.7	7.0	19