

FIGURES

FIG. 1:

Entry	Experiment	Isolated Yield (%)	Isolated Residue (%) ^{b)}	Morphology by XRPD	Comment
1	Distillative MTBE-removal with methanol. "Precipitation" by addition to water.	90		amorphous	According to standard procedure. Good precipitation, comparable to acetone.
2	Distillative MTBE-removal with ethanol (water free; denaturated with toluene). "Precipitation" by addition to water.	91		amorphous	According to standard procedure. Good precipitation, comparable to acetone.
3	Distillative MTBE-removal with acetonitrile. "Precipitation" by addition to water.	91		amorphous	According to standard procedure. Good precipitation, comparable to acetone.
4	Distillative MTBE-removal with acetone. Product precipitation by addition to water.	92		amorphous	Standard procedure.
5	Inverted precipitation: water addition to acetone solution.	80		amorphous	Sticky material on flask wall; scraping off and further agitation was necessary in order to obtain solid material.
6	Inverted precipitation: water addition to acetonitrile solution.	73		amorphous	Sticky material on flask wall; scraping off and further agitation was necessary in order to obtain solid material.
7	"Drum dryer-simulation": utilization of methanol		64	amorphous	60°C bath temperature; 300 --> 50 mbar, final foaming; residue scraped off the glass wall.
8	"Drum dryer-simulation": utilization of ethanol (water free; denaturated with toluene).		49	amorphous	60°C bath temperature; 250 --> 20 mbar, sudden foaming at 30 mbar; residue scraped off the glass wall.
9	"Drum dryer-simulation": utilization of acetonitrile.		49	amorphous	60°C bath temperature; 200 --> 20 mbar, final foaming; residue scraped off the glass wall.
10	"Drum dryer-simulation": utilization of DCM.		66	amorphous	60°C bath temperature; 900 --> 50 mbar, final foaming; residue scraped off the glass wall.
11	"Drum dryer-simulation": utilization of MTBE.		98	amorphous	60°C bath temperature; 800 --> 50 mbar, final foaming; residue scraped off the glass wall.

FIG. 2:

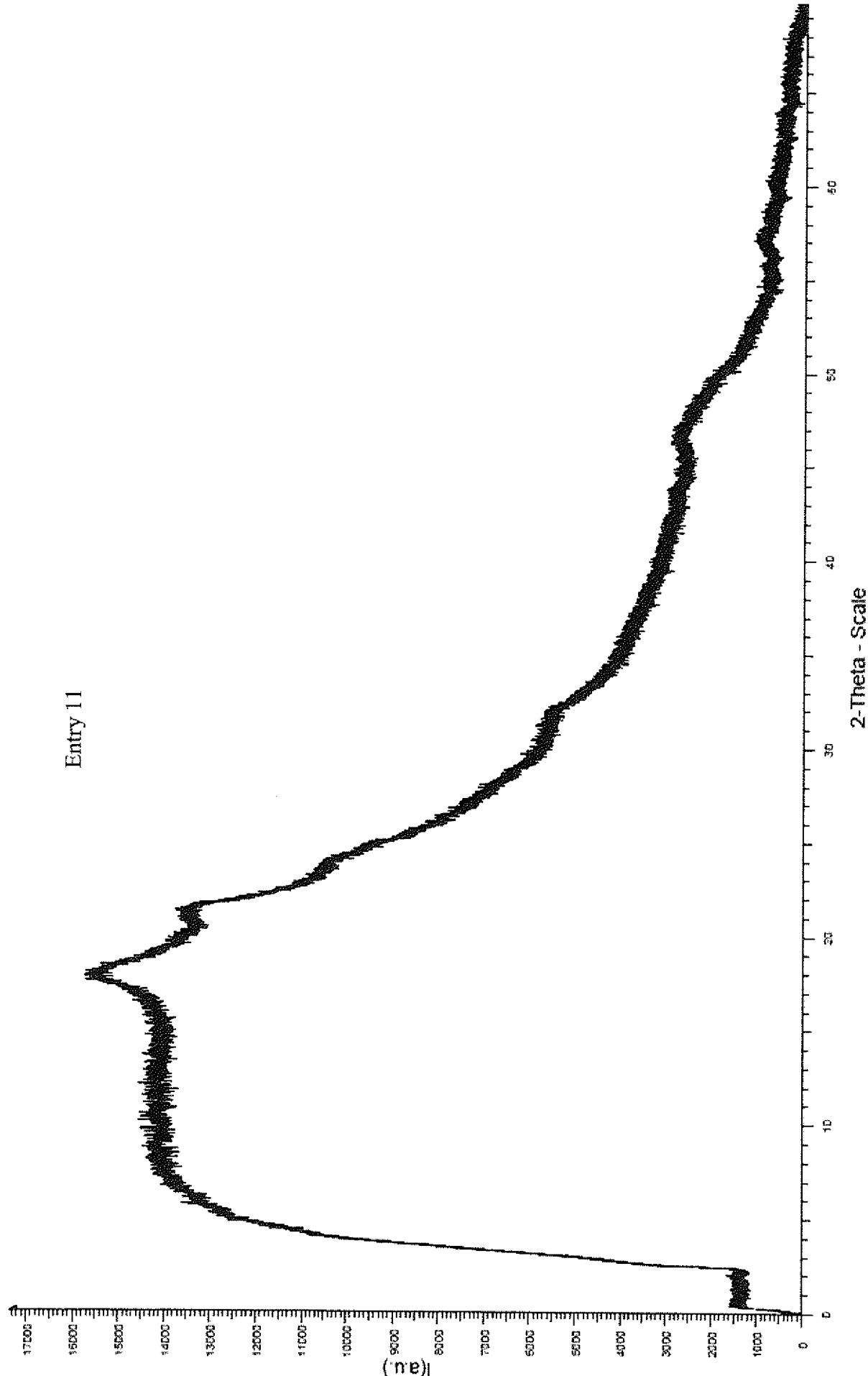
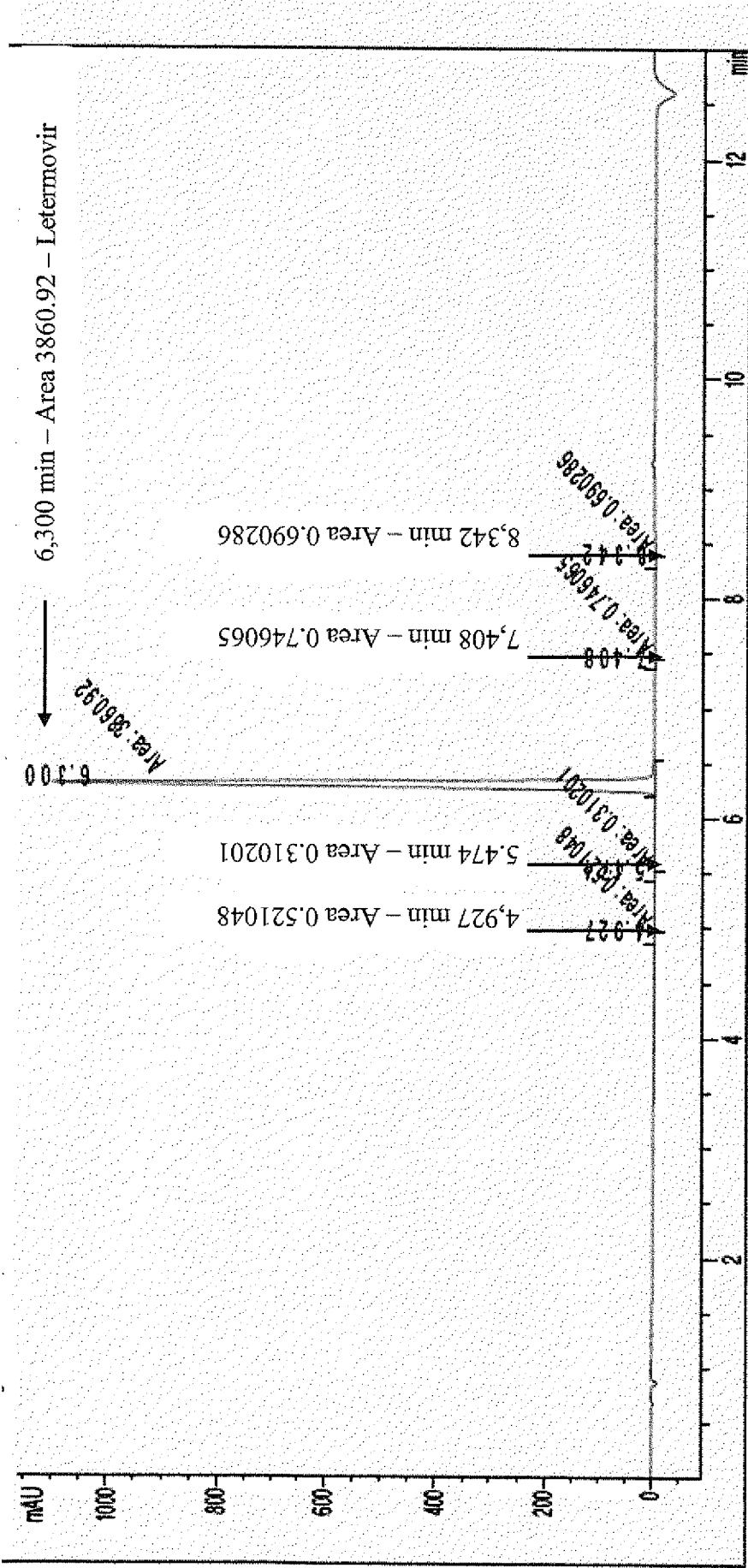


FIG. 3:

DAD1 B, Sig=260, 4 Ref=off



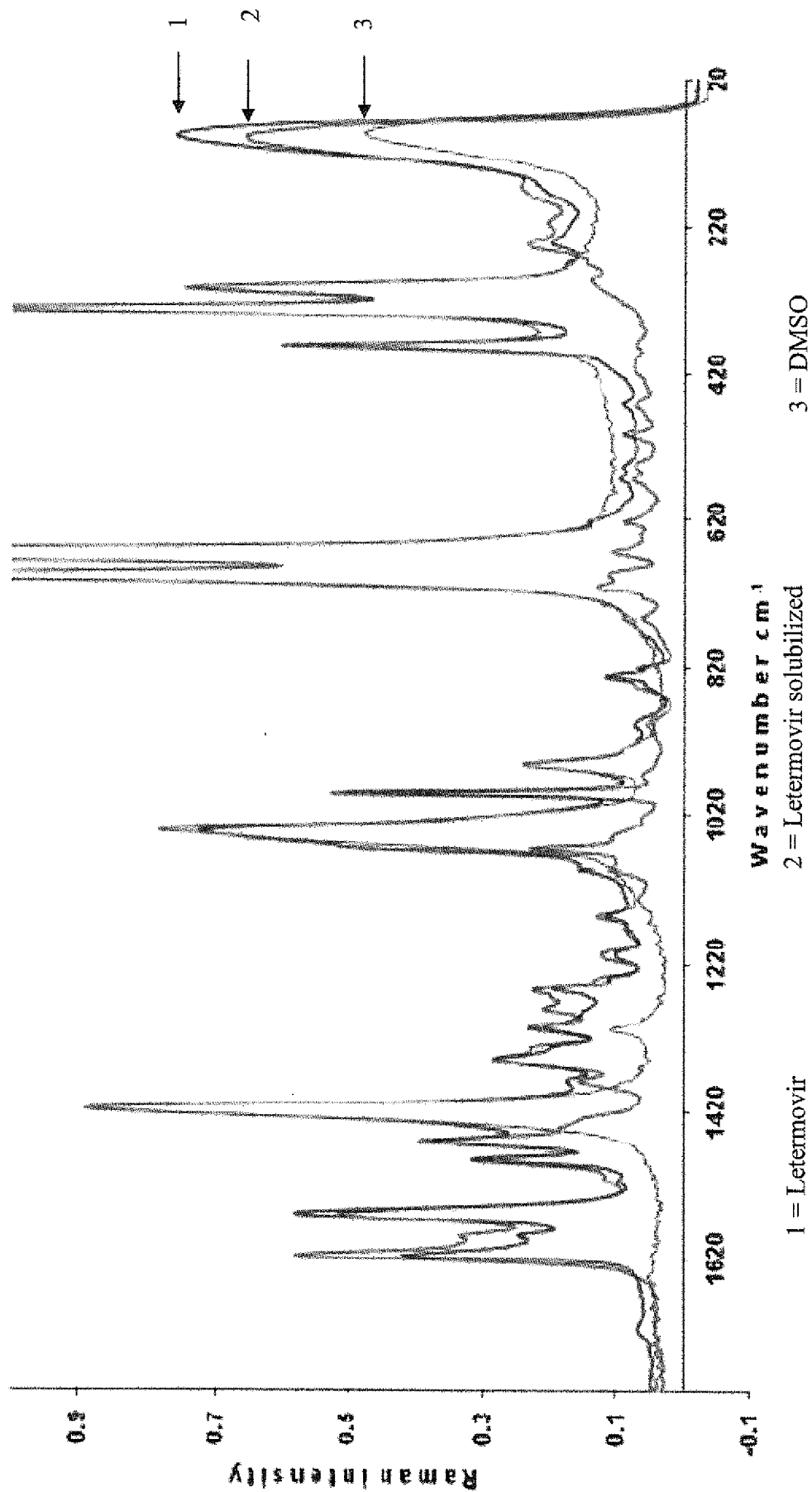


FIG. 4:

FIG. 5:

Aqueous Media	Letermovir (mg/ml)
Water	0.4
5 % Human serum albumin in water	5.5

FIG. 6:

Buffer pH	Letermovir (mg/ml)
pH 1	16.9
pH 2	3.5
pH 3	0.8
pH 4	0.4
pH 5	0.3
pH 6	0.2
pH 7	0.4
pH 8	7.7
pH 9	25.5
pH 10	51.4
pH 11	69.6
pH 12	91.3

FIG. 7a:

Pharmacokinetics of Letemovir (mean $\pm$ SD, t_{max} : median [range])	Cohort 1: 30 mg Letemovir 30 min iv infusion	Cohort 1: 30 mg Letemovir oral
n	12 ^a	12 ^b
C_{max}, ng/mL	1209 $\pm$ 235.3	363.5 $\pm$ 118.4
t_{max}, h	0.50 (0.50-0.50)	1.50 (1.00-3.00)
AUC_{0-last}, ng*h/mL	1980 $\pm$ 473.5	1544 $\pm$ 478.9
AUC_{0-∞}, ng*h/mL	2245 ^c $\pm$ 353.4 ^c	1802 ^d $\pm$ 298.8 ^d
λ_z, 1/h	0.05837 ^c $\pm$ 0.01335 ^c	0.04983 ^d $\pm$ 0.01593 ^d
t_{1/2α}, h	12.66 ^c $\pm$ 4.082 ^c	15.49 ^d $\pm$ 5.869 ^d
CL(/F), L/h	13.66 ^c $\pm$ 2.215 ^c	17.07 ^d $\pm$ 2.857 ^d
V_D (/F), L	251.5 ^c $\pm$ 92.34 ^c	382.2 ^d $\pm$ 175.2 ^d
MRT, h	5.543 ^c $\pm$ 0.6608 ^c	8.509 ^d $\pm$ 1.919 ^d

^a n=8 for AUC_{0- ∞} , λ_z , t_{1/2term}, CL, V_D and MRT^b n=9 for AUC_{0- ∞} , ng*h/mL, λ_z , t_{1/2term}, CL/F, V_D /F and MRT^c Accurate determination not possible in 4 subjects^d Accurate determination not possible in 6 subjects

FIG. 7b:

Parameter	LS means		LS means ratio, %	90% CI, % ^c	period	p-value sequence	treatment
	30 mg Letemovir, 30 min iv infusion	30 mg Letemovir, oral					
AUC_{0-last}, ng*h/mL^a	1924	1459	75.82	68.40-84.04	0.4707	0.4719	0.0006*
AUC_{0-∞}, ng*h/mL^b	2158	1771	82.07	74.53-90.37	0.2929	0.1322	0.0072*

^a n=12 for 30 min iv infusion and oral Letemovir^b n=8 for 30 min iv infusion and oral Letemovir^c 90% confidence intervals

* Statistically significant difference

FIG. 8b)

[illegible]

FIG. 8c)

[illegible]

FIG. 9a)

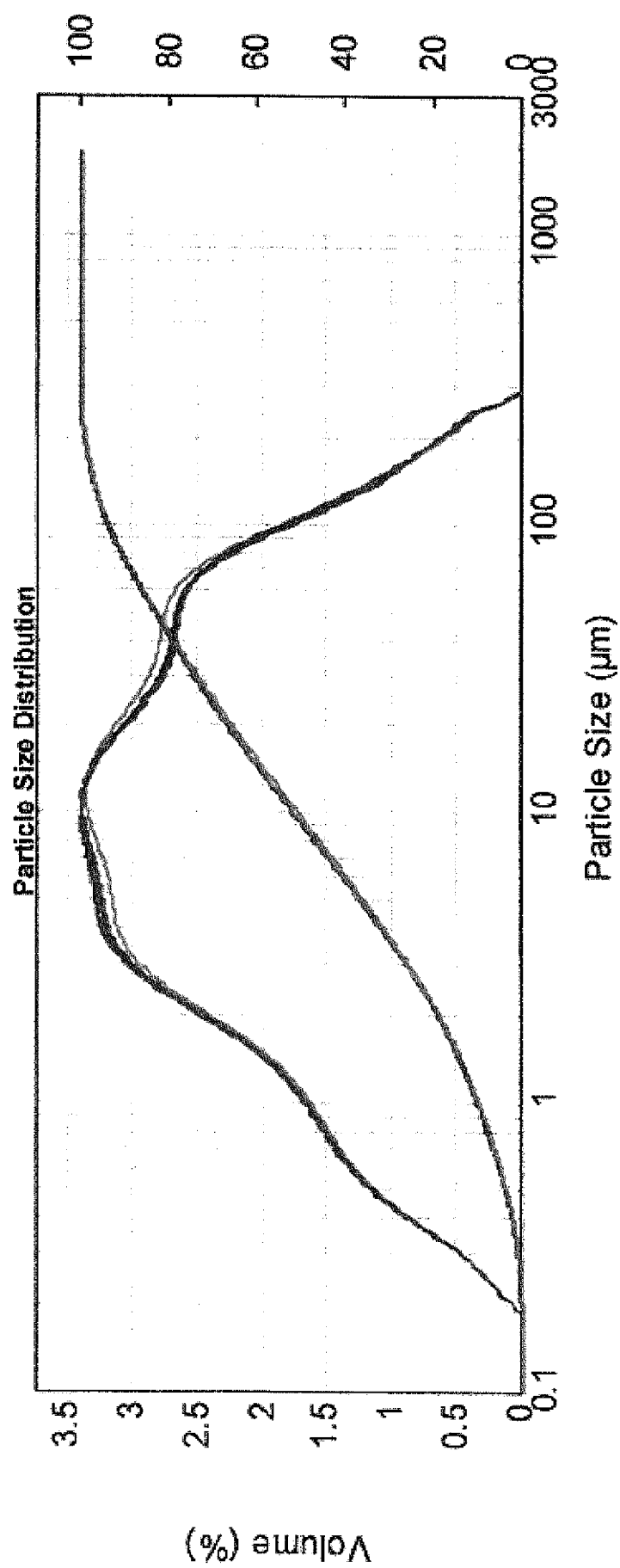


FIG. 9b)

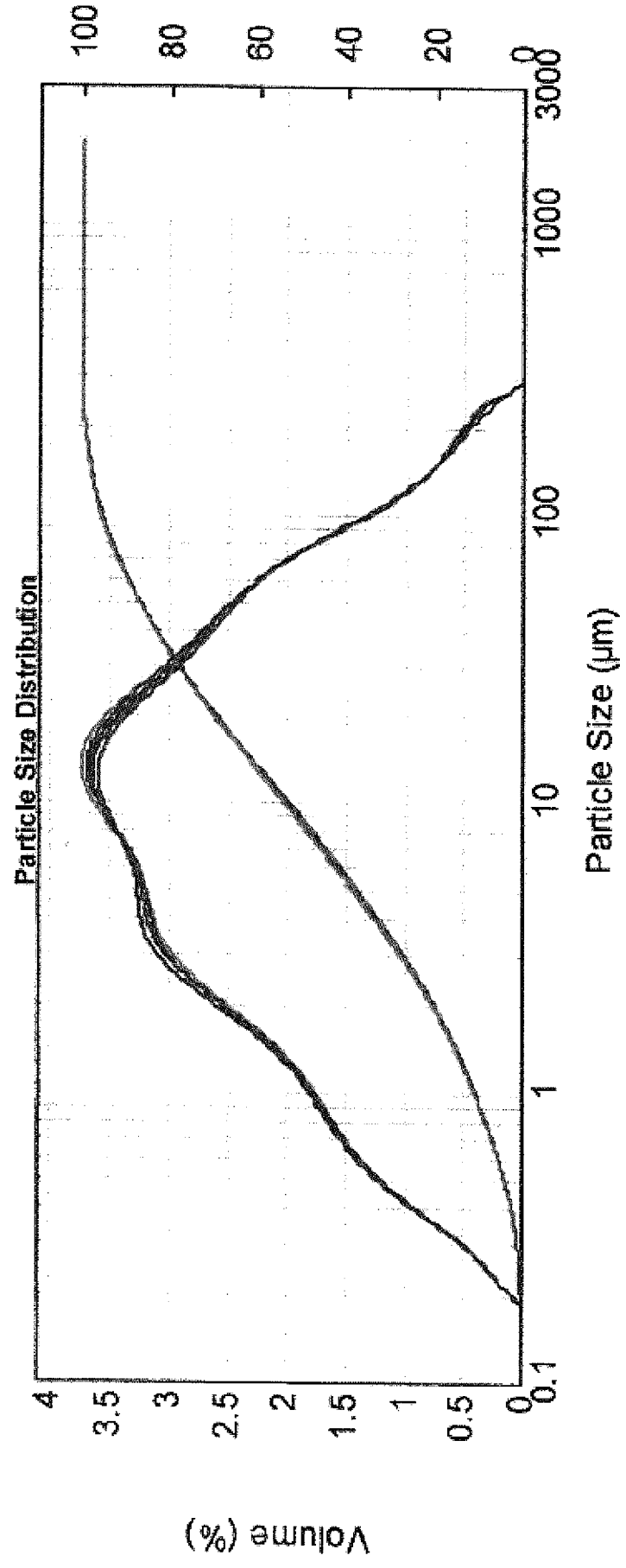


FIG. 9c)

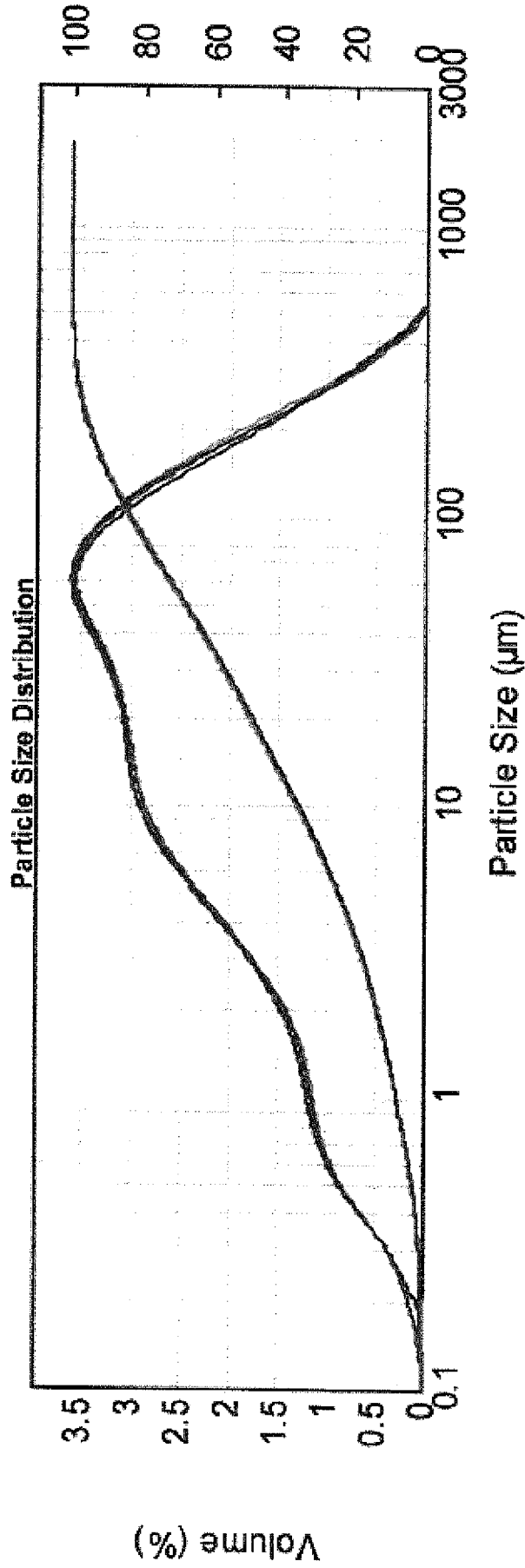


FIG. 10

Test Parameters/Specification	initial	12 months	24 months	36 months	Valuation
Appearance white to yellow or brown solid	white solid	white solid	almost white solid	white solid	no change
Purity Related substances HPLC *					
Di-p-toluoyl tartaric acid $\leq 0.10\%$	0.01%	< 0.01%	< 0.01%	< 0.05% (< 0.01%)	no change
Quinazolyldipiperazine $\leq 0.10\%$	< 0.01%	0.01%	0.01%	< 0.05% (0.01%)	no change
Quinazolyldipiperazine $\leq 0.10\%$	0.01%	0.01%	< 0.02%	< 0.05% (0.02%)	no change
each unspecified impurity $\leq 0.10\%$	RRT %	RRT %	RRT %	RRT %	
	< 0.01%				
RRT – relative retention time reorting level: 0.01% (unit 24 month) / 0.05%		1.10 1.65	0.86 1.09 1.53	0.01 0.01 0.01	0.84 1.09 (0.01) (0.01)
		0.01 0.01			no change
Total $\leq 1.5\%$	0.02%	0.04%	0.06%	< 0.05%	no change
Purity Enantiomeric excess (HPLC) EE $\geq 98.8\%$	99.9%	99.9%	99.9%	99.9%	no change
Purity Water content	1.05%	0.78%	0.83%	0.77%	no change
Purity Appearance of the solution $\leq BY_5$ or Y_5 or B_5	< BY_5 , < Y_5 , < B_5	next > BY_7 , next Y_7 , < B_9	next BY_7 , next Y_7 , between B_5 and B_9	< BY_5 , next B_9	
Assay HPLC 97.0% - 102.0%, calculated to anhydrous and solvent free substance	99.5%	99.2%	98.6%	98.2%	no change
Microbiological purity	conforms	not tested	not tested	not tested	--

FIG. 11

Test Parameters	initial	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	Valuation
Appearance white to yellow or brown solid	almost white solid	white solid	almost white solid	almost white solid	almost white solid	white solid	white solid	white solid	white solid	no change
Purity Related substances HPLC *										
Di-p-toluoyl tartaric acid	0.04%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	0.01%	< 0.01%	< 0.01%	
Quinazolyloperazine	0.02%	0.03%	0.03%	< 0.01%	0.02%	0.02%	0.02%	0.03%	0.03%	
Quinazolyloperazine	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	
each unspecified impurity										
≤ 0.10%										
rel. RT										
0.52	< 0.01%	< 0.01%	< 0.01%	0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	
0.84	< 0.01%	0.02%	0.02%	0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	0.01%	
1.10	< 0.01%	0.03%	0.03%	0.03%	0.02%	< 0.01%	< 0.01%	< 0.01%	0.01%	
1.13	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	0.03%	0.02%	
1.21	< 0.01%	< 0.01%	< 0.01%	< 0.01%	< 0.01%	0.03%	< 0.01%	0.03%	0.02%	
1.56	< 0.01%	0.01%	0.01%	< 0.01%	< 0.01%	0.01%	< 0.01%	< 0.01%	< 0.01%	
1.63	< 0.01%	< 0.01%	0.01%	< 0.01%	< 0.01%	< 0.01%	0.01%	< 0.01%	0.02%	
Total	0.06%	0.09%	0.10%	0.08%	0.04%	0.06%	0.04%	0.10%	0.13%	no significant changes
Enantiomeric excess (HPLC) EE ≥ 98.8%	99.9%	99.9%	99.9%	99.8%	99.8%	99.8%	99.8%	99.8%	99.8%	no change
Water content	0.92%	0.63%	0.62%	0.51%	0.73%	0.36%	0.48%	0.59%	0.51%	slight decrease
Appearance of the solution ≤ BY ₅ or Y ₅ or B ₅	< BY ₅ , < Y ₅ , < B ₅	= BY ₇ , < Y ₇ , < B ₇	< BY ₇ , next Y ₇ , = B ₇	< BY ₇ , next Y ₇ , < B ₇	< BY ₅ , next Y ₇ , = B ₇	< BY ₇ , next Y ₇ , = B ₇	< BY ₇ , next Y ₇ , = B ₇	< BY ₇ , next Y ₇ , = B ₇	< BY ₇ , next Y ₇ , = B ₇	no change
Assay HPLC 97.0% - 102.0% water and solvent-free substance	100.7%	100.8%	99.8%	101.2%	99.6%	99.8%	100.4%	98.4%	101.1%	no change

* reporting level: 0.01%

