

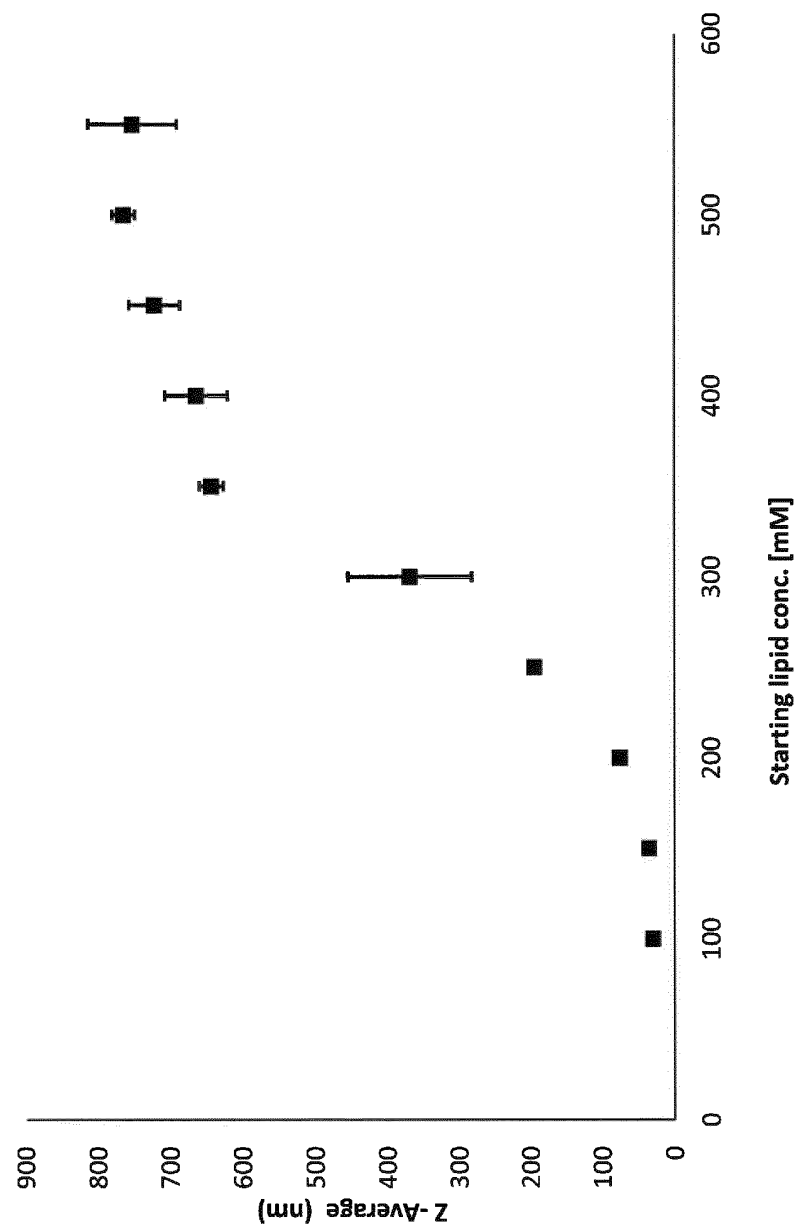


Figure 1

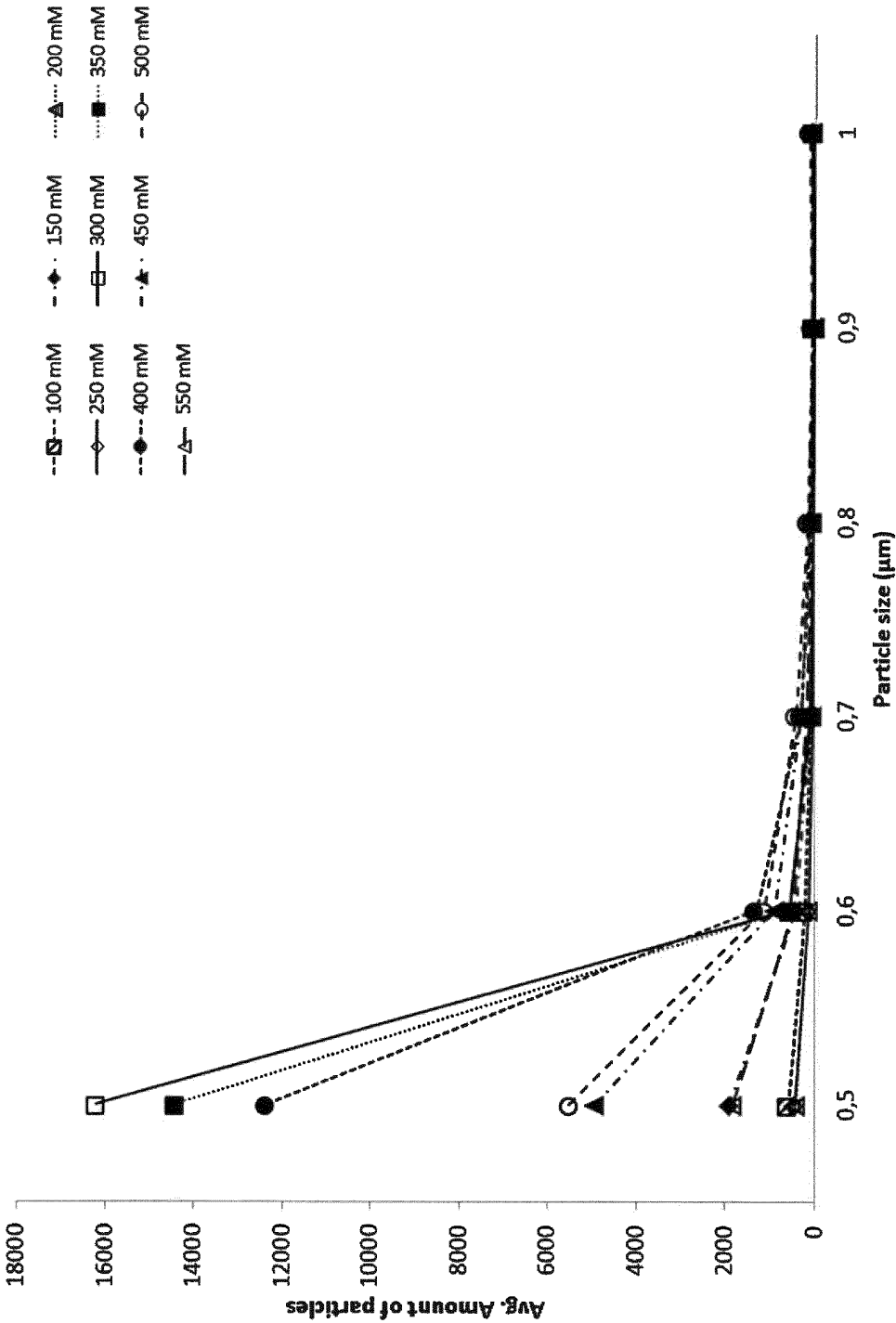


Figure 2

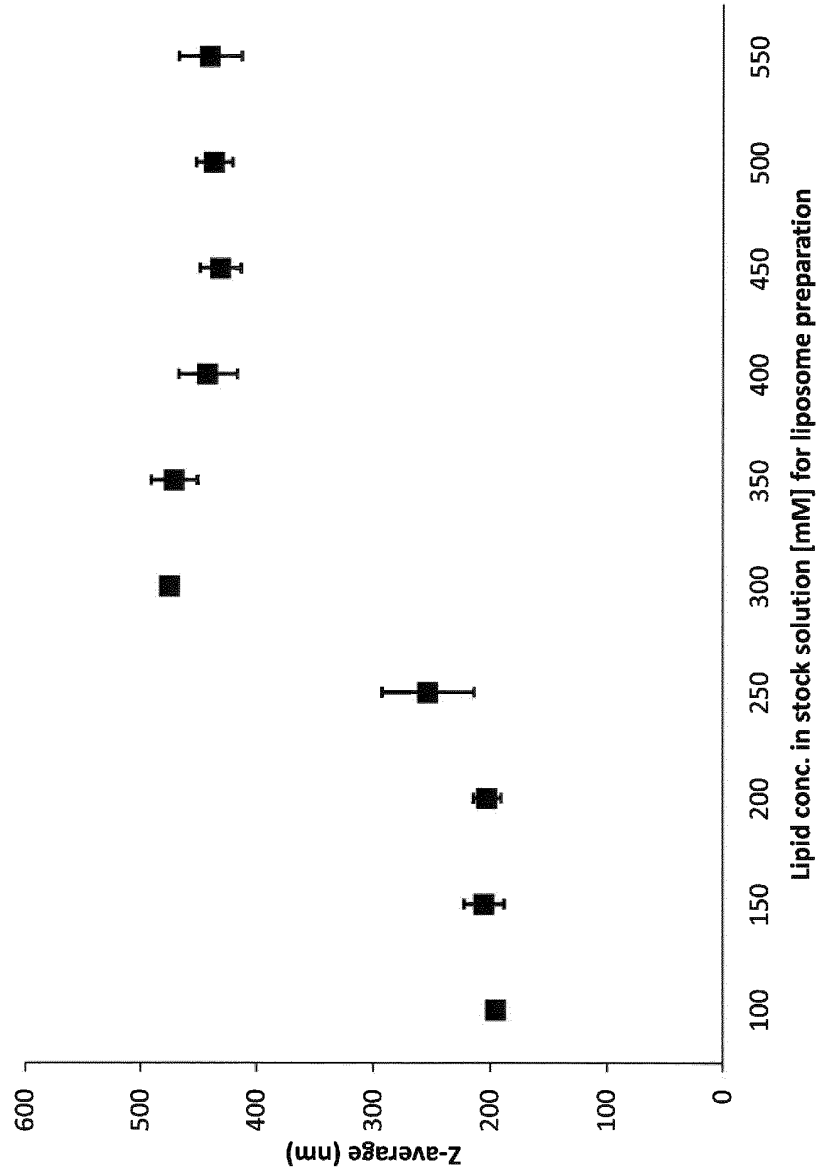


Figure 3

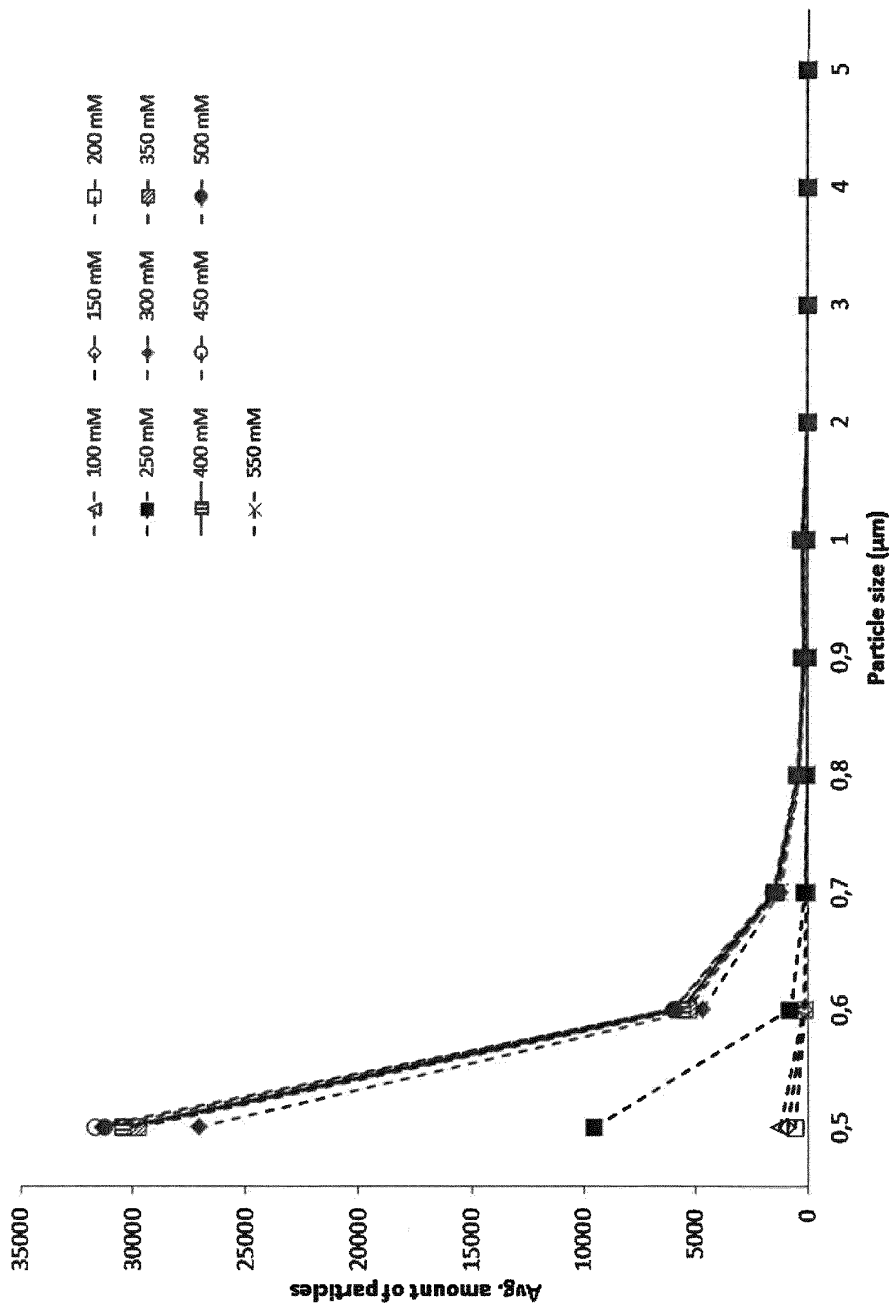


Figure 4

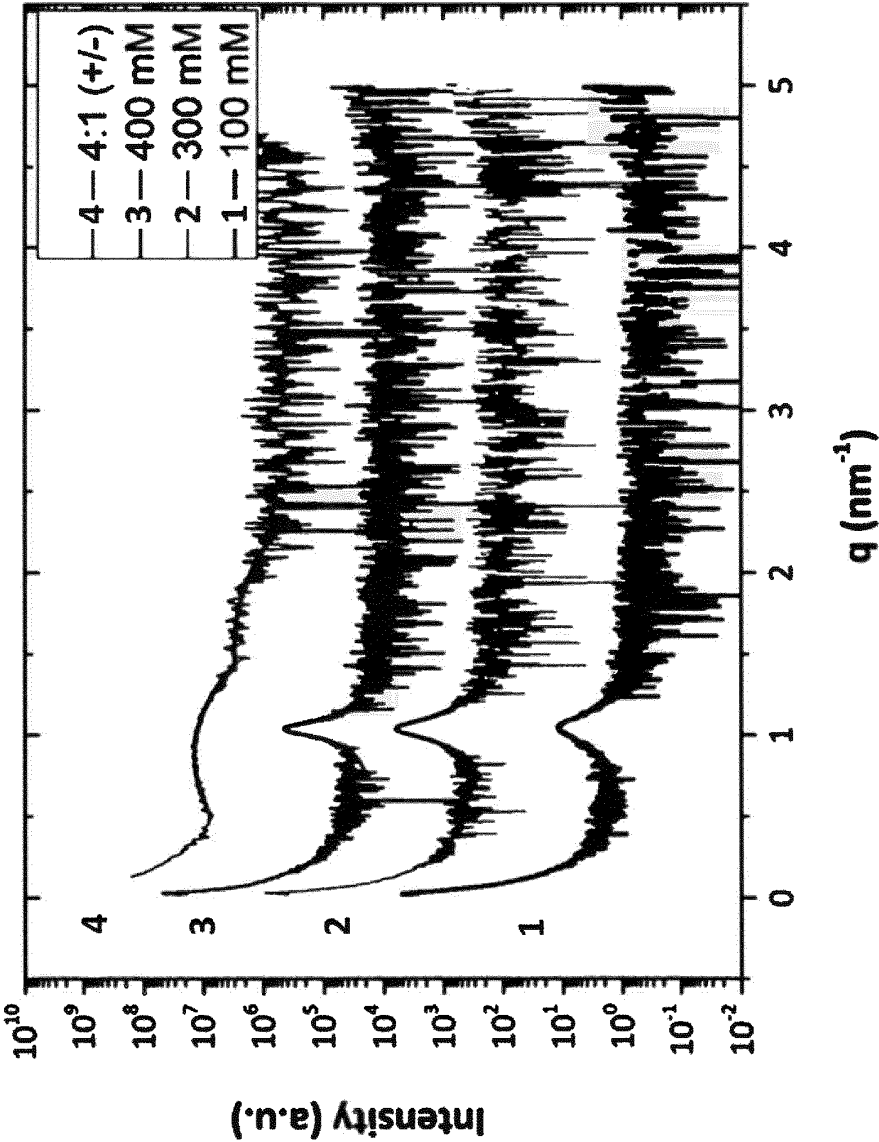


Figure 5

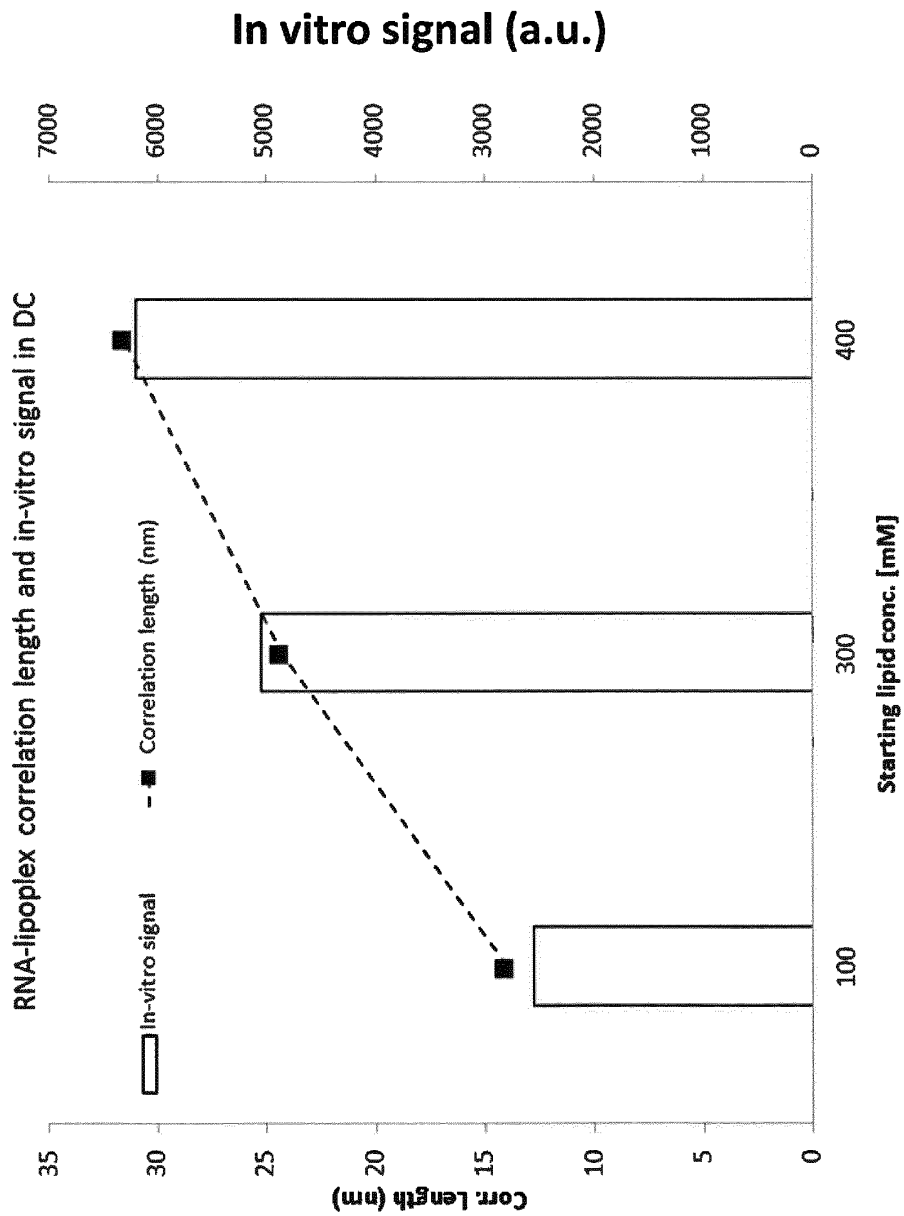


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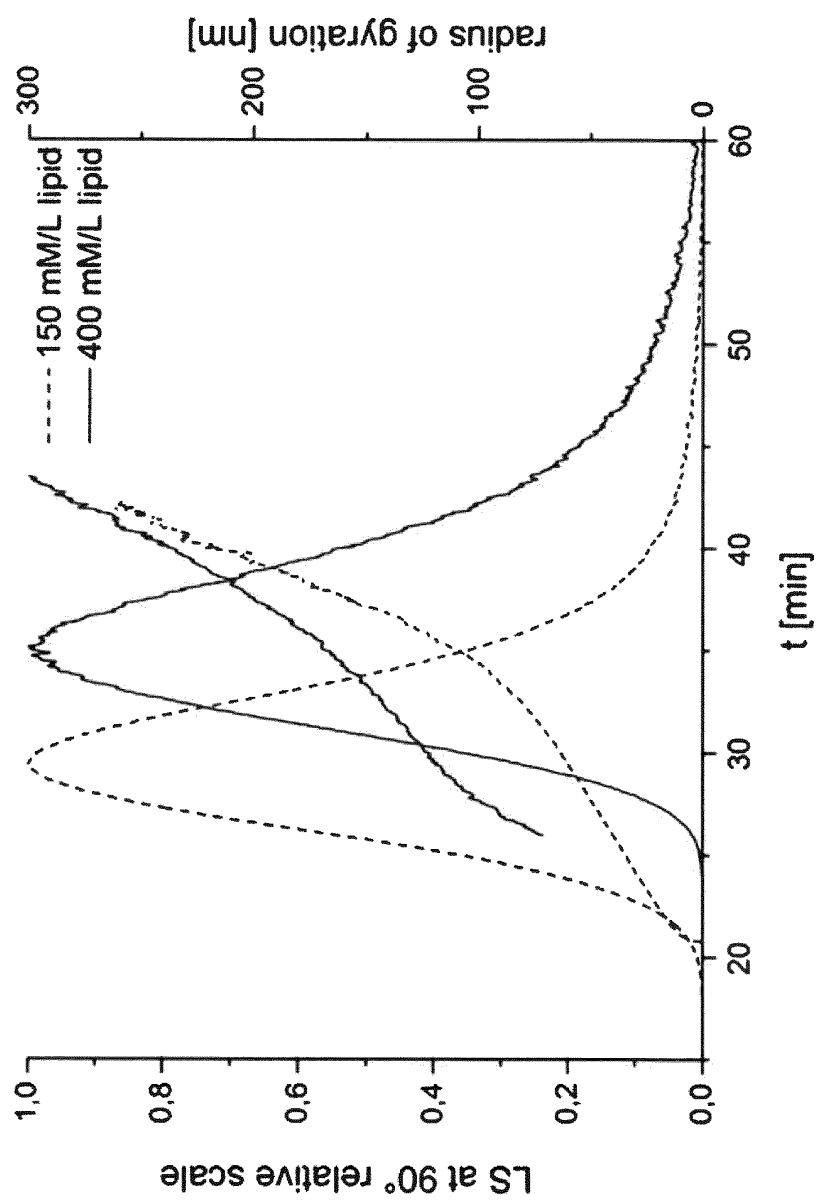


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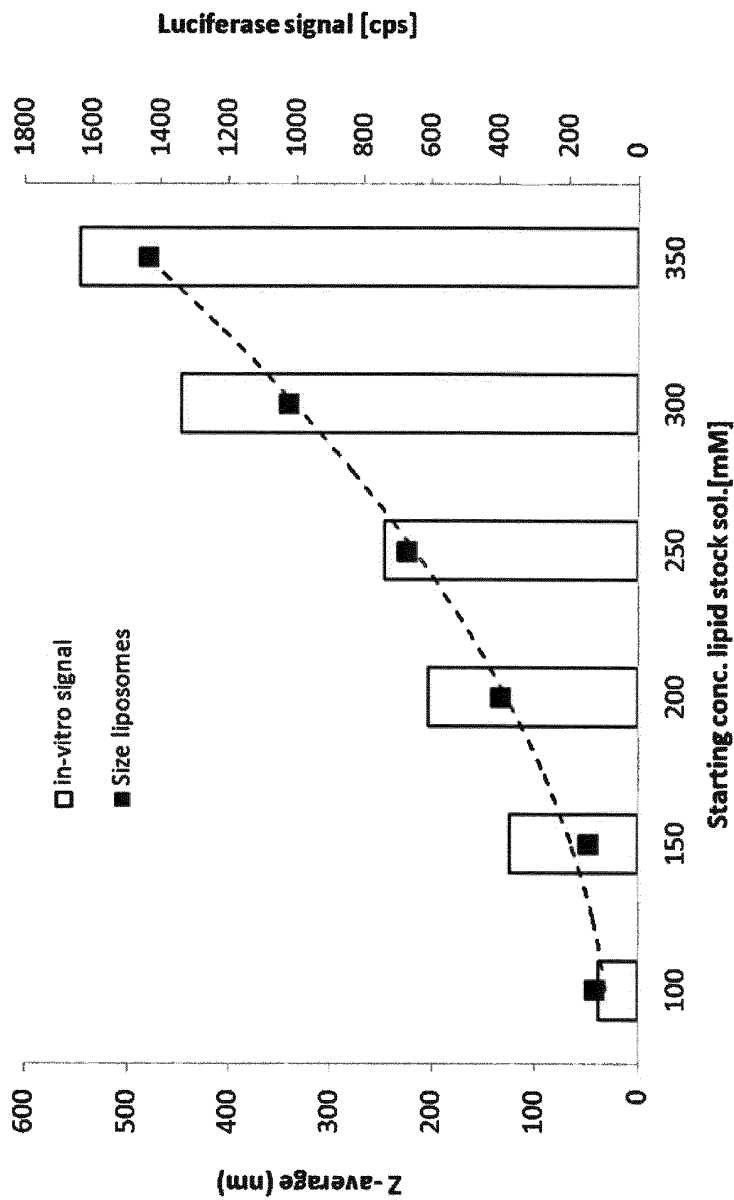


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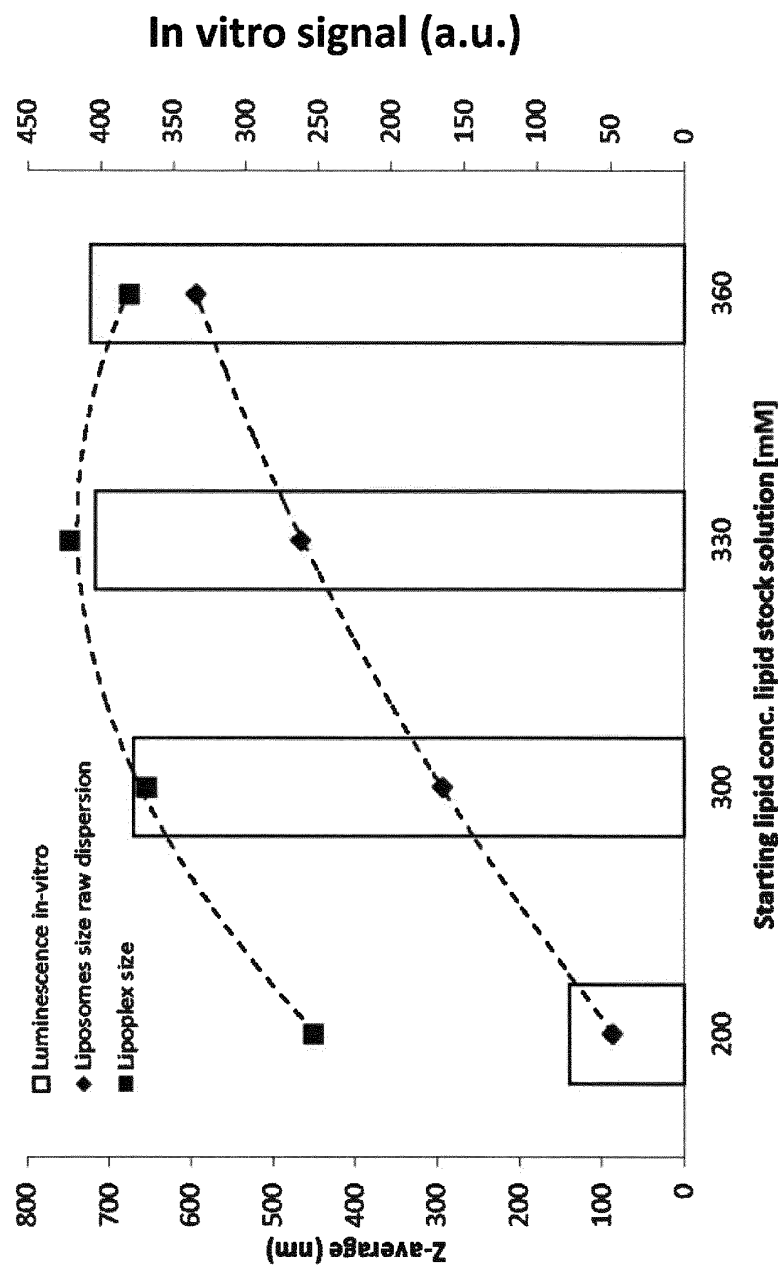


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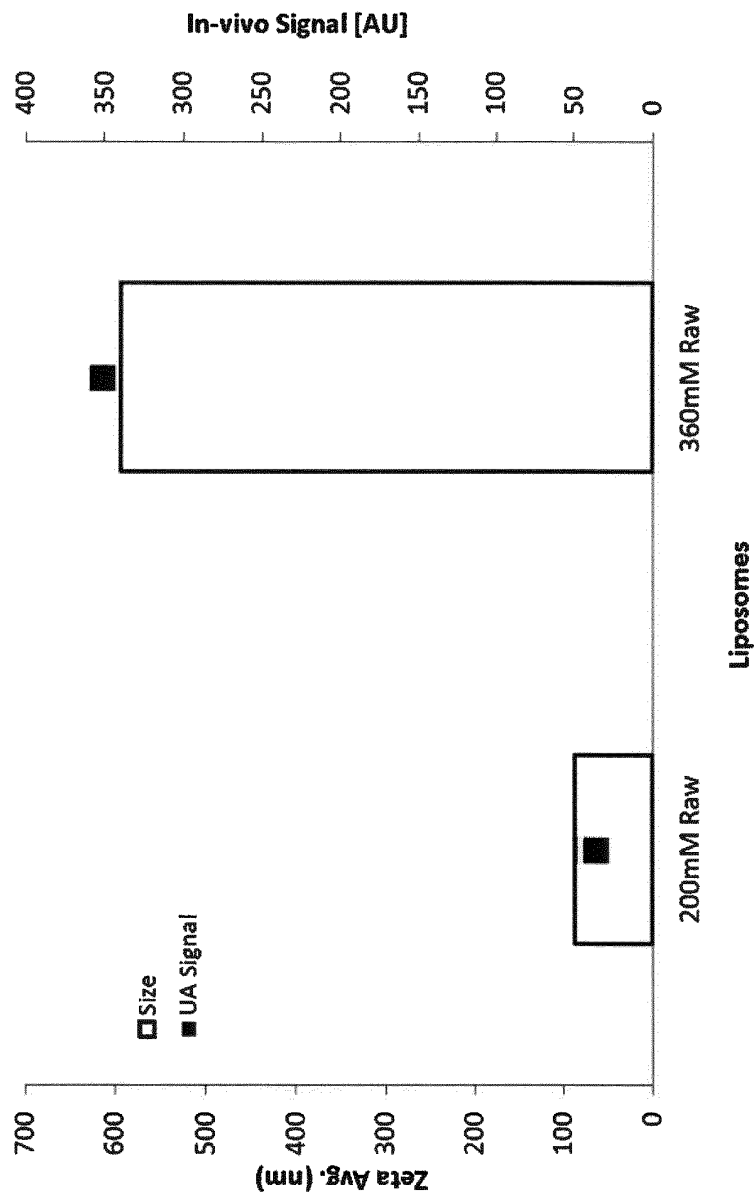


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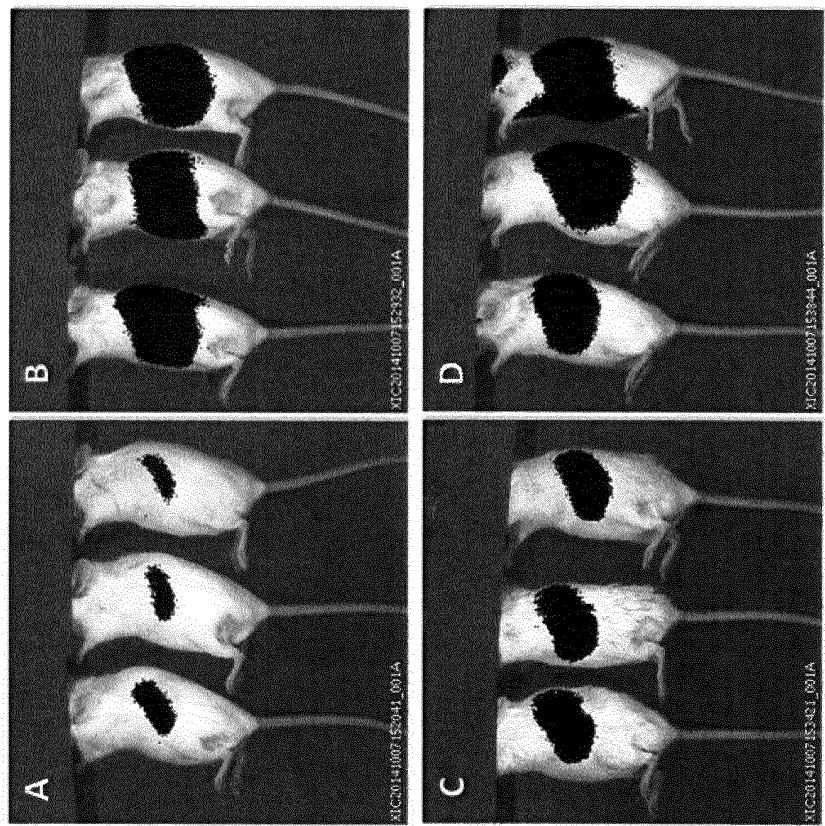


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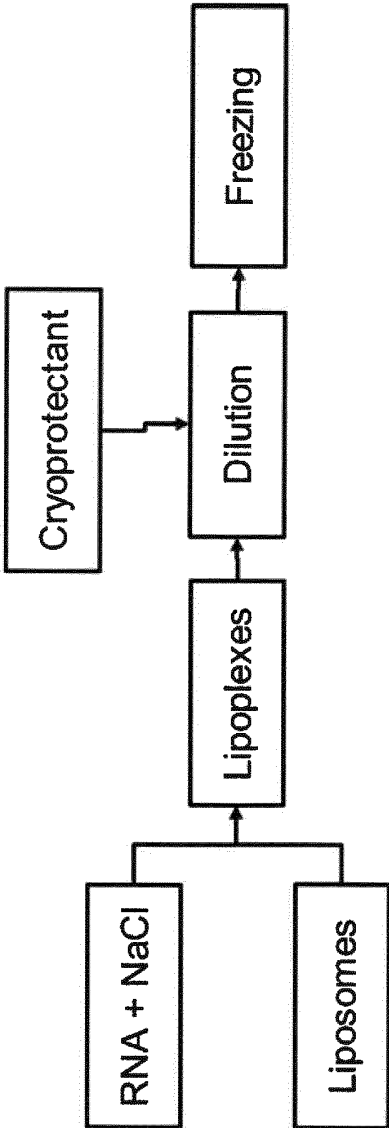


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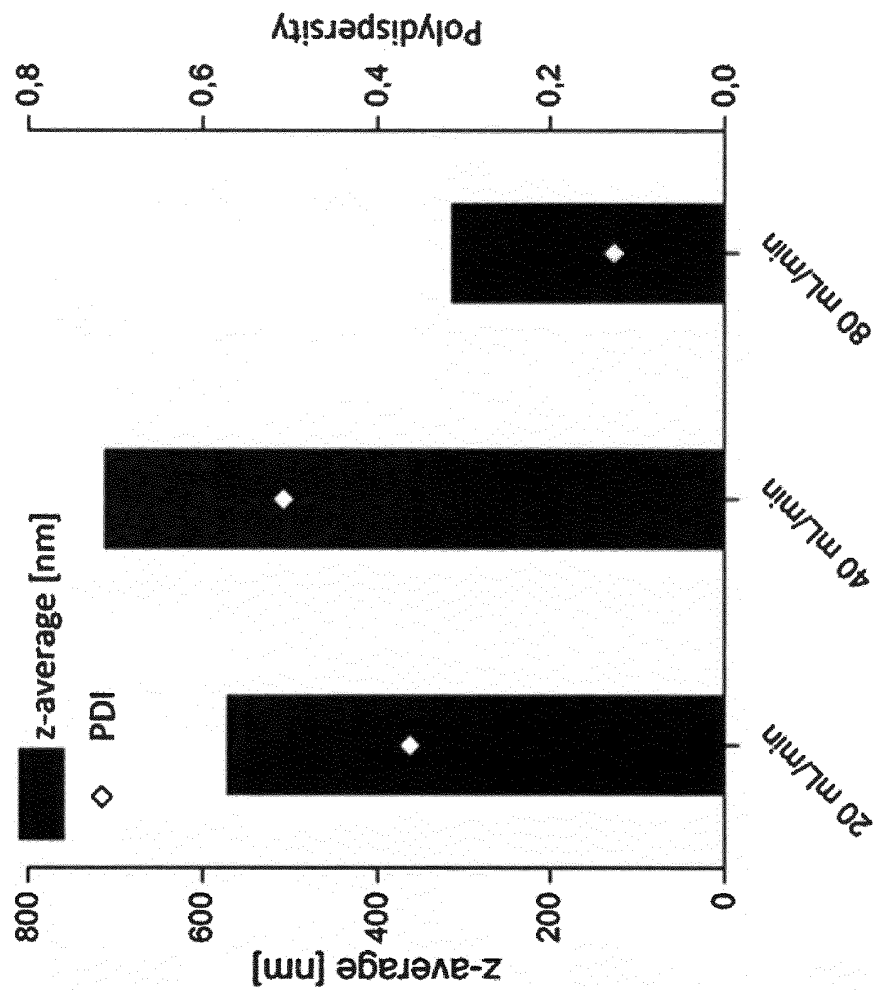


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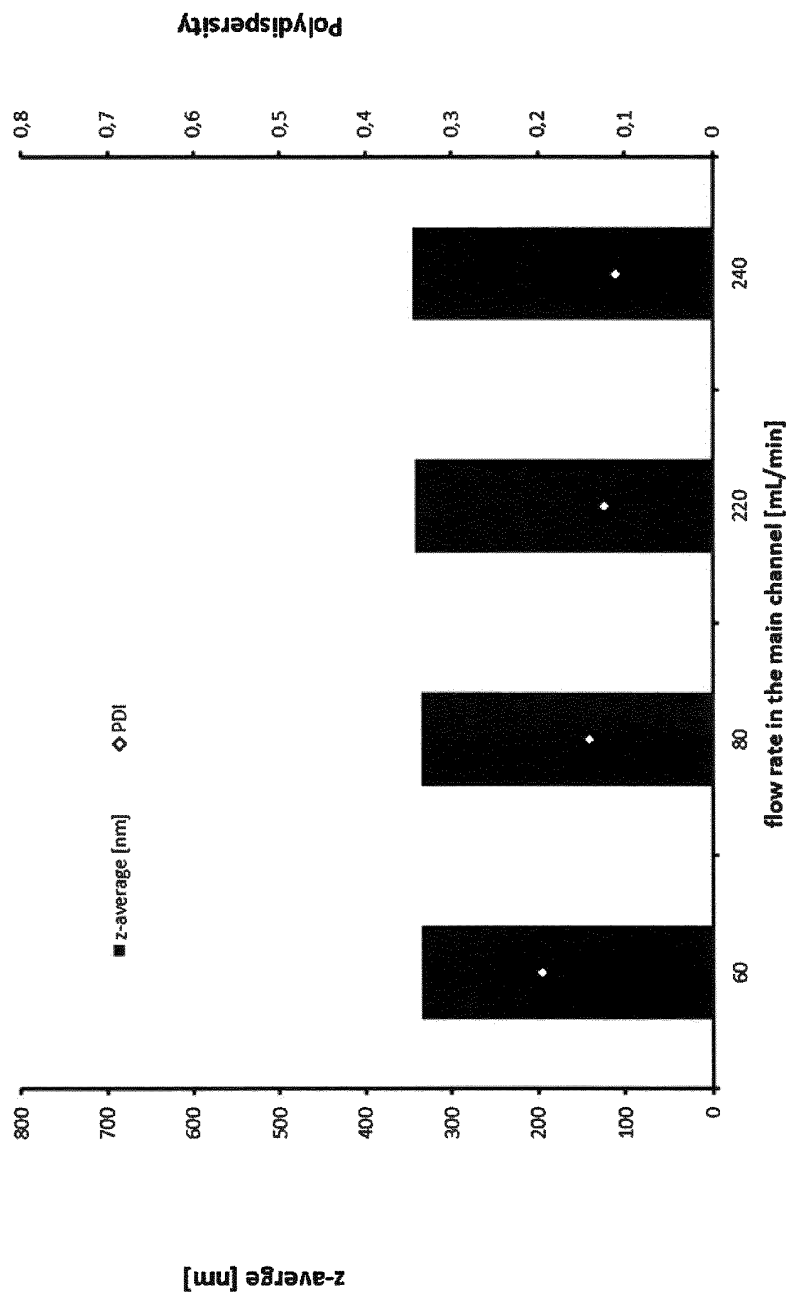


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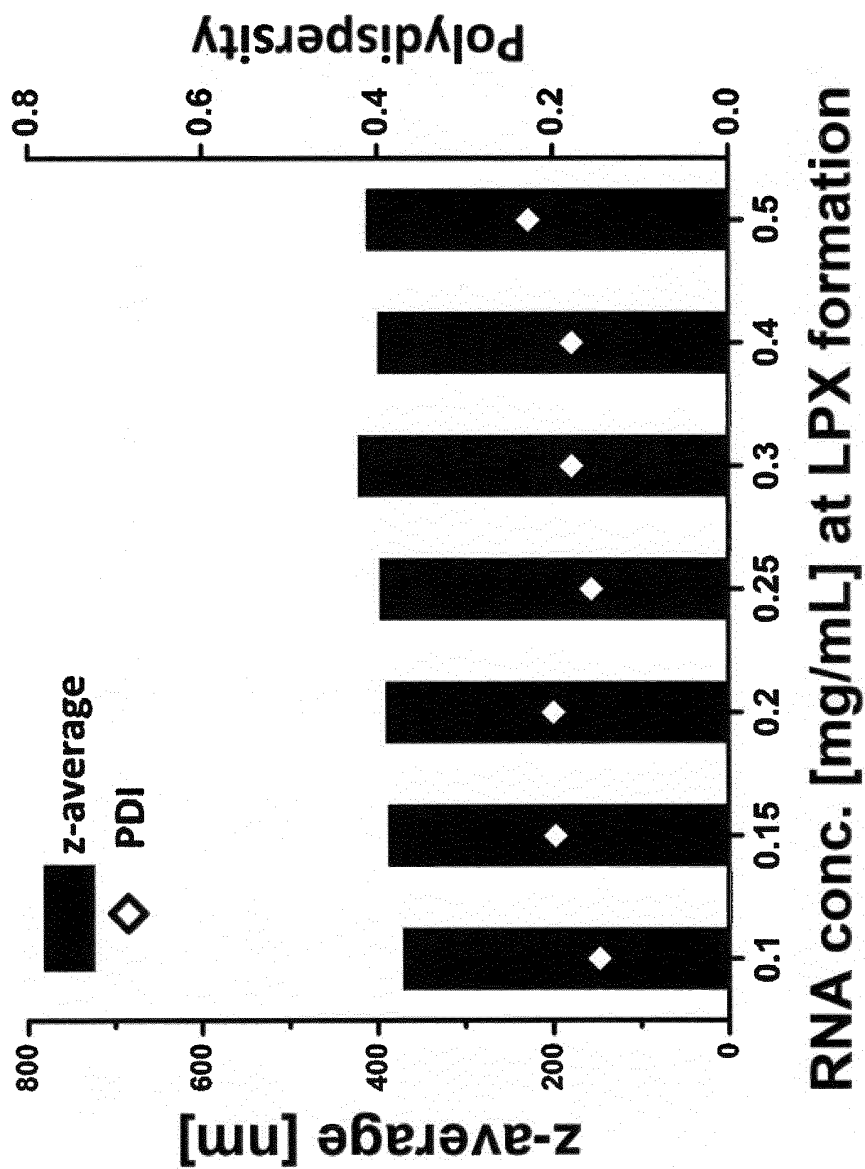


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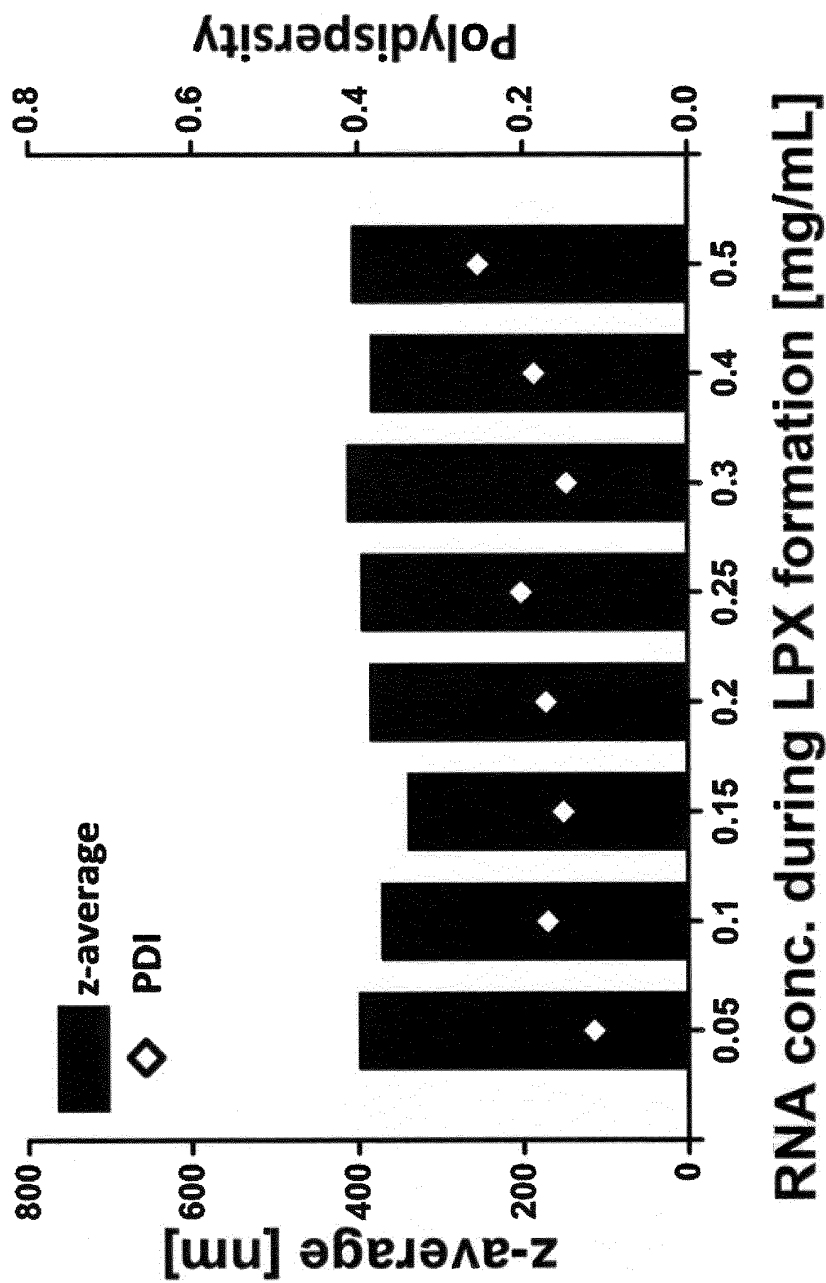


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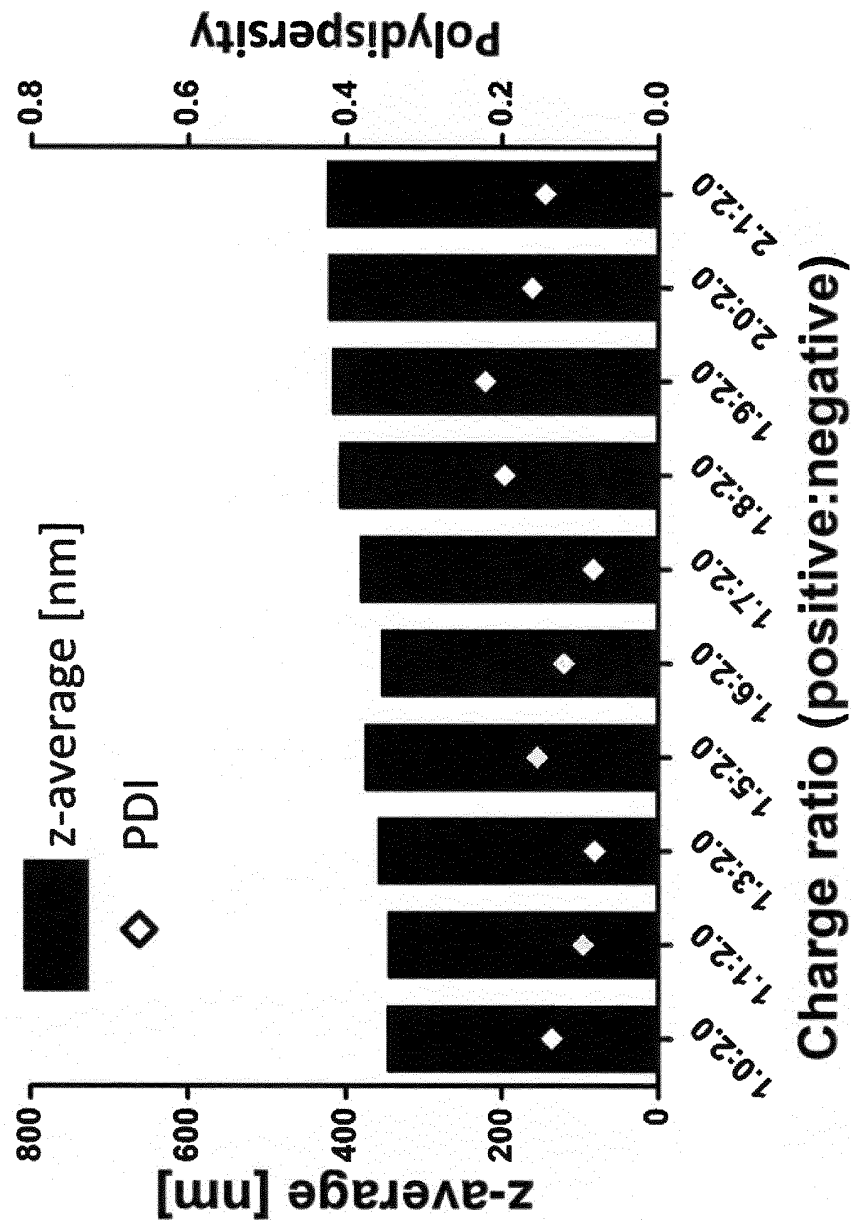


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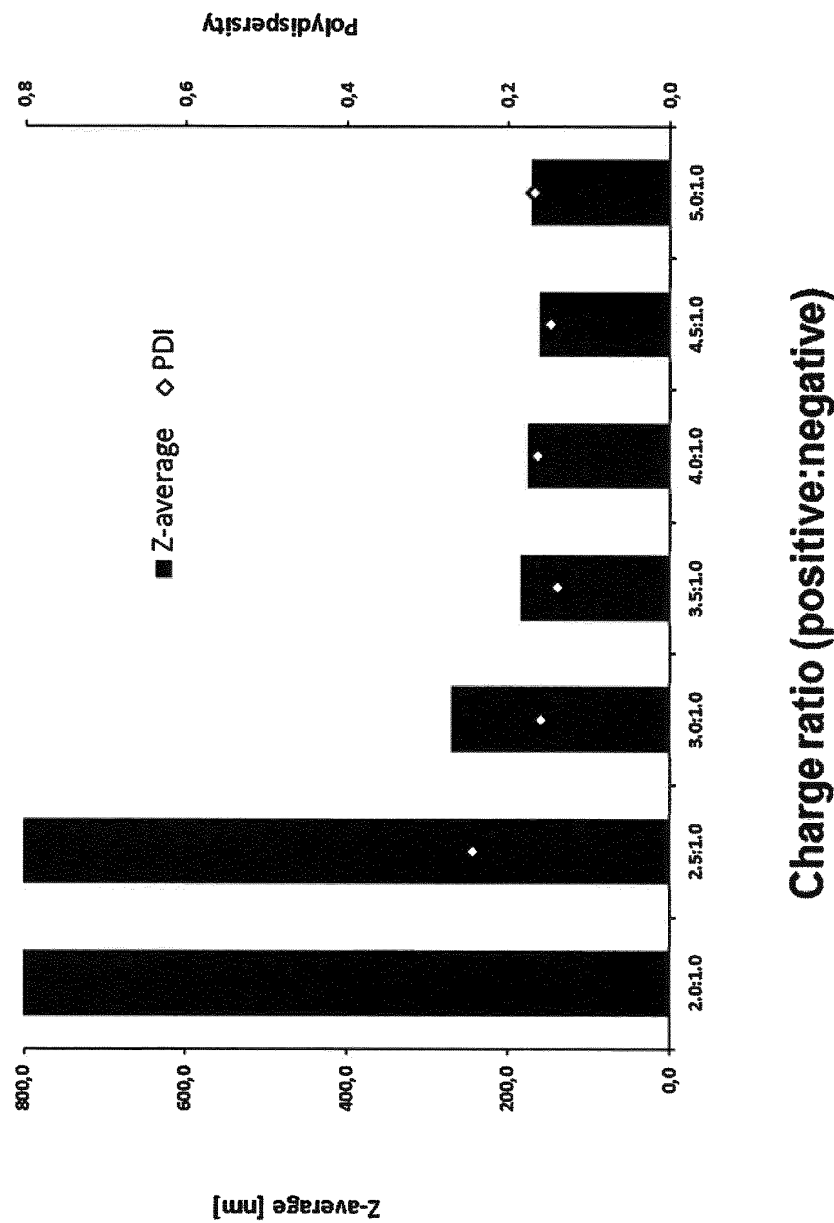


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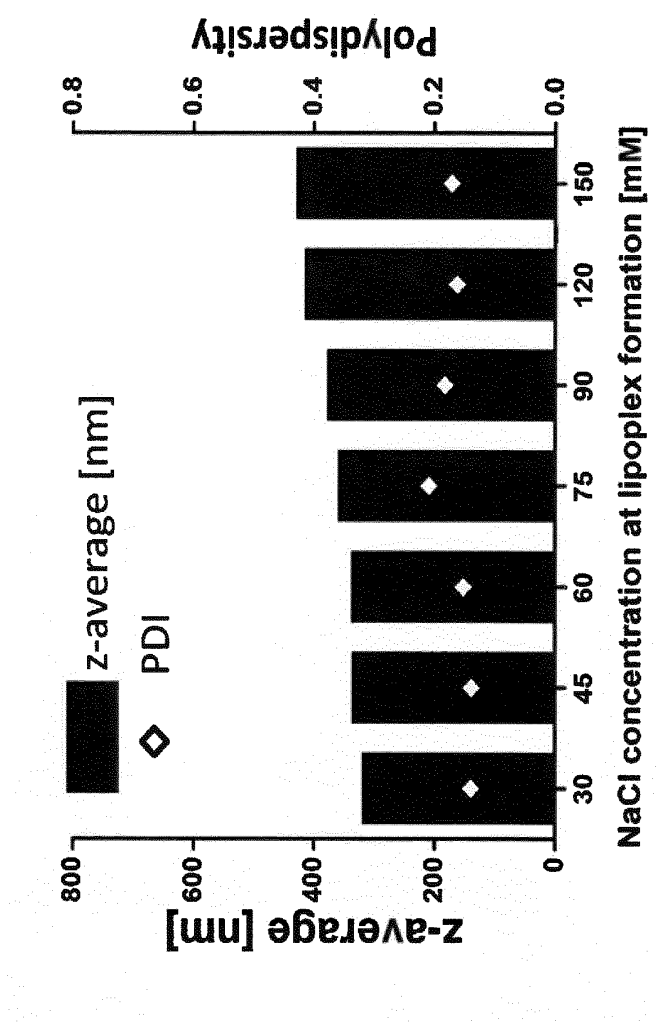


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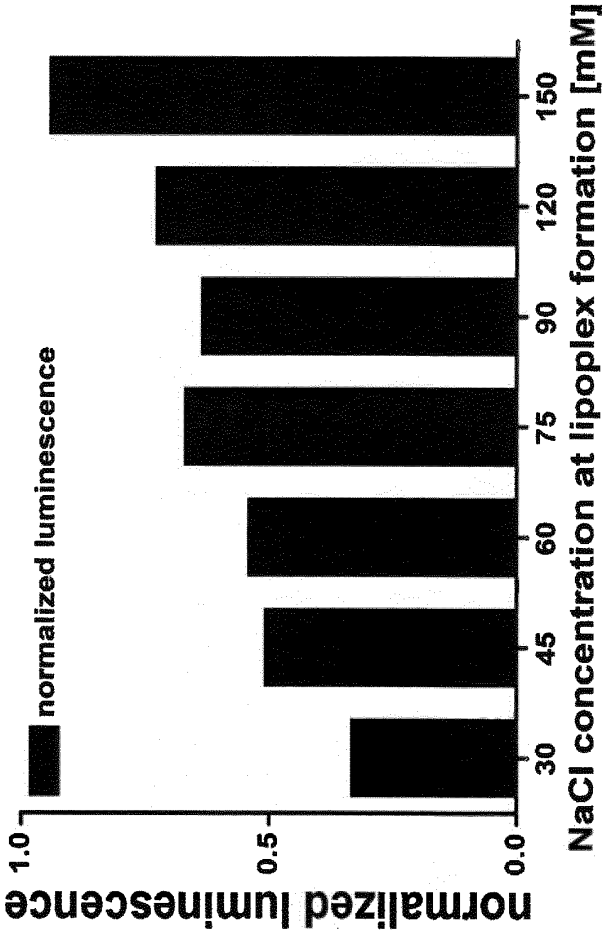


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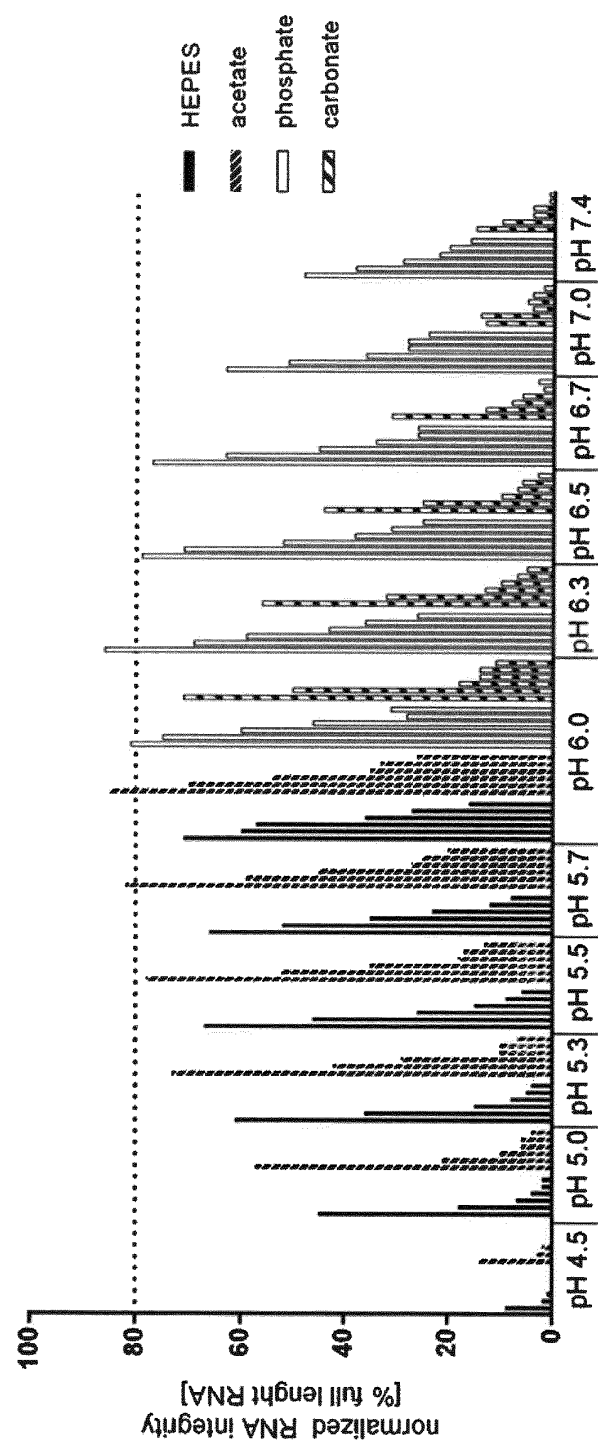


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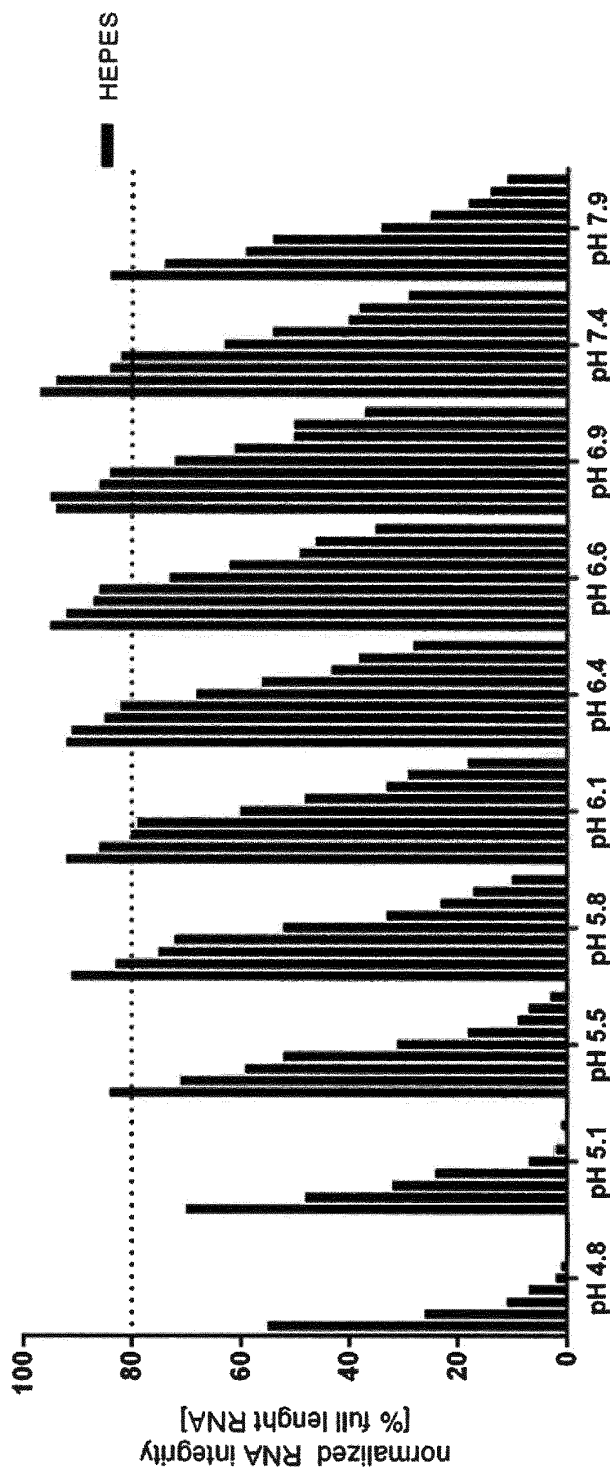


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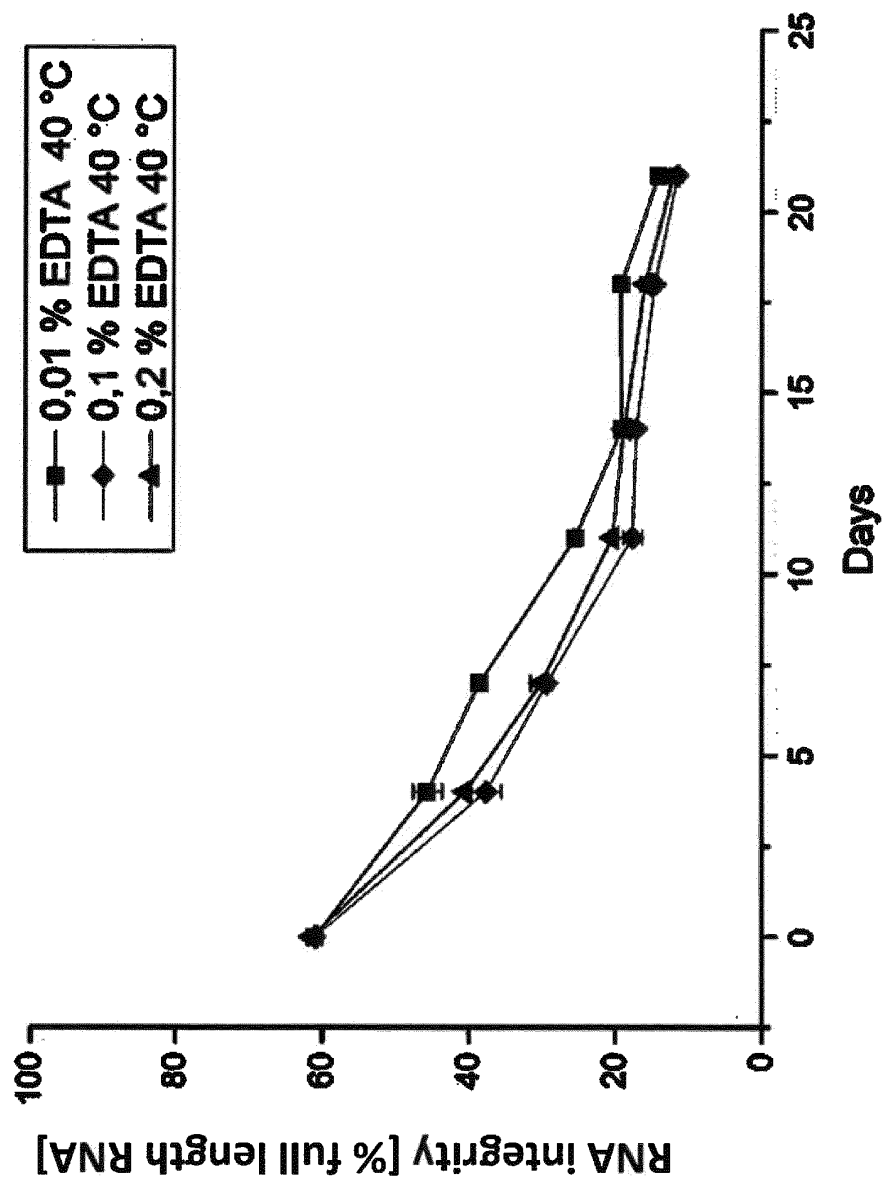


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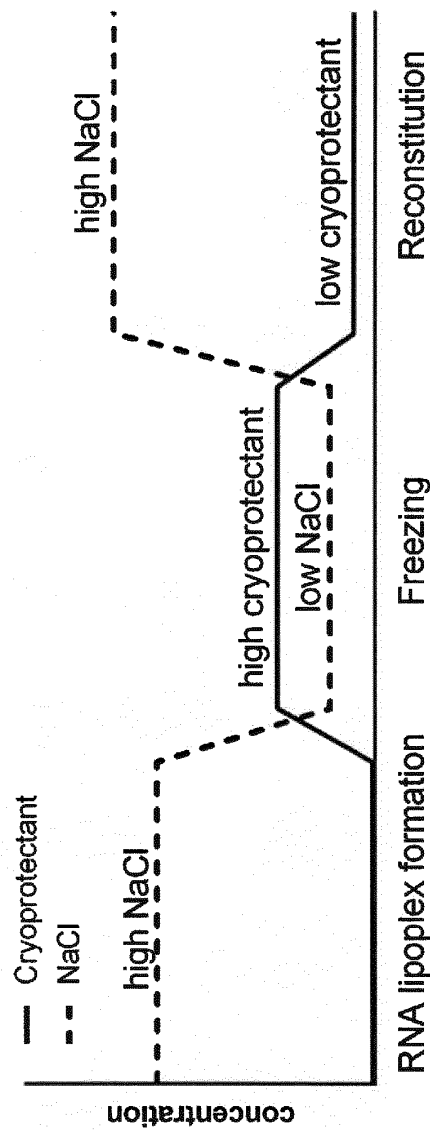


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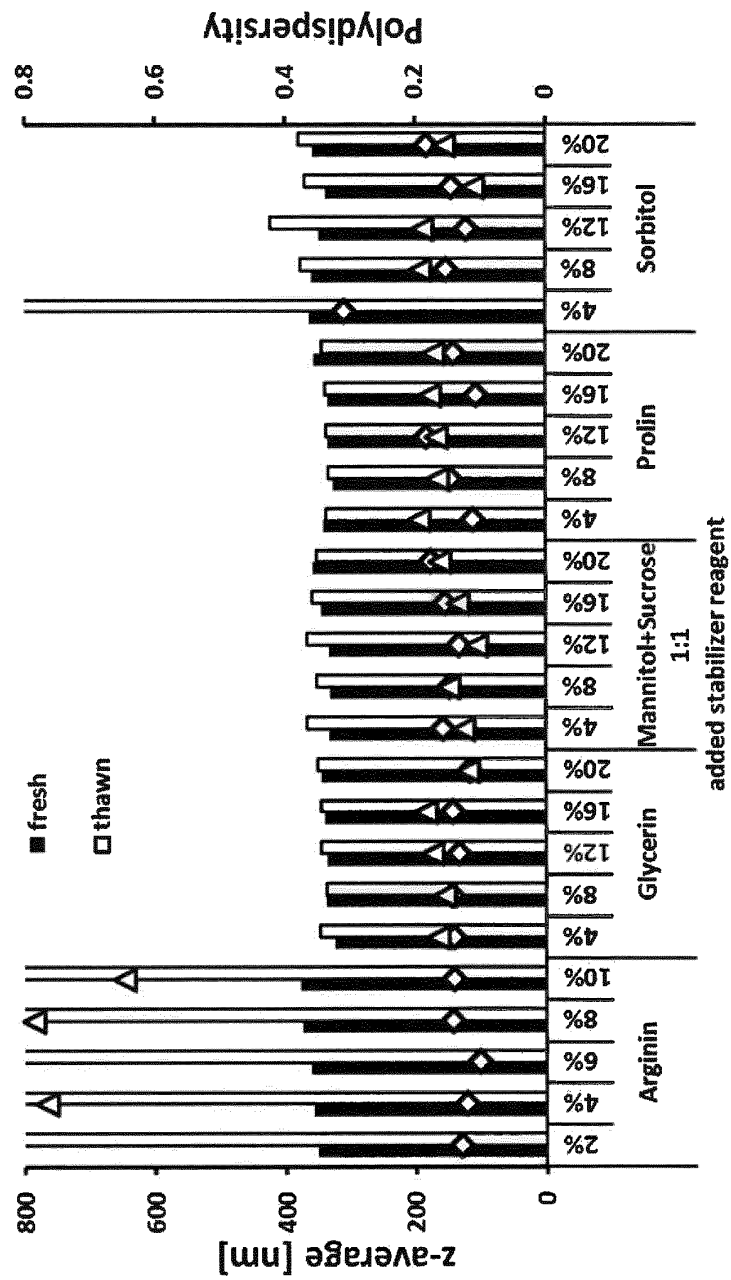


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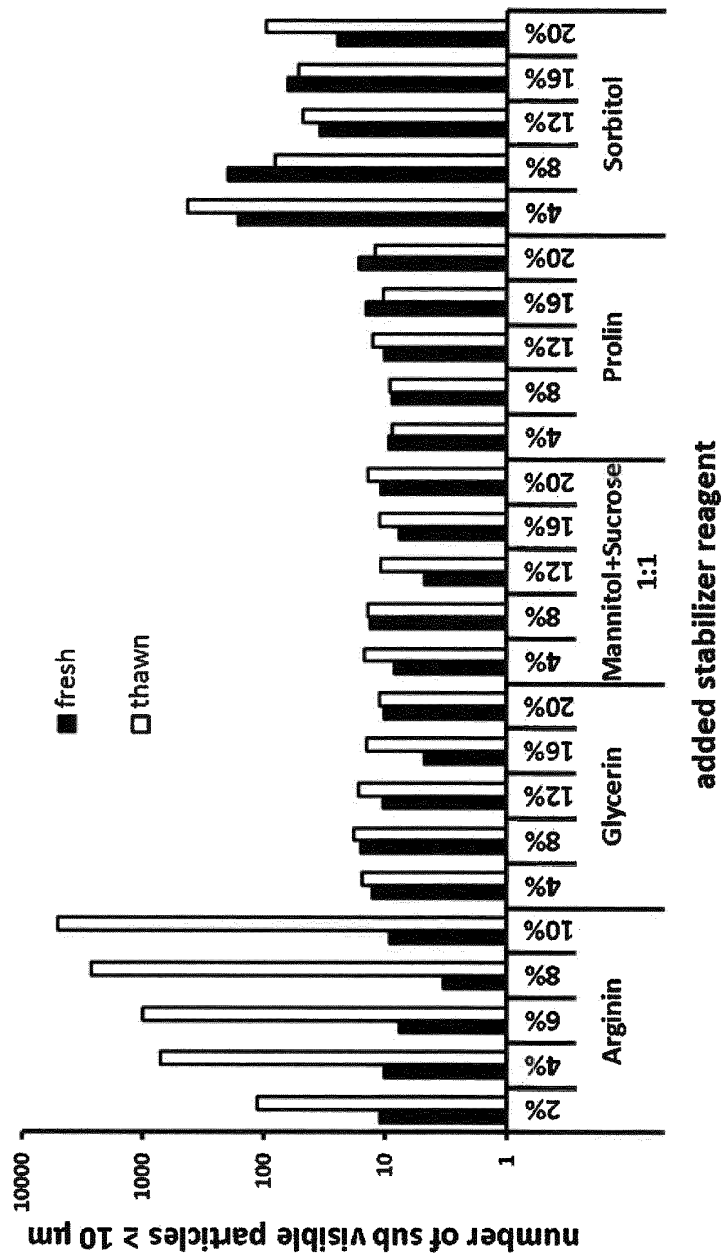


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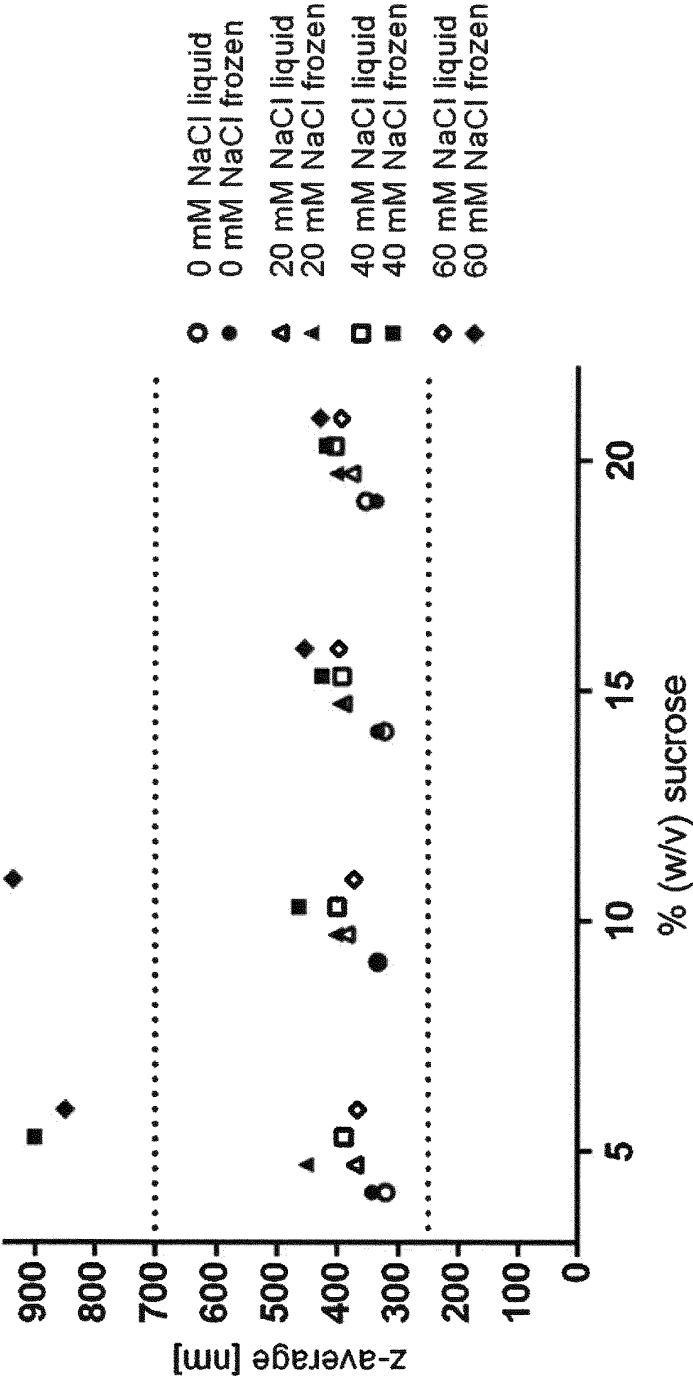


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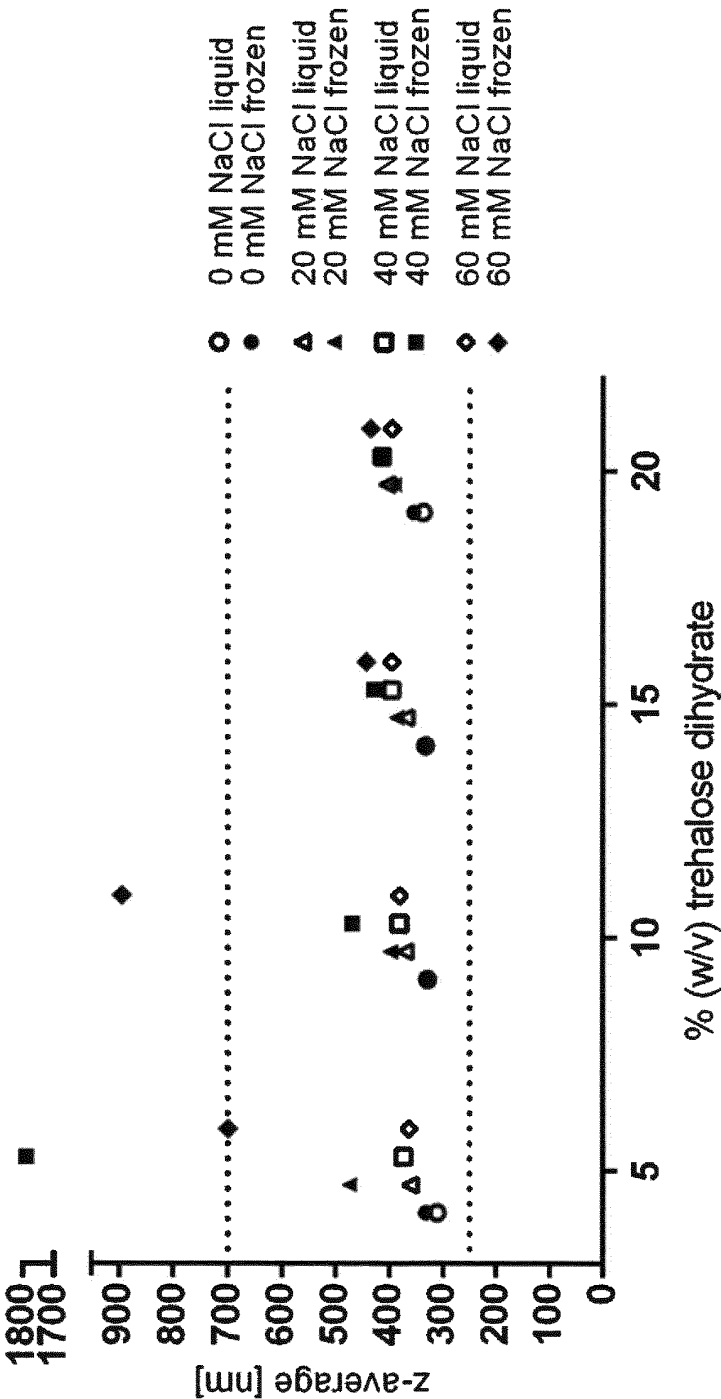


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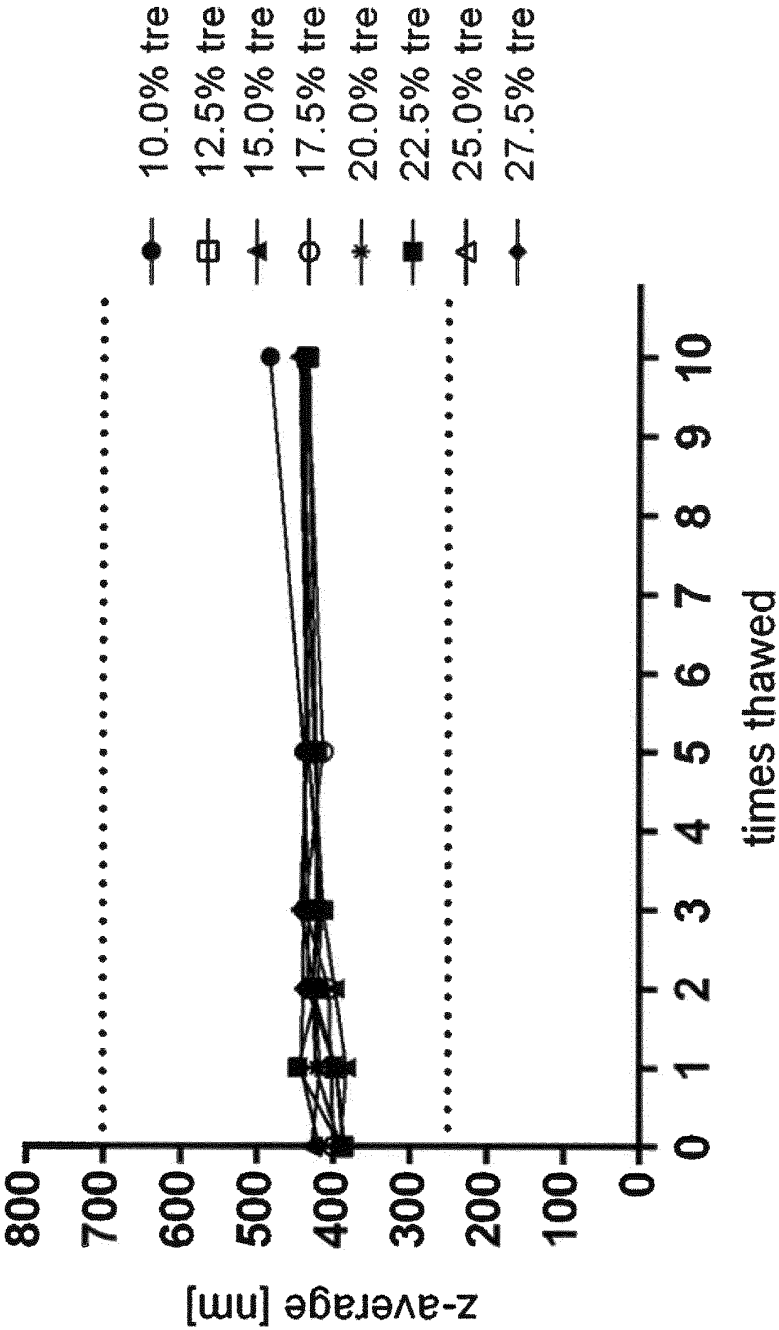


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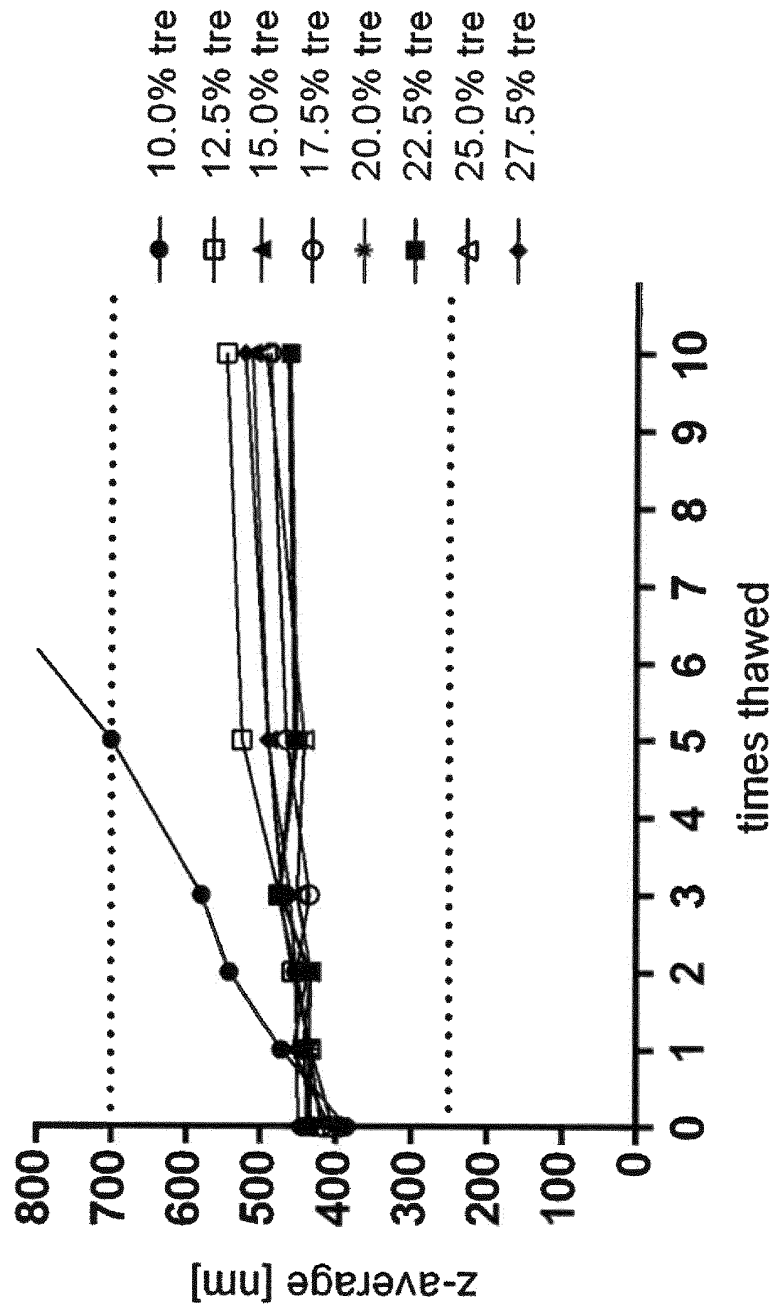


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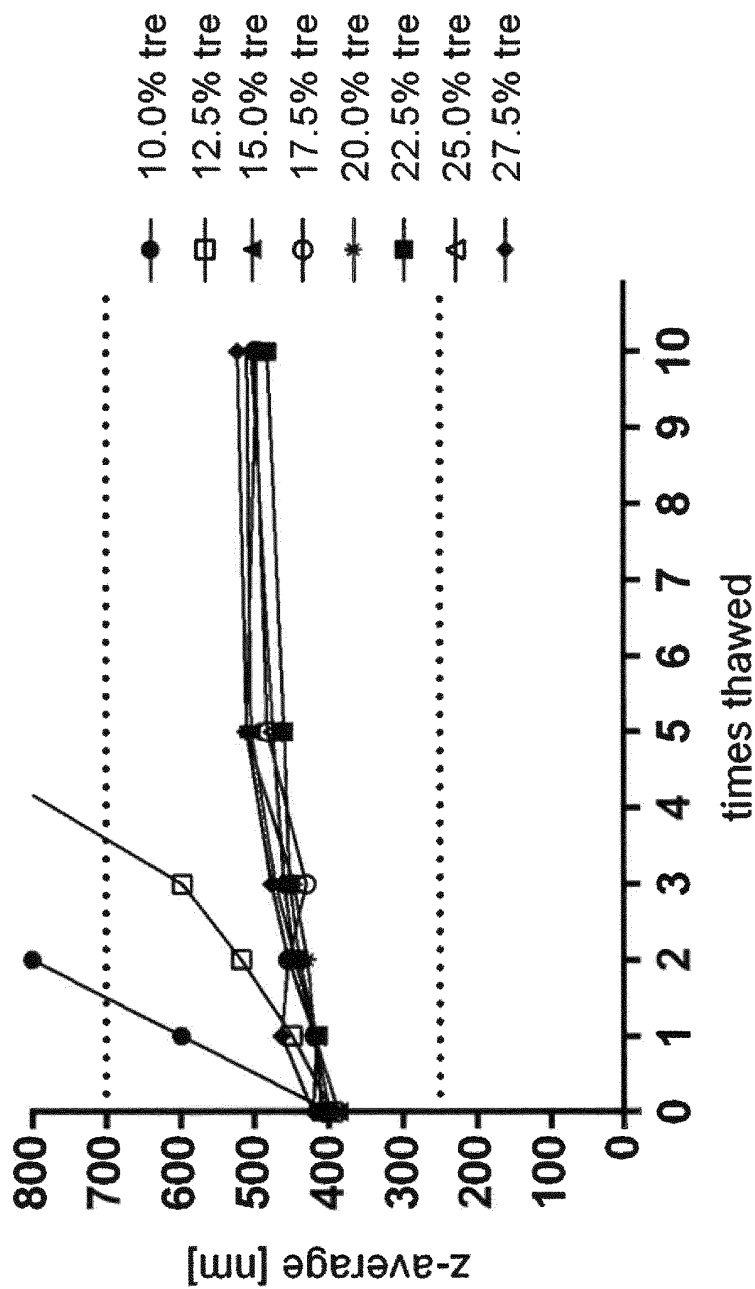


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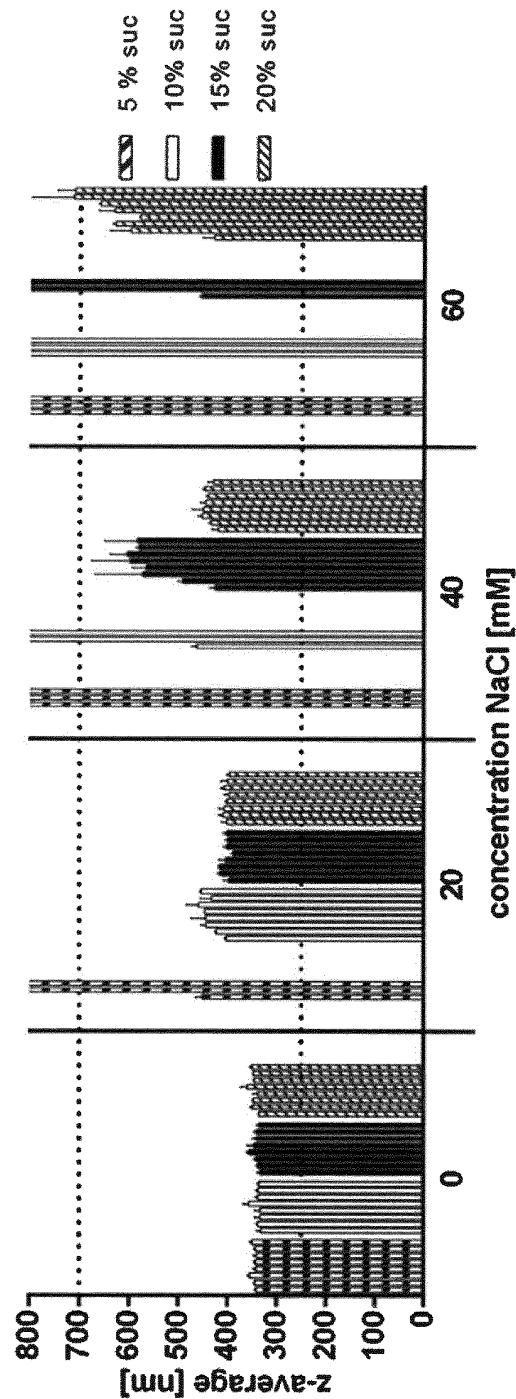


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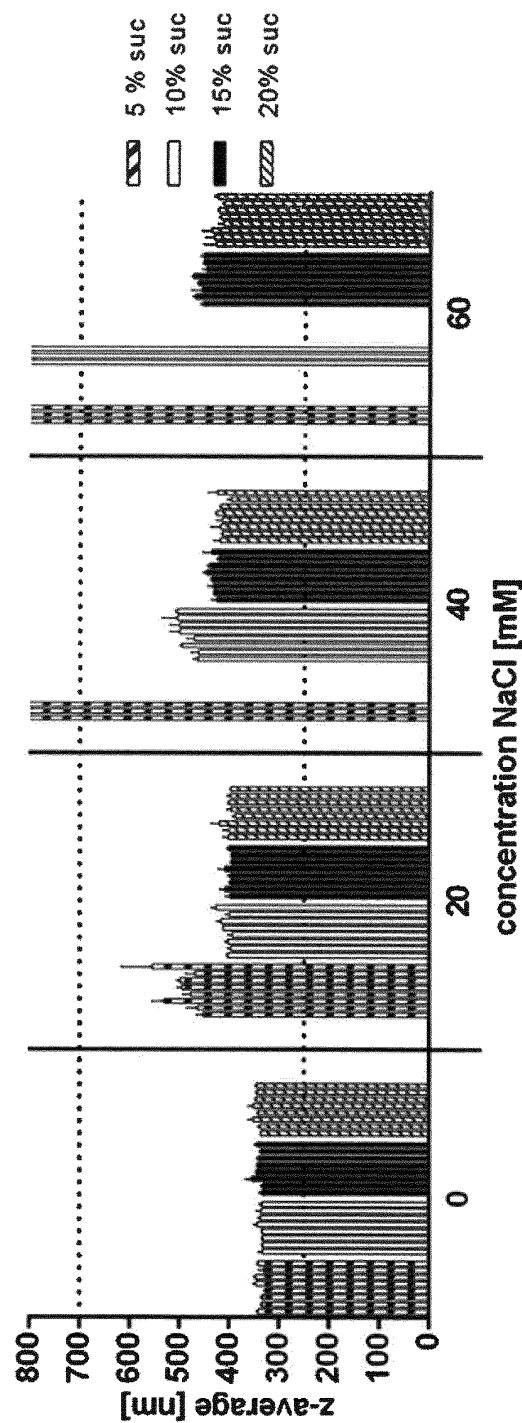


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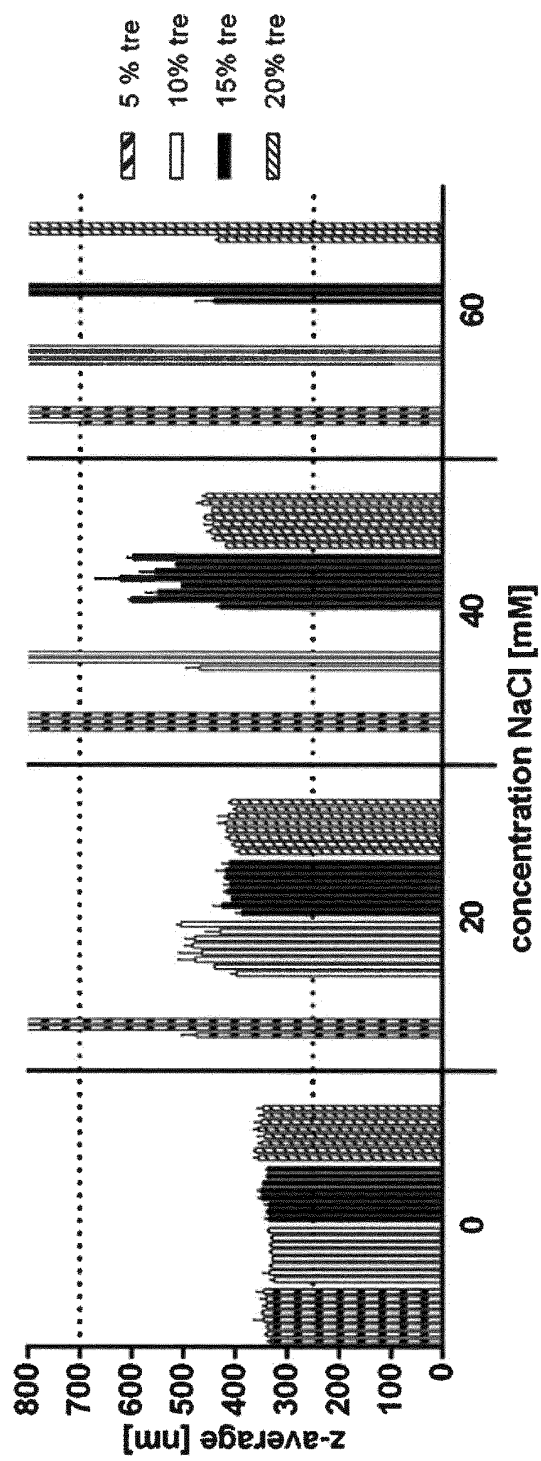


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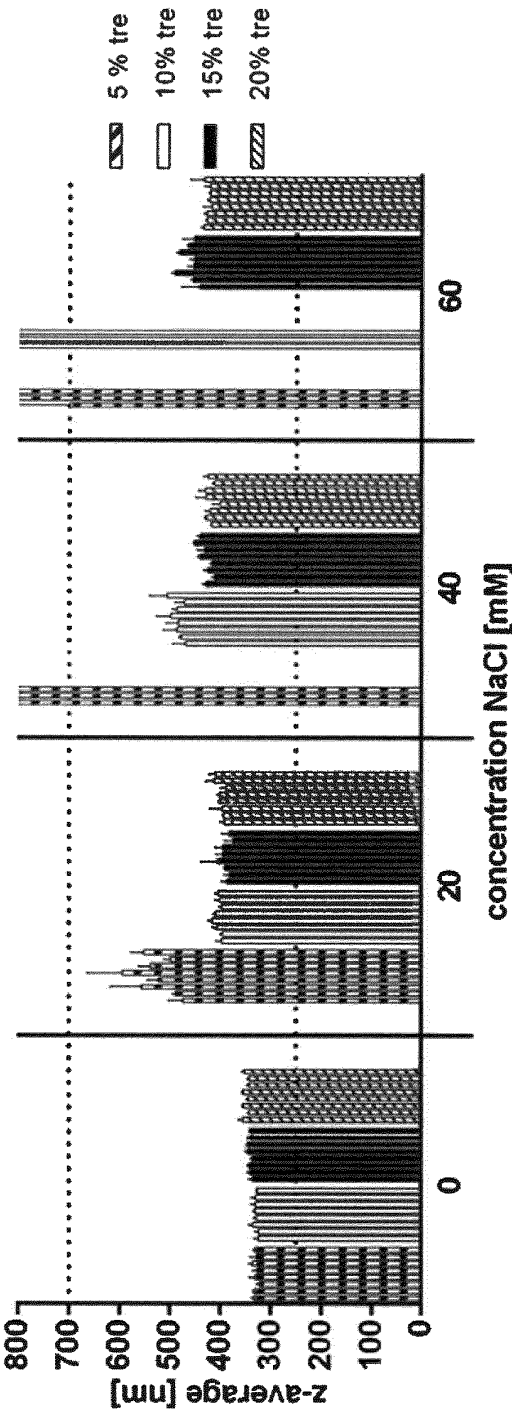


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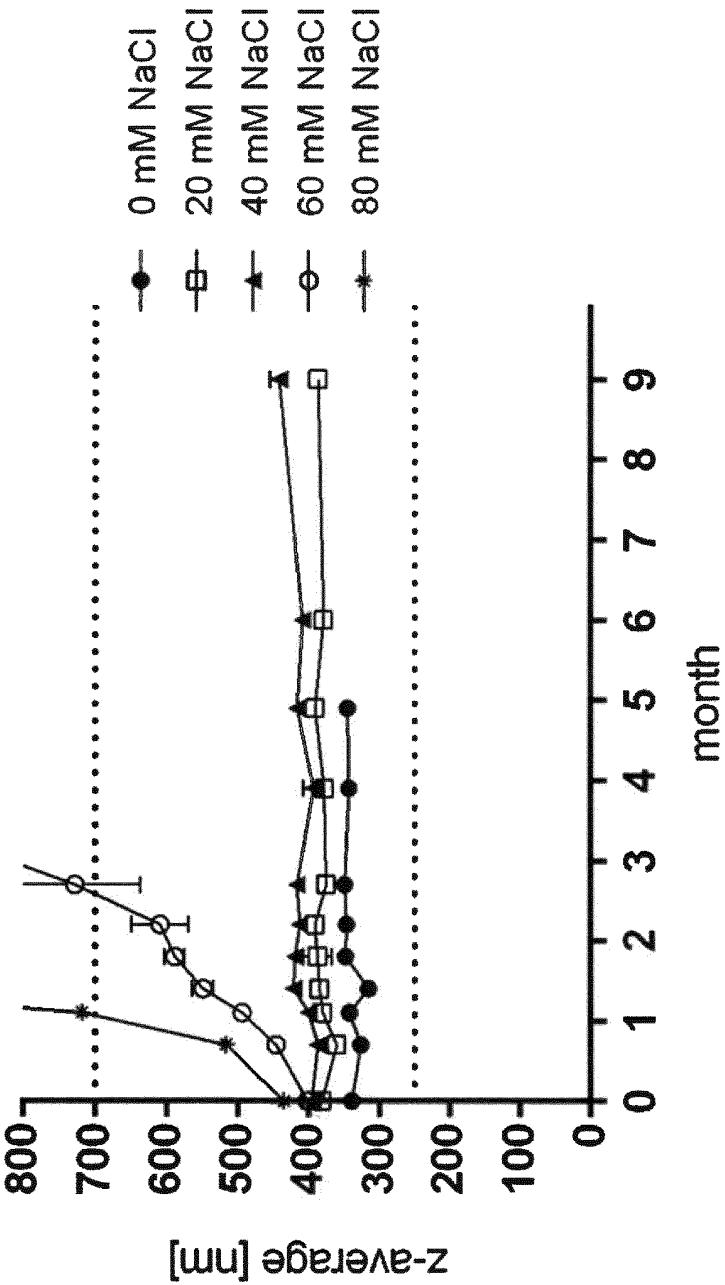


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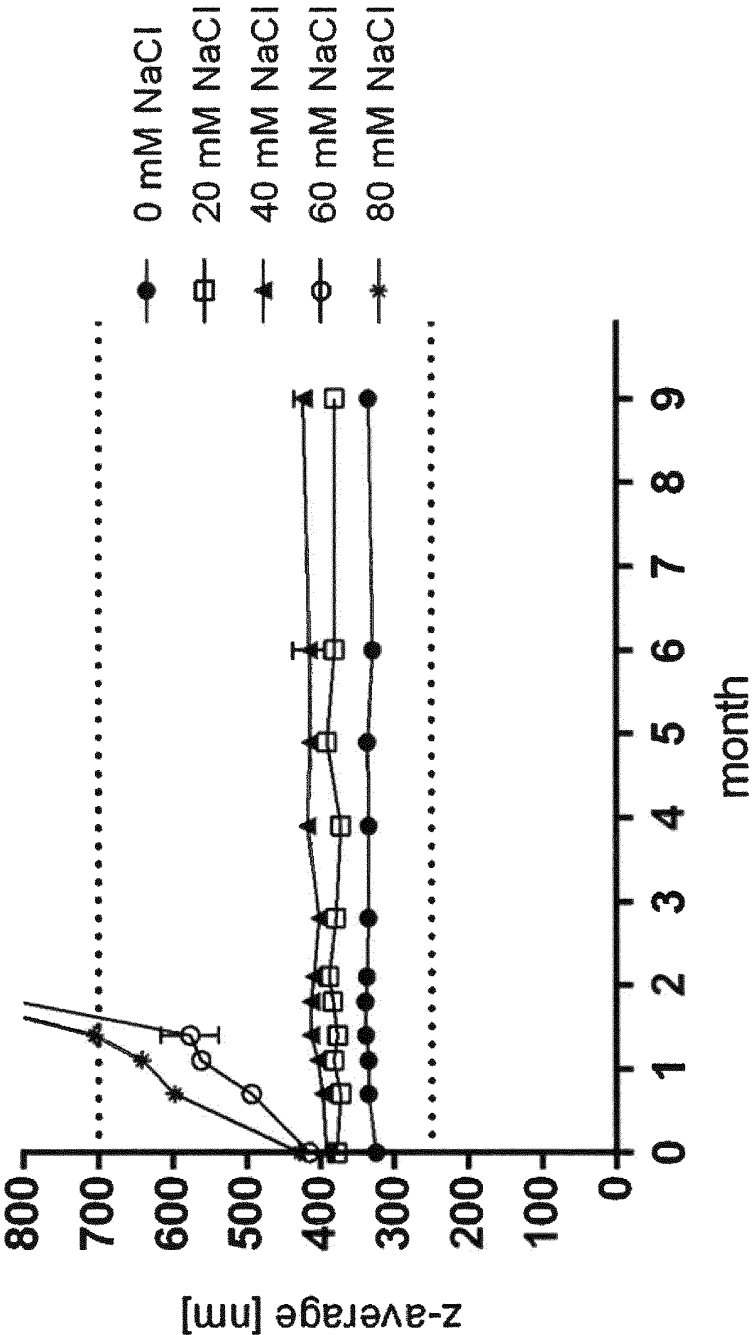


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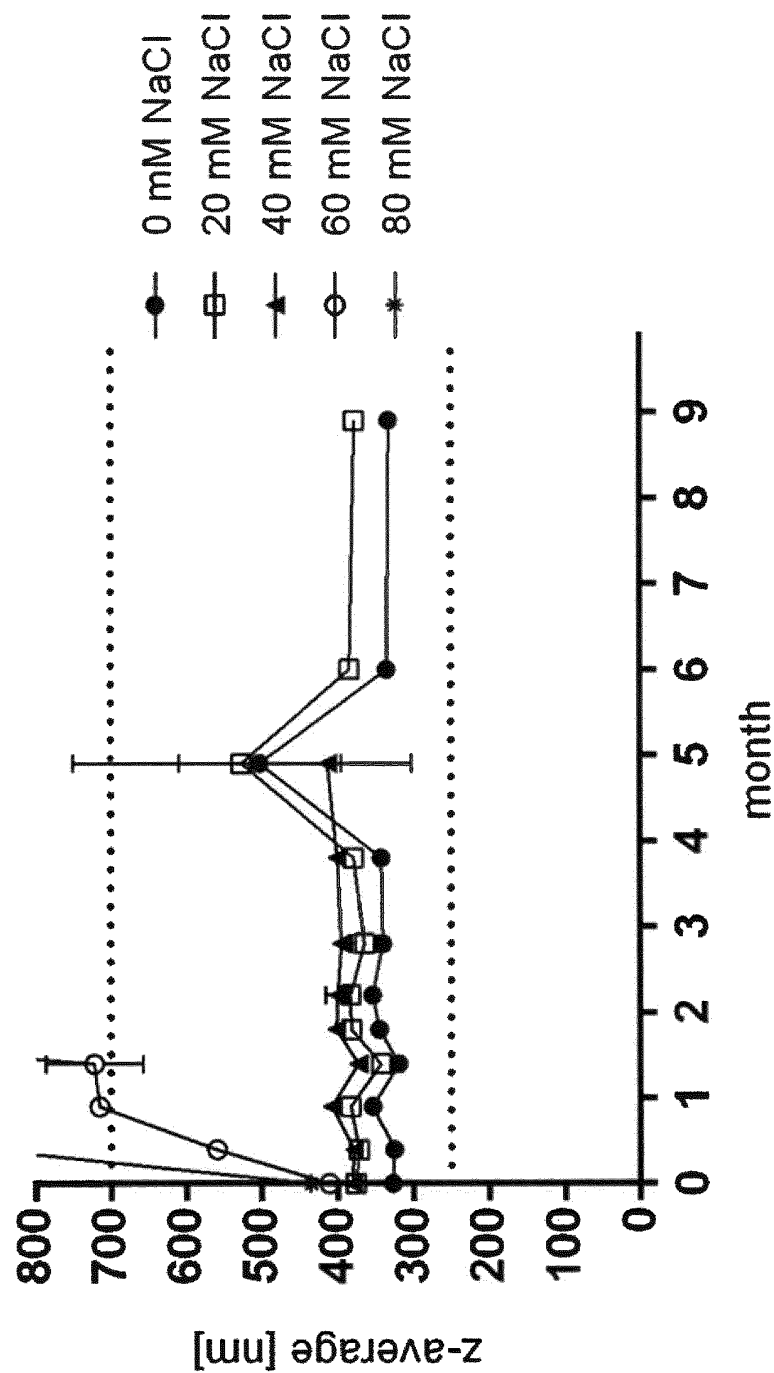


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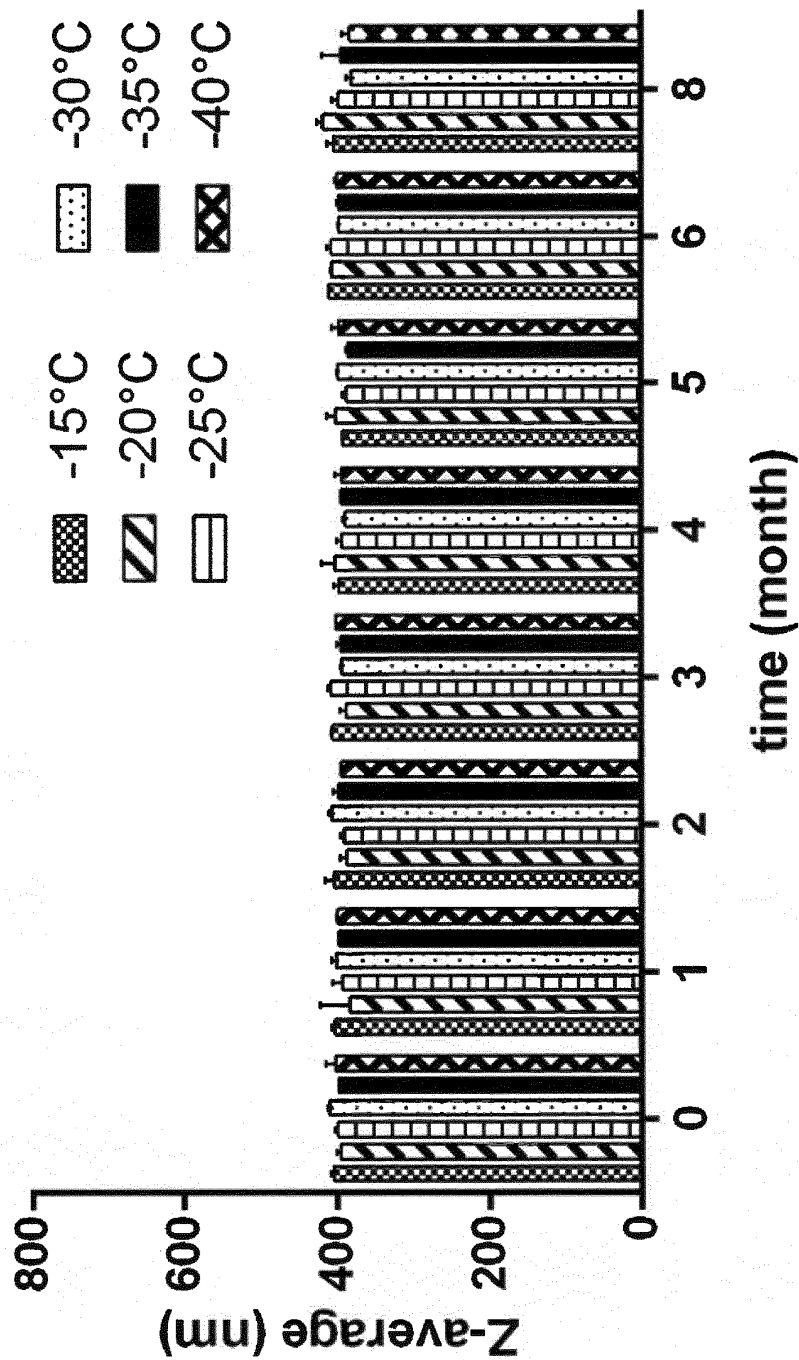


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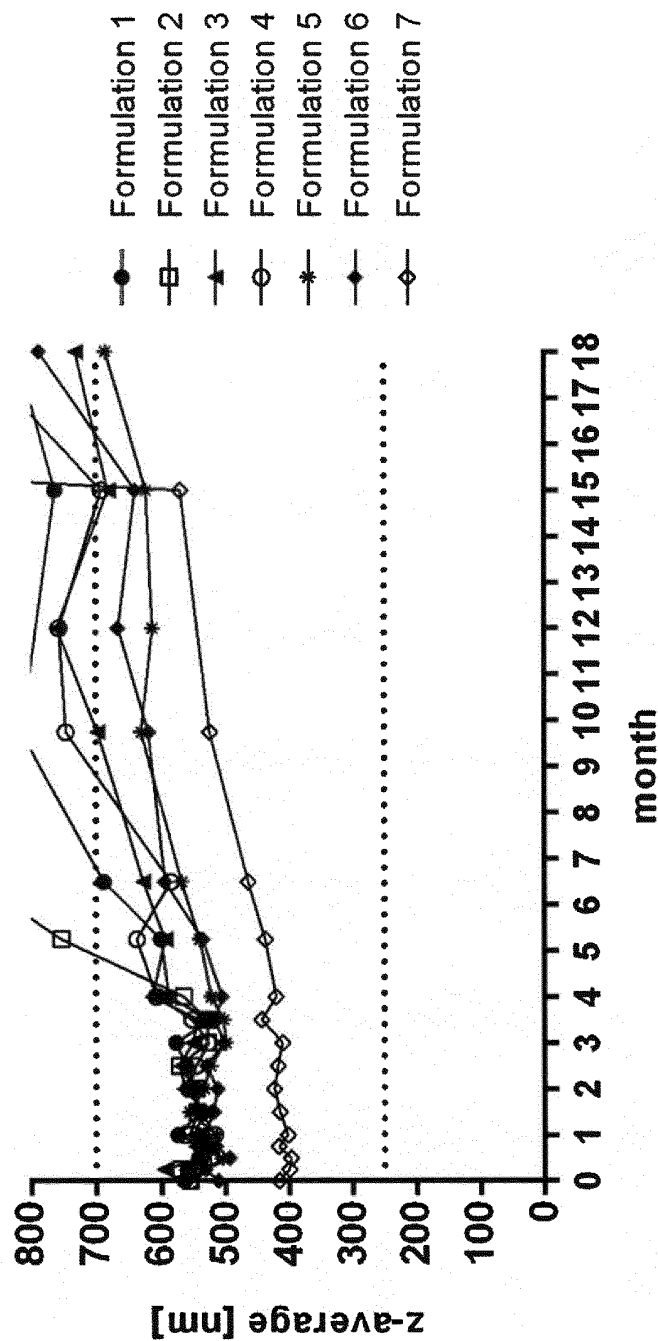


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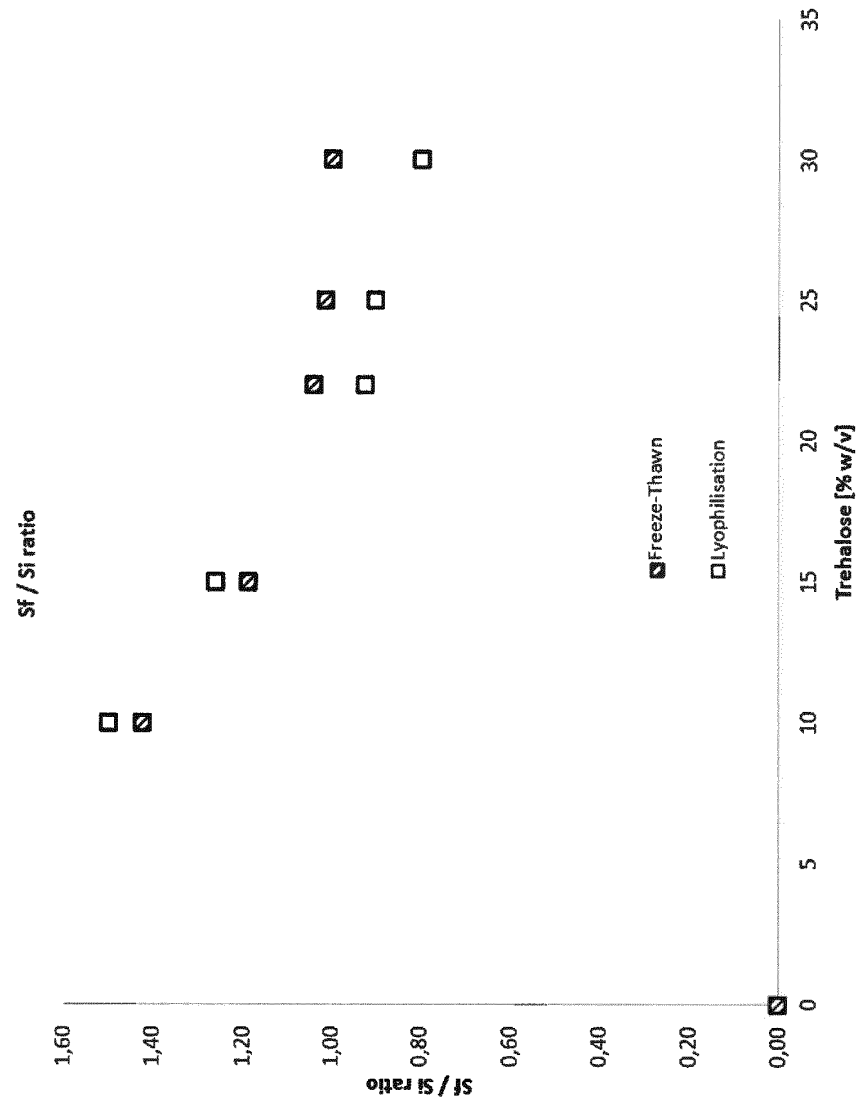


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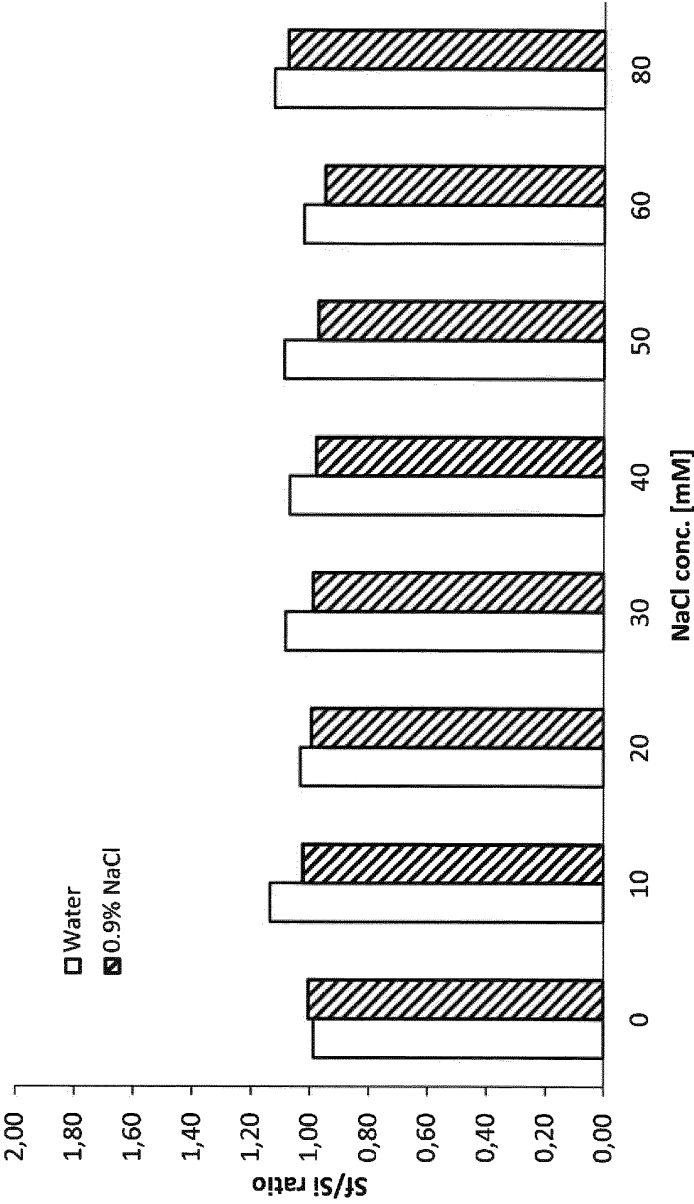


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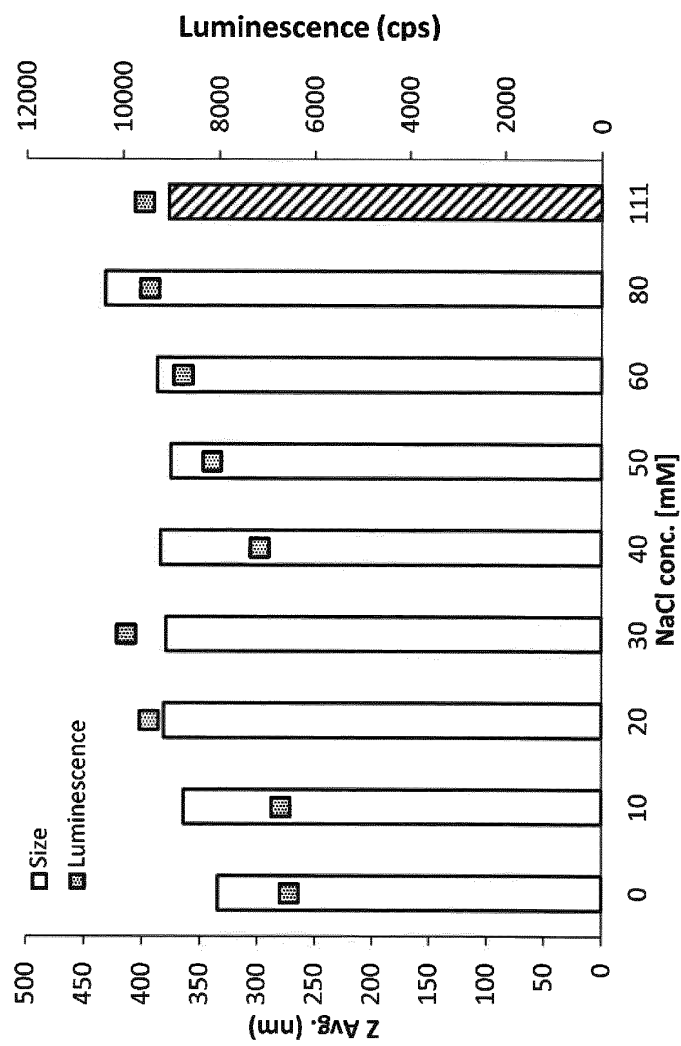


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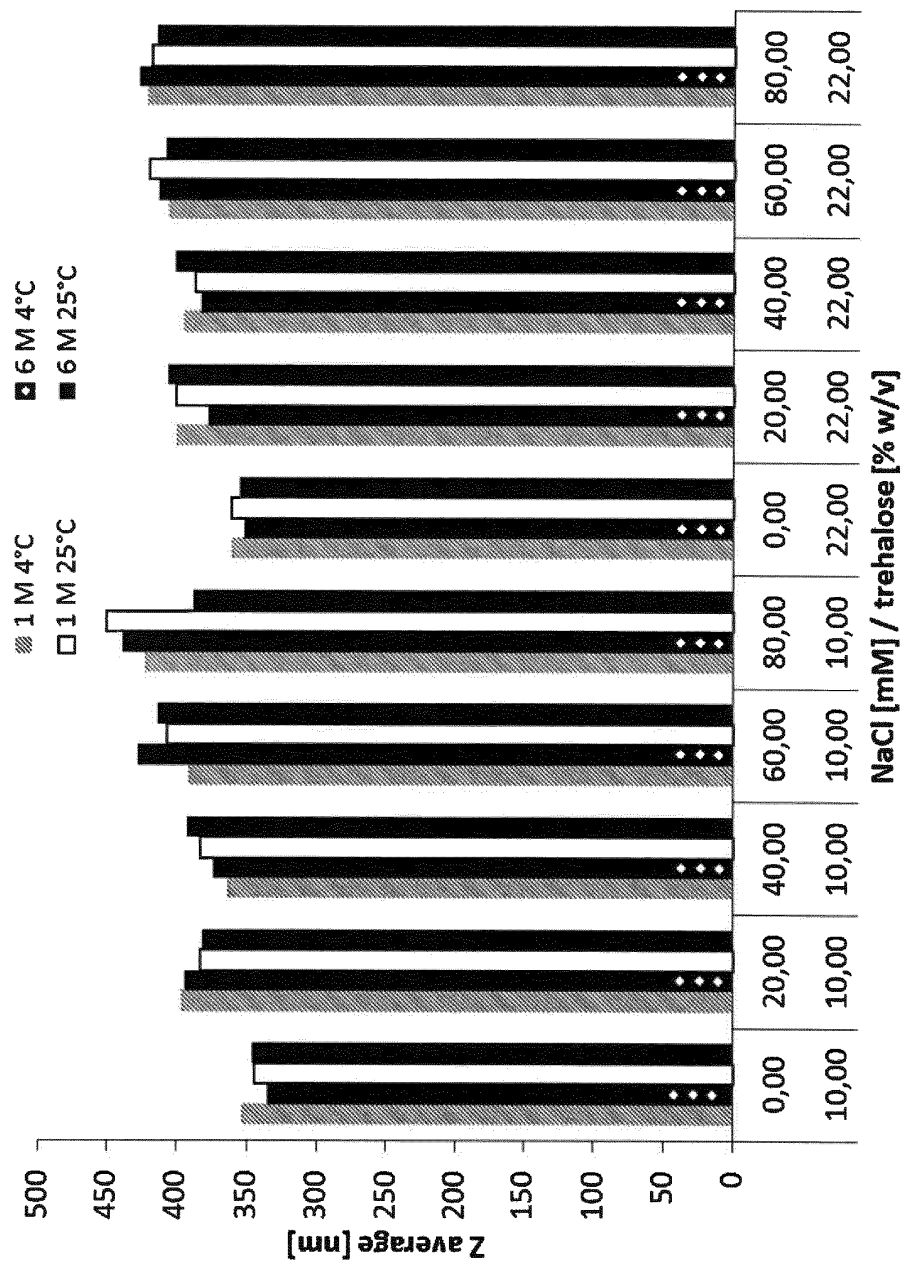


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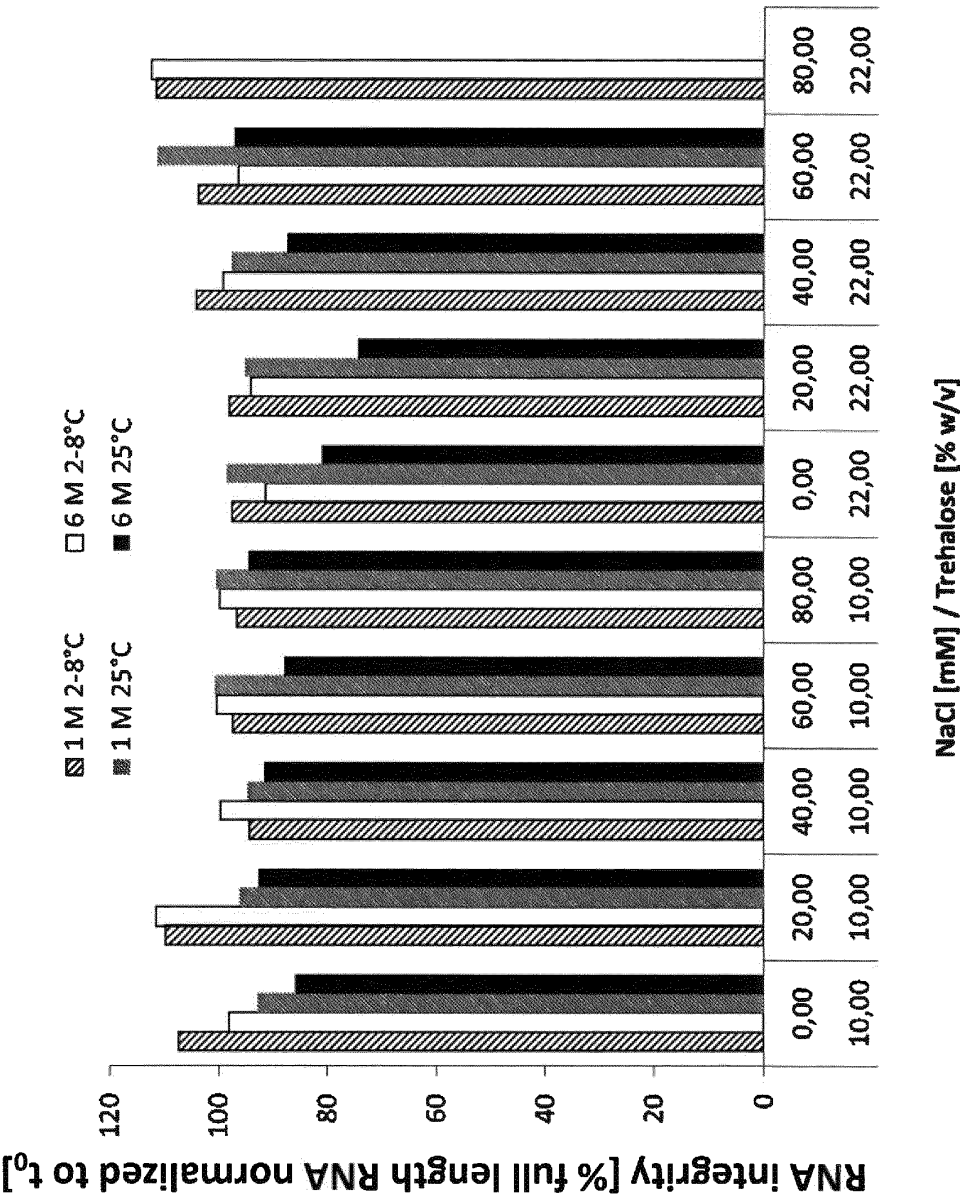


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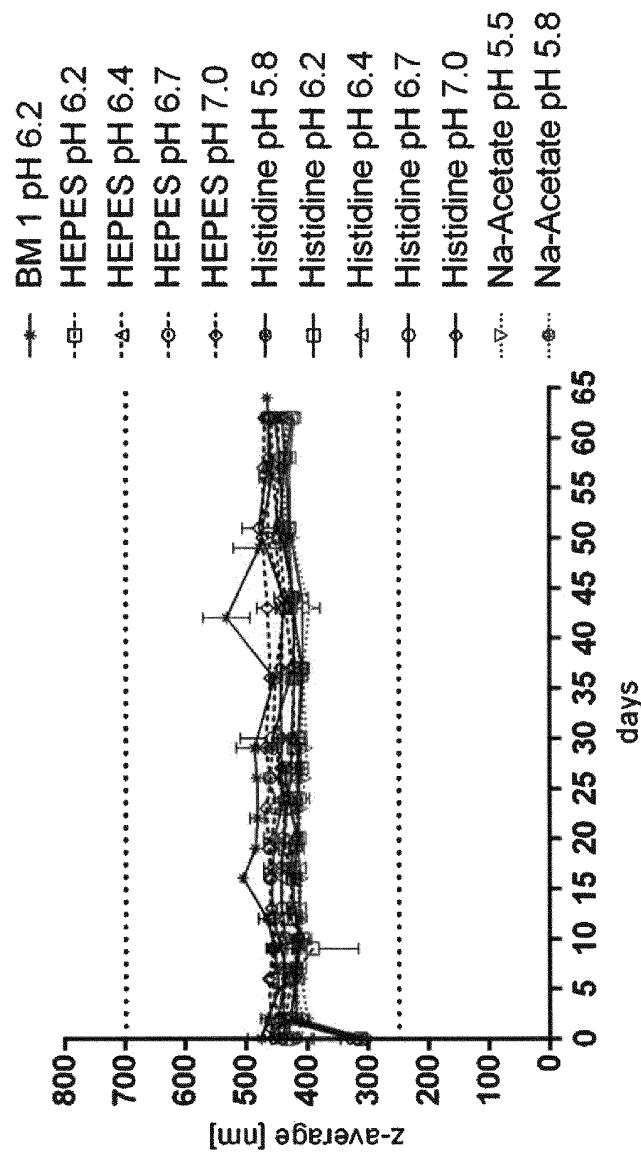


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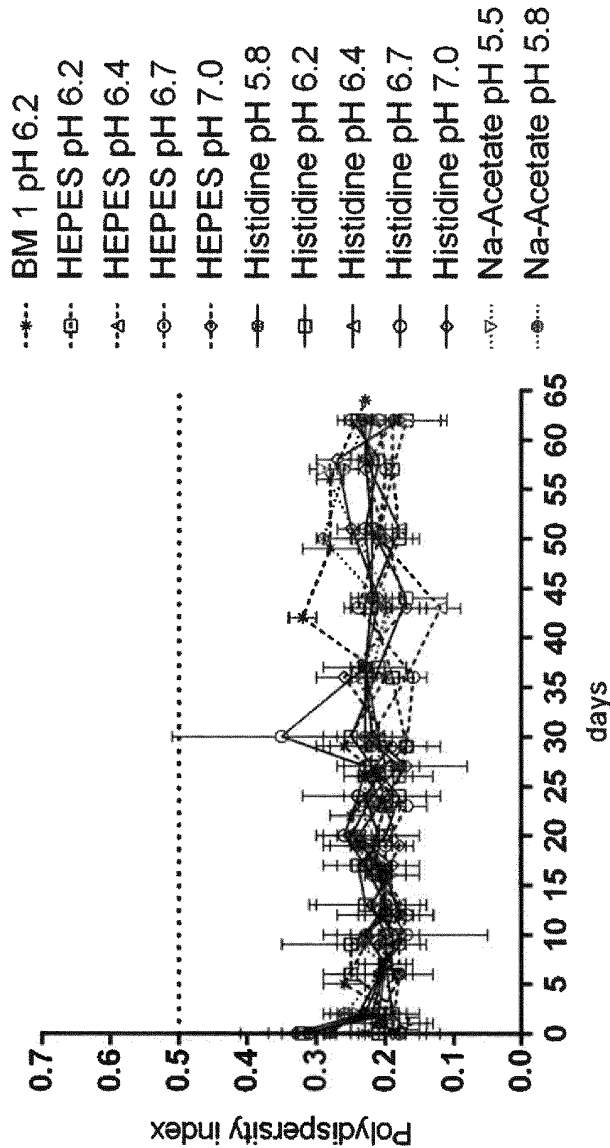


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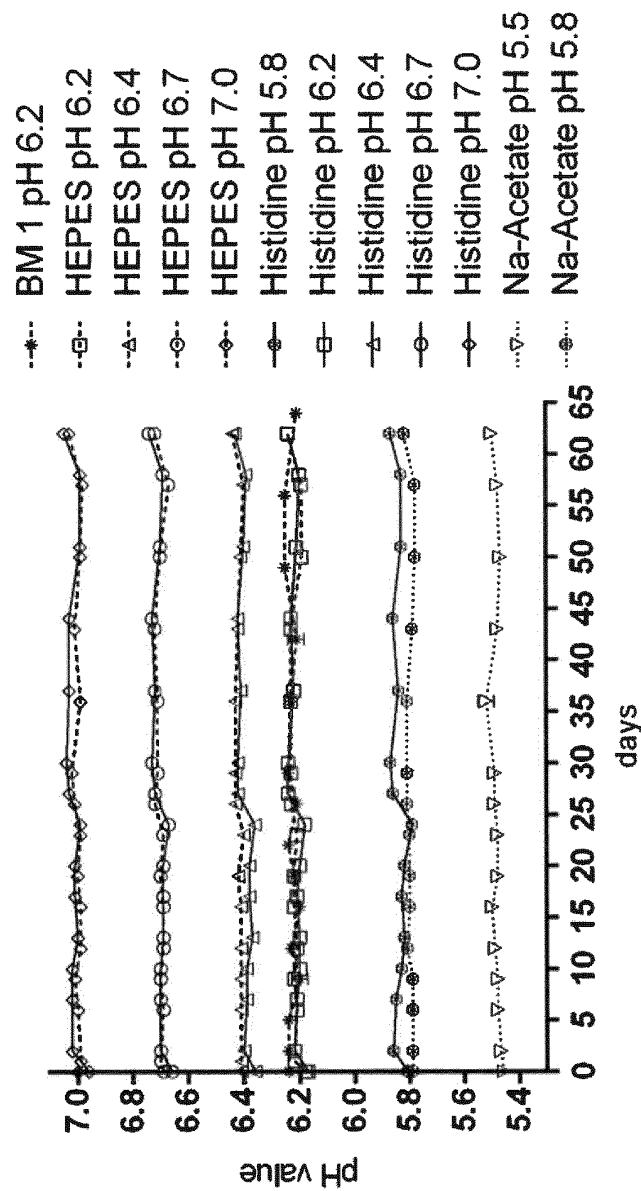


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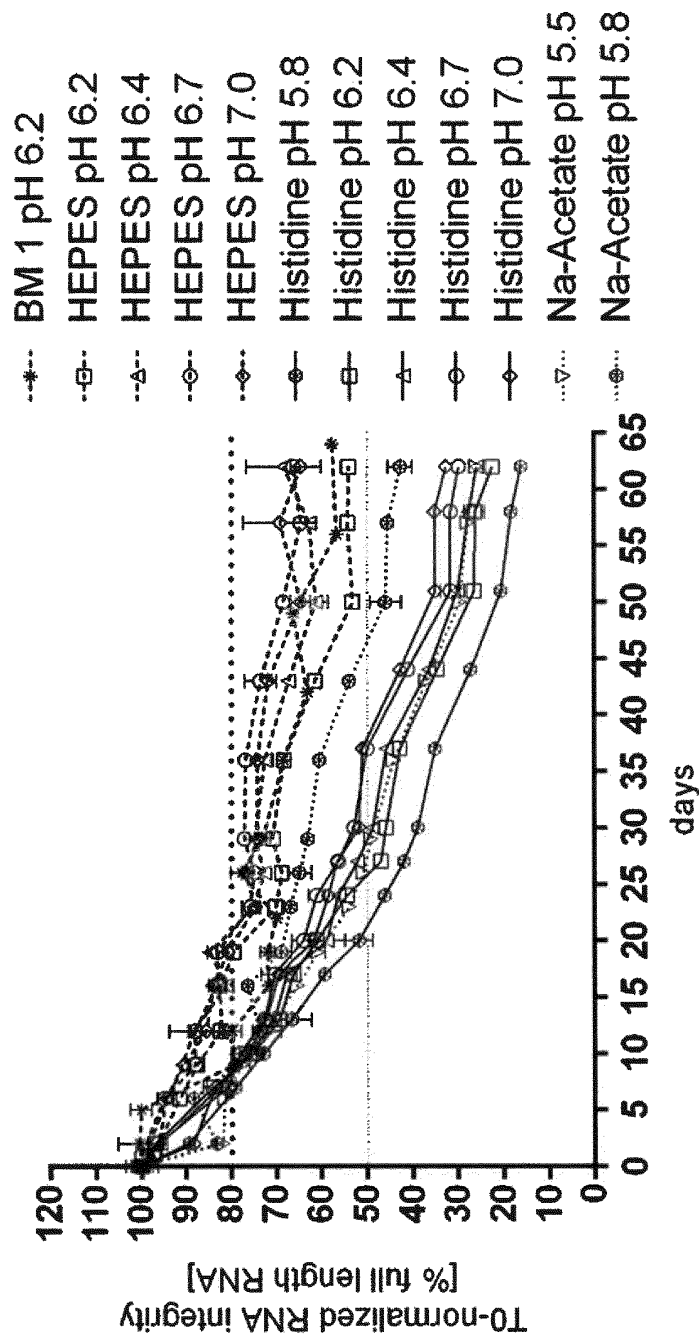


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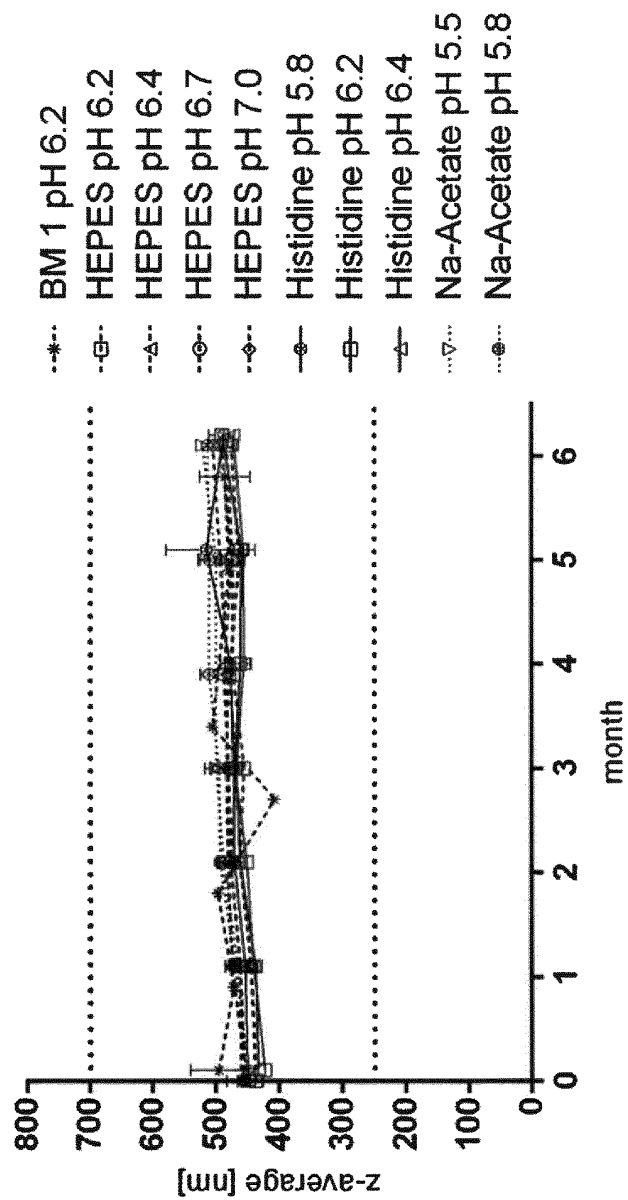


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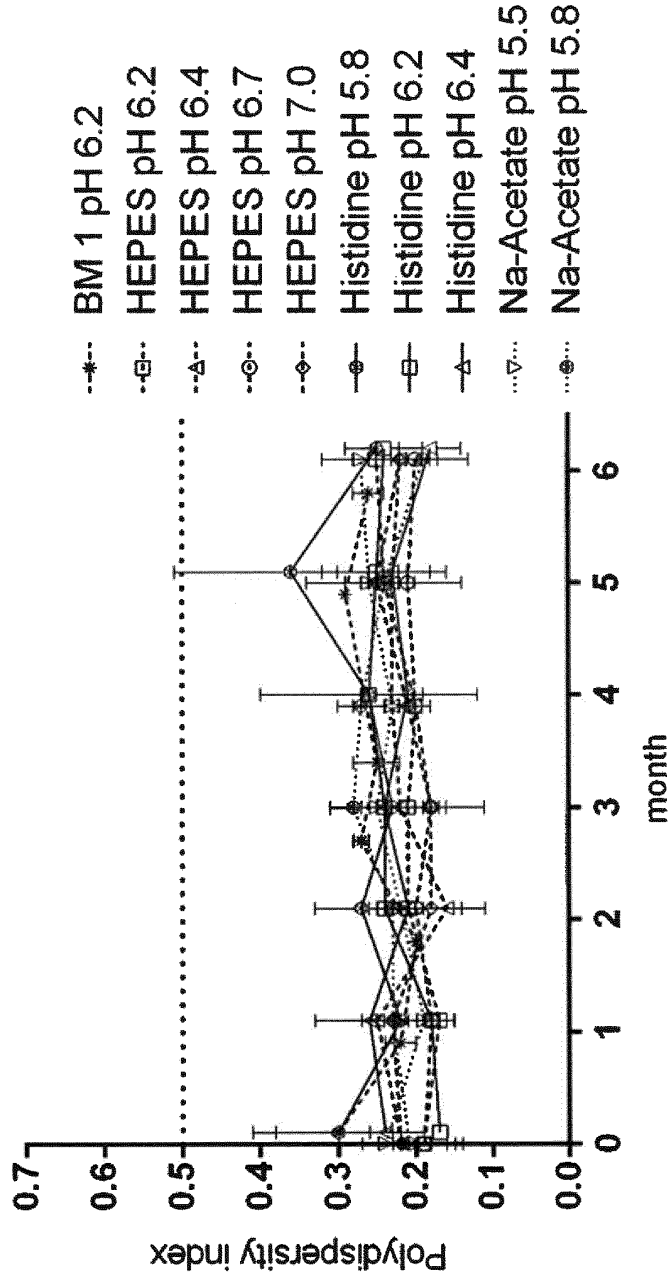


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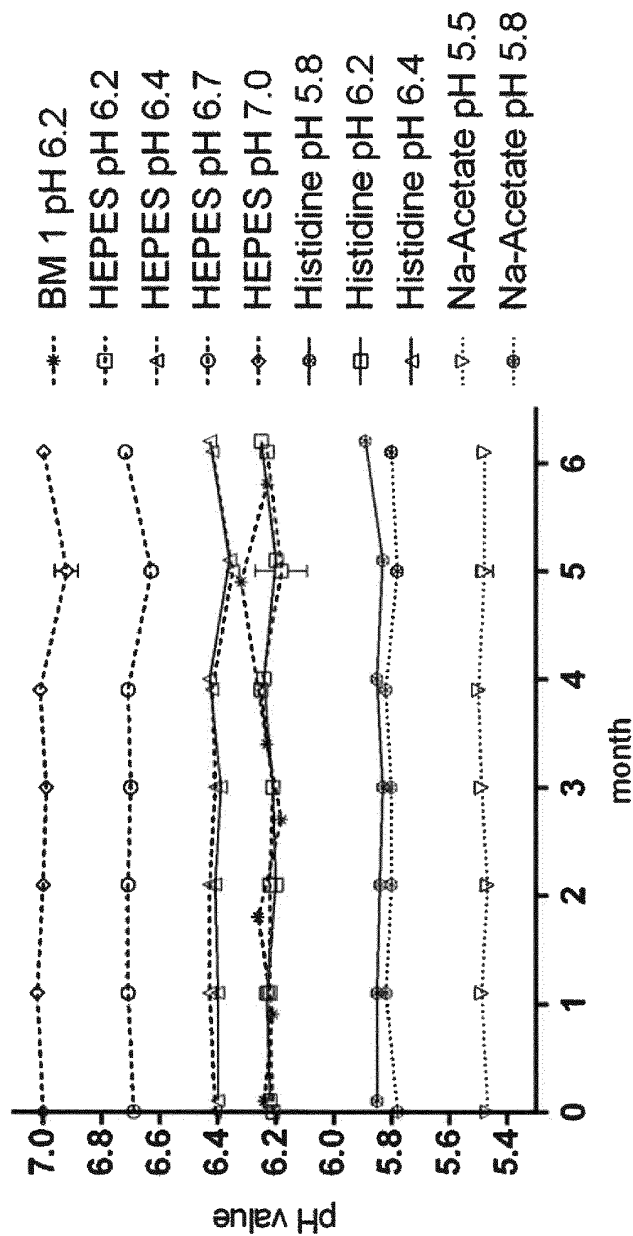


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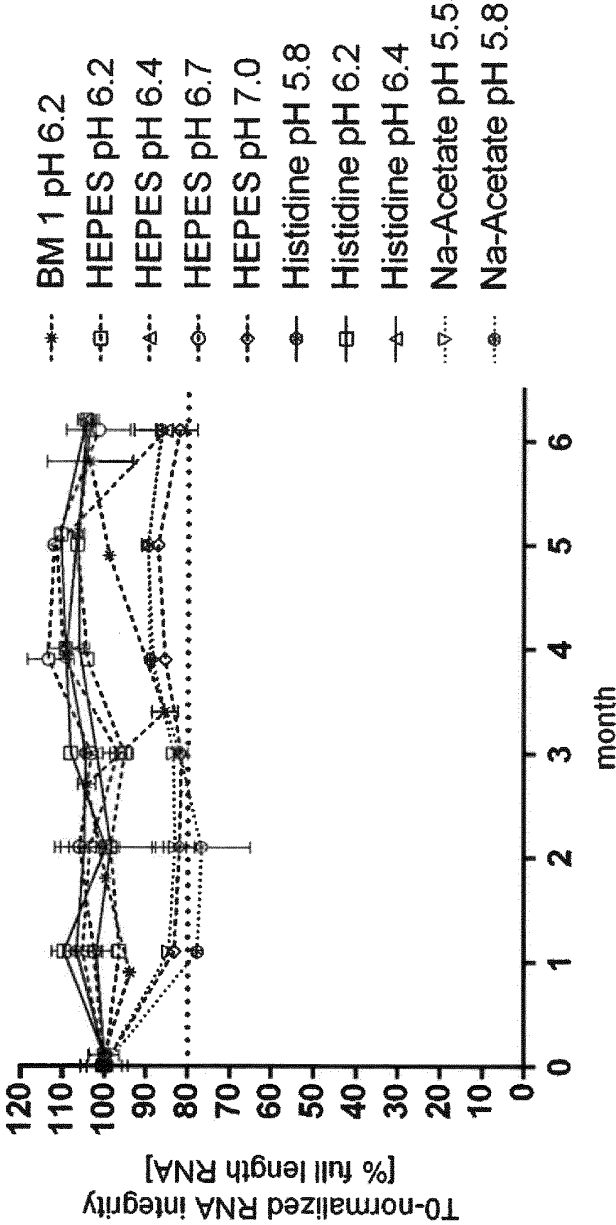


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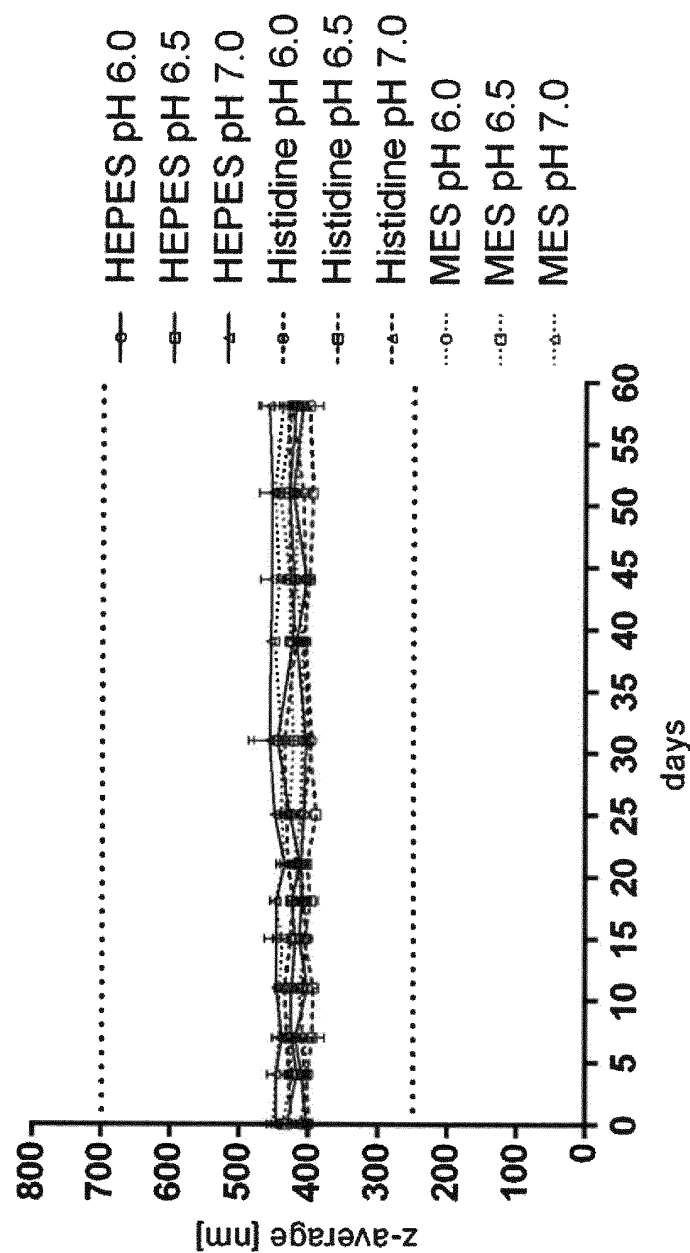


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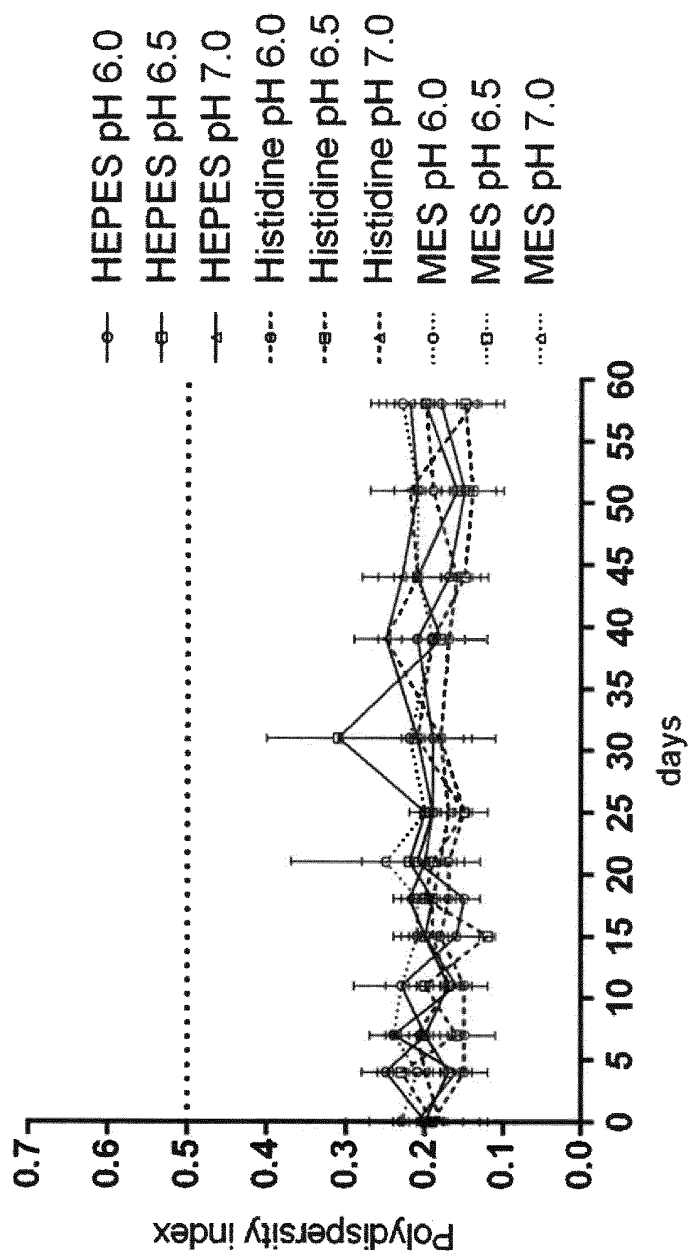


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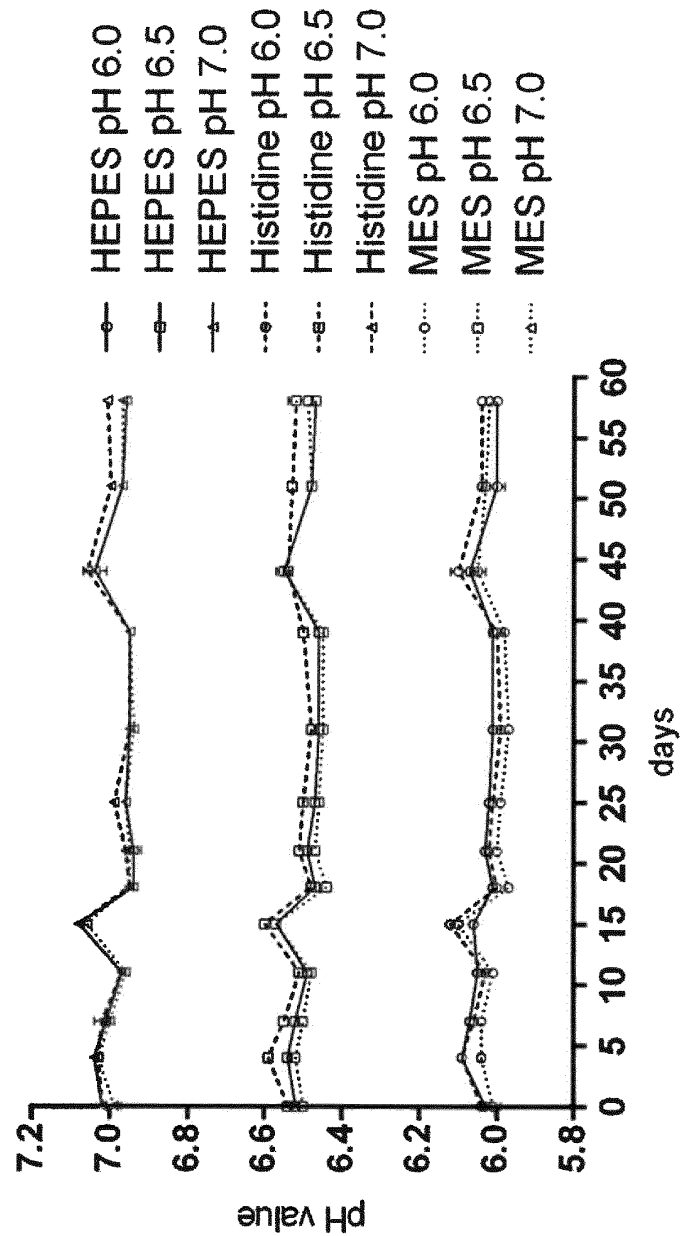


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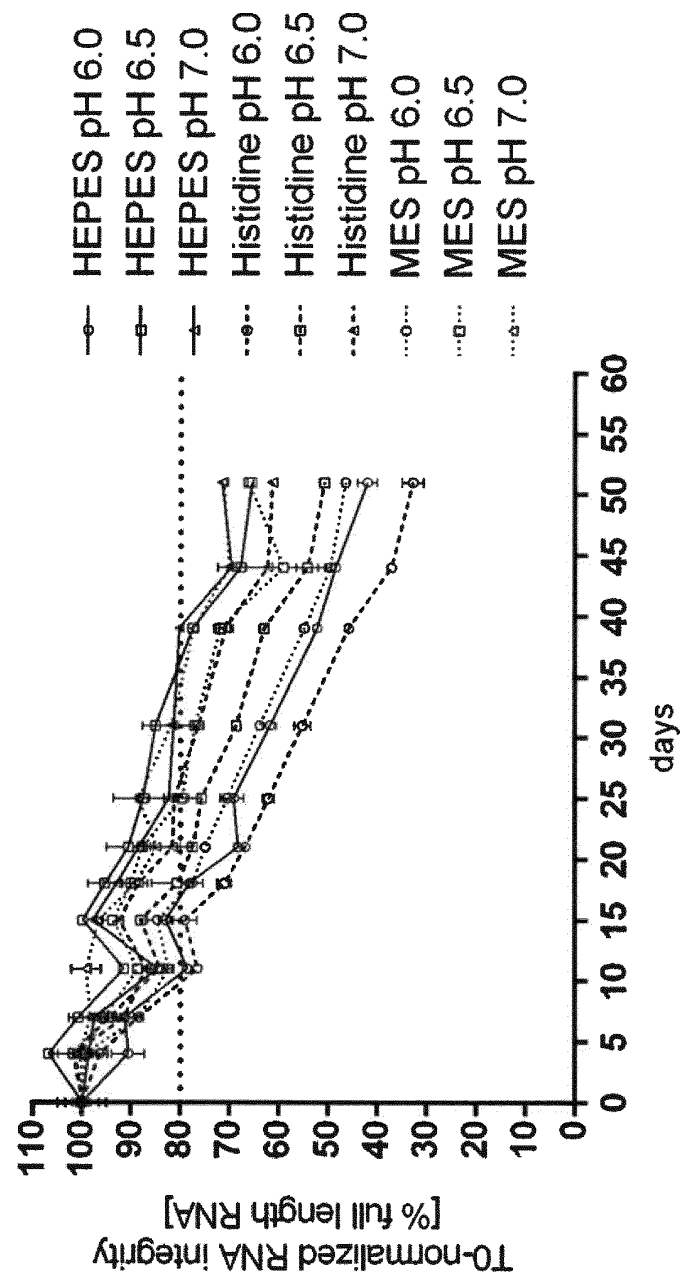


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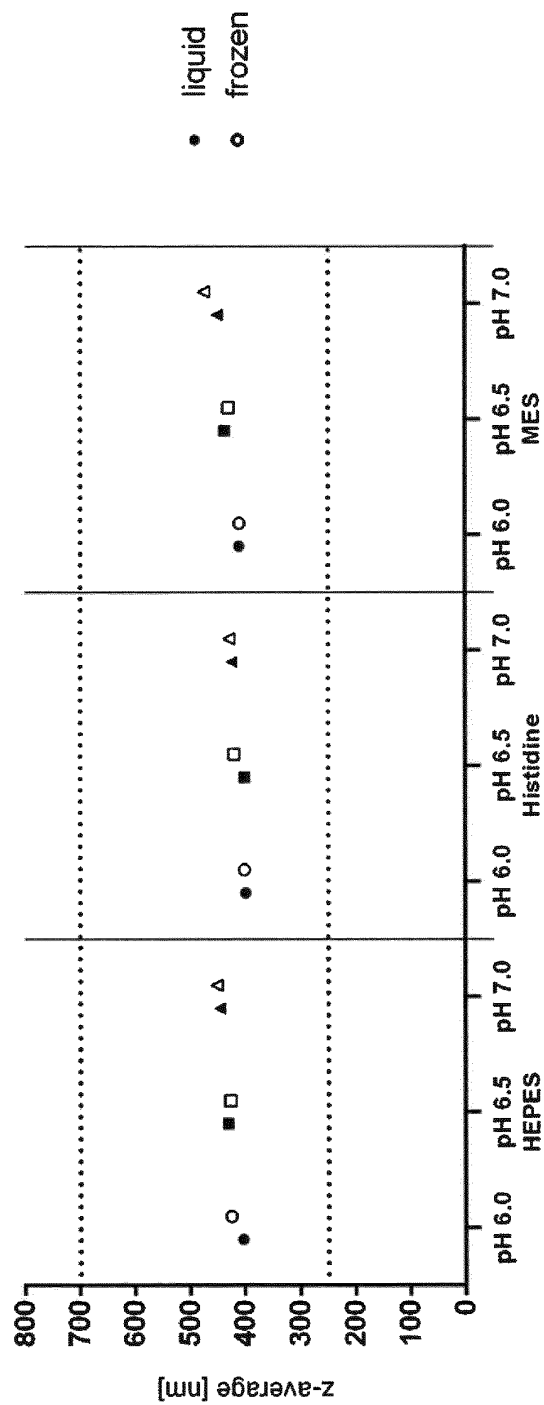


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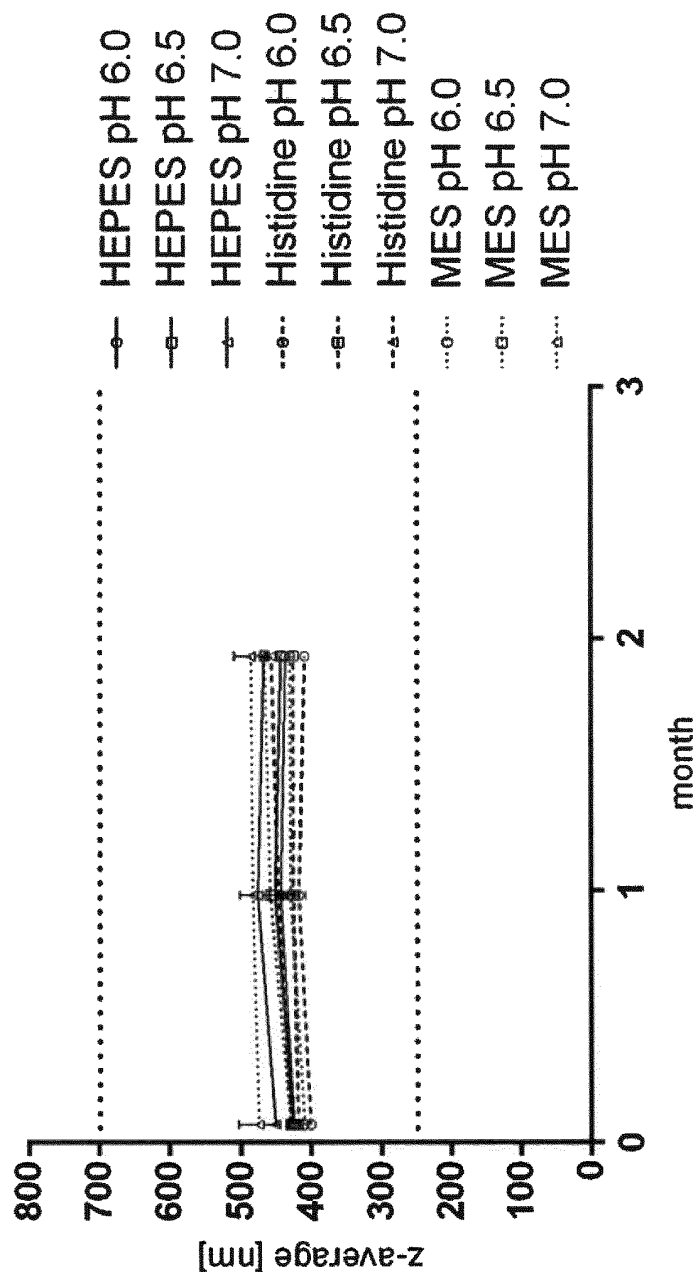


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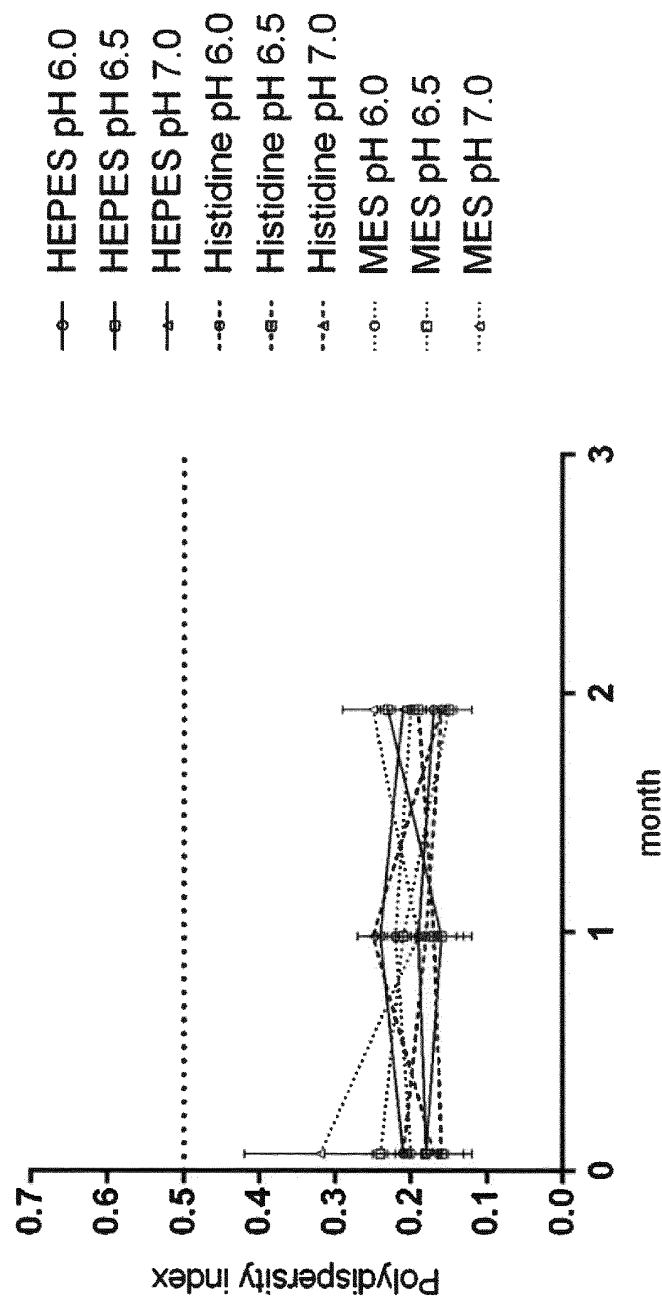


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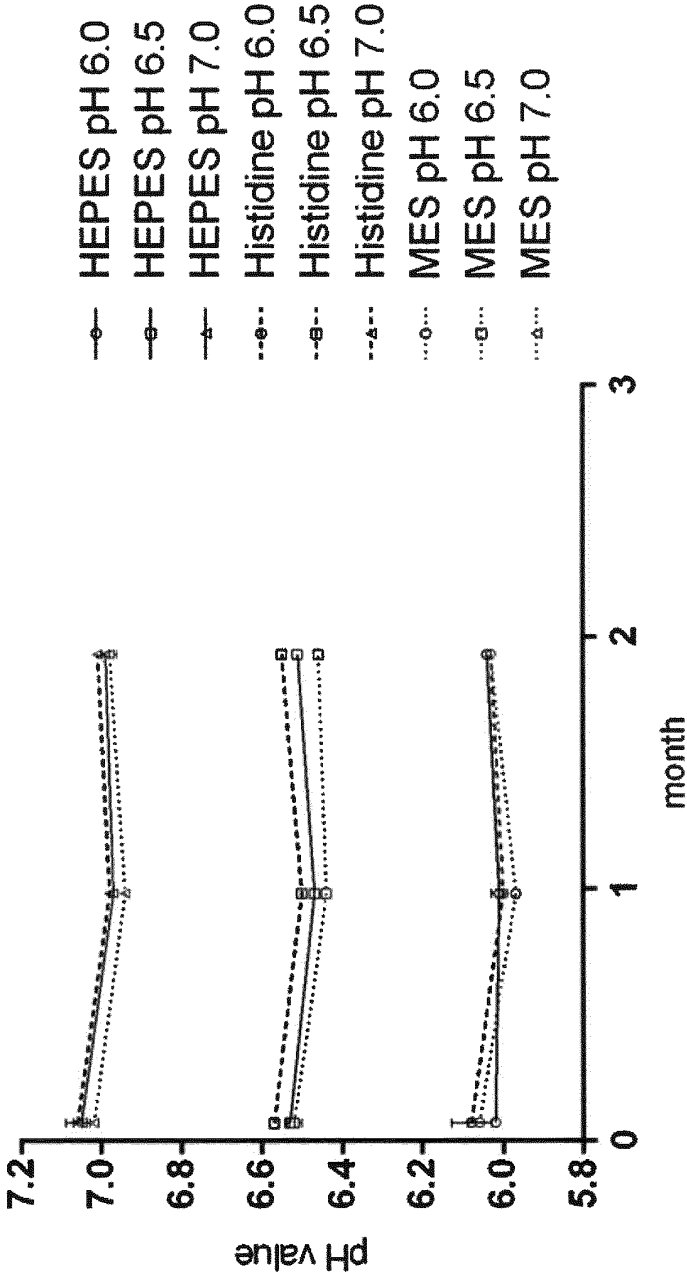


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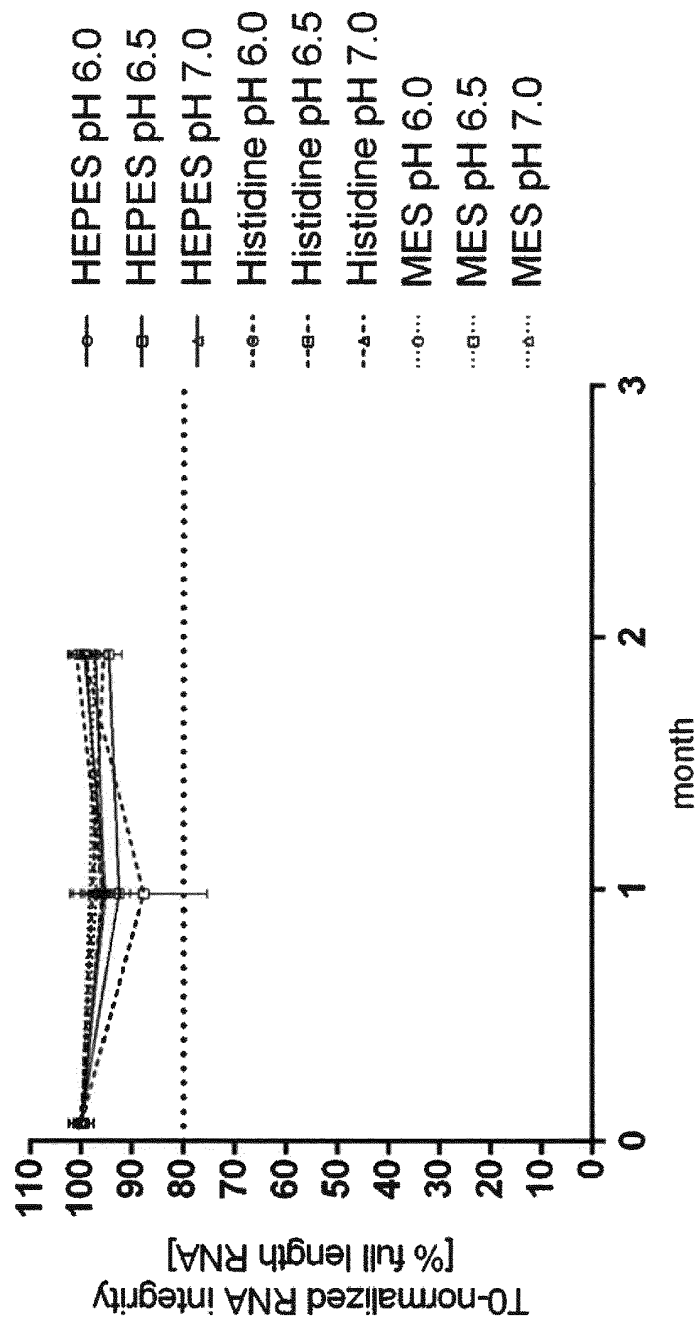


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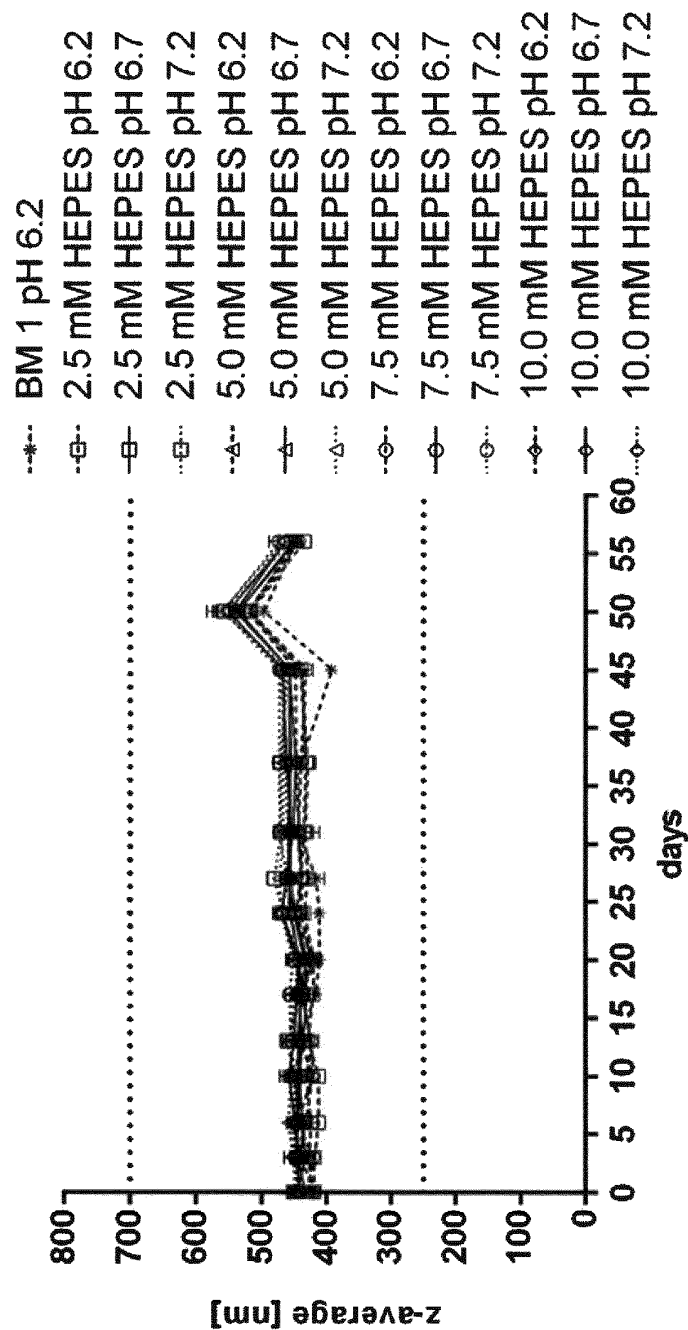


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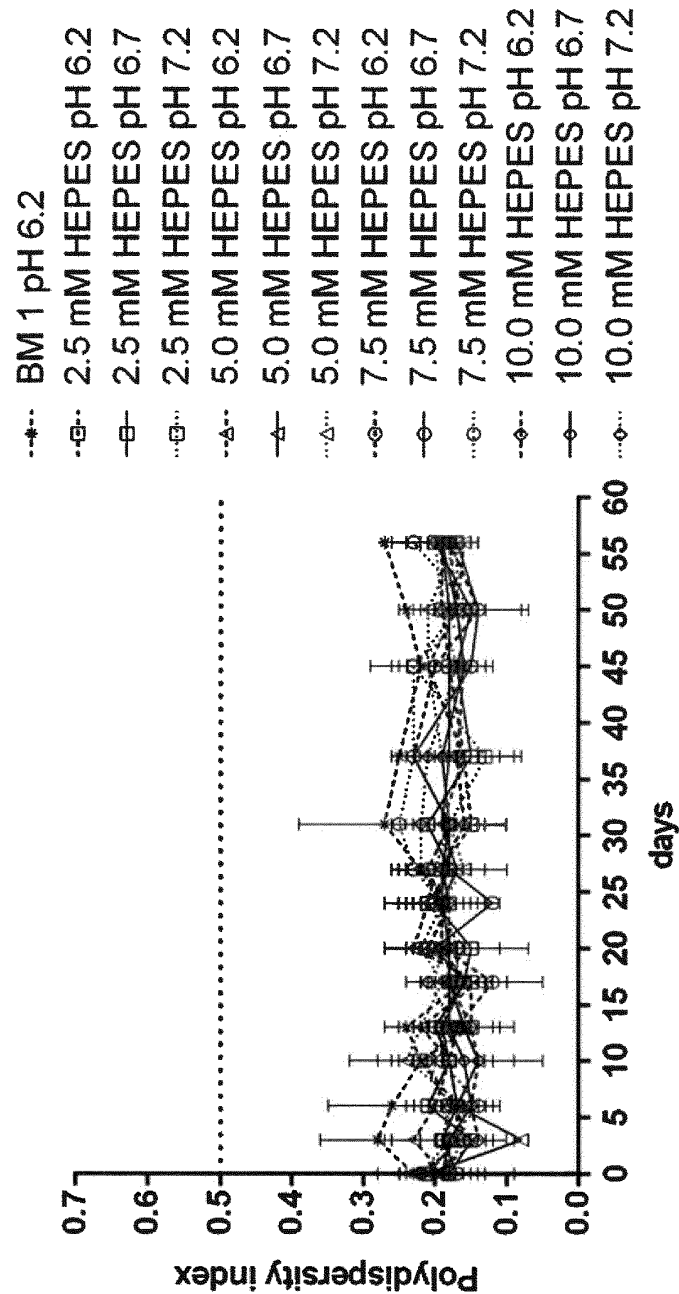


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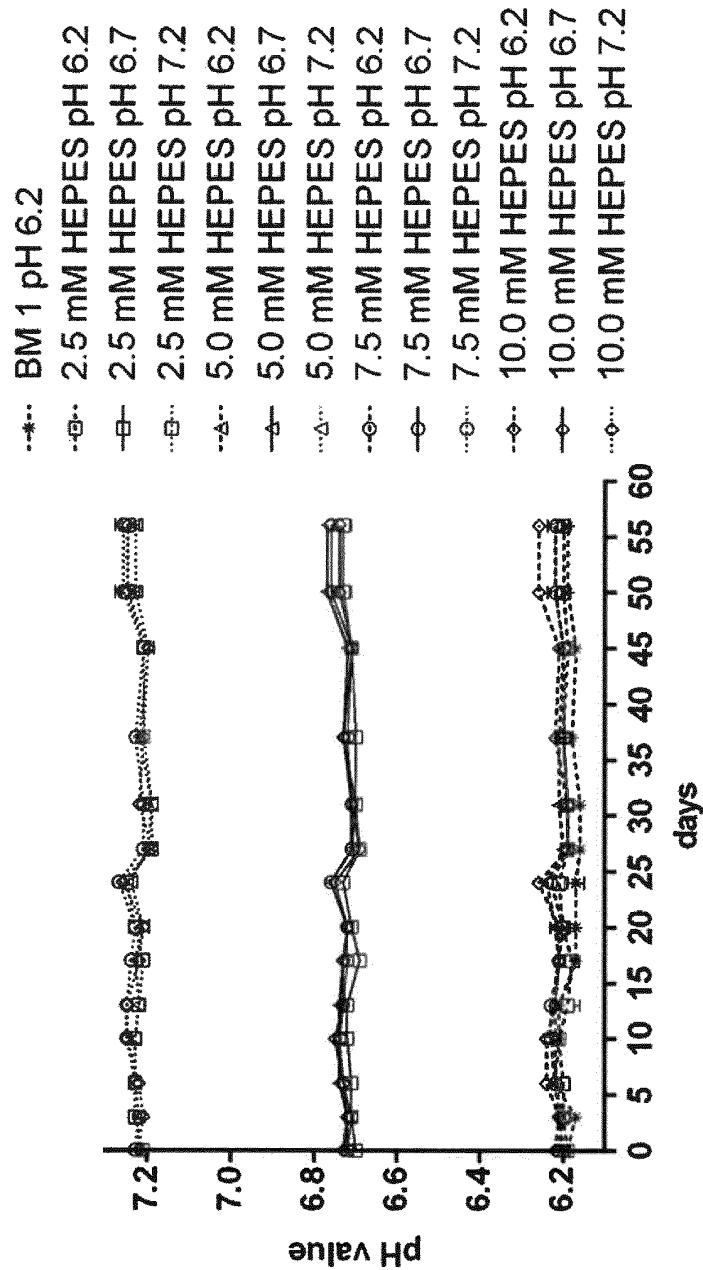


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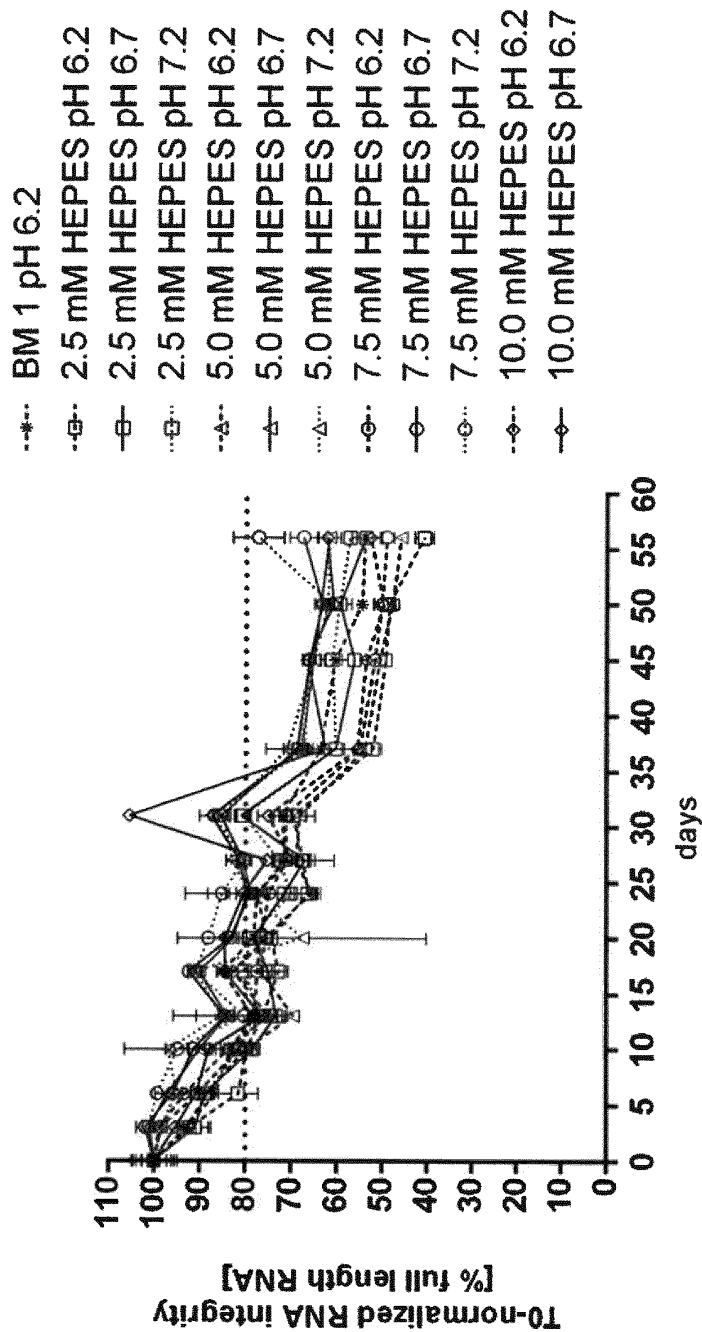


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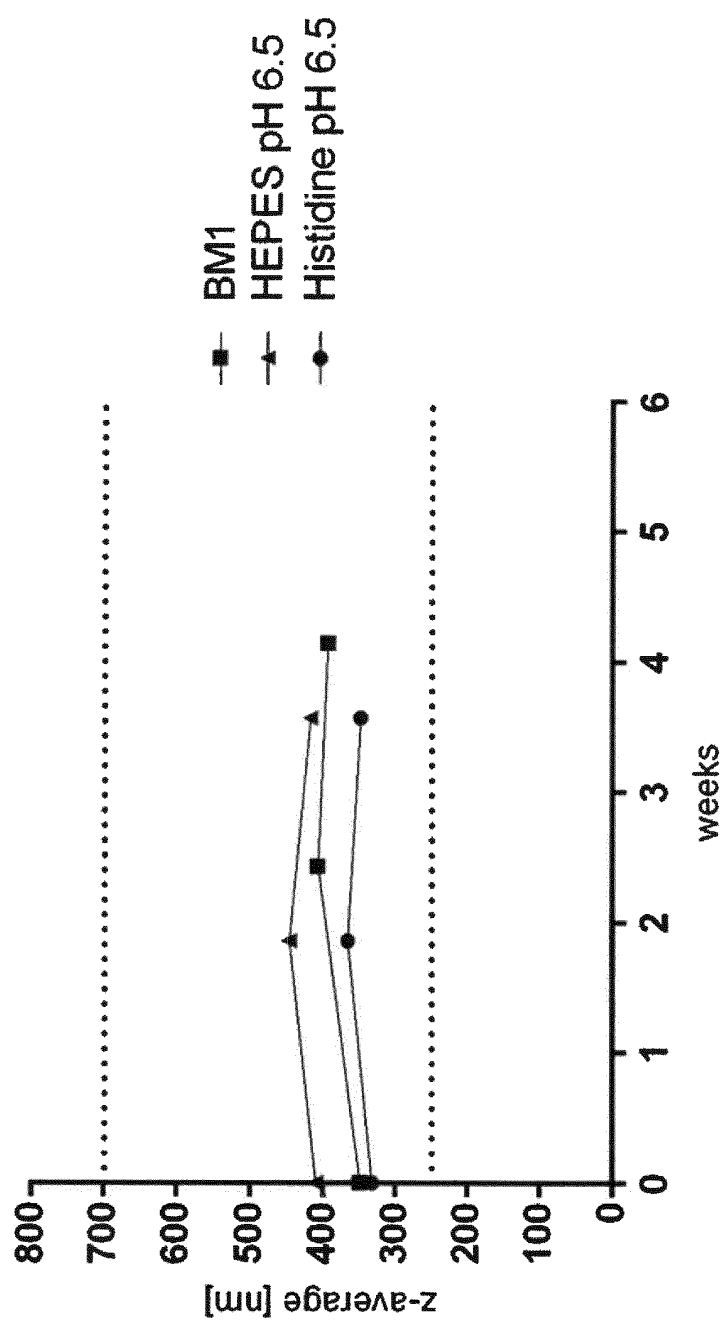


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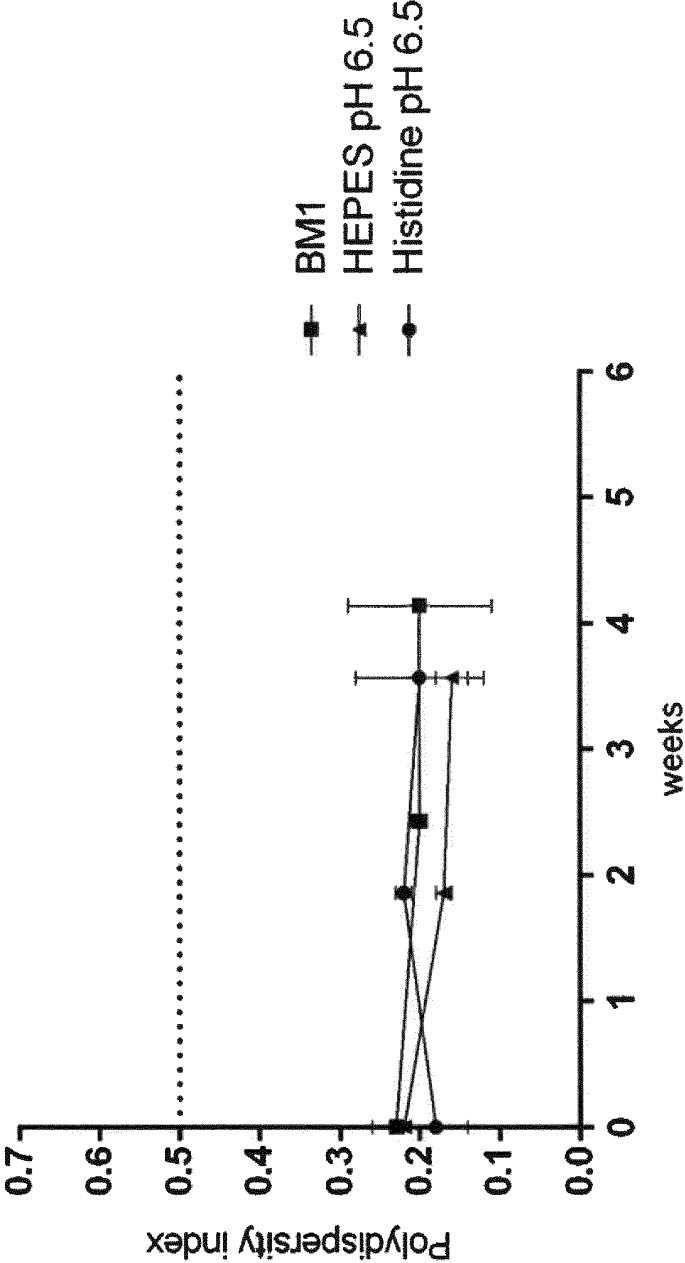


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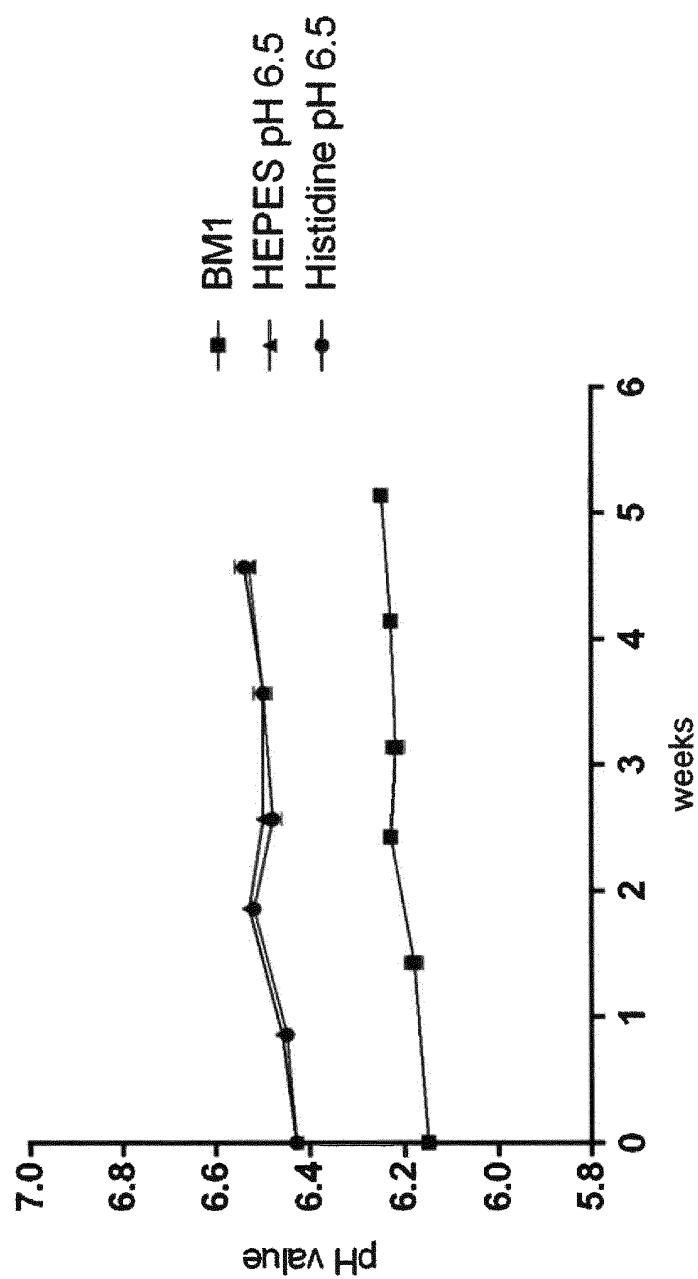


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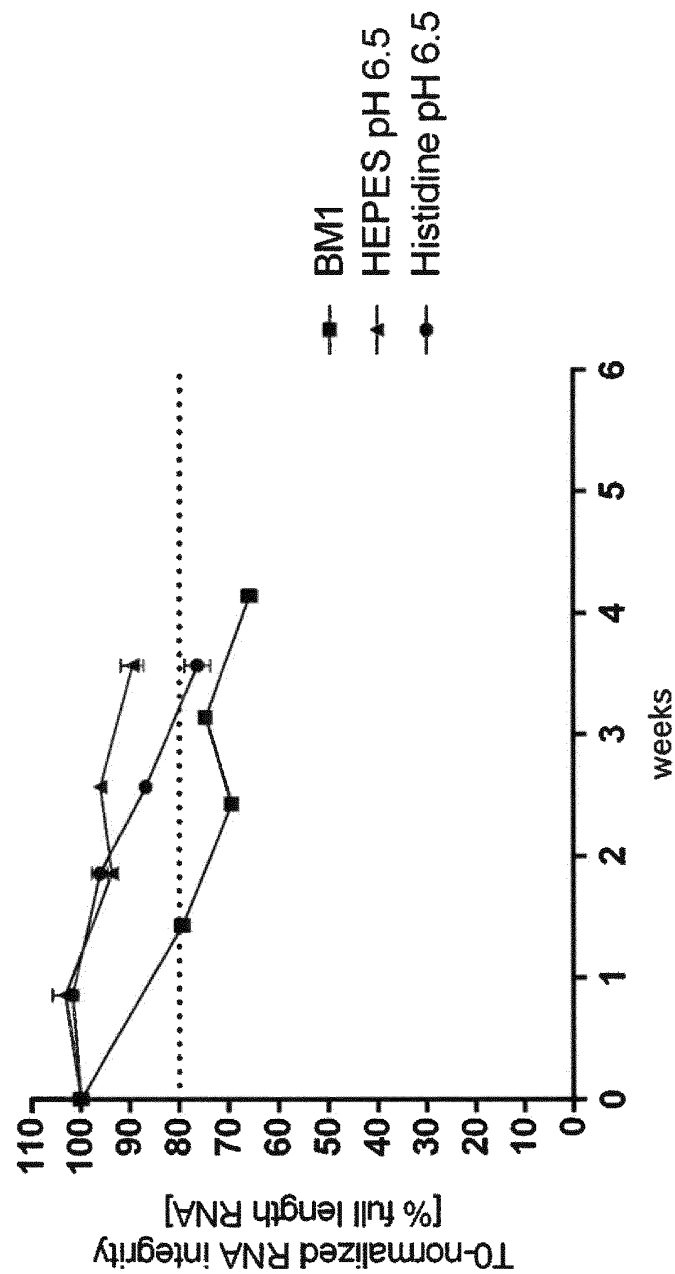


Figure 70

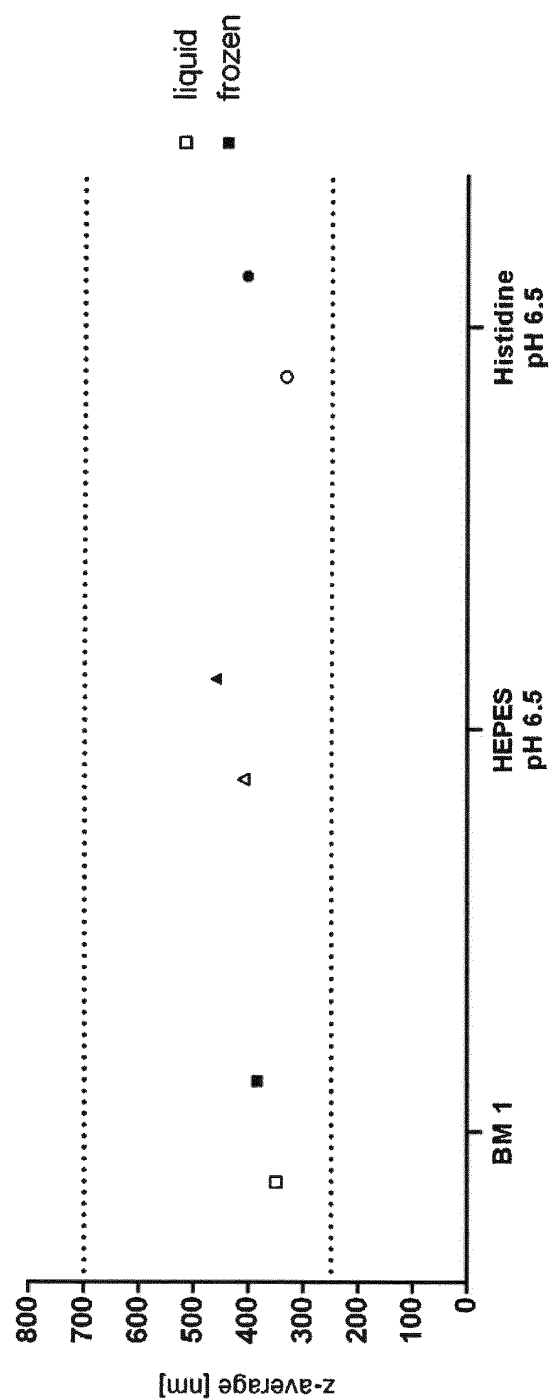


Figure 71

A

Formulation Component	Purpose	Current Formulation ¹		Proposed Formulation ²
		Before Diluent Addition	After Diluent Addition	
RNA	API	50 µg/mL	10 µg/mL	25 µg/mL
DOTMA	Drug Delivery	0.066 mg/mL	0.013 mg/mL	0.033 mg/mL
DOPE	Drug Delivery	0.037 mg/mL	0.007 mg/mL	0.018 mg/mL
HEPES	Buffer	7.5 mM	1.5 mM	5.0 mM
EDTA	Buffer/Chelator	2.5 mM	0.5 mM	2.5 mM
Sucrose	Cryoprotectant	220 mg/mL	44 mg/mL	130 mg/mL
NaCl	RNA Conditioner	20 mM	127 mM	8.2 mM
AcOH	DOPE stabilization	0 mM	0 mM	0.1 mM
pH	RNA stability	6.2	6.2	6.7

¹ DP diluted 5X with Sodium Chloride for Injection prior to administration² No dilution prior to administration**B**

Formulation Component	Purpose	Investigated range in DP		Proposed Formulation
		Minimum	Maximum	
RNA	API	20 µg/mL	30 µg/mL	25 µg/mL
DOTMA	Drug Delivery	0.026 mg/mL	0.039 mg/mL	0.033 mg/mL
DOPE	Drug Delivery	0.014 mg/mL	0.021 mg/mL	0.018 mg/mL
HEPES	Buffer	0 mM	10.0 mM	5.0 mM
EDTA	Buffer/Chelator	0 mM	3.5 mM	2.5 mM
Sucrose	Cryoprotectant	60 mg/mL	180 mg/mL	130 mg/mL
NaCl	RNA Conditioner	6.5 mM	10.5 mM	8.2 mM
AcOH	DOPE stabilization	0 mM	0.73 mM	0.1 mM
pH	RNA Stability	5.5	7.2	6.7

Figure 72

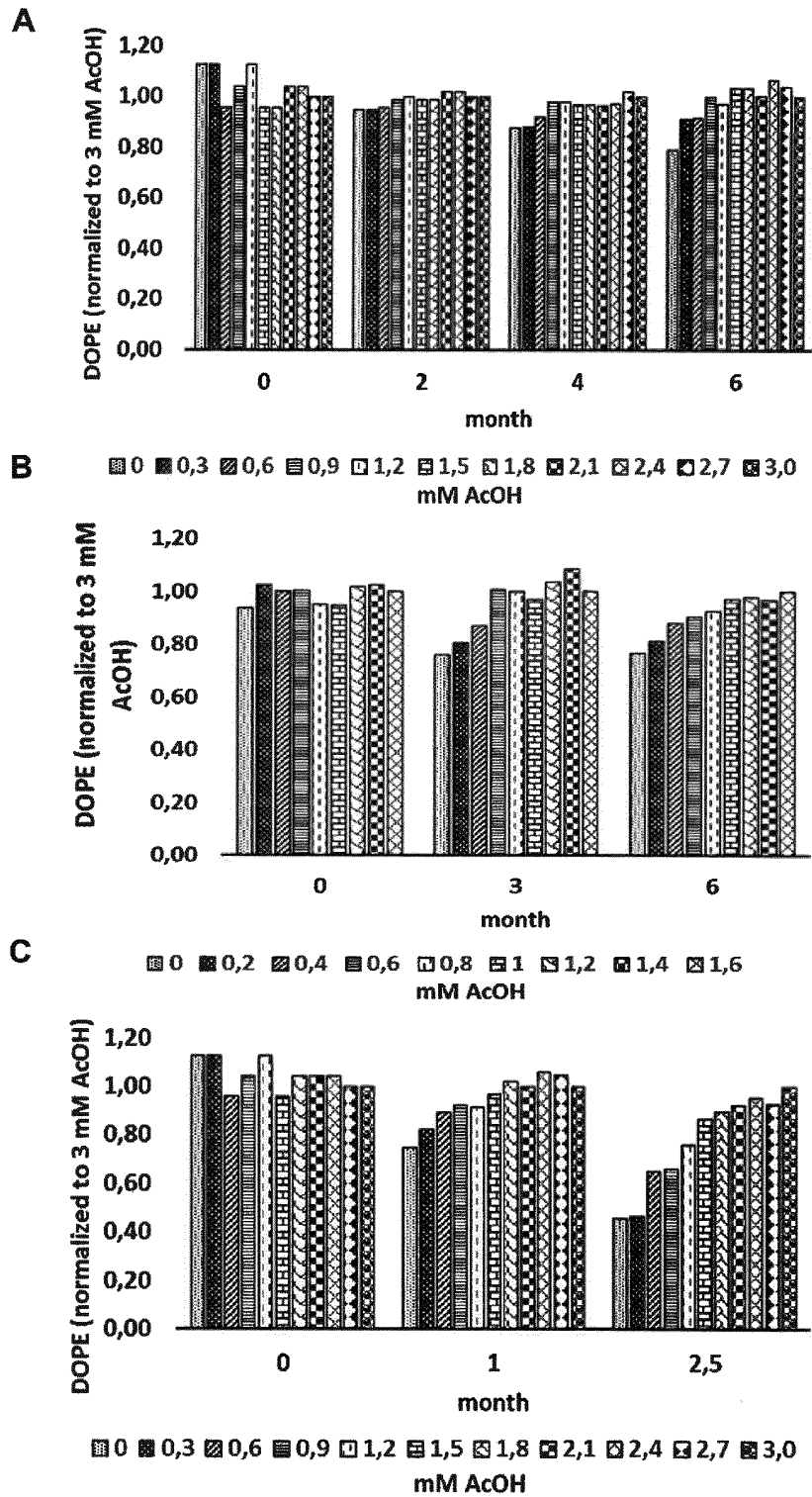


Figure 73

Formulation Component	Purpose	Current Formulation ¹		Proposed new DS formulation
		Before Dilution (nominal)	After WFI and Saline Addition	
RNA	API	0.42 mg/mL	0.26-0.36 mg/mL	0.26-0.36 mg/mL ¹
HEPES	Buffer	18 mM	12.8-17.3 mM	18 mM
EDTA	Buffer/Chelator	18 mM	12.8-17.3 mM	18 mM
NaCl	RNA Conditioner	n.a.	100 mM	100 mM
pH	RNA stability	6.2	6.2	7.0

¹ RNA concentration to be adjusted to respective DOTMA concentration; range applies to current DOTMA specification in liposomes

Figure 74

RNA Concentration in DP	Two DP Vials				One DP Vial			
	Dose Volume per Vial (mL)				Dose Volume (mL)			
	15	25	50	100	15	25	50	100
Dose (µg)								
20 µg/mL	0.38	0.63	1.25	2.50	0.75	1.25	2.50	5.00
25 µg/mL	0.30	0.50	1.00	2.00	0.60	1.00	2.00	4.00

Figure 75

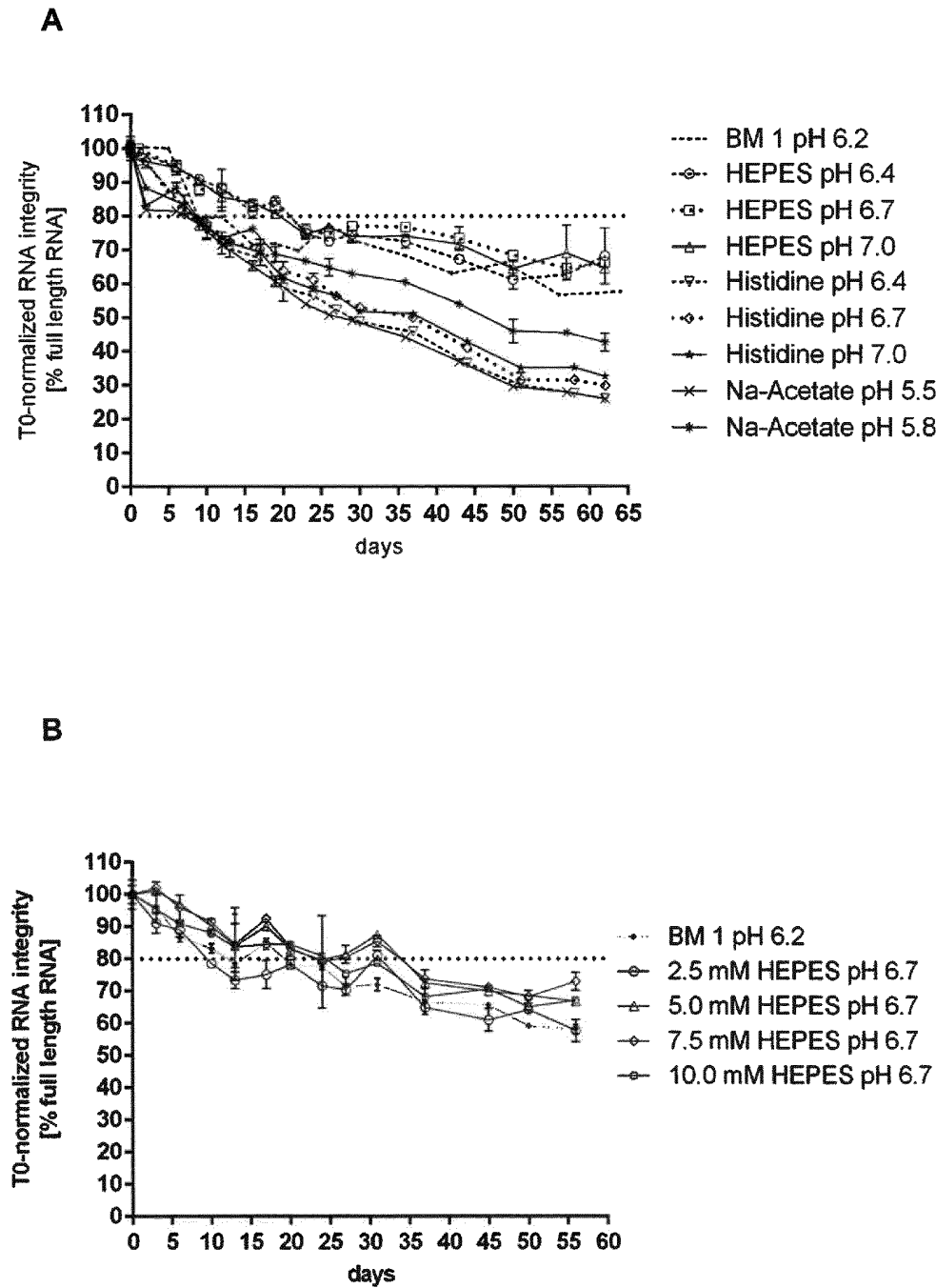


Figure 76

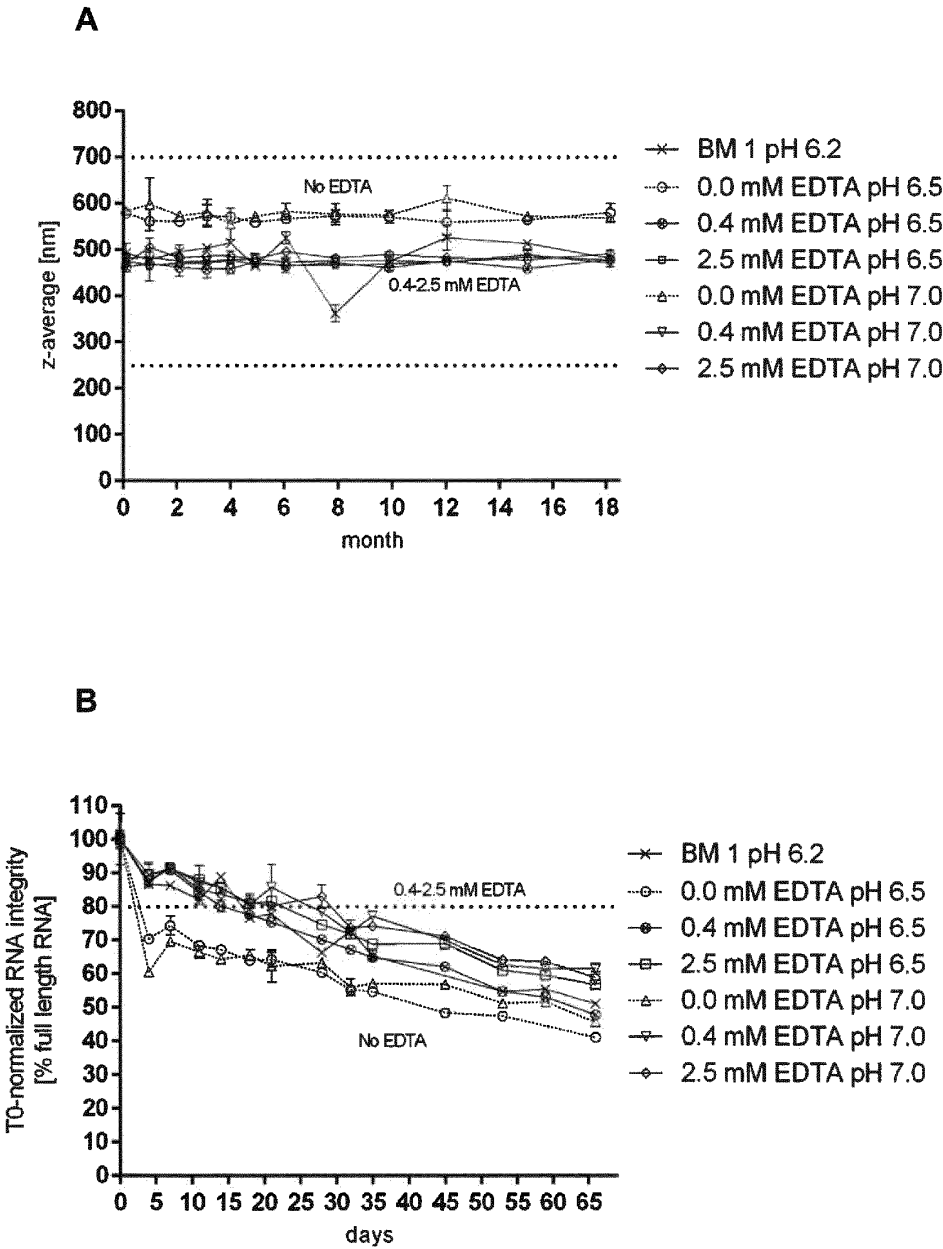


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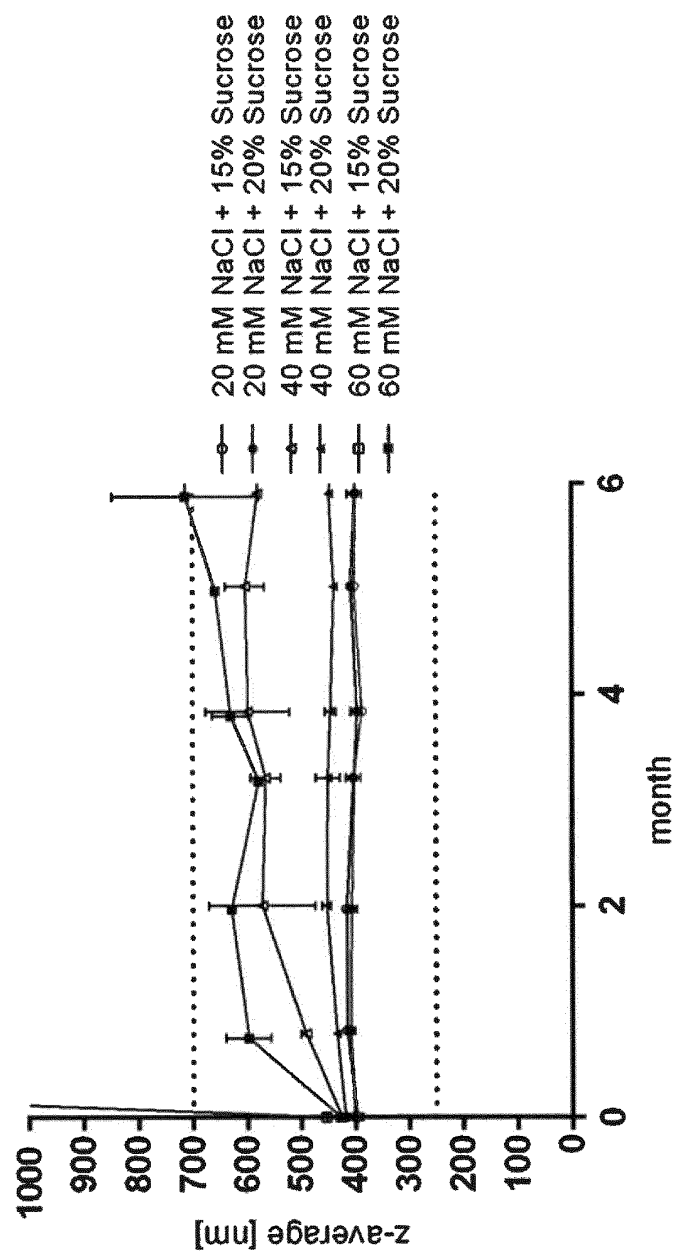


Figure 78

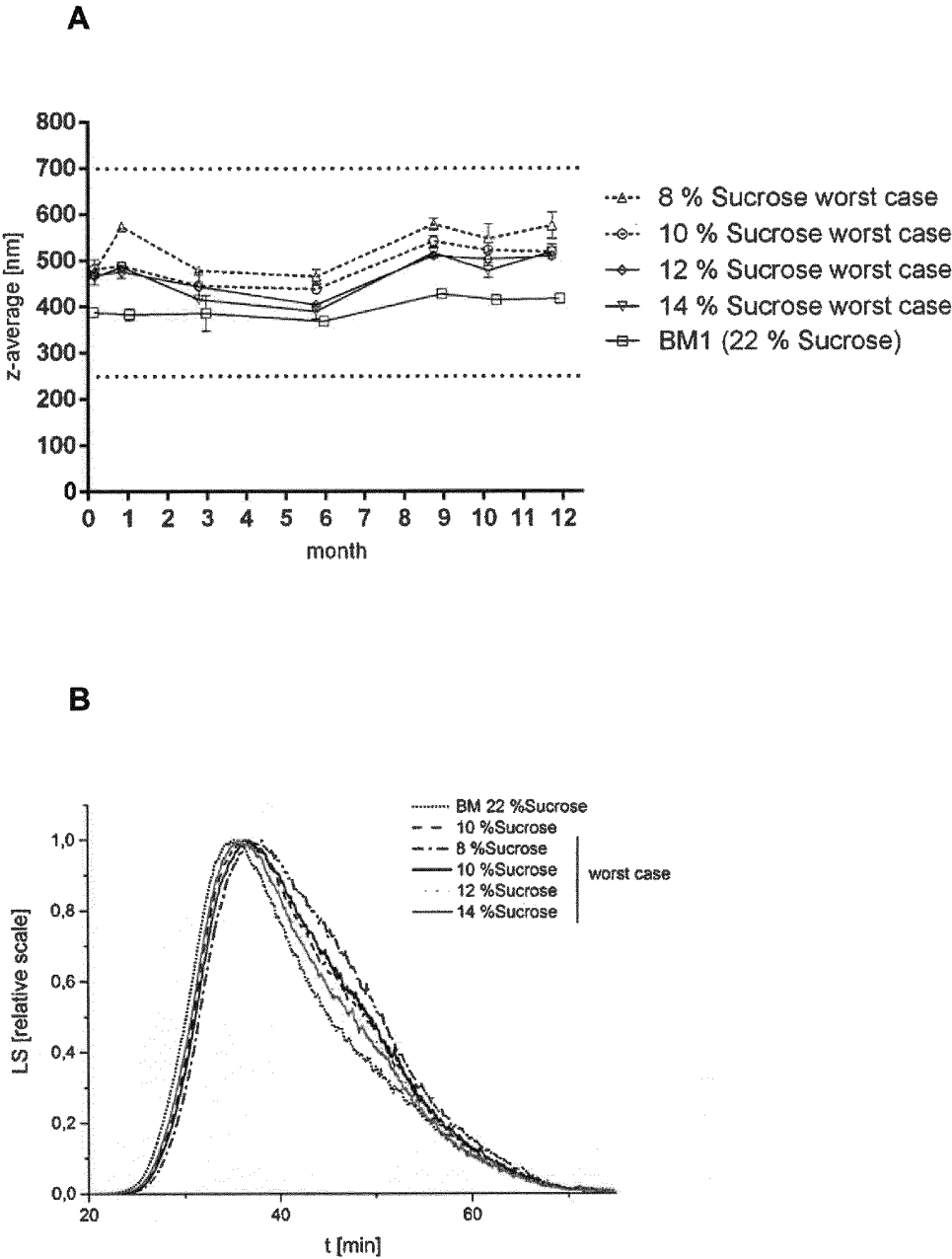


Figure 79

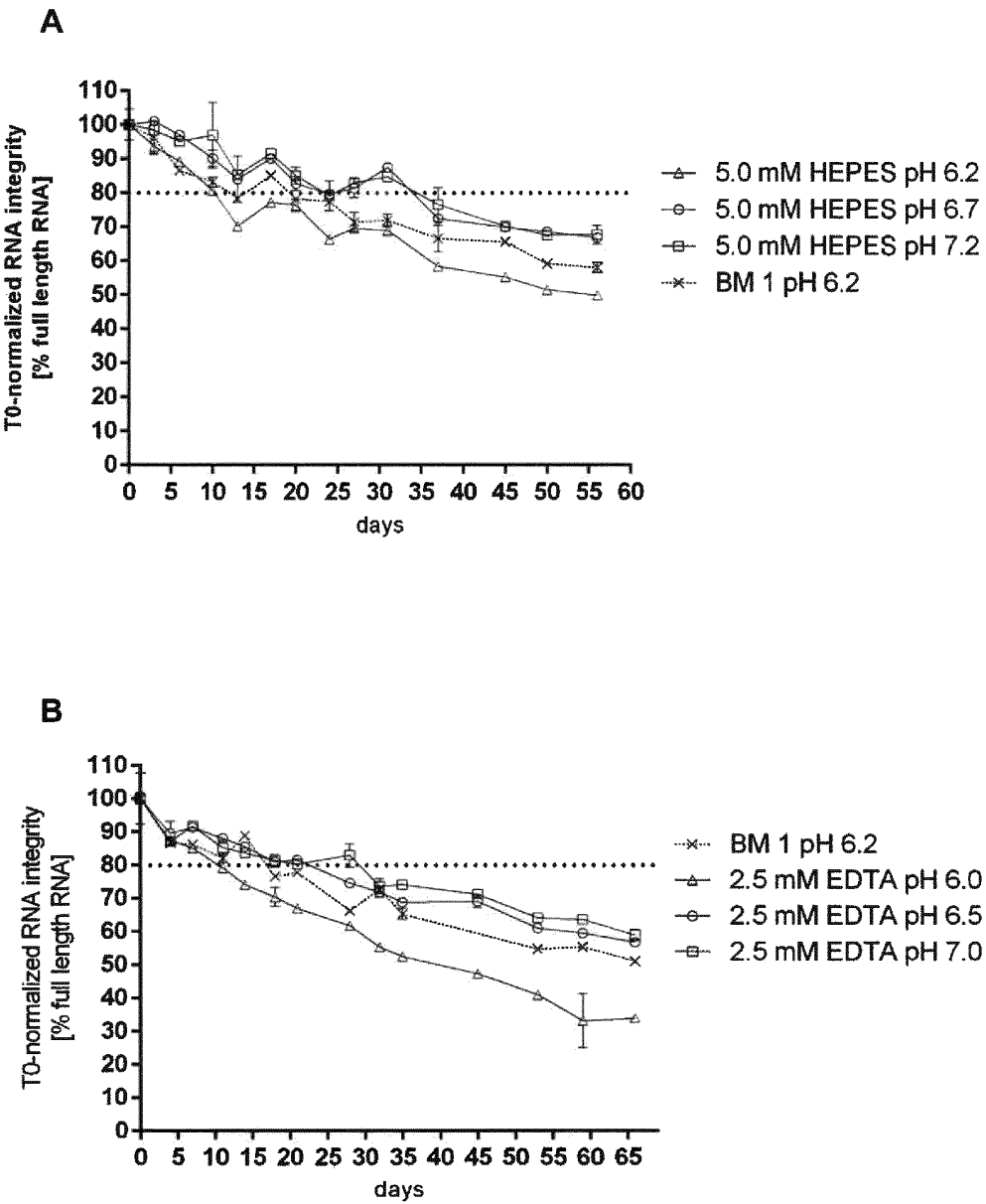


Figure 80

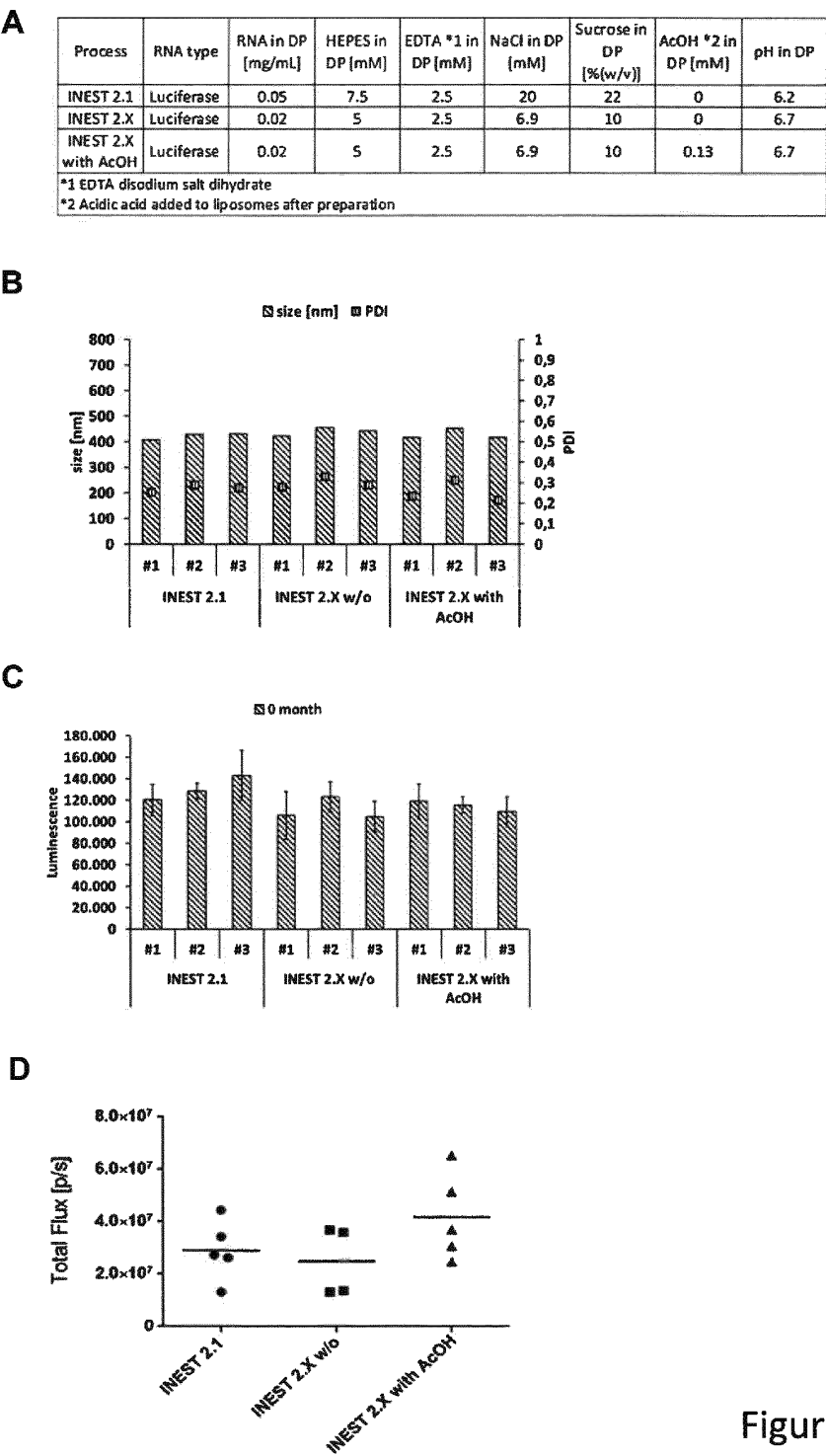


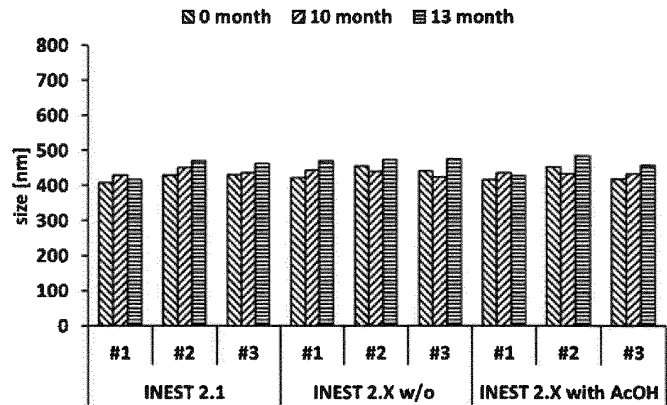
Figure 81

A

Process	RNA type	RNA in DP [mg/mL]	HEPES in DP [mM]	EDTA *1 in DP [mM]	NaCl in DP [mM]	Sucrose in DP [% (w/v)]	AcOH *2 in DP [mM]	pH in DP
INEST 2.1	Luciferase	0.05	7.5	2.5	20	22	0	6.2
INEST 2.X	Luciferase	0.02	5	2.5	6.9	10	0	6.7
INEST 2.X with AcOH	Luciferase	0.02	5	2.5	6.9	10	0.13	6.7

*1 EDTA disodium salt dihydrate
*2 Acidic acid added to liposomes after preparation

B



C

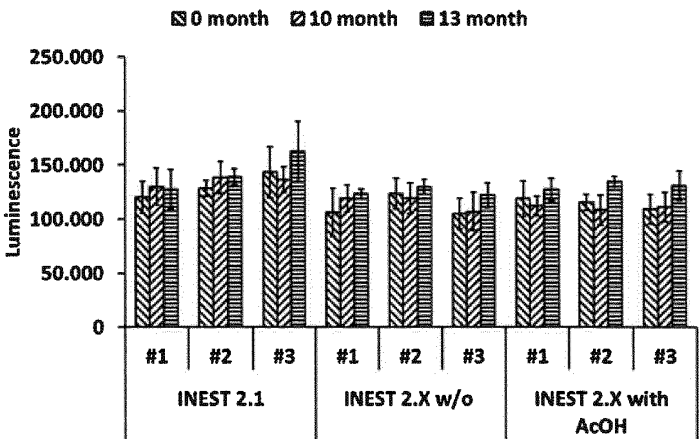


Figure 82