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(54) **READY-TO-USE POTASSIUM PHOSPHATES
IN SODIUM CHLORIDE SOLUTIONS**

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9/08 (2013.01)

(57) **ABSTRACT**

A ready-to-use (RTU) potassium phosphates in sodium
chloride solution for phosphorus replacement therapy
includes potassium phosphate and sodium chloride at a fixed
volume with 15 mmol/100 mL phosphorus and 22 mEq/100
mL potassium and less than 50 mcg/L aluminum.

Amneal Exhibit 1006, Page 1 of 41
Amneal Pharmaceuticals, Inc. v. Nivagen Pharmaceuticals, Inc.
IPR2025-00731

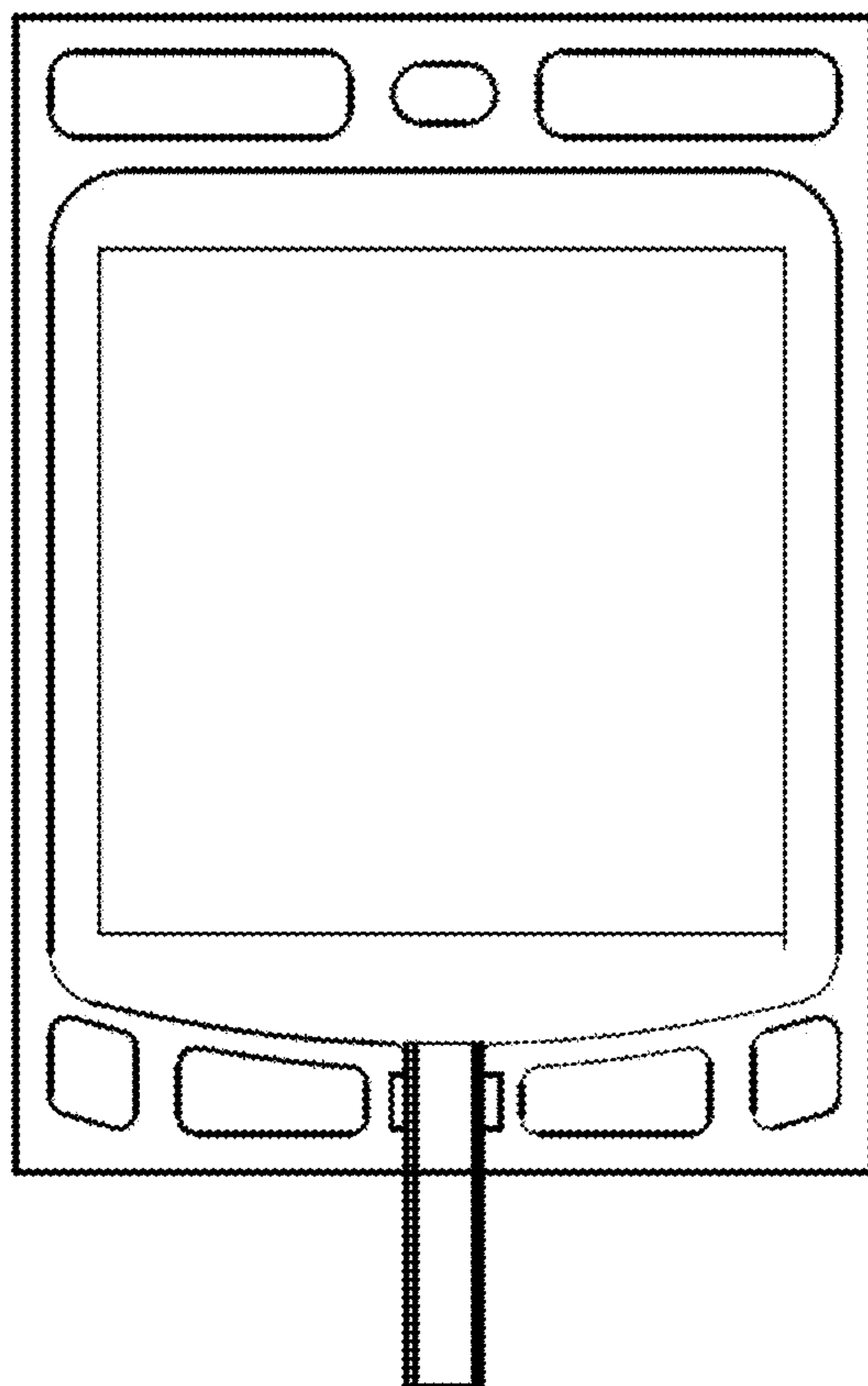


FIG.1

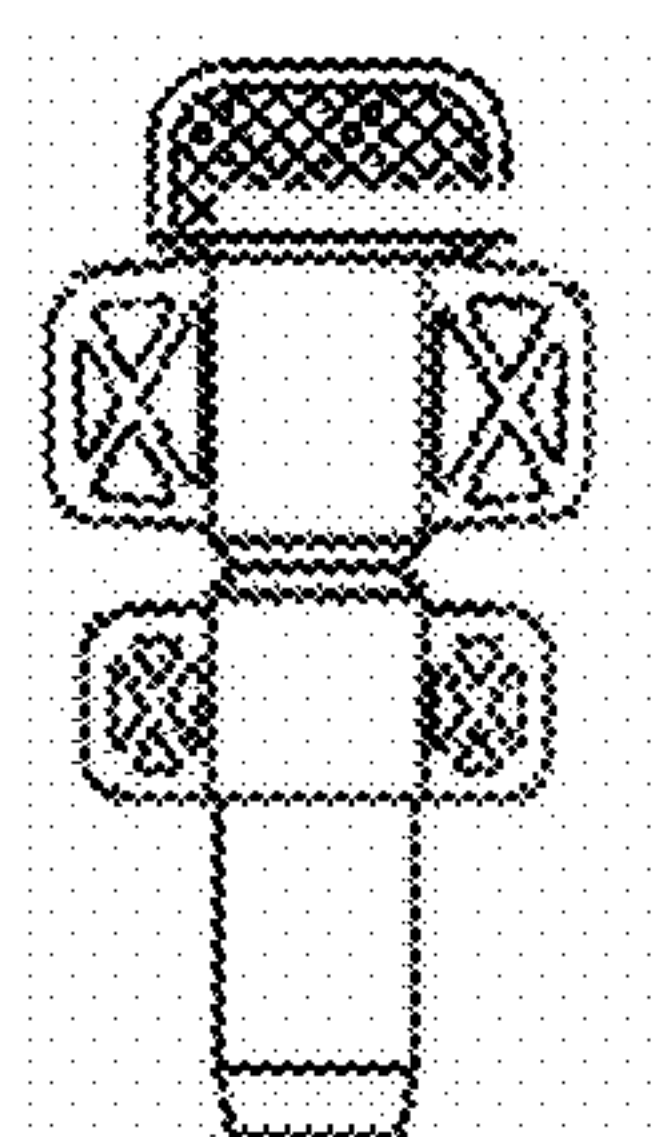


FIG.2



FIG.3

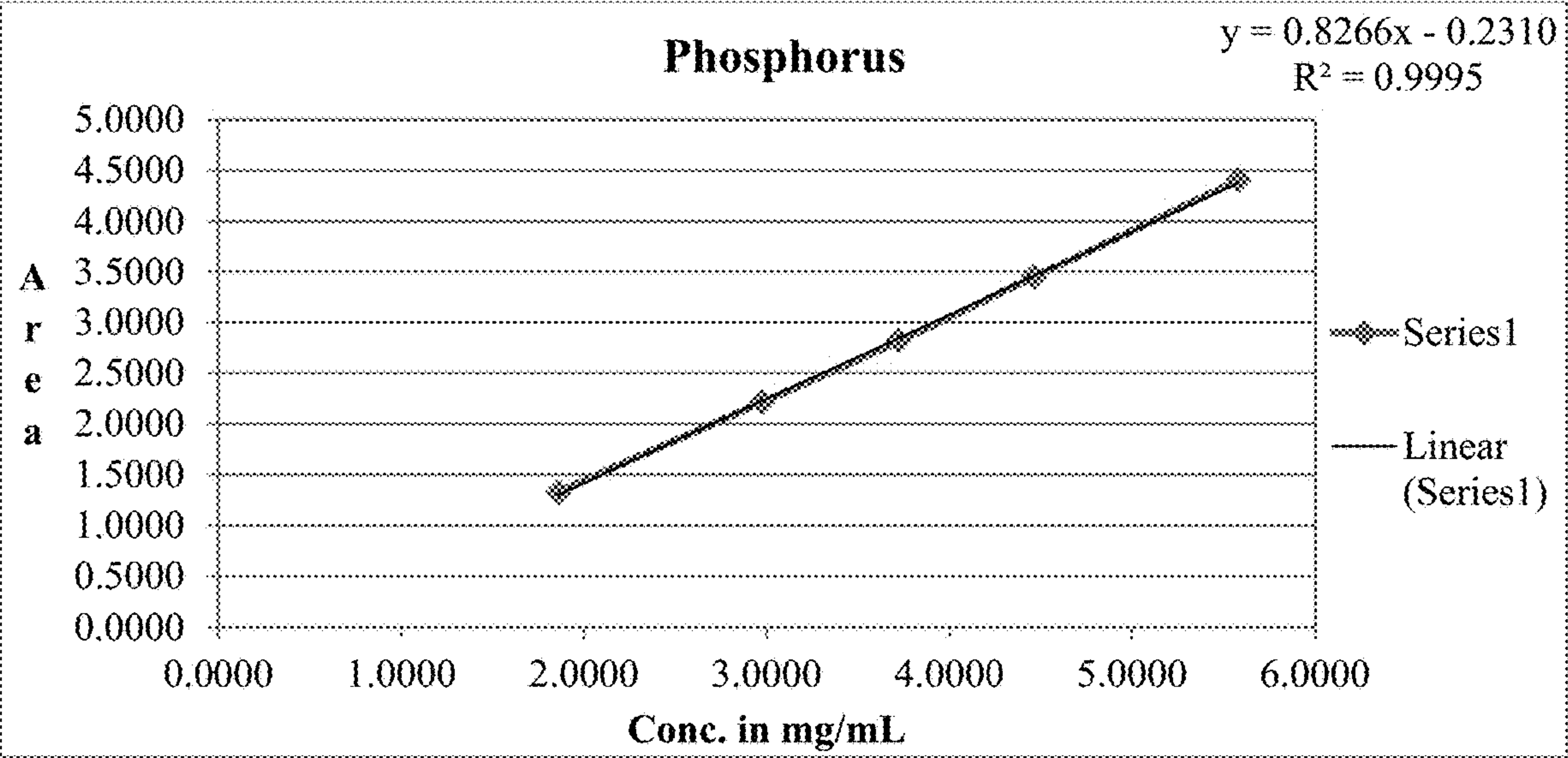


FIG.4

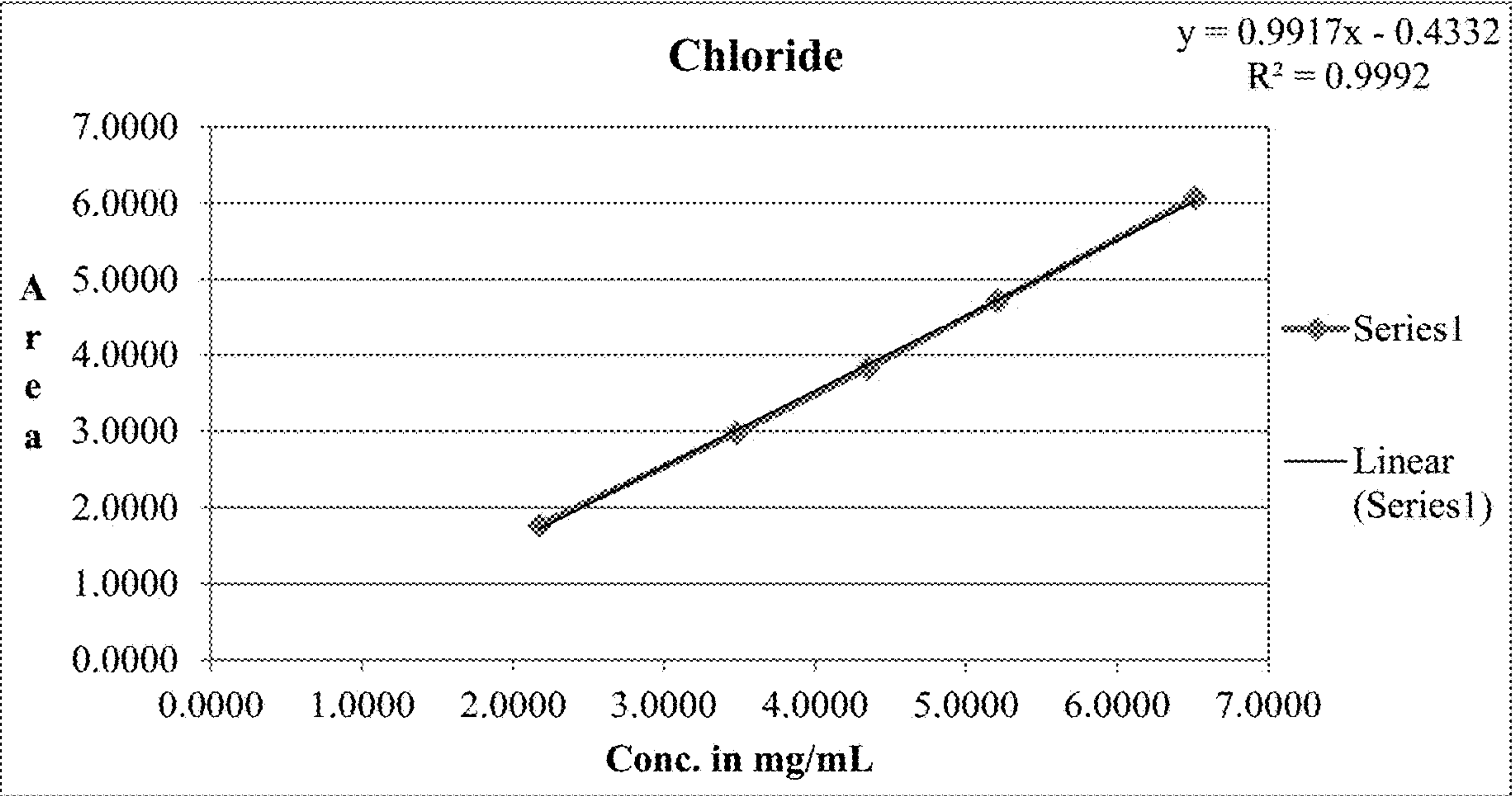


FIG.5

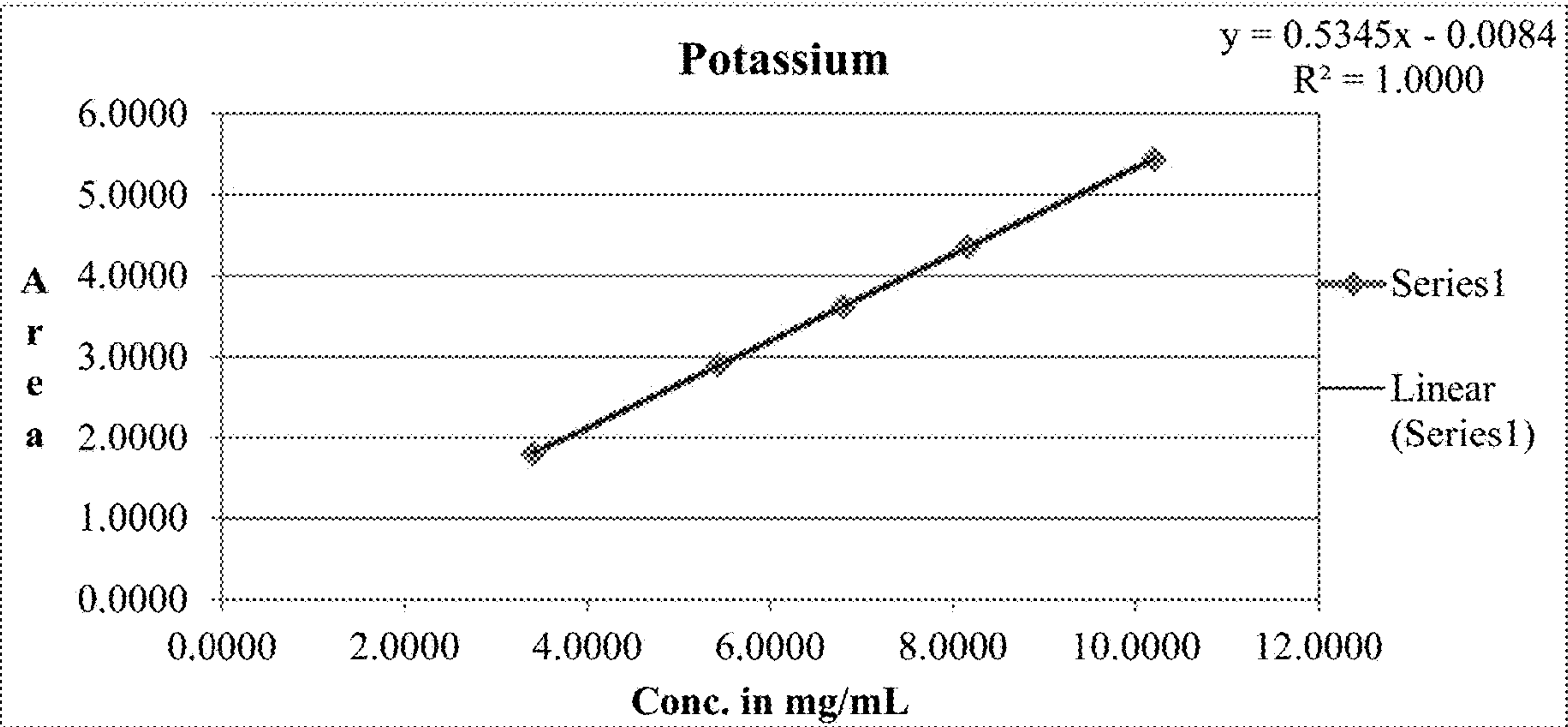


FIG.6

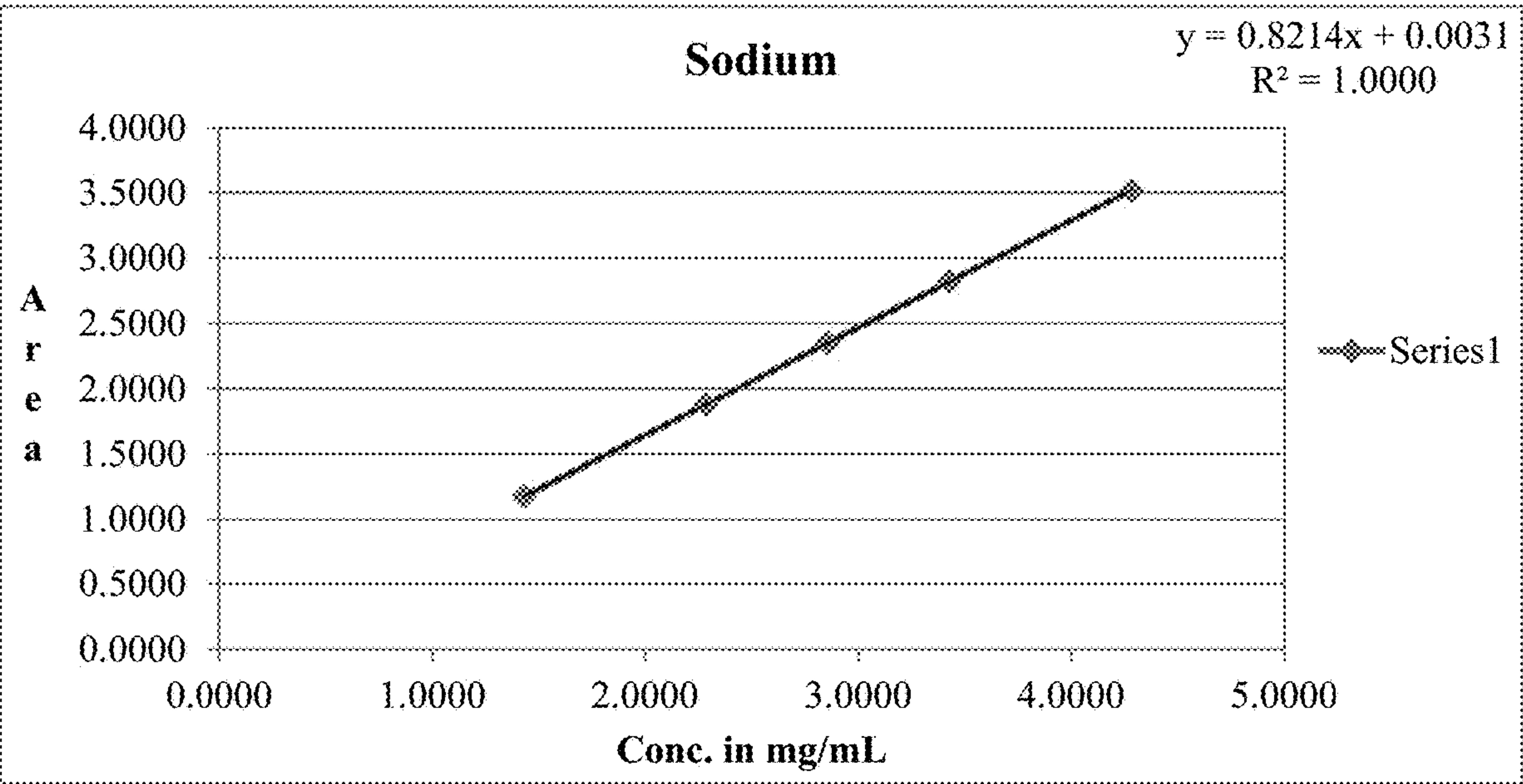


FIG.7

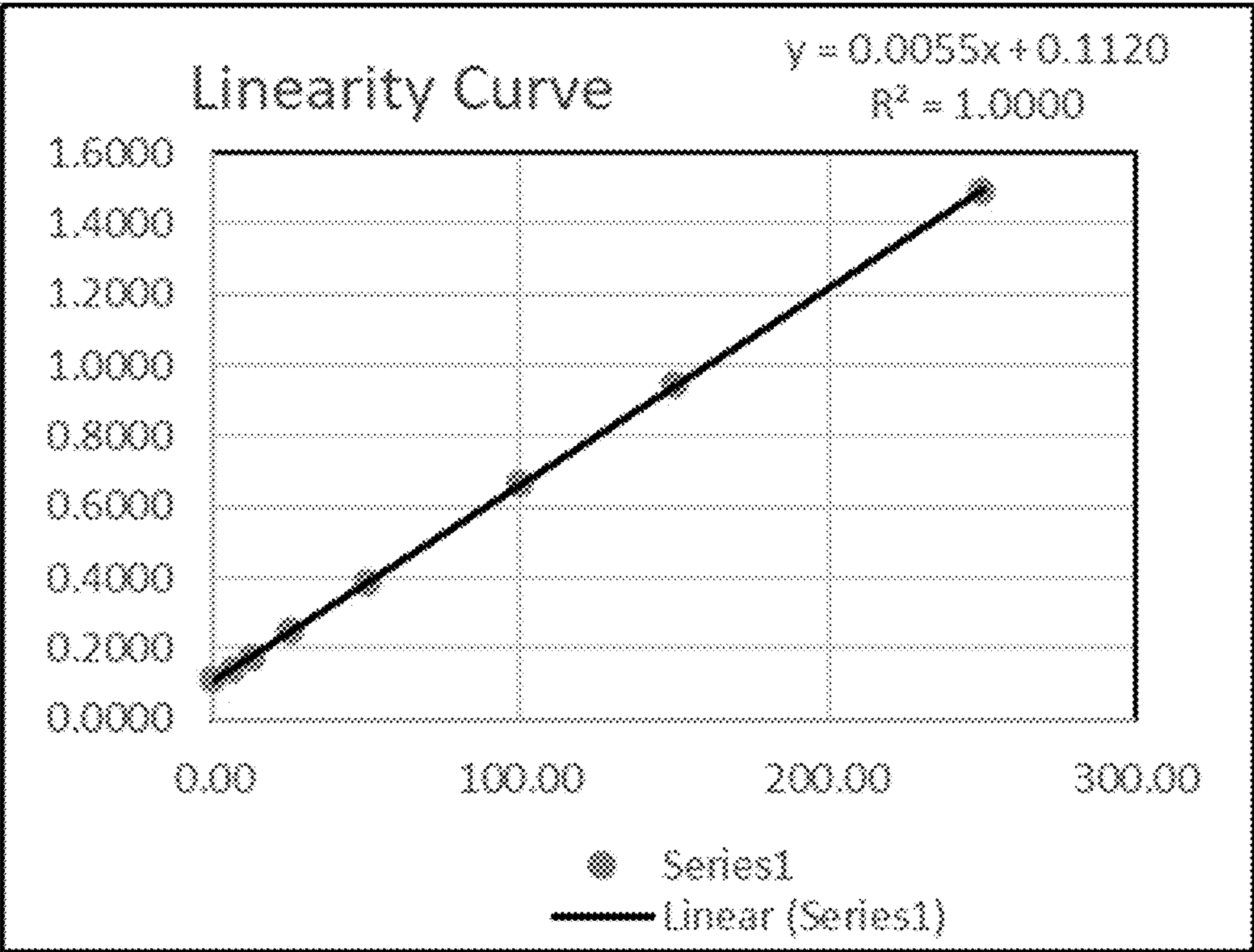


FIG.8

B. No. #NPD2052										
Autoclave @ 121°C for 15 Minutes										
TechnoFlex 1T PP Bag + Al Pouch										
Test		Condition								
		Bulk Solution	Initial	3M 25/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15	
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH of Solution		6.543	6.551	6.61	6.56	6.62	6.56	6.57		Not Analyzed (Sample sent to Samova for AI content development at 3 months)
Osmolality (mOsm/kg)		576	569	565	606	592	588	595		
LPC	10µm	227	553	113	427	80	233	187		
	25µm	20	13	7	13	13	7	0		
Assay of Anions	% Phosphorus	101.0	101.0	98.0	99.1	94.4	101.6	99.5		
	% Chloride	102.0	101.8	96.7	101.2	92.5	102.3	99.1		
Assay of Cations	% Potassium	102.2	102.0	98.6	98.3	94.3	101.7	98.6		
	% Sodium	99.8	99.7	99.1	100.5	92.8	101.6	98.5		
TechnoFlex 1T PP Bag (Without Al Pouches)										
Test		Condition								
		Bulk Solution	Initial	3M 25/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15	
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH of Solution		6.543	6.551	6.58	6.58	6.57	6.56	6.54	6.54	
Osmolality (mOsm/kg)		576	569	571	608	622	578	560	615	
LPC	10µm	227	553	227	440	940	140	407	280	
	25µm	20	13	20	7	20	0	27	13	
Assay of Anions	% Phosphorus	101.0	101.0	99.3	100.5	101.0	101.7	101.4	110.2	
	% Chloride	102.0	101.8	98.4	99.0	8.0	99.8	100.4	108.0	
Assay of Cations	% Potassium	102.2	102.0	100.5	99.6	100.3	99.9	99.8	106.0	
	% Sodium	99.8	99.7	100.9	98.5	102.7	99.7	99.7	107.7	
* CCS- A Clear colorless solution, free from visible foreign particles										

FIG.9

Autoclave @ 121°C for 15 Minutes											
Grifols 1T PP Bag + Al Pouch											
Test		Condition									
		Bulk Solution	Initial	3M 25/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15		
Assay of Anions	% Phosphorus	101.0	100.9	98.8	98.8	95.0	100.3	100.0	100.3		
	% Chloride	102.0	101.9	98.4	97.7	94.6	99.3	99.0	98.6		
Assay of Cations	% Potassium	102.2	101.8	99.9	98.1	96.0	99.7	98.7	98.6		
	% Sodium	99.8	99.4	100.9	96.9	94.6	99.2	98.6	98.2		
Grifols 1T PP Bag (Without Al Pouches)											
Test		Condition									
		Bulk Solution	Initial	3M 25/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15		
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS		
	pH of Solution	6.543	6.548	6.62	6.36	6.58	6.39	6.56	6.36		
LPC	Osmolality (mOsm/kg)	576	579	574	604	626	581	591	628		
	10µm	227	187	107	60	387	193	173	107		
Assay of Anions	25µm	20	0	7	0	27	7	33	33		
	% Phosphorus	101.0	100.9	99.5	100.8	102.0	102.8	102.1	111.8		
Assay of Cations	% Chloride	102.0	101.9	99.2	99.0	100.5	100.6	101.0	109.7		
	% Potassium	102.2	101.8	101.2	99.7	102.9	100.4	100.7	109.6		
	% Sodium	99.8	99.4	101.8	98.7	101.3	99.8	100.4	109.3		
* CCS- A Clear colorless solution, free from visible foreign particles											

FIG.9 cont'd

Autoclave @ 121°C for 15 Minutes											
TechnoFlex 2T PP Bag + Al Punch											
Test		Condition									
		Bulk Solution	Initial	3M 25/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15		
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution		6.543	6.549	6.61	6.63	6.58	6.54	6.57	6.58		
Osmolality (mOsm/kg)		576	570	568	601	569	577	577	572		
LPC	10µm	227	287	360	893	183	520	180	100		
	25µm	20	17	30	33	20	47	27	13		
Assay of Anions	% Phosphorus	101.0	101.6	98.5	98.4	97.9	100.3	98.7	100.5		
	% Chloride	102.0	102.6	97.7	97.5	96.2	99.4	97.7	98.6		
Assay of Cations	% Potassium	102.2	102.5	99.7	97.7	98.3	99.5	97.4	98.9		
	% Sodium	99.8	100.1	100.2	96.7	96.6	99.0	97.3	98.6		
TechnoFlex 2T PP Bag (Without Al Punches)											
Test		Condition									
		Bulk Solution	Initial	3M 25/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15		
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution		6.543	6.549	6.63	6.58	6.6	6.57	6.57	6.58		
Osmolality (mOsm/kg)		576	570	573	604	620	584	583	615		
LPC	10µm	227	287	133	333	1867	167	240	460		
	25µm	20	17	7	7	20	0	7	13		
Assay of Anions	% Phosphorus	101.0	101.6	98.8	100.1	103.0	109.2	102.5	109.5		
	% Chloride	102.0	102.6	98.2	99.2	102.1	112.4	101.0	107.4		
Assay of Cations	% Potassium	102.2	102.5	100.6	99.4	104.1	100.4	100.7	107.3		
	% Sodium	99.8	100.1	101.1	98.5	102.3	100.0	100.5	107.0		
* CCS- A Clear colorless solution, free from visible foreign particles											

FIG.9 cont'd

Autoclave @ 121°C for 15 Minutes											
Bausch TT PP Bag + Al Pouch											
Test		Condition									
		Bulk Solution	Initial	3M 15/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15		
Description*	pH of Solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
		6.543	6.555	6.63	6.62	6.59	6.55	6.58	6.58		
Osmolality (mOsm/kg)	LPC	576	572	567	599	591	582	580	581		
		227	153	127	427	240	153	240	333		
Assay of Anions	25µm	20	13	13	20	0	7	7	7		
		% Phosphorus	101.0	101.6	98.0	98.9	96.8	101.2	100.0	100.8	
Assay of Cations	% Chloride	102.0	102.6	97.7	102.6	95.9	99.3	98.8	99.2		
		% Potassium	102.2	102.4	99.6	98.8	103.2	99.7	98.7	99.3	
Assay of Cations	% Sodium	99.8	100.2	100.3	102.0	96.3	99.0	98.5	99.0		
		Bausch TT PP Bag (Without Al Pouches)									
Test		Condition									
		Bulk Solution	Initial	3M 15/40	3M 30/65	3M 40/15	6M 25/40	6M 30/65	6M 40/15		
Description*	pH of Solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
		6.543	6.555	6.62	6.56	6.62	6.59	6.56	6.56		
Osmolality (mOsm/kg)	LPC	576	572	571	610	625	578	593	618		
		227	153	193	93	40	127	247	240		
Assay of Anions	25µm	20	13	0	0	0	0	0	20		
		% Phosphorus	101.0	101.6	96.8	99.5	102.1	104.2	102.3	109.7	
Assay of Cations	% Chloride	102.0	102.6	96.2	98.8	100.8	104.1	100.6	108.0		
		% Potassium	102.2	102.4	98.6	98.7	103.1	100.7	100.0	107.7	
Assay of Cations	% Sodium	99.8	100.2	99.1	98.1	102.1	100.5	99.9	107.2		
		* CCS - A Clear colorless solution, free from visible foreign particles									

FIG.9 cont'd

Autoclave @ 121°C for 15 Minutes											
TechnoFlex 1T PVC Bag + AI Pouch											
Test		Condition									
		Bulk Solution	Initial	3M 15/40	3M 30/65	3M 40/15	6M 15/40	6M 30/65	6M 40/15	6M 15/40	6M 40/15
Description*	pH of Solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		6.543	6.550	6.61	6.57	6.57	6.57	6.57	6.57	6.57	6.56
Osmolality (mOsm/kg)	LPC	576	573	573	606	606	594	589	581		
		227	153	267	600	360	313	193	87		
Assay of Anions	10µm	20	13	13	33	7	0	7	7		
		25µm									
Assay of Cations	% Phosphorus	101.0	101.9	99.4	99.7	100.5	102.6	101.3	102.9		
		% Chloride	102.0	103.1	98.8	98.8	99.4	101.1	100.5	101.2	
Assay of Cations	% Potassium	102.2	102.3	100.7	99.1	101.6	102.1	99.7	101.3		
		% Sodium	99.8	100.1	101.3	98.2	99.8	100.7	99.6	100.9	
TechnoFlex 2T PVC Bag (Without AI Pouches)											
Test		Condition									
		Bulk Solution	Initial	3M 15/40	3M 30/65	3M 40/15	6M 15/40	6M 30/65	6M 40/15	6M 15/40	6M 40/15
Description*	pH of Solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		6.543	6.550	6.61	6.6	6.6	6.55	6.55	6.45		
Osmolality (mOsm/kg)	LPC	576	573	607	657	946	636	649	1092		
		227	153	320	253	147	933	260	161		
Assay of Anions	10µm	20	13	20	13	27	7	13	7		
		25µm									
Assay of Cations	% Phosphorus	101.0	101.9	104.7	110.4	142.7	123.2	113.7	224.2		
		% Chloride	102.0	103.1	104.4	109.8	141.5	116.1	112.3	222.7	
Assay of Cations	% Potassium	102.2	102.3	107.1	110.1	145.3	112.7	111.9	218.7		
		% Sodium	99.8	100.1	107.6	109.4	142.4	112.3	111.7	217.7	
* CCS- A Clear colorless solution, free from visible foreign particles											

FIG.9 cont'd

B. No. #NPD2092												
Autoclave @ 121°C for 15 Minutes												
TechnoFlex 1T PP Bag + Al Pouch												
Test	Condition											
	Bulk Solution	Initial	1M 1-8	1M 15/40	1M 30/65	1M 40/15	6M 1-8	6M 15/40	6M 30/65	6M 40/15		
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS		
pH of Solution	6.61	6.58	6.59	6.1	6.62	6.56	6.67	6.66	6.67	6.69		
Osmolality (mOsm/kg)	574	569	577	580	577	581	573	575	578	575		
LPC	10µm	240	213	160	503	207	487	433	327	347		
	25µm	7	7	0	20	20	20	53	7	13		
Assay of Anions	% Phosphorus	100.8	98.9	97.7	98.3	98.1	98.8	99.9	101.2	101.4		
	% Chloride	99.0	105.4	96.1	96.1	96.1	100.7	101.5	101.8	100.7		
Assay of Cations	% Potassium	101.1	98.4	98.8	97.4	92.7	101.1	100.6	101.5	101.7		
	% Sodium	101.5	98.1	98.3	96.8	92.7	100.3	99.8	102.2	100.8		
* CCS- A Clear colorless solution, free from visible foreign particles												
Autoclave @ 121°C for 15 Minutes												
Grifols 1T PP Bag + Al Pouch												
Test	Condition											
	Bulk Solution	Initial	1M 1-8	1M 15/40	1M 30/65	1M 40/15	6M 1-8	6M 15/40	6M 30/65	6M 40/15		
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS		
pH of Solution	6.61	6.55	6.58	6.57	6.59	6.60	6.69	6.69	6.67	6.70		
Osmolality (mOsm/kg)	574	572	579	575	578	581	572	573	571	573		
LPC	10µm	153	307	1573	527	333	273	287	473	180		
	25µm	7	20	73	53	33	33	27	67	27		
Assay of Anions	% Phosphorus	101.5	97.3	98.3	92.9	97.3	100.7	100.9	100.3	101.2		
	% Chloride	99.0	106.4	94.2	95.1	95.5	101.1	103.3	103.2	102.1		
Assay of Cations	% Potassium	101.1	100.2	97.1	98.5	98.7	100.6	100.7	100.5	100.7		
	% Sodium	101.5	98.9	96.8	98.0	98.2	97.4	99.9	98.7	99.9		
* CCS- A Clear colorless solution, free from visible foreign particles												

FIG.10

B. No.8XPD11881															
Aseptik Filling															
Infused (PolyoxaPH145) IT PP Bag + A1 Pouch															
Test	Condition														
	Bulk Solution	Bulk IM 1-8	Bulk IM 40/15	Bulk IM 2-8	Bulk IM 40/15	Initial	IM 25/40	IM 40/15	IM 1-8	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH of Solution	6.52														
Osmolality (mOsm/kg)	380														
LPC	10µm	Not Applicable													
	25µm	Not Applicable													
Assay of Anions	% Phosphorus	97.5	101.4	103.2	101.5	115.6	100.2	96.9	100.9	102.4	101.3	102.6	102.7	102.8	
	% Chloride	96.5	99.4	101.7	100.2	115.0	98.3	98.1	101.1	105.9	102.7	100.7	101.5	101.5	
Assay of Cations	% Potassium	102.1	100.6	101.5	99.1	112.0	100.3	100.9	101.2	102.8	106.4	106.0	100.5	101.2	
	% Sodium	101.1	101.2	103.9	98.8	111.8	100.6	100.4	101.4	102.6	101.0	98.1	98.4	100.3	
* CCS- A Clear colorless solution, free from visible foreign particles															
Aseptik Filling															
Haemofluors (M312A) IT PP Bag + A1 Pouch															
Test	Condition														
	Bulk Solution	Bulk IM 2-8	Bulk IM 40/15	Bulk IM 2-8	Bulk IM 40/15	Initial	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH of Solution	6.58														
Osmolality (mOsm/kg)	380														
LPC	10µm	Not Applicable													
	25µm	Not Applicable													
Assay of Anions	% Phosphorus	97.5	101.4	103.2	101.5	115.9	100.9	101.5	101.8	102.6	102.5	102.7	102.8	103.1	
	% Chloride	96.5	99.4	101.7	100.2	115.0	98.7	99.4	103.4	103.1	101.9	101.4	101.8	101.9	
Assay of Cations	% Potassium	102.1	100.9	103.5	98.1	112.6	100.8	101.6	100.8	101.8	101.2	100.6	100.8	101.1	
	% Sodium	101.1	101.2	103.9	98.8	111.8	101.5	102.0	101.6	101.9	101.3	99.7	99.8	100.6	
* CCS- A Clear colorless solution, free from visible foreign particles															

FIG.11

Aspirin Filling															
Technoflex 11 PP Bag - All Pouch															
Test		Condition													
Description*	Bulk Solution	Bulk_1M 2-8	Bulk_1M 40/15	Bulk_6M 2-8	Bulk_6M 40/15	Initial	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 40/15	6M 2-8	6M 25/40	6M 30/65	6M 40/15
		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.58	Not applicable													
Osmolality (mOsm/kg)	580														
LPC	Not Applicable														
Assay of Anions	% Phosphorus	97.2	101.4	105.2	101.5	115.9	100.2	99.9	102.3	102.5	100.9	103.3	103.4	102.7	102.3
	% Chloride	96.5	99.4	101.7	100.2	115.0	98.2	98.3	100.4	104.0	101.9	102.2	102.0	101.4	101.3
Assay of Cations	% Potassium	102.1	100.9	102.5	99.1	112.0	100.9	100.6	102.9	101.5	99.6	101.2	101.1	100.6	101.0
	% Sodium	101.3	101.2	103.9	98.8	111.8	103.6	101.1	96.7	98.2	95.3	100.1	100.2	99.7	100.1
* CCS - A Clear colorless solution, free from visible foreign particles															
Aspicare 20 121°C for 15 Minutes (Ambient Pressure: Max. 3.18 bar, Min. 3.00 bar)															
Infomed (PacTec APP1145) 11 PP Bag - All Pouch															
Test		Condition													
Description*	Bulk Solution	Bulk_1M 2-8	Bulk_1M 40/15	Bulk_6M 2-8	Bulk_6M 40/15	Initial	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 40/15	6M 2-8	6M 25/40	6M 30/65	6M 40/15
		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.58	Not applicable													
Osmolality (mOsm/kg)	580														
LPC	Not Applicable														
Assay of Anions	% Phosphorus	97.3	101.4	103.2	101.5	115.0	100.2	99.1	100.9	100.6	101.1	103.6	103.6	103.0	102.7
	% Chloride	96.5	99.4	101.7	100.2	115.0	98.1	97.2	102.7	102.1	102.3	101.4	102.9	102.6	102.4
Assay of Cations	% Potassium	102.1	100.9	103.5	99.1	112.0	100.3	98.7	100.0	99.8	102.5	100.8	103.2	100.8	101.1
	% Sodium	101.1	101.2	103.9	98.8	111.8	101.6	100.3	100.7	100.3	102.4	100.1	101.2	100.3	100.9
* CCS - A Clear colorless solution, free from visible foreign particles															

FIG.11 cont'd

Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.14 bar , Min-3.08 bar)																
Bacteroflex (M312A) IT PP Bag + AI Pouch																
Condition																
Test	Bulk Solution	Bulk IM 2-8	Bulk IM 40:15	Bulk IM 2-8	Bulk IM 40:15	Initial	IM 25:40	IM 40:15	IM 2-8	IM 25:40	IM 40:15	IM 2-8	IM 25:40	IM 40:15	IM 2-8	IM 40:15
		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
Description*	pH of Solution	6.59	Not Applicable													
	Osmolality (mOsm/kg)	580	Not Applicable													
LPC	18µm	Not Applicable	Not Applicable													
	15µm	Not Applicable	Not Applicable													
Assay of Anions	% Phosphorus	97.3	101.4	103.2	101.5	115.9	99.6	99.8	101.8	102.0	101.4	102.7	103.8	103.8	103.2	103.2
	% Chloride	96.5	99.4	101.7	109.2	115.0	97.2	97.5	103.5	103.4	103.4	103.5	103.1	102.7	103.6	103.6
Assay of Cations	% Potassium	102.1	109.9	105.5	99.1	112.9	99.4	100.2	101.5	101.0	99.9	101.0	101.9	101.5	102.1	102.1
	% Sodium	101.1	101.2	103.9	94.8	111.8	100.3	100.8	102.1	101.5	100.3	100.7	101.3	100.9	102.0	102.0
* CCS - A Clear colorless solution, free from visible foreign particles.																
Autoclave @ 121°C for 5 Minutes (Autoclave Pressure: Max-3.19 bar , Min-2.98 bar)																
Tectaflex IT PP Bag + AI Pouch																
Condition																
Test	Bulk Solution	Bulk IM 2-8	Bulk IM 40:15	Bulk IM 2-8	Bulk IM 40:15	Initial	IM 25:40	IM 40:15	IM 2-8	IM 25:40	IM 40:15	IM 2-8	IM 25:40	IM 40:15	IM 2-8	IM 40:15
		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
Description*	pH of Solution	6.58	Not Applicable													
	Osmolality (mOsm/kg)	580	Not Applicable													
LPC	18µm	Not Applicable	Not Applicable													
	25µm	Not Applicable	Not Applicable													
Assay of Anions	% Phosphorus	97.3	101.4	103.2	101.5	115.9	99.5	98.3	101.2	101.6	102.5	102.5	101.9	102.6	102.4	102.4
	% Chloride	96.5	99.4	101.7	100.2	115.0	97.6	97.6	101.7	101.6	102.6	101.8	102.2	101.7	102.3	102.3
Assay of Cations	% Potassium	102.1	109.9	105.5	99.1	112.9	100.4	100.4	101.1	101.2	100.9	100.7	101.1	100.7	101.0	101.0
	% Sodium	101.1	101.2	103.9	98.8	111.8	100.9	101.1	95.7	96.7	96.5	100.2	100.6	100.2	100.6	100.6
* CCS - A Clear colorless solution, free from visible foreign particles.																

FIG.11 cont'd

Autoclave @ 115°C for 20 Minutes (Autoclave Pressure: Max-2.61 bar , Min-2.45 bar)															
Infomed (PolybioAPP1145) 11 PP Bag + All Pouch															
Condition															
Test	Bulk Solution	Bulk IM 2-8	Bulk IM 40/15	Bulk_6M 2-8	Bulk_6M 40/15	Initial	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
	Not Applicable														
pH of Solution	6.58														
Osmolality (mOsm/kg)	586														
LPC	10µm														
	25µm														
Assay of Anions	% Phosphorus	97.3	101.4	103.2	101.5	115.9	101.6	100.5	101.1	101.1	102.2	102.2	102.5	103.9	
	% Chloride	96.5	99.4	101.7	100.2	115.0	98.5	102.2	102.6	102.6	102.8	101.5	100.9	101.8	
Assay of Cations	% Potassium	102.1	100.9	103.5	99.1	112.0	99.6	100.0	101.1	101.1	100.2	100.1	98.8	100.5	
	% Sodium	101.1	101.2	103.9	98.8	111.8	100.3	100.6	100.3	100.4	101.2	100.1	100.3	100.9	
* CCS- A Clear colorless solution, free from visible foreign particles															
Autoclave @ 115°C for 20 Minutes (Autoclave Pressure: Max-2.61 bar , Min-2.45 bar)															
HaenselPharm (M312A) 11 PP Bag + All Pouch															
Condition															
Test	Bulk Solution	Bulk IM 2-8	Bulk IM 40/15	Bulk_6M 2-8	Bulk_6M 40/15	Initial	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	IM 2-8	IM 25/40	IM 40/15	
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
	Not Applicable														
pH of Solution	6.58														
Osmolality (mOsm/kg)	586														
LPC	10µm														
	25µm														
Assay of Anions	% Phosphorus	97.3	101.4	103.2	101.5	115.9	101.8	100.9	101.1	101.6	101.6	101.9	102.5	103.9	
	% Chloride	96.5	99.4	101.7	100.2	115.0	99.7	98.7	102.3	103.1	102.8	102.3	100.7	101.4	
Assay of Cations	% Potassium	102.1	100.9	103.5	99.1	112.0	99.5	100.5	100.6	101.0	100.9	100.6	99.6	100.0	
	% Sodium	101.1	101.2	103.9	98.8	111.8	100.1	101.1	100.0	100.6	100.5	99.5	98.3	98.5	
* CCS- A Clear colorless solution, free from visible foreign particles															

FIG.11 cont'd

Autoclave @ 115°C for 28 Minutes (Autoclave Pressure: Max: 2.61 bar, Min: 2.45 bar)																
Testoaflex 11 RF Bag - 41 Pouch																
Test		Condition														
Description*		Bulk Solution	Bulk IM 2-9	Bulk IM 48/15	Bulk 603 2-8	Bulk 604 49/15	Initial	IM 25/40	IM 40/15	3M 2-9	3M 25/40	3M 40/15	603 2-8	603 25/40	603 30/65	603 40/15
pH of Solution		CCS	CCS	CCS	CCS	CCS	CCS	6.52	6.51	6.5	6.6	6.6	6.57	6.57	6.57	6.58
Osmolality (mOsm/kg)		580	Not Applicable													
LFC	10µm	Not Applicable														
	25µm	Not Applicable														
Assay of Anions	% Phosphate	97.3	101.4	103.2	101.5	115.9	94.0	101.0	101.3	103.3	102.4	101.5	103.6	102.5	102.8	103.0
	% Chloride	96.5	99.4	103.7	100.2	115.0	97.3	99.5	98.1	104.0	102.6	102.9	101.1	100.8	101.0	101.8
Assay of Cations	% Potassium	102.1	106.0	105.5	99.1	112.0	102.9	100.2	100.0	102.2	106.2	106.3	99.9	99.6	99.7	100.1
	% Sodium	101.1	101.2	103.8	94.8	111.8	102.0	101.0	100.8	97.3	96.0	96.4	98.6	94.3	98.2	98.2
* CCS: A Clear colorless solution, free from visible foreign particles																

FIG.11 cont'd

B. No. #192073_11													
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.18 bar , Min-2.98 bar)													
Hicmed6arm (M112A) IT PP Bag + AlPouch													
Test		Initial	1M 1.8	1M 25/40	1M 40/15	3M 2.8	3M 25/40	3M 30/65	3M 40/15	6M 2.8	6M 25/40	6M 30/65	6M 40/15
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution		6.56	6.61	6.60	6.58	6.66	6.65	6.66	6.67	6.59	6.58	6.58	6.58
Osmolality (mOsm/kg)		569	579	581	589	576	580	578	577	579	577	575	573
LPC	10µm	433	980	553	220	240	187	107	207	337	173	300	20
	25µm	13	47	20	7	13	9	13	13	7	26	7	0
Assay of Anions	% Phosphorus	100.9	98.7	98.8	99.4	102.5	104.9	104.7	103.4	98.6	100.2	99.0	99.6
	% Chloride	100.0	97.3	97.8	98.5	101.8	104.1	104.0	102.9	99.3	100.8	99.5	100.2
Assay of Cations	% Potassium	101.8	102.7	103.4	103.0	100.0	101.0	101.7	100.7	101.6	100.0	99.2	99.8
	% Sodium	100.7	101.9	102.3	103.0	99.0	101.0	100.8	99.9	100.3	100.6	98.0	98.6
* CCS- A Clear colorless solution, free from visible foreign particles													

FIG.12

B. No. 8XPO11806														
Aseptic Filling														
HaemoPharm (M312) IT PP Bag + Al Pouch														
Test		Condition												
Description*	Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 30/65	3M 40/15	6M 2-8	6M 25/40	6M 30/65	6M 40/15	
	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.60	6.52	6.60	6.60	6.66	6.56	6.56	6.56	6.56	6.59	6.58	6.6	6.6	
Osmolality (mOsm/kg)		561	577	576	577	574	576	578	574	572	580	579	580	
LPC	Not Applicable	267	367	347	253	87	127	140	140	309	309	160	300	
		47	33	13	13	7	13	29	9	7	7	13	27	
Assay of Anions	% Phosphorus	101.2	100.6	101.6	103.3	103.0	103.4	100.5	102.3	103.2	103.7	103.8	103.0	
	% Chloride	100.0	101.2	100.9	101.0	104.1	104.2	101.3	103.1	102.8	103.5	103.7	103.3	
Assay of Cations	% Potassium	101.1	102.2	102.8	104.3	101.5	101.6	99.3	101.1	100.0	100.4	100.5	101.5	
	% Sodium	101.6	101.6	102.3	103.6	101.8	102.0	99.6	101.4	99.3	100.0	100.2	101.4	
* CCS- A Clear colorless solution, free from visible foreign particles														
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.24 bar , Min-2.99 bar)														
HaemoPharm (M312) IT PP Bag + Al Pouch														
Test		Condition												
Description*	Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 30/65	3M 40/15	6M 2-8	6M 25/40	6M 30/65	6M 40/15	
	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH of Solution	6.60	6.52	6.67	6.67	6.66	6.54	6.56	6.56	6.53	6.58	6.6	6.59	6.61	
Osmolality (mOsm/kg)		563	577	575	578	554	577	573	583	572	580	574	574	
LPC	Not Applicable	307	393	893	447	87	80	153	60	307	1040	300	127	
		13	0	20	20	0	0	27	0	13	20	7	13	
Assay of Anions	% Phosphorus	101.7	97.0	98.7	100.8	102.1	102.6	102.5	104.2	102.4	103.9	102.5	103.7	
	% Chloride	100.6	101.1	103.3	102.7	102.5	103.4	103.3	105.0	102.2	103.8	102.3	103.5	
Assay of Cations	% Potassium	101.8	100.1	101.4	103.0	100.8	101.0	101.0	102.3	99.4	100.8	101.7	100.5	
	% Sodium	102.3	99.7	100.8	102.5	100.8	101.4	101.1	102.5	98.7	100.0	98.7	98.9	
* CCS- A Clear colorless solution, free from visible foreign particles														

FIG.13

B. No. 838021887														
Aseptic Filling														
Hemopharm (R312) 11 PP Bag + Al Pouch														
Test	Condition													
	Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	3M 15/40	3M 30/65	3M 40/15	GM 2-8	GM 25/40	GM 30/65	GM 40/15	GM 40/15
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.58	6.65	6.56	6.57	6.58	6.48	6.48	6.49	6.49	6.58	6.59	6.59	6.6	6.6
Osmolality (mOsm/kg)		575	573	574	576	549	573	578	577	565	567	568	568	568
LPC	10µm	Not Applicable												
	25µm	7	6.67	0	46.67	13	13	33	20	13	47	33	7	7
Assay of Anions	% Phosphorus	101.9	102.2	104.0	103.1	98.9	98.2	99.3	99.0	100.0	102.0	102.4	101.9	101.9
	% Chloride	101.5	101.8	104.6	103.2	100.0	99.2	100.7	100.2	101.1	102.2	102.6	102.1	102.1
Assay of Cations	% Potassium	99.4	99.7	101.6	101.6	102.2	99.1	100.2	99.6	100.0	101.0	101.4	101.0	101.0
	% Sodium	98.8	99.1	100.9	101.7	99.6	97.0	98.1	97.6	100.6	101.5	101.9	101.6	101.6
* CCS- A Clear colorless solution, free from visible foreign particles														
Infused (Polyvin APP114S) 11 PP Bag + Al Pouch														
Test	Condition													
	Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 30/65	3M 40/15	GM 2-8	GM 25/40	GM 30/65	GM 40/15	GM 40/15
Description*	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.58	6.67	6.57	6.56	6.56	6.49	6.49	6.5	6.5	6.58	6.58	6.58	6.58	6.58
Osmolality (mOsm/kg)		573	571	575	576	573	580	582	574	560	577	579	578	578
LPC	10µm	Not Applicable												
	25µm	6	360	133.33	13.33	20	20	7	40	7	7	27	47	47
Assay of Anions	% Phosphorus	101.9	102.5	100.5	102.0	99.1	97.4	98.5	98.5	105.2	103.5	105.5	103.4	103.4
	% Chloride	101.5	102.2	100.4	102.1	100.5	98.7	99.6	99.7	103.5	103.7	103.8	103.8	103.8
Assay of Cations	% Potassium	99.4	100.1	99.7	100.9	100.4	99.1	100.7	99.7	101.9	103.8	101.5	101.6	101.6
	% Sodium	98.8	98.4	98.3	100.8	97.2	95.9	97.7	96.2	102.5	102.5	102.3	102.1	102.1
* CCS- A Clear colorless solution, free from visible foreign particles														

FIG.14

Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.15 bar , Min-2.97 bar)														
HemoPharm (M312) II PP Bag + Al Pouch														
Test		Condition												
		Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	M3 15/40	M3 30/65	M3 40/15	6M 2-8	6M 25/40	6M 30/65	6M 40/15
Description*	pH of Solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		6.58	6.63	6.57	6.58	6.57	6.49	6.49	6.49	6.48	6.59	6.59	6.59	6.59
Osmolality (mOsm/kg)	LPC	Not Applicable	577	581	572	574	578	575	580	578	569	588	570	586
			473	313.33	2991.33	646.67	147	147	253	106	71	260	419	60
Assay of Anions	% Phosphorus	Not Applicable	20	40	26	46.67	13	7	27	7	27	20	40	7
			102.1	103.9	103.7	104.0	102.1	98.9	98.7	100.9	102.3	103.0	103.2	102.1
Assay of Cations	% Chloride	Not Applicable	102.9	105.4	103.9	104.9	103.5	103.4	99.7	103.6	102.5	103.4	103.4	102.3
			98.9	103.1	102.1	103.0	102.6	99.9	99.9	101.8	100.8	101.0	101.2	100.9
Assay of Cations	% Potassium	Not Applicable	99.3	101.1	102.2	102.6	101.1	97.6	97.3	98.5	101.1	101.5	101.7	101.5
			98.8	101.1	102.2	102.6	101.1	97.6	97.3	98.5	101.1	101.5	101.7	101.5
* CCS- A Clear colorless solution, free from visible foreign particles														
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.29 bar , Min-2.97 bar)														
Infomed (Polyvin APP1148) II PP Bag + Al Pouch														
Test		Condition												
		Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	M3 15/40	M3 30/65	M3 40/15	6M 2-8	6M 25/40	6M 30/65	6M 40/15
Description*	pH of Solution	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
		6.58	6.65	6.57	6.57	6.57	6.5	6.49	6.5	6.49	6.58	6.58	6.58	6.58
Osmolality (mOsm/kg)	LPC	Not Applicable	573	569	569	569	573	572	572	576	570	579	573	571
			120	303.33	833.33	3186.67	173	127	353	107	107	120	147	367
Assay of Anions	% Phosphorus	Not Applicable	7	20	15.35	91.33	13	7	27	7	13	0	13	20
			101.6	105.1	104.4	104.3	98.2	98.5	98.4	98.8	103.8	102.8	103.1	102.8
Assay of Cations	% Chloride	Not Applicable	101.6	105.3	106.7	105.2	99.7	99.6	99.5	99.9	104.0	103.0	103.3	103.9
			98.6	101.4	104.1	103.2	99.7	103.3	99.2	99.7	102.1	101.3	101.4	101.1
Assay of Cations	% Potassium	Not Applicable	99.6	101.4	104.1	103.2	99.7	103.3	99.2	99.7	102.1	101.3	101.4	101.1
			98.8	101.1	103.1	103.4	102.6	96.1	100.8	96.2	96.1	102.3	101.6	101.8
* CCS- A Clear colorless solution, free from visible foreign particles														

FIG.14 cont'd

B. No. 67XPC011808														
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.15 bar , Min-2.95 bar)														
HemoPharm (M012) IT PP Bag + Al Patch														
Test		Condition												
Description*	Bulk Solution	Initial	IM 2-8	IM 25-40	IM 40-15	3M 2-8	3M 25-40	3M 30-65	3M 40-15	6M 2-8	6M 25-40	6M 30-65	6M 40-15	
	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.57	6.68	6.58	6.59	6.58	6.88	6.56	6.56	6.57	6.61	6.61	6.62	6.61	6.61
Osmolality (mOsm/kg)		574	576	575	574	582	572	572	574	578	576	575	575	578
LPC	Not Applicable	240	366.67	166.67	273.33	747	267	273	400	340	193	67	60	60
	18µm	7	20	6.67	26	67	26	13	26	13	13	0	0	0
Assay of Anions	% Phosphate	101.8	102.1	103.3	102.5	102.0	100.5	103.6	103.3	101.6	102.3	102.2	102.8	102.8
	% Chloride	101.8	102.2	102.2	101.6	100.6	101.3	100.9	101.3	102.1	102.6	104.2	102.9	102.9
Assay of Cations	% Potassium	100.5	98.9	100.2	99.5	100.4	101.8	101.6	102.1	100.8	101.2	103.0	101.6	101.6
	% Sodium	99.8	98.4	98.0	97.6	98.8	98.7	98.6	99.1	101.1	101.4	101.4	101.7	101.7
* CCS- A Clear colorless solution, free from visible foreign particles														
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.20 bar , Min-3.00 bar)														
Infomed (Pabrin APF1113S) IT PP Bag + Al Patch														
Test		Condition												
Description*	Bulk Solution	Initial	IM 2-8	IM 25-40	IM 40-15	3M 2-8	3M 25-40	3M 30-65	3M 40-15	6M 2-8	6M 25-40	6M 30-65	6M 40-15	
	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution	6.57	6.68	6.58	6.59	6.59	6.58	6.57	6.58	6.59	6.62	6.62	6.61	6.61	6.61
Osmolality (mOsm/kg)		573	572	572	570	571	575	574	574	577	572	575	575	575
LPC	Not Applicable	327	300	920	1226.67	340	440	213	107	140	319	167	180	180
	18µm	7	13.33	60	33.33	0	0	0	7	33	20	0	27	27
Assay of Anions	% Phosphate	101.8	103.0	103.2	103.2	102.0	101.0	100.2	100.8	102.4	103.2	103.5	102.8	102.8
	% Chloride	101.8	105.2	102.7	102.5	101.5	99.3	98.8	99.1	102.7	103.1	103.9	103.0	103.0
Assay of Cations	% Potassium	100.5	103.2	100.6	100.3	101.3	99.6	98.9	99.2	101.3	101.8	102.4	101.5	101.5
	% Sodium	99.8	99.4	97.2	98.4	98.7	98.2	96.4	96.2	101.3	101.6	102.2	101.5	101.5
* CCS- A Clear colorless solution, free from visible foreign particles														

FIG.15

B. No.#NPD11812												
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.24 bar , Min-2.99 bar)												
Infomed (Nexcel M312) IT PP Bag + Al Pouch												
Test		Condition										
		Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 30/65	3M 40/15		
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution		6.53	6.54	6.56	6.62	6.61	6.59	6.56	6.55	6.57	6.57	6.57
Osmolality (mOsm/kg)		573	574	570	565	569	568	572	572	568	572	568
LPC	10µm	67	320	720	380	520	227	227	1125	187	7	7
	25µm	0	20	106.67	53.33	33.33	0	7	33	7	33	7
Assay of Anions	% Phosphorus	101.7	101.6	98.5	98.1	98.9	101.1	100.9	100.0	100.6	99.5	99.5
	% Chloride	99.7	99.4	99.2	98.7	99.5	98.9	99.2	98.8	99.5	99.9	99.6
Assay of Cations	% Potassium	101.7	101.5	99.2	98.9	99.8	100.1	100.3	99.9	99.6	99.1	98.4
	% Sodium	99.3	99.2	98.8	97.3	98.2	98.8	99.1	98.9	98.4	99.1	98.4
* CCS- A Clear colorless solution, free from visible foreign particles												
Autoclave @ 121°C for 15 Minutes (Autoclave Pressure: Max-3.24 bar , Min-2.99 bar)												
Infomed (Polycrine APP1145) IT PP Bag + Al Pouch												
Test		Condition										
		Bulk Solution	Initial	IM 2-8	IM 25/40	IM 40/15	3M 2-8	3M 25/40	3M 30/65	3M 40/15		
Description*		CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH of Solution		6.53	6.54	6.55	6.54	6.54	6.57	6.56	6.56	6.58	6.58	6.58
Osmolality (mOsm/kg)		573	575	570	570	570	568	566	566	570	570	570
LPC	10µm	67	153	1526.67	2053.33	1193.33	993	647	647	153	287	153
	25µm	0	0	6.67	13.33	20	13	13	13	0	27	0
Assay of Anions	% Phosphorus	101.7	101.2	98.8	98.0	97.8	100.6	100.7	100.7	100.5	99.8	100.5
	% Chloride	99.7	99.2	99.9	98.4	98.4	99.8	98.6	98.6	98.4	98.6	98.4
Assay of Cations	% Potassium	101.7	101.2	99.9	98.6	98.5	100.9	99.6	99.9	99.6	99.6	99.6
	% Sodium	99.3	98.9	98.3	97.1	96.9	99.9	98.4	98.6	98.4	98.4	98.4
* CCS- A Clear colorless solution, free from visible foreign particles												

FIG.16

Engineering Batch_Lot#21070832 (Finished Product)					
Autoclave @ 121°C for 15 Minutes					
Infomed (Nexcel M312) IT PP Bag + Al Pouch					
Test		Condition			
		Bulk Solution			Initial
		Sampling Time: 5 Minutes	Sampling Time: 10 Minutes	Sampling Time: 15 Minutes	
Description*		CCS	CCS	CCS	CCS
pH of Solution		6.64	6.63	6.64	6.61
Osmolality (mOsm/kg)		559	556	555	566
LPC	10µm	1006.67	466.67	300	60
	25µm	66.67	40	13.33	0
Assay of Anions	% Phosphorus	98.7	98.2	97.8	98.6
	% Chloride	98.9	98.7	98.0	98.9
Assay of Cations	% Potassium	99	98.7	97.8	99.0
	% Sodium	97.3	96.7	95.9	97.3
* CCS- A Clear colorless solution, free from visible foreign particles					
Autoclave @ 121°C for 15 Minutes					
Infomed (Polycine APP114S) IT PP Bag + Al Pouch					
Test		Condition			
		Bulk Solution			Initial
		Sampling Time: 5 Minutes	Sampling Time: 10 Minutes	Sampling Time: 15 Minutes	
Description*		CCS	CCS	CCS	CCS
pH of Solution		6.64	6.63	6.64	6.61
Osmolality (mOsm/kg)		559	556	555	564
LPC	10µm	1006.67	466.67	300	260
	25µm	66.67	40	13.33	46.67
Assay of Anions	% Phosphorus	98.7	98.2	97.8	98.8
	% Chloride	98.9	98.7	98.0	98.9
Assay of Cations	% Potassium	99	98.7	97.8	99.5
	% Sodium	97.3	96.7	95.9	97.5
* CCS- A Clear colorless solution, free from visible foreign particles					

FIG.17

Aseptic Filling					
Infomed (Nexcel M312) 1T PP Bag + Al Pouch					
Test		Condition			
		Bulk Solution			Sampling: Beginning
		Sampling Time: 5 Minutes	Sampling Time: 10 Minutes	Sampling Time: 15 Minutes	
Description*		CCS	CCS	CCS	CCS
pH of Solution		6.64	6.63	6.64	6.61
Osmolality (mOsm/kg)		559	556	555	562
LPC	10µm	1006.67	466.67	300	66.67
	25µm	66.67	40	13.33	0
Assay of Anions	% Phosphorus	98.7	98.2	97.8	99.7
	% Chloride	98.9	98.7	98.0	99.9
Assay of Cations	% Potassium	99	98.7	97.8	99.5
	% Sodium	97.3	96.7	95.9	97.8
* CCS- A Clear colorless solution, free from visible foreign particles					
Aseptic Filling					
Infomed (Polycine APP114S) 1T PP Bag + Al Pouch					
Test		Condition			
		Bulk Solution			Sampling: Beginning
		Sampling Time: 5 Minutes	Sampling Time: 10 Minutes	Sampling Time: 15 Minutes	
Description*		CCS	CCS	CCS	CCS
pH of Solution		6.64	6.63	6.64	6.61
Osmolality (mOsm/kg)		559	556	555	560
LPC	10µm	1006.67	466.67	300	453.33
	25µm	66.67	40	13.33	33.33
Assay of Anions	% Phosphorus	98.7	98.2	97.8	98.3
	% Chloride	98.9	98.7	98.0	98.4
Assay of Cations	% Potassium	99	98.7	97.8	98.3
	% Sodium	97.3	96.7	95.9	96.3
* CCS- A Clear colorless solution, free from visible foreign particles					

FIG.17 cont'd

Engineering Batch_Lot#21070832 (Placebo)					
Autoclave @ 121°C for 15 Minutes					
Infomed (Nexcel M312) IT PP Bag + Al Pouch					
Test		Condition			Initial
		Bulk Solution			
		Sampling Time: 5 Minutes	Sampling Time: 10 Minutes	Sampling Time: 15 Minutes	
Description*		NA			CCS
pH of Solution					6.28
Osmolality (mOsm/kg)					289
LPC	10µm				813.33
	25µm				13.33
Assay of Anions	% Phosphorus				NA
	% Chloride				100.0
Assay of Cations	% Potassium				NA
	% Sodium				99.1
* CCS- A Clear colorless solution, free from visible foreign particles					
Autoclave @ 121°C for 15 Minutes					
Infomed (Polycine APP114S) IT PP Bag + Al Pouch					
Test		Condition			Initial
		Bulk Solution			
		Sampling Time: 5 Minutes	Sampling Time: 10 Minutes	Sampling Time: 15 Minutes	
Description*		NA			CCS
pH of Solution					6.3
Osmolality (mOsm/kg)					287
LPC	10µm				806.67
	25µm				6.67
Assay of Anions	% Phosphorus				NA
	% Chloride				100.9
Assay of Cations	% Potassium				NA
	% Sodium				99.4
* CCS- A Clear colorless solution, free from visible foreign particles					

FIG.17 cont'd

**READY-TO-USE POTASSIUM PHOSPHATES
IN SODIUM CHLORIDE SOLUTIONS**

[0001] This application claims priority to our copending U.S. provisional application with the Ser. No. 63/090,518, which was filed Oct. 12, 2020, and which is incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The field of the invention is compositions and methods for potassium phosphates solutions for injection, especially as it relates to such solutions with ultra-low concentrations of aluminum where the solutions are packaged in a ready-to-use container at volumes and concentrations suitable for direct administration to a patient.

BACKGROUND

[0003] The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] All publications identified herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0005] Hypophosphatemia is a clinical condition in which serum phosphate concentrations are less than 2.5 mg/dL (0.81 mmol/L). Causes for such condition can include alcohol use disorder, burns, starvation, and diuretic use, and symptoms include muscle weakness, respiratory failure, heart failure, and seizures and coma can occur. In most cases, the treatment for hypophosphatemia is phosphorus replacement therapy with an intravenous (IV) infusion rate of phosphates that must be adjusted to the patient's age and particular need. Phosphorus replacement therapy is generally administered via peripheral venous catheter or central venous catheter and at a rate according to the maximum recommended concentration and infusion rate as is shown in Table 1 (Maximum Recommended Daily Concentration of Potassium Phosphates Injection By Age and Route of Administration (Peripheral vs. Central)) and Table 2 (Maximum Recommended Infusion Rate of Potassium Phosphates Injection For Adults and Pediatric Patients 12 Years of Age and Older), where the term 'Phosphorus' is equivalent with 'Phosphate' (PO_4^{3-} anion).

TABLE 1		
Patient Population	Peripheral Venous Catheter	Central Venous Catheter
Adults and Pediatric Patients (12 Years of Age and Older)	Phosphorus 6.8 mmol/100 mL (Potassium 10 mEq/100 mL)	Phosphorus 18 mmol/100 mL (Potassium 26.4 mEq/100 mL)
Pediatric Patients (Less than 12 Years of Age)	Phosphorus 0.27 mmol/10 mL (Potassium 0.4 mEq/10 mL)	Phosphorus 0.55 mmol/10 mL (Potassium 0.8 mEq/10 mL)

TABLE 2	
Route of Administration	Maximum Infusion Rate
Peripheral Venous Catheter	Phosphorus 6.8 mmol/hour (Potassium 10 mEq/hour)
Central Venous Catheter	Phosphorus 15 mmol/hour (Potassium 22 mEq/hour)

[0006] Currently approved phosphorus replacement products of potassium phosphorus for IV administration may require continuous electrocardiographic (ECG) monitoring as serious cardiac reactions may occur as well as pulmonary embolisms due to pulmonary vascular precipitates. These serious cardiac and pulmonary risk factors render the accuracy of the concentration and infusion rate of the potassium phosphate critical for patient safety. Furthering these risks, the currently approved potassium phosphorus products are supplied and stored as concentrates and will therefore require aseptic compounding for the needed infusion rate, thereby increasing the risk of error and contamination. While care and monitoring may be implemented to avoid miscalculations, contamination, and serious adverse effects, preparing the IV solution by dilution and programming the correct infusion rate for administration often takes time and additional oversight. Furthermore, in most cases separate preparations are required for each of the central venous and peripheral venous administrations.

[0007] In addition, there are also potential risks with respect to chemical stability and aluminum toxicity, especially in patients with renal impairment. As is well known, phosphate solutions may be subject to crystallization and precipitation, which is exacerbated in the presence of oxygen. For that reason, concentrated solutions must be used within several hours as any remaining volume of such solutions after even limited exposure to oxygen is prone to crystallization and precipitation. To reduce the risk of crystallization during storage, deoxygenated preparations can be prepared as is described in CN106265499. However, such formulations were nevertheless concentrates and as such failed to avoid many of the difficulties associated with concentrates. With respect to levels of aluminum it should be recognized that while most currently used products are below the maximum allowed aluminum level as determined by the Federal Drug Administration (FDA), some of these aluminum concentrations may nevertheless be toxic in impaired patients. Attempts have been made to produce potassium phosphate compositions with decreased concentrations of aluminum as is disclosed, for example, in U.S. Ser. No. 10/632,150. However, the products described in the '150 patent are still concentrates, and problems associated with such forms remain. Moreover, many of the known concentrated compositions include varying amounts of potassium in the form of potassium dihydrogen phosphate and potassium hydrogen phosphate and may not provide a

proper ratio of these critical components, nor do these compositions provide a tonicity agent.

[0008] Therefore, there is still a need for potassium phosphates solutions with reduced aluminum content where such solutions are in a ready-to-administer formulation suitable for phosphorus replacement therapy, and where such solutions have sufficient storage stability.

SUMMARY OF THE INVENTION

[0009] The inventive subject matter is directed to various compositions and methods of ready-to-use (RTU) potassium phosphates solutions for intravenous administration to patients in need thereof. Advantageously, the solutions presented herein exhibit excellent storage stability over extended periods of time, include a suitable tonicity agent, have a desirable phosphate to potassium ratio, and have an aluminum content that is equal or less than 50 mcg/L. Such solutions will not require any dilution or other manipulation to adjust the solution to a required phosphate and/or potassium concentration and can be administered as a single unit at a rate of administration that will not require specific calculations.

[0010] In one aspect of the inventive subject matter, the inventors contemplate an isotonic sterile ready-to-use (RTU) aqueous potassium phosphates solution that comprises potassium phosphates and sodium chloride, wherein the solution includes 15 mmol/100 ml phosphorus (0.15 mmol/mL) and equal or less than 50 mcg/L aluminum.

[0011] In some embodiments, the potassium phosphates comprise potassium dihydrogen phosphate (KH_2PO_4) and potassium hydrogen phosphate (K_2HPO_4), wherein the potassium dihydrogen phosphate is present in the solution an amount of about 1,120 mg/100 ml (8.2 mmol/100 ml) phosphorus wherein the potassium hydrogen phosphate is present in the solution in an amount of about 1,180 mg/100 ml (6.8 mmol/100 ml) phosphorus, and/or wherein potassium is present in the solution in an amount of about 22 mEq/100 mL. Preferably, but not necessarily, sodium chloride is present in the solution in an amount of about 900 mg/100 ml, and/or the solution has a pH of between 6.2 and 6.8.

[0012] In further embodiments, the solution may have, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a liquid particle count of no more than 360 and 30 for particles at 15 and 25 micrometer size, respectively. Moreover, the solution may have, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in phosphorus of no more than 1% absolute, and/or the solution may have, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in potassium of no more than 2% absolute. It is further generally preferred that the solution is packaged in a flexible (e.g., polyolefin) container, typically at a volume of 100 mL, and the flexible polyolefin container may further be contained in a secondary metallized overwrap.

[0013] Therefore, in still further contemplated aspects, the inventors contemplate a sterile ready-to-use (RTU) premixed pharmaceutical product stored in a flexible polymeric container. While not limiting to the inventive subject matter, the pharmaceutical product may include potassium phosphates in an aqueous sodium chloride solution, containing (a) less than 50 mcg/L aluminum, (b) about 15 mmol/100 ml phosphorus, and (c) about 22 mEq/100 mL potassium.

[0014] Most typically, the potassium phosphates comprise potassium dihydrogen phosphate (KH_2PO_4) and potassium hydrogen phosphate (K_2HPO_4), wherein the potassium dihydrogen phosphate is present in the solution an amount of about 1,120 mg/100 ml (8.2 mmol/100 ml) phosphorus, and wherein the potassium hydrogen phosphate is present in the solution in an amount of about 1,180 mg/100 ml (6.8 mmol/100 ml) phosphorus. It is further preferred that sodium chloride is present in the aqueous sodium chloride solution in an amount of about 900 mg/100 ml.

[0015] The premixed pharmaceutical product in the flexible polymeric container preferably has a volume of 100 mL, and it is further preferred that the flexible polymeric container is enclosed in a secondary metallized overwrap. Therefore, in some embodiments, the premixed pharmaceutical product will comprise about 4.65 mg/mL of phosphorus (0.15 mmol/mL), about 8.50 mg/mL of potassium (0.22 mEq/mL), about 3.57 mg/mL of sodium, and about 5.43 mg/mL of chloride.

[0016] In a still further aspect of the inventive subject matter, the inventors also contemplate a method of administering phosphates to a patient in need of phosphorus replacement therapy, and contemplated methods include a step of administering, without prior dilution, an isotonic, sterile, and ready-to-use (RTU) solution comprising potassium phosphates and sodium chloride solution from a flexible container to the patient at a rate of infusion and by a route of administration corresponding to the patient's age and degree of need of phosphorus replacement. Most typically, the solution comprises about 15 mmol/100 ml phosphorus, about 22 mEq/100 mL potassium, and less than 50 mcg/L aluminum. In further contemplated embodiments, the rate of infusion is 6.8 mmol phosphates per hour or 15 mmol phosphates per hour, and/or the route of administration is a central venous catheter. Furthermore, it is contemplated that the solution can be administered after extended storage (e.g., storage for at least 3 months at 25° C. and 40% relative humidity).

[0017] Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawing figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 is an exemplary schematic showing a flexible pouch configuration for storage of the solutions presented herein.

[0019] FIG. 2 is an exemplary schematic of a double winged stopper for use with a container of FIG. 1.

[0020] FIG. 3 is an exemplary flow chart for producing an exemplary solution presented herein.

[0021] FIG. 4 is an exemplary linearity curve for determination of phosphorus using ion chromatography.

[0022] FIG. 5 is an exemplary linearity curve for determination of chloride using ion chromatography.

[0023] FIG. 6 is an exemplary linearity curve for determination of potassium using ion chromatography.

[0024] FIG. 7 is an exemplary linearity curve for determination of sodium using ion chromatography.

[0025] FIG. 8 is an exemplary linearity curve for determination of aluminum using Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

[0026] FIGS. 9-17 are tables providing results for stability conditions for exemplary phosphorus solution as presented herein in various container materials.

DETAILED DESCRIPTION

[0027] The inventors have now discovered that potassium phosphates solutions can be prepared that are storage stable, sterile, and ready-to-use (RTU), and as such avoid all of the drawbacks of heretofore known concentrated potassium phosphates solutions that required prior manipulation and had no significant shelf life. Moreover, the potassium phosphates solutions presented herein also exhibit a desirably low aluminum concentration and provide phosphates and potassium at ratios that are suitable for facile administration. Still further, the solutions according to the inventive subject matter are preservative free and have osmolality and pH suitable for direct administration.

[0028] For example, 100 mL of the RTU solution may be packaged into a flexible polymeric container to thereby provide in a sodium chloride solution about 15 mmol total phosphates and about 22 mEq potassium for injection, wherein the RTU solution has equal or less than 50 micrograms/liter (mcg/L or $\mu\text{g/L}$) aluminum. It should be appreciated that such RTU solution allows for simple and direct administration to a patient without the need for further dilution or other manipulation, and that such solution can be infused via a pump at a single infusion rate to thereby deliver appropriate quantities of phosphates and potassium. Moreover, and as described in more detail below, the solutions as presented herein also exhibit excellent storage stability (i.e., will not be subject to crystallization and precipitation and remain free of microbial growth). Having the specified quantities of phosphates and potassium will advantageously enable administration to an adult or pediatric patient via peripheral venous administration or central venous administration.

[0029] Therefore, especially preferred premixed pharmaceutical products that provide a desirable phosphates to potassium ratio will be prepared such that the solution will contain in water 11.2 KH_2PO_4 and 11.8 mg/mL K_2HPO_4 for a total 0.15 mmol/mL of phosphates, and 9 mg/mL sodium chloride. Notably, such solutions will not only result in a pH suitable for injection (i.e., pH between 6.0 and 7.0), but also result in a ratio of potassium to phosphorus and overall quantities of potassium and phosphorus desirable or necessary for direct injection.

[0030] In this context it is noted that the term “ready-to-use” or “RTU” when used in conjunction with the solutions presented herein refers to a solution that can be directly administered to a patient without prior need for dilution or other adjustment such as addition of saline or other tonicity agent). Viewed from a different perspective, a “ready-to-use” or “RTU” solution can be delivered from a storage container via peripheral or central catheter to a patient without additional manipulation of the solution in the storage container. Therefore, the terms “ready-to-use” and “RTU” are interchangeably used with the term “ready-to-administer”. Moreover, the term “phosphorus” is used interchangeably with the term “phosphate” or “phosphates” and refers to the PO_4^{3-} anion, regardless of its protonation state and/or presence of counterion(s). Thus, the term phosphorus can refer to K_2HPO_4 , KH_2PO_4 , HPO_4^{2-} , and/or PO_4^{3-} . Still further, the term “aluminum” as used herein refers to both aluminum ions (e.g., Al^{3+}) as well as metallic aluminum.

Likewise, the terms “sodium” and “potassium” as used herein refer to the cationic forms of sodium (Na^+) and potassium (K^+).

[0031] In addition to the contemplated RTU potassium phosphates in sodium chloride solution being more efficient, effective, and safe (e.g., less risk of contamination) to prepare and administer, the potassium phosphates in sodium chloride solution also has preferably less than 50 mcg/L aluminum. However, contemplated solutions are also suitable that have less than 100 mcg/L, less than 90 mcg/L, less than 80 mcg/L, less than 70 mcg/L, less than 60 mcg/L, or less than 55 mcg/L aluminum. More preferably, the potassium phosphates in sodium chloride solution has an aluminum content of no more than 50 mcg/L, not more than 49 mcg/L, not more than 48 mcg/L, not more than 47 mcg/L, not more than 46 mcg/L, 45 mcg/L, 44 mcg/L, 43 mcg/L, 42 mcg/L, 41 mcg/L, 40 mcg/L, 39 mcg/L, 38 mcg/L, 37 mcg/L, 36 mcg/L, 35 mcg/L, 34 mcg/L, 33 mcg/L, 32 mcg/L, 31 mcg/L, 30 mcg/L, 29 mcg/L, 28 mcg/L, 27 mcg/L, 26 mcg/L, 25 mcg/L, 24 mcg/L, 23 mcg/L, 22 mcg/L, 21 mcg/L, or 20 mcg/L, and even less (8 mcg/L). Therefore, and most typically, the contemplated potassium phosphates in sodium chloride solution has equal or less than 50 mcg/L, or equal or less than 40 mcg/L, or equal or less than 50 mcg/L aluminum.

[0032] Therefore, in exemplary embodiments, the RTU potassium phosphates in sodium chloride solution includes potassium dihydrogen phosphate (KH_2PO_4) and potassium hydrogen phosphate (K_2HPO_4). Typically, the potassium dihydrogen phosphate is at an amount of about 1120 mg/100 ml (8.2 mmol/100 ml of phosphorus) and the potassium hydrogen phosphate is at an amount of about 1180 mg/100 ml (6.8 mmol/100 ml of phosphorus). Additionally, the sterile RTU aqueous potassium phosphates in sodium chloride solution includes the sodium chloride at an amount of about 900 mg/100 ml.

[0033] Moreover, it is pointed out that contemplated methods of making aqueous potassium phosphates in sodium chloride solutions for phosphorus replacement therapy include adding potassium hydrogen phosphate, potassium dihydrogen phosphate, and sodium chloride to water, wherein each of these components does not contain more than 5 part per million (ppm) or more than 4 ppm, or more than 3 ppm, or more than 2 part per million (ppm, approximately 0.7 mmol/100 ml), or more than 1 ppm aluminum. Accordingly, and in contrast to the currently available products, aluminum content is reduced from the starting materials, thereby avoiding any further compounding of aluminum levels and decreasing the levels of total aluminum in the solutions presented herein.

[0034] In still further contemplated aspects, it is preferred that the solutions presented herein are stored in an autoclavable flexible container that is most typically fabricated from a polymeric material. Notably, and as shown in more detail below, the inventors also discovered that type of polymeric material may have an impact on chemical and storage stability. For example, some polymeric materials were prone to produce higher quantities of crystallized material and/or precipitates (e.g., at an average particle size of about 10 micron or 25 micron), whereas certain other materials were unexpectedly prone to water loss due to water vapor permeability, particularly at extended periods of storage (e.g., one to several months). Therefore, the inventors also used secondary overwraps that contained the pri-

mary packaging materials to help maintain predetermined concentration of all solutes. Among other materials, particularly preferred overwrap materials comprised polymeric composite films with at least one metal (e.g., aluminum) layer.

[0035] With respect to suitable polymeric autoclavable containers, various materials are deemed suitable for use herein, and especially preferred polymeric materials include polysulfone, polycarbonate, polypropylene, polyethylene (LDPE or HDPE), ethylene/propylene copolymers, polyolefins, acrylic-imide copolymers, polyester (e.g., PET, PEN and the like), Teflon, Nylon, acetal (Delrin), polymethylpentene, PVDC, ethylvinylacetate, polyvinyl chloride, and polyolefins. Notably, polyolefin containers remained transparent and dimensionally stable, even after autoclaving and were as such preferred. As will be readily appreciated, the polymeric containers can be prepared in numerous form factors, however, flexible bags are especially preferred. Likewise, the volume of the polymeric container may change considerably. However, it is typically preferred that the container has a volume that accommodates the volume of solution required for a single and complete administration of the solutions presented herein. Therefore, a particularly preferred internal volume of the container is 100 mL. Moreover, it should be appreciated that the polymeric container will have a single or a double port that is typically sealed with a stopper as is well known in the art. FIG. 1 depicts an exemplary flexible container with 100 mL internal volume, and FIG. 2 depicts an exemplary double winged stopper that can be used with the container of FIG. 1.

[0036] Most typically, the potassium phosphates in sodium chloride solution in the flexible container will be sterilized in the container by steam sterilization (e.g., autoclaving, 121° C. for about 15 minutes), preferably without altering the thermal properties of the film layers, ports, and closure system as well as maintaining the integrity of the flexible container. In more typical embodiments, the pre-mixed or ready-to-use stable pharmaceutical, formulation of potassium phosphates in sodium chloride at 15 mmol/100 ml of Phosphorus is packaged in a non-PVC plastic container with ports and container closure systems, which is terminally sterilized at a temperature of at least about 110° C. to 130° C. via autoclaving with a dwelling time ranging from 7 to 30 minutes.

[0037] Within these embodiments, it is preferred that the autoclaving temperature ranges from 110 to 130° C. The autoclaving temperature can be at a minimum temperature of 111° C., 112° C., 113° C., 114° C., 115° C., 116° C., 117° C., 118° C., 119° C., 120° C., or 121° C., and the maximum temperature can be 130° C., 129° C., 128° C., 127° C., 126° C., 125° C., 124° C., 123° C., 122° C., 121° C., or 120° C., inclusive of all ranges and sub-ranges embraced therein. Therefore, typical ranges for the autoclaving temperature may be include from 111 to 131° C., or from 117 to 125° C. Within these embodiments, it is preferred that the autoclaving time range from 7 to 60 minutes. The autoclaving time can be at a minimum of 7 minutes, 9 minutes, 11 minutes, 13 minutes or 15 minutes and the maximum autoclaving time can be 60 minutes, 45 minutes 30 minutes, 28 minutes, 26 minutes, 25 minutes, 24 minutes, 22 minutes, or 20 minutes, inclusive of all ranges and sub-ranges embraced therein. Exemplary ranges for the autoclaving time include

from 7 to 60 minutes, or from 8 to 45 minutes, or from 9 to 30 minutes, or from 10 to 25 minutes, or from 15 to 20 minutes.

[0038] FIG. 3 depicts an exemplary process of making a RTU phosphates solution that includes the steps of adding potassium hydrogen phosphate to water at a concentration of 1180 mg/100 ml with stirring, wherein the potassium hydrogen phosphate contains no more than 2 ppm aluminum, adding potassium dihydrogen phosphate to the water at a concentration of 1120 mg/100 ml with stirring, wherein the potassium dihydrogen phosphate contains no more than 2 ppm aluminum, and adding sodium chloride to the water at a concentration of 900 mg/100 ml with stirring, wherein the sodium chloride contains no more than 0.2 ppm aluminum, thereby forming the aqueous potassium phosphates in sodium chloride solution.

[0039] In additional or alternative embodiments, the method of making the aqueous potassium phosphates in sodium chloride solution includes filter sterilizing a fixed volume of the aqueous potassium phosphates in sodium chloride solution into a flexible container. Typically, a fixed volume of the solution is 100 ml provided to a sterile flexible container (e.g., an IV bag). With the fixed volume of the solution dispensed in the flexible container, the flexible container may be terminally sterilized. Preferably, the terminal sterilization is autoclaving to sterility. For storage and/or transport of the terminally sterilized flexible container of RTU aqueous potassium phosphates in sodium chloride solution, the flexible container may be placed inside an aluminum pouch for protective storage and transport.

[0040] In contrast to current practice where remaining concentrated phosphates solutions after withdrawal must be discarded after 24-48 hours (due to crystallization and/or precipitation issues), the inventors unexpectedly discovered that the RTU solutions could remain chemically stable and did not undergo microbial spoilage where RTU solutions were packaged and autoclaved in the package. Most typically, stability and/or concentration of the cations and anions was further promoted where the autoclaved container was packaged into a secondary container (typically containing a metal foil such as aluminum) and/or where the space between the containers was flushed with nitrogen or other inert gas to remove oxygen before sealing the secondary (overwrap) container. The inventors also observed that the type of polymer had at least some influence on storage stability and dimensional stability under autoclaving conditions.

[0041] Based on stability studies performed by the inventors, contemplated solutions can be stored for extended periods such as at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months, at least 3 months, at least 6 months, at least 1 year, and even longer without significant changes in the product composition. Such storage can be performed under refrigerated conditions (e.g., 2-8° C.), at ambient conditions (e.g., 25° C., 40% relative humidity), at warm conditions (e.g., 30° C., 65% relative humidity), and even at accelerated storage conditions (e.g., 40° C., 15% relative humidity).

[0042] For example, the inventors observed that the solutions may have, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a liquid particle count of no more than 400, or no more than 360, or no more than 330, or no more than 300, or no more than 170, or no more than 150, or no more than 120, or no more than 100 for

particles at 25 micrometer size and no more than 30, or no more than 25, or no more than 20, or no more than 17, or no more than 14, or no more than 10 for particles at 15 micrometer size. Alternatively, or additionally, the solutions may have, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in phosphorus and/or potassium content of no more than +/-3% (absolute), or no more than +/-2.5% (absolute), or no more than +/-2.0% (absolute), or no more than +/-1.5% (absolute), or no more than +/-1.0% (absolute), or no more than +/-0.8% (absolute), or no more than +/-0.6% (absolute), relative to initial conditions. Likewise, the solutions may have, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in sodium and/or chloride of no more than +/-2.5% (absolute), or no more than +/-2.0% (absolute), or no more than +/-1.5% (absolute), or no more than +/-1.0% (absolute), or no more than +/-0.8% (absolute), or no more than +/-0.6% (absolute), or no more than +/-0.4% (absolute), relative to initial conditions.

[0043] Notably, the inventive RTU aqueous potassium phosphates in sodium chloride solution may be efficiently administered to a patient in need of phosphorus replacement therapy. Advantageously, the method includes easily administering the sterile ready-to-use (RTU) potassium phosphates in sodium chloride solution from the flexible container to the patient at a rate of infusion and by a route of administration corresponding to the patient’s age and degree of need of phosphorus replacement. As the flexible container comprises a fixed volume (e.g., 100 ml) of the sterile RTU potassium phosphates in sodium chloride solution includes 15 mmol/100 ml Phosphorus, administration to adult or pediatric patients by peripheral venous catheter or central venous catheter may be readily accomplished based on programming the infusion rate accordingly.

[0044] In preferred embodiments, the rate of infusion of the sterile RTU potassium phosphates in sodium chloride solution into the patient is selected from 6.8 mmol/hour or 15 mmol/hour. In typical embodiments, the sterile RTU potassium phosphates in sodium chloride solution is administered to an adult or pediatric patient 12 years of age and older by peripheral venous catheter at 6.8 mmol/hour. In more preferred embodiments, the concentration of phosphates administered by peripheral venous catheter is not more than 6.8 mmol/100 ml in adult patients or pediatric patient 12 years of age and older and not more than 2.7 mmol/100 ml in pediatric patients less than 12 years of age.

[0045] In other typical embodiments, the sterile RTU potassium phosphates in sodium chloride solution is administered to an adult or pediatric patient 12 years of age and older by central venous catheter at 15 mmol/hour. In more preferred embodiments, the concentration of phosphates administered by central venous catheter is not more than 18 mmol/100 ml in adult patients or pediatric patient 12 years of age and older and not more than 5.5 mmol/100 ml in pediatric patients less than 12 years of age.

Examples

[0046] Formulation of ingredients for potassium phosphates in sodium chloride injection 15 mmol/100 ml solution. As set forth in Tables 3-4 below, exemplary amounts of potassium phosphate monobasic (potassium dihydrogen phosphate, KH₂PO₄), potassium phosphate dibasic (potassium hydrogen phosphate, K₂HPO₄) are the active pharmaceutical ingredients (API), thereby serving an active func-

tion. For a 15 mmol/100 ml concentration of phosphorus, 11.2 mg/mL KH₂PO₄ and 11.8 mg/mL K₂HPO₄ are added to water with mixing as disclosed herein. The deionized water is to volume (quantum satis (Q. S.)), which for the ready-to-use (RTU) formulation disclosed herein, is fixed at 100 ml. Sodium chloride (NaCl) is an admixture carrier and tonicity agent having a IIG limit of 0.9" weight/volume (w/v). Accordingly, for a 100 ml solution, 900 mg of NaCl is added.

[0047] Table 5 provides specifications for Monobasic Potassium Phosphate, Table 6 provides specifications for Dibasic Potassium Phosphate, Table 7 provides specifications for Sodium Chloride, and Table 8 provides specifications for Potassium Phosphates in Sodium Chloride Injection, RTU.

TABLE 3

Table 3: Formulation of potassium phosphates in sodium chloride injection solution (15 mmol/100 ml of Phosphorus and 22 mEq/100 mL of Potassium)			
Active and Excipient Details	IIG Limit (mg/mL)	Function	Formulation
Potassium Phosphate monobasic	Not Applicable	Active	11.2 mg
Potassium Phosphate dibasic	Not Applicable	Active	11.8 mg
Sodium Chloride	0.9% w/v	Admixture carrier	9 mg
Water for Injection/Deionized Water	Q.S. to mL	Vehicle	100 mL

TABLE 4

Table 4: Batch formulation of potassium phosphates injection solution (15 mmol/100 ml of Phosphorus and 22 mEq/100 mL of Potassium) in 1 liter (1000 mL). Formulation for Bulk solution of Potassium Phosphates in Sodium Chloride Injection, RTU		
Active and Excipient Details	Formulation	
	Batch Size: 1000 mL	
	Composition per mL	Batch Qty. per 1000 mL
Potassium Phosphate monobasic	11.2 mg	11.2 g or 11200 mg
Potassium Phosphate dibasic	11.8 mg	11.8 g or 11800 mg
Sodium Chloride	9 mg	9 g or 9000 mg
Water for Injection/Deionized Water	1 mL	1000 mL

TABLE 5

Table 5: Specification of Monobasic Potassium Phosphate API			
Sr. No.	Test	Specification	Reference
1.	Description	Colorless crystals or white, granular or crystalline powder	USP
2.	Solubility	Freely soluble in water; practically insoluble in alcohol	USP
3.		Identification tests	
3.1.	Potassium	Meet the requirement	USP<191>
3.2.	Phosphate	Meet the requirement	USP <191>
4.	LOD@105° C.	Not more than 1.0%	USP monograph
5.	Assay	Not less than 98.0% and Not more than 100.5% on the dried basis	USP monograph
6.	Insoluble substances	Not more than 0.2% (NMT 20 mg)	USP monograph
7.		Impurities	
7.1.	Arsenic	Not more than 3 ppm (NMT 3 µg/g)	USP <211>, Method I
7.2.	Lead	Not more than 5 ppm (NMT 5 µg/g)	USP <251>
7.3.	Limit of Fluoride	Not more than 0.001% (NMT 10 µg/g)	USP monograph
8.	Aluminum content	Not more than 2 ppm	In-House
9.	Bacterial Endotoxin	Not more than 0.1 EU/mg of Monobasic Potassium phosphate	USP <85>
10.		Microbial Enumeration Tests	
	Total Aerobic Microbial Count (TAMC)	Not more than 1000 cfu/g	USP <61> & <1111>
	Total Combined Yeasts and Molds Count (TYMC)	Not more than 100 cfu/g	
11.	Total Coliforms	Negative	USP <62> & <1111>
12.	Residual Solvents	Meets the requirement	USP

TABLE 6

Table 6: Specification of Dibasic Potassium Phosphate API			
Sr. No.	Test	Specification	Reference
1.	Description	Colorless or white, somewhat hygroscopic, granular powder.	USP
2.	Solubility	Freely soluble in water; very slightly soluble in alcohol.	USP
3.		Identification tests	
3.1.	Potassium	Meet the requirement	USP<191>
3.2.	Phosphate	Meet the requirement	USP <191>
4.	LOD@105° C.	1.0% of its weight.	USP <731>
5.	pH (5%)	8.5-9.6	USP <791>
6.	Assay	Not less than 98.0% and Not more than 100.5% on the dried basis	USP monograph
7.		Impurities	
7.1.	Insoluble substances	The weight of the residue is Not more than 20 mg (Not more than 0.2%).	USP monograph
7.2.	Carbonate	NMT a few bubbles are evolved.	USP monograph
7.3.	Chloride and Sulfate, Chloride	Shows no more chloride than corresponds to 0.40 mL of 0.020 N hydrochloric acid (Not more than 0.03%)	USP <221>
7.4.	Chloride and Sulfate, Sulfate	Shows no more sulfate than corresponds to 0.20 mL of 0.020 N sulfuric acid (Not more than 0.1%)	USP <221>
7.5.	Arsenic	Not more than 3 ppm (3 µg/g)	USP <211>, Method I
7.6.	Iron	Any red color produced within 1 h is not darker than that of a control prepared from 1 mL of Standard Iron Solution: Not more than 30 ppm (0.003%)	USP <241>
7.7.	Sodium	A solution (1 in 10) tested on a platinum wire imparts no pronounced yellow color to a nonluminous flame.	USP monograph
7.8.	Limit of Fluoride	Not more than 0.001% (10 µg/g)	USP monograph
7.9.	Limit of Monobasic/Tribasic salt	A blue color is produced, which is changed to yellow (with a greenish tinge) by the addition of NMT 0.4 mL of 1 N hydrochloric acid.	USP monograph
8.	Aluminum content	Not more than 2 ppm	In-House

TABLE 6-continued

Table 6: Specification of Dibasic Potassium Phosphate API			
Sr. No.	Test	Specification	Reference
9.	Bacterial Endotoxin	Not more than 0.1 EU/mg of Dibasic Potassium phosphate	USP <85>
Microbial Enumeration Tests			
10.	Total Aerobic Microbial Count (TAMC)	Not more than 1000 cfu/g	USP <61> & <1111>
	Total Combined Yeasts and Molds Count (TYMC)	Not more than 100 cfu/g	
11.	Total Coliforms	Negative	USP <62> & <1111>
12.	Residual Solvents	Meets the requirement	USP

TABLE 7

Table 7: Specification of Sodium Chloride			
Sr. No.	Test	Specification	Reference
1.	Description	Colorless, cubic crystals or white crystalline powder. Has a saline taste	USP
2.	Solubility	Freely soluble in water; soluble in glycerin; slightly soluble in alcohol	USP
3.	Identification tests		
3.1.	Sodium	Meet the requirement	USP<191>
3.2.	Chloride	Meet the requirement	USP <191>
4.	LOD@105° C.	0.5% of its weight.	USP <731>
5.	Assay	Not less than 99.0% and Not more than 100.5% on the dried basis	USP monograph
6.	Appearance of Solution	Meet the requirement	USP monograph
7.	Acidity or Alkalinity	Meet the requirement	USP monograph
8.	Impurities		
8.1.	Aluminum (Al)	Not more than 0.2 ppm	USP monograph
8.2.	Arsenic	Not more than 1 ppm	USP <211>, Method 1
8.3.	Barium	Should be complies	USP monograph
8.4.	Ferrocyanide	Should be complies	USP monograph
8.5.	Iodide	Should be complies	USP monograph
8.6.	Iron	Not more than 2 ppm	USP monograph
8.7.	Bromides	Not more than 100 ppm	USP monograph
8.8.	Phosphates	Not more than 25 ppm	USP monograph
8.9.	Potassium	Not more than 500 ppm	USP monograph
8.10.	Magnesium and Alkaline Earth Metals (as Ca)	Not more than 100 ppm	USP monograph
8.11.	Nitrite (Absorbance Value)	Not more than 0.01%	USP monograph
8.12.	Sulfate	Not more than 200 ppm	USP monograph
9.	Sterility	Meets the requirement	USP<71>
10.	Bacterial Endotoxin	Not more than 0.1 EU/mg of Dibasic Potassium phosphate	USP <85>
11.	Residual Solvents	Meets the requirement	USP

TABLE 8

Table 8: Specification of Potassium Phosphates in Sodium Chloride Injection, RTU				
Sr. No.	Test	Release Specification	Shelf Life Specification	Reference
1.	Description	clear colorless solution, free from visible particles	clear colorless solution, free from visible particles	In-House
2.	Identification tests			
7.1	Potassium	Meet the requirement	Not Applicable	USP<191>
7.2	Phosphate	Meet the requirement	Not Applicable	USP <191>
7.3	Sodium	Meet the requirement	Not Applicable	USP<191>
7.4	Chloride	Meet the requirement	Not Applicable	USP <191>
3.	pH	Between 6.0 and 7.0	Between 6.0 and 7.0	In-House
4.	Osmolality	550-700 mOsmol/kg	550-700 mOsmol/kg	USP <785>
5.	Aluminum content	Not more than 50 µg/L	Not more than 50 µg/L	In-house
6.	Particulate matter			
3.1	A) Visible particles			USP<790>
	Visual inspection	Should be free of visible particles	Should be free of visible particles	

TABLE 8-continued

Table 8: Specification of Potassium Phosphates in Sodium Chloride Injection, RTU				
Sr. No.	Test	Release Specification	Shelf Life Specification	Reference
3.2	B) Sub-visible Particles (By Light Obscuration method)			USP<788>, Method-I; B
	10 µm size particles	Not more than 6000 particles per container	Not more than 6000 particles per container	
	25 µm size particles	Not more than 600 particles per container	Not more than 600 particles per container	
7.	Container content for Injections	Not less than 100.0 mL	Not less than 100.0 mL	USP<697>
8.	Assay of Potassium (Label Claim: Each 100 mL bag contains 8.50 mg/mL of Potassium)	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house
9.	Assay of Phosphorus (Label Claim: Each 100 mL bag contains 4.65 mg/mL of Phosphorus)	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house
10.	Assay of Sodium (Label Claim: Each 100 mL bag contains 3.57 mg/mL of Sodium)	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house
11.	Assay of Chloride (Label Claim: Each 100 mL bag contains 5.43 mg/mL of Chloride)	Not less than 95.0% and Not more than 105.0%	Not less than 90.0% and Not more than 110.0%	In-house
12.	Sterility	Meets the requirement	Meets the requirement	USP<71>
13.	Bacterial endotoxins	Not more than 1.10 USP EU/mg	Not more than 1.10 USP EU/mg	USP<85>
14.	Residual Solvents	Meets the requirement	Not Applicable	USP<467> (Option 1)
15.	Container Closure integrity test	Meets the requirement	Meets the requirement	USP<1207.2>

[0048] Ion Chromatography Methods:

[0049] Assay of Anions (Phosphorus and Chloride) and Cations (Potassium and Sodium) By Ion Chromatography: All the solution preparations (Mobile Phase, Standard, Sample) should be prepared in plastic ware (Volumetric flask, beakers, pipette tips, eluent bottles, etc.).

[0050] Preparation of Mobile Phases:

[0051] Mobile Phase for Anions (9 mM Na2CO3): Take 18.0 mL of Dionex Sodium Carbonate concentrate (0.5M) and dilute to 1000 mL with IC grade water (18.2 MΩ·cm, 0.22 µm filtered), mixed well and degas it for 10 minutes. Purge the solution with helium at 8-10 psi for 10 minutes. After purging blanket/pressurize the container with helium at 8-10 psi for 10 minutes.

[0052] Mobile Phase for Cations (20 mm Methanesulfonic Acid (MSA)): Take 50.0 mL of Dionex CS12A Eluent concentrate (0.4M Methanesulfonic Acid) and dilute to 1000 mL with IC grade water (18.2 MΩ·cm, 0.22 µm filtered), mixed well and degas it for 10 minutes.

[0053] Diluent: Use IC grade water (18.2 MΩ·cm, 0.22 µm filtered) as Diluent.

[0054] IC Conditions: The liquid chromatography equipped with conductivity detector, an injector and a data processor.

[0055] Chromatographic Conditions for Anions are shown in Table 9.

TABLE 9

Parameters	Conditions
Guard Column	Dionex IonPac RFIC AG9-HC (2 × 50 mm)
Column	Dionex IonPac RFIC AS9-HC (2 × 250 mm)

TABLE 9-continued

Parameters	Conditions
Flow rate	0.4 mL/min.
Detector	Suppressed conductivity
Injection volume	50 µL
Run time	15 Minutes
Cell Temperature	30° C.
Sample Cooler Temp.	25° C.
Suppressor	AERS 500e 2 mm (constant voltage & recycle mode) (18 mA)

[0056] Chromatographic Conditions for Anions are shown in Table 10.

TABLE 10

Parameters	Conditions
Guard Column	Dionex IonPac RFIC CG12A (4 × 50 mm)
Column	Dionex IonPac RFIC CS12A (4 × 250 mm)
Flow rate	0.7 mL/min.
Detector	Suppressed conductivity
Injection volume	50 µL
Run time	15 Minutes
Cell Temperature	30° C.
Sample Cooler Temp.	25° C.
Suppressor	CDRS 600 4 mm (constant voltage & recycle mode) (41 mA)

[0057] Preparation of Analytical Solutions:

[0058] Preparation of Standard Solution-1 Set-1 (For Anions): Transfer 0.465 mL of Phosphate Phosphorus Standard Solution for IC and 0.543 mL of Chloride Standard Solution for IC into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. Further diluted 5.0

mL above solution into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. (This solution contains 3.720 µg/mL of Phosphorus and 4.344 µg/mL of Chloride).

[0059] Preparation of Standard Solution-1 Set-2 (For Anions): Transfer 0.465 mL of Phosphate Phosphorus Standard Solution for IC and 0.543 mL of Chloride Standard Solution for IC into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. Further diluted 5.0 mL above solution into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. (This solution contains 3.720 µg/mL of Phosphorus and 4.344 µg/mL of Chloride).

[0060] Preparation of Standard solution-2 Set-1 (For Cations): Transfer 0.850 mL of Potassium Standard Solution for IC and 0.357 mL of Sodium Standard Solution for IC into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. Further diluted 5.0 mL above solution into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. (This solution contains 6.800 µg/mL of Potassium and 2.856 µg/mL of Sodium).

[0061] Preparation of Standard solution-2 Set-2 (For Cations): Transfer 0.850 mL of Potassium Standard Solution for IC and 0.357 mL of Sodium Standard Solution for IC into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. Further diluted 5.0 mL above solution into 25 mL of plastic volumetric flask made up to the mark with diluent, mixed well. (This solution contains 6.800 µg/mL of Potassium and 2.856 µg/mL of Sodium).

[0062] Preparation of Sample Solution: Transfer 1.0 mL of Finished Product into 100 mL of plastic volumetric flask made up to the mark with diluent, mixed well. Further diluted 4.0 mL above solution into 50 mL of plastic volumetric flask made up to the mark with diluent, mixed well. (This solution contains 3.720 µg/mL of Phosphorus, 4.344 µg/mL of Chloride, 6.800 µg/mL of Potassium and 2.856 µg/mL of Sodium).

[0063] Injection Sequence for Anions is shown in Table 11:

TABLE 11

Sr. No.	Solution Name	Number of Injection
1.	Column Condition	3
2.	Diluent	1
3.	Standard Solution-1 Set-1 (For Anions)	6
4.	Standard Solution-1 Set-2 (For Anions)	2
5.	Diluent	1
6.	Sample Solution-1 to 6	2
7.	Diluent	1
8.	Bracketing Standard Solution-1 Set-1 (For Anions)	1 (Inject after 6 Test Samples)

[0064] Injection Sequence for Anions is shown in Table 12:

TABLE 12

Sr. No.	Solution Name	Number of Injection
1.	Column Condition	3
2.	Diluent	1
3.	Standard Solution-2 Set-1 (For Cations)	6

TABLE 12-continued

Sr. No.	Solution Name	Number of Injection
4.	Standard Solution-2 Set-2 (For Cations)	2
5.	Diluent	1
6.	Sample Solution-1 to 6	2
7.	Diluent	1
8.	Bracketing Standard Solution-2 Set-1 (For Cations)	1 (Inject after 6 Test Samples)

[0065] System Suitability Requirements are shown in Table 13:

Parameter	Phosphorus Peak	Chloride Peak	Potassium Peak	Sodium Peak
Z	Z	Z	Z	Z
% Correlation between Standard Solution Set-1 and Set-2	No Less Than 98.0 and No More Than 102.0			
% RSD of Standard	No More Than 2.0			
USP tailing of standard	No More Than 2.0			
USP plate count of standard	No More Than 2000			
Overall % RSD of Standard	No More Than 2.0			

[0066] Calculate the % correlation in standard solution and report the value. If any peak response identified in Diluent at principal peaks then mean the peak response of each individual principal peak from all the diluent injected in sequence and subtract that individual peak response from Standard and Sample respectively.

[0067] % Correlation between Standard Solution Set-1 and Set-2 is calculated as

$$\frac{Rstd\ 2}{Rstd\ 1} \times \frac{Vstd\ 1}{Vstd\ 2} \times 100$$

[0068] Where Rstd 1 is Average Peak area of each individual peak in Standard Solution Set-1, Rstd 2 is Average Peak area of each individual peak in Standard Solution Set-2, Vstd 1 is Dilution of Standard Solution Set-1, and Vstd 2 is Dilution of Standard Solution Set-2.

[0069] Calculations

[0070] Calculate the Assay in test solution and report the value. Note: If any peak response identified in Diluent at principal peaks then mean the peak response of each individual principal peak from all the diluent injected in sequence and subtract that individual peak response from Standard and Sample respectively.

[0071] % Assay is calculated as follows:

$$\frac{Ru}{Rs} \times \frac{Vs}{25} \times \frac{5.0}{25} \times \frac{100}{Vt} \times \frac{50}{4.0} \times \frac{P}{L.C.}$$

[0072] Where Ru is Average Peak area of each individual peak in Sample Solution, Rs is Average Peak area of each individual peak in Standard Solution Set-1, Vs is Volume of each Anion Standards (Phosphorus and Chloride) and Cat-

ion Standards (Potassium and Sodium) (in mL), Vt is Volume of Sample Solution (in mL), P is Potency of each individual Standard, and L.C. is Label Claim of each Anions and Cations as follows: Phosphorus (Anion)-4.65 mg/mL, Chloride (Anion)-5.43 mg/mL, Potassium (Cation)-8.50 mg/mL, and Sodium (Cation)-3.57 mg/mL.

[0073] Validation for Ion Chromatography:

[0074] The Ion Chromatographic process was then tested and validated, and exemplary results are shown in FIGS. 4-7 depicting excellent linearity in the relevant range for the various ions. More specifically, FIG. 4 depicts the linearity curve for phosphorus, FIG. 5 depicts the linearity curve for chloride, FIG. 6 depicts the linearity curve for potassium, and FIG. 7 depicts the linearity curve for sodium, and Table 13 provides exemplary results from these linearity curves.

TABLE 13

Name	Anions		Cations	
	Phosphorus	Chloride	Potassium	Sodium
Correlation coefficient	0.9998	0.9996	1.0000	1.0000
R ² Value	0.9995	0.9992	1.0000	1.0000
Slope of regression line	0.8266	0.9917	0.5345	0.8214
Y intercept	-0.2310	-0.4332	-0.0084	0.0031

[0075] Tables 14-17 provide further data for the accuracies for phosphorus (Table 14), chloride (Table 15), potassium (Table 16), and sodium (Table 17).

TABLE 14

Sr No.	Sample name	Amount added	Amount recovered	% Recovery
1	Accuracy Level-50% Set-1	2.3483	2.3752	101.1
2	Accuracy Level-50% Set-2	2.3489	2.3674	100.8
3	Accuracy Level-50% Set-3	2.3513	2.3592	100.3
	Mean			100.7
	STD Dev			0.4
	% RSD			0.4
1	Accuracy Level-100% Set-1	4.6924	4.6986	100.1
2	Accuracy Level-100% Set-2	4.6967	4.7287	100.7
3	Accuracy Level-100% Set-3	4.6987	4.7609	101.3
	Mean			100.7
	STD Dev			0.6
	% RSD			0.6
1	Accuracy Level-150% Set-1	7.0437	7.0506	100.1
2	Accuracy Level-150% Set-2	7.0428	7.0125	99.6
3	Accuracy Level-150% Set-3	7.0436	7.0702	100.4
	Mean			100.0
	STD Dev			0.4
	% RSD			0.4

TABLE 15

Sr No.	Sample name	Amount added	Amount recovered	% Recovery
1	Accuracy Level-50% Set-1	2.7056	2.7676	102.3
2	Accuracy Level-50% Set-2	2.7079	2.7514	101.6
3	Accuracy Level-50% Set-3	2.7050	2.7540	101.8
	Mean			102.0
	STD Dev			0.5
	% RSD			0.5
1	Accuracy Level-100% Set-1	5.4170	5.5163	101.8
2	Accuracy Level-100% Set-2	5.4148	5.5327	102.2
3	Accuracy Level-100% Set-3	5.4067	5.5532	102.7
	Mean			102.0
	STD Dev			0.3
	% RSD			0.3

TABLE 15-continued

Sr No.	Sample name	Amount added	Amount recovered	% Recovery
1	Accuracy Level-150% Set-1	8.1173	8.2750	101.9
2	Accuracy Level-150% Set-2	8.1221	8.2221	101.2
3	Accuracy Level-150% Set-3	8.1206	8.2802	102.0
	Mean			101.7
	STD Dev			0.4
	% RSD			0.4

TABLE 16

Sr No.	Sample name	Amount added	Amount recovered	% Recovery
1	Accuracy Level-50% Set-1	4.2860	4.2825	99.9
2	Accuracy Level-50% Set-2	4.2890	4.2816	99.8
3	Accuracy Level-50% Set-3	4.2875	4.2808	99.8
	Mean			99.8
	STD Dev			0.1
	% RSD			0.1
1	Accuracy Level-100% Set-1	8.5660	8.5052	99.3
2	Accuracy Level-100% Set-2	8.5716	8.5544	99.8
3	Accuracy Level-100% Set-3	8.5774	8.6057	100.3
	Mean			99.8
	STD Dev			0.5
	% RSD			0.5
1	Accuracy Level-150% Set-1	12.8574	12.8679	100.1
2	Accuracy Level-150% Set-2	12.8568	12.7590	99.2
3	Accuracy Level-150% Set-3	12.8577	12.8449	99.9
	Mean			99.7
	STD Dev			0.5
	% RSD			0.5

TABLE 17

Sr No.	Sample name	Amount added	Amount recovered	% Recovery
1	Accuracy Level-50% Set-1	1.7779	1.7785	100.0
2	Accuracy Level-50% Set-2	1.7795	1.7730	99.6
3	Accuracy Level-50% Set-3	1.7776	1.7744	99.8
	Mean			99.8
	STD Dev			0.3
	% RSD			0.3
1	Accuracy Level-100% Set-1	3.5597	3.5414	99.5
2	Accuracy Level-100% Set-2	3.5583	3.5502	99.8
3	Accuracy Level-100% Set-3	3.5530	3.5647	100.3
	Mean			99.7
	STD Dev			0.2
	% RSD			0.2
1	Accuracy Level-150% Set-1	5.3342	5.3404	100.1
2	Accuracy Level-150% Set-2	5.3374	5.3049	99.4
3	Accuracy Level-150% Set-3	5.3364	5.3340	100.0
	Mean			99.8
	STD Dev			0.4
	% RSD			0.4

[0076] Table 18 depicts exemplary results for cation and anion recovery.

TABLE 18

Ions	Recovery Levels	Mean % Recovery	% RSD
Phosphorus	50% Level	100.7	0.4
	100% Level	100.7	0.6
	150% Level	100.0	0.4
Chloride	50% Level	102.0	0.5
	100% Level	102.0	0.3
	150% Level	101.7	0.4

TABLE 18-continued

Ions	Recovery Levels	Mean % Recovery	% RSD
Potassium	50% Level	99.8	0.1
	100% Level	99.8	0.5
	150% Level	99.7	0.5
Sodium	50% Level	99.8	0.3
	100% Level	99.7	0.2
	150% Level	99.8	0.4

[0077] In conclusion, it should therefore be appreciated that the above test method established that the method is specific, linear, accurate, precise, robust and stable. Based on solution stability data (data not shown), it was concluded that standard solution are stable up to 168 Hrs at room temperature, that sample solutions are stable up to 168 Hrs at room temperature, and that mobile phases were stable up to 72 Hrs at room temperature under continuous chromatographic conditions.

[0078] Aluminum Detection

[0079] In a similar manner, the inventors set further out to detect and quantify aluminum levels in the solutions presented herein, and FIG. 8 depicts an exemplary linearity curve for aluminum in the potassium phosphates solutions presented herein. Table 19 provides exemplary results for Accuracy & Method Precision at 100% Spiked Level by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

TABLE 19

Accuracy & Method Precision @ 100% Spiked Level					
Sets/Levels	% Recovery	Average % Recovery	AVG.	SD	% RSD
LOQ_25%_Set-1	113.84	113.92	105.75	9.8281	9.3
	113.99				
LOQ_25%_Set-2	109.62	110.06			
	110.50				
LOQ_25%_Set-3	93.04	93.26			
	93.48				
50%_Set-1	104.27	103.36	104.44	3.5114	3.4
	102.45				
50%_Set-2	101.87	101.25			
	100.63				
50%_Set-3	108.41	108.70			
	108.99				
100%_Set-1	99.52	99.77	99.76	4.5208	4.5
	100.02				
100%_Set-2	99.66	100.01			
	100.35				
100%_Set-3	95.48	96.02			
	96.57				
100%_Set-4	99.33	100.35			
	101.37				
100%_Set-5	107.55	107.97			
	108.39				
100%_Set-6	93.73	94.42			
	95.12				
200%_Set-1	99.74	99.67	97.29	2.9961	3.1
	99.59				
200%_Set-2	99.59	98.53			
	97.47				
200%_Set-3	94.70	93.68			
	92.65				
400%_Set-1	96.32	96.07	95.77	0.3961	0.4
	95.82				
400%_Set-2	95.55	95.38			
	95.21				
400%_Set-3	96.08	95.87			
	95.65				

[0080] Stability Studies

[0081] For the stability studies, the inventors investigated stability of a phosphorus solution containing saline that was prepared according to FIG. 3 from water and potassium dihydrogen phosphate (KH₂PO₄), potassium hydrogen phosphate (K₂HPO₄), and sodium chloride (NaCl), wherein the potassium dihydrogen phosphate was present in the solution an amount of about 1,120 mg/100 ml (8.2 mmol/100 ml), wherein the potassium hydrogen phosphate was present in the solution in an amount of about 1,180 mg/100 ml (6.8 mmol/100 ml), and wherein the sodium chloride was present in the solution in an amount of about 900 mg/100 ml. Thus, the solution contained 15 mmol/100 ml phosphorus (0.15 mmol/mL), 22 mEq/100 mL potassium, and had an aluminum content of about 30 mcg/L. Table 20 provides an overview of the packaging materials used and filling/auto-claving conditions employed.

TABLE 20

Potassium Phosphates in Sodium Chloride Injection (15 mmol/100 mL of Phosphorus and 22 mEq/100 mL of Potassium) Secondary packaging for all samples was an aluminum pouch (PET/ALU/PET/PP) and bag fill volume was 100 mL							
Bag Source	Bag Film Material	Bag Material	Bag Injection Port	Bag Injection Port material	Bag Tube Material	Batch No. (Stability Batches and Results)	Sterilization Method
TechnoFlex	PP Film/Layflat Inerta 103 (0.20-NCT)	PP	1	Twist off Port 823-PP INERTA016	PP-4618 Ø 6.15 × 8.2 Tube-NCT	NPO2052 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
						NPO2092 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
						NPO21001 (6 Months)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes)
TechnoFlex	PP Film/Layflat Inerta 103 (0.20-NCT)	PP	2	Twist off Port 823-PP INERTA016 and Injection Port	PP-4618 Ø 6.15 × 8.2 Tube-NCT	NPO2052 (6 Months),	Terminal Sterilization (121° C. for 15 Minutes)
						NPO2092 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
TechnoFlex	PVC/Layflat MediPack-3222 (0.32-NCT)	PVC	2	Twist off 450 Welded PVC 3222 and Injection Port	PVC-3227 Ø 6.15 × 8.2 Tube-NCT	NPO2052 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
Grifols	Not Available	PP	1	PP Plug for Twist off	Not Available	NPO2052 (6 Months), NPO2092 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
Bausch	APP 114S 200 µm Film 160 mm Width	PP	2	PP Plug for Twist off and Injection Port	APP 107 Tubing Ø 8.2 × 6.2	NPO2052 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
HaemoPharm	NEXCEL M312A Film (Sealed Air) 135 × 0.40	Polyolefins	1	PP Plug for Twist off in Melitek	Raumedic Tube Ø 6.2 × 8.3	NPO21001 (6 Months)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes), Terminal Sterilization (115° C. for 20 Minutes)
						B#192073__11 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
HaemoPharm	NEXCEL M312 Film (Sealed Air) 135 × 0.40	Polyolefins	1	PP Plug for Twist off in Melitek	Raumedic Tube Ø 6.2 × 8.3	NPO21006 (6 Months)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes)
						NPO21007 (6 Months)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes)
						NPO21008 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)

TABLE 20-continued

Potassium Phosphates in Sodium Chloride Injection (15 mmol/100 mL of Phosphorus and 22 mEq/100 mL of Potassium) Secondary packaging for all samples was an aluminum pouch (PET/ALU/PET/PP) and bag fill volume was 100 mL							
Bag Source	Bag Film Material	Bag Material	Bag Injection Port	Bag Injection Port material	Bag Tube Material	Batch No. (Stability Batches and Results)	Sterilization Method
Informed Fluids	APP114S Film (Polycine) 135 × 0.20	Polyolefins	1	1963/SM - winged spike port	APP107 Tubing Ø 6.8 × 8.8 Roll	NPO21001 (6 Months)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes), Terminal Sterilization (115° C. for 20 Minutes)
						NPO21007 (6 Months)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes)
						NPO21008 (6 Months)	Terminal Sterilization (121° C. for 15 Minutes)
						NPO21012 (up to 3 Months)	Terminal Sterilization (121° C. for 15 Minutes)
						Engineering Batch Lot#21070832 (Initial)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes)
Informed Fluids	NEXCEL M312 Film (Sealed Air) 135 × 0.20	Polyolefins	1	1963/SM - winged spike port	COEX TUBE PP/EVA Ø 6.8 × 8.8 Roll	NPO21012 (up to 3 Months)	Terminal Sterilization (121° C. for 15 Minutes)
						Engineering Batch Lot#21070832 (Initial)	Aseptic Filling, Terminal Sterilization (121° C. for 15 Minutes)

[0082] Stability was determined for all samples over various time periods and temperatures as is indicated in the respective “Stability Batches and Results”, with detailed results shown in FIGS. 9-17. More specifically, FIG. 9 depicts stability conditions and results for Stability Batch NPO2052, FIG. 10 depicts stability conditions and results for Stability Batch NPO2092, FIG. 11 depicts stability conditions and results for Stability Batch NPO21001, FIG. 12 depicts stability conditions and results for Stability Batch B #192073_11, FIG. 13 depicts stability conditions and results for Stability Batch NPO21006, FIG. 14 depicts stability conditions and results for Stability Batch NPO21007, FIG. 15 depicts stability conditions and results for Stability Batch NPO21008, FIG. 16 depicts stability conditions and results for Stability Batch NPO21012, and FIG. 17 depicts stability conditions and results for Stability Batch Engineering Batch Lot #21070832. All formulations listed in FIGS. 9-17 had an aluminum content of less than 50 mcg/L, with most formulations having an aluminum concentration of between about 7-27 mcg/L.

[0083] As can be readily seen from the results, the materials of the primary container did exert some influence on

storage stability as evidenced by the liquid particle count (LPC) for particle size measurements at 10 and 25 micron. In addition, as can also be seen with certain materials, the presence of an overwrap substantially reduce loss of water via vapor phase as evidenced by the cation and anion concentrations.

[0084] In some embodiments, the numbers expressing quantities of ingredients, properties such as concentration, reaction conditions, and so forth, used to describe and claim certain embodiments of the invention are to be understood as being modified in some instances by the term “about.” Accordingly, in some embodiments, the numerical parameters set forth in the written description and attached claims are approximations that can vary depending upon the desired properties sought to be obtained by a particular embodiment. The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein.

[0085] As used herein, the term “administering” a pharmaceutical composition or drug refers to both direct and

indirect administration of the pharmaceutical composition or drug, wherein direct administration of the pharmaceutical composition or drug is typically performed by a health care professional (e.g., physician, nurse, etc.), and wherein indirect administration includes a step of providing or making available the pharmaceutical composition or drug to the health care professional for direct administration (e.g., via injection, infusion, oral delivery, topical delivery, etc.). It should further be noted that the terms “prognosing” or “predicting” a condition, a susceptibility for development of a disease, or a response to an intended treatment is meant to cover the act of predicting or the prediction (but not treatment or diagnosis of) the condition, susceptibility and/or response, including the rate of progression, improvement, and/or duration of the condition in a subject.

[0086] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. “such as”) provided with respect to certain embodiments herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0087] As used in the description herein and throughout the claims that follow, the meaning of “a,” “an,” and “the” includes plural reference unless the context clearly dictates otherwise. Also, as used in the description herein, the meaning of “in” includes “in” and “on” unless the context clearly dictates otherwise. As also used herein, and unless the context dictates otherwise, the term “coupled to” is intended to include both direct coupling (in which two elements that are coupled to each other contact each other) and indirect coupling (in which at least one additional element is located between the two elements). Therefore, the terms “coupled to” and “coupled with” are used synonymously.

[0088] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms “comprises” and “comprising” should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C . . . and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

What is claimed is:

1. An isotonic sterile ready-to-use (RTU) aqueous potassium phosphates solution, comprising potassium phosphates and sodium chloride, wherein the solution comprises 15 mmol/100 ml phosphorus (0.15 mmol/mL) and equal or less than 50 mcg/L aluminum.

2. The solution of claim 1, wherein the potassium phosphates comprise potassium dihydrogen phosphate

(KH_2PO_4) and potassium hydrogen phosphate (K_2HPO_4), wherein the potassium dihydrogen phosphate is present in the solution an amount of about 1,120 mg/100 ml or 8.2 mmol/100 ml of Phosphorus and wherein the potassium hydrogen phosphate is present in the solution in an amount of about 1,180 mg/100 ml or 6.8 mmol/100 ml of Phosphorus.

3. The solution of claim 1, wherein the potassium is present in the solution in an amount of about 22 mEq/100 mL.

4. The solution of claim 1, wherein the sodium chloride is present in the solution in an amount of about 900 mg/100 ml.

5. The solution of claim 1, wherein the solution has a pH of between 6.2 and 6.8.

6. The solution of claim 1, wherein the solution has, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a liquid particle count of no more than 360 and 30 for particles at 15 and 25 micrometer size, respectively.

7. The solution of claim 1, wherein the solution has, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in phosphorus of no more than 1% absolute.

8. The solution of claim 1, wherein the solution has, after autoclaving and storage of at least 3 months at 25° C. and 40% relative humidity, a change in potassium of no more than 2% absolute.

9. The solution of claim 1, wherein the solution is packaged in a flexible polyolefin container, optionally at a volume of 100 mL.

10. The solution of claim 1, wherein the flexible polyolefin container is further contained in a secondary metallized overwrap.

11. A sterile ready-to-use (RTU) premixed pharmaceutical product stored in a flexible polymeric container, wherein the pharmaceutical product comprises a potassium phosphates in an aqueous sodium chloride solution containing (a) less than 50 mcg/L aluminum, (b) about 15 mmol/100 ml phosphorus, and (c) about 22 mEq/100 mL potassium.

12. The pharmaceutical product of claim 11, wherein the potassium phosphates comprise potassium dihydrogen phosphate (KH_2PO_4) and potassium hydrogen phosphate (K_2HPO_4), wherein the potassium dihydrogen phosphate is present in the solution an amount of about 1,120 mg/100 ml or 8.2 mmol/100 ml of Phosphorus, and wherein the potassium hydrogen phosphate is present in the solution in an amount of about 1,180 mg/100 ml or 6.8 mmol/100 ml of Phosphorus.

13. The pharmaceutical product of claim 12, wherein the sodium chloride is present in the aqueous sodium chloride solution in an amount of about 900 mg/100 ml.

14. The pharmaceutical product of claim 11, wherein the premixed pharmaceutical product in the flexible polymeric container has a volume of 100 mL.

15. The pharmaceutical product of claim 11, wherein the flexible polymeric container is enclosed in a secondary metallized overwrap.

16. The pharmaceutical product of claim 11, wherein the premixed pharmaceutical product comprises about 4.65 mg/mL of phosphorus (0.15 mmol/mL), about 8.50 mg/mL of potassium (0.22 mEq/mL), about 3.57 mg/mL of sodium, and about 5.43 mg/mL of chloride.

17. A method of administering phosphates to a patient in need of phosphorus replacement therapy, comprising:

administering, without prior dilution, an isotonic, sterile, and ready-to-use (RTU) solution comprising potassium phosphates and sodium chloride solution from a flexible container to the patient at a rate of infusion and by a route of administration corresponding to the patient's age and degree of need of phosphorus replacement; wherein the solution comprises about 15 mmol/100 ml phosphorus, about 22 mEq/100 mL potassium, and less than 50 mcg/L aluminum.

18. The method of claim **17**, wherein the rate of infusion is 6.8 mmol phosphates per hour or 15 mmol phosphates per hour.

19. The method of claim **17**, wherein the route of administration is a central venous catheter.

20. The method of claim **17**, wherein the solution is administered after storage of at least 3 months at 25° C. and 40% relative humidity.

* * * * *