

Extended Stability of Sodium Phosphate Solutions in Polyvinylchloride Bags.



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BACKGROUND

Concentrated sodium phosphate injections provide 3mmol of phosphate per mL and 4 mmol of sodium per mL. At this concentration the solution is considered a risk to patient safety and must be sufficiently diluted, thoroughly mixed, and infused slowly enough to prevent phlebitis, hypernatremia, hyperphosphatemia and changes to calcium metabolism. As a result many pharmacy departments have been preparing dilute solutions of sodium phosphate solutions, frequently in the range of 30 mmol/L to 150 mmol/L of phosphate.

While we are not aware of any literature that aqueous solutions of sodium or phosphate degrades, there is also no supporting published evidence documenting stability in IV solutions to allow the establishment of a beyond use date (BUD). However, in assigning a reasonable BUD, which is frequently extended to provide convenience and reduce wastage, some additional factors must be considered. These include sodium phosphate solubility, storage temperature, the effect of water loss through a PVC bag and USP Chapter 797 recommendations.

OBJECTIVES

The objective of this study was to evaluate the stability of both sodium and phosphate in admixtures of 30 mmol/L (phosphate) and 150 mmol/L (phosphate) from sodium phosphate in 5% dextrose in water or 0.9% sodium chloride solutions stored in PVC bags at both room temperature (23C) and 4C over 63 days. During the study PVC bags were stored with the over-wrap removed.

During the 63-day study period, the concentration of sodium and phosphate was determined on 12 study days, the weight of PVC bags was recorded and solutions were visually inspected for particulate matter and any visual changes.

METHODS

MEASUREMENT OF SODIUM AND PHOSPHATE

Both sodium and phosphate concentrations in the diluted IV solutions were determined using established methods. Sodium was measured by indirect Ion Selective Electrode (ISE) based on a sodium-selective PVC Membrane, while inorganic phosphate was measured based on the formation of ammonium phosphomolybdate complex, $(\text{NH}_4)_3[\text{PO}_4(\text{MoO}_3)_{12}]$, monitored spectrophotometrically at wavelength of 340 nm. Both methods were routinely quality-controlled by using commercial materials at two different concentrations, giving long term imprecision (CVs) of 0.83-1.67% for sodium and 2.49-3.22% for phosphate.

ASSAY VALIDATION

To test the accuracy and reproducibility of measured concentrations of sodium and phosphate, a solution containing 250.15 mmol/L of sodium and 75 mmol/L of phosphate was prepared. Five samples were tested in duplicate and the accuracy and reproducibility of the measured concentrations calculated on five consecutive days.

STABILITY STUDY

On study-day zero, 16 x 100 mL PVC bags containing 150 mmol/L of phosphate (8 solutions in D5%W and 8 in NS), and 16 - x 250 mL PVC bags containing 30 mmol/L of phosphate (8 solutions in 5% dextrose, 8 in NS) were prepared. Solutions were stored at 4°C and room temperature (23°C), unprotected from fluorescent room light and with the over-wrap removed. On each study day (0, 2, 7, 9, 16, 21, 23, 28, 30, 35, 50 and 63), the sodium and phosphate concentrations were determined. Bags were also inspected visually for a precipitate, visual changes, and the weight of the bag determined.

DATA REDUCTION AND STATISTICAL ANALYSIS

Linear regression and multiple linear regression were used to determine if there was an association between the observed concentration and study days, solution type, concentrations or temperature. The 95% confidence interval of the percent remaining on the last study day was calculated. Analysis of variance was used to test differences in concentration on different study days, solution type, concentration and temperature. The five-percent level was used as the *a priori* cut-off for significance.

Assay Validation

Phosphate measurements, based on 5 samples with a nominal concentration of 75 mmol/L were accurate (mean bias of -1.17% [range -6.12% to 3.15 percent]; mean absolute bias of 2.86%) and reproducible (mean CV 0.86%). Sodium was also measured accurately (mean bias of -1.98% [range -5.66% to -0.86%]; mean absolute bias 1.98%) and reproducible (mean CV 0.58%) based on 5 samples with a nominal concentration of 250.15 mmol/L.

Physical Stability and Bag Weights.

Over the 63-day study period all solutions remained clear and colourless without visible signs of precipitate or particulate matter.

PVC Bag Volume	Surface Area	Loss of weight over 63 Days	
		4°C	23°C
100 mL	176 cm ²	1.2 gm	3.5 gm
250 mL	256 cm ²	1.8 gm	4.7 gm
Loss mg/cm ² /day		0.123 – 0.144	0.288 – 0.311

With the over-wrap removed, these changes in weight due to the loss of water are sufficient to increase the concentration of sodium and phosphate in study bags by between 0.82% to 3.45% over the 63 day study period. The observed percent loss per day, determined by linear regression-is listed in Tables 1 and 2.

Sodium Phosphate Stability

The initial concentration and the percent remaining observed on each study day during the study period for sodium and phosphate are listed in Tables 1 and 2, respectively.

In both Tables 1 and 2, the 95% confidence interval for the degradation rate for both sodium and phosphate includes a rate of zero (%/day). The intersection of the lower limit of the 95% CI of the slope and 90%, indicates that concentrations will remain greater than 90% for more than 63 days.

Table 1. Percent Remaining¹ of Sodium During Storage

Expected Sodium Concentration (mmol/L)	346.3		200.0		200.0		192.5		192.5		40.0		40.0	
	Observed Initial Concentration (mmol/L)	342.0±0.4	340.0±0.7	193.0±0.6	194.3±0.4	191.7±0.3	192.5±0.4	38.7±1.3	38.7±1.3					
Study Day	100 mL NS 4°C	100 mL NS 23°C	100 mL D5W 4°C	100 mL D5W 23°C	250 mL NS 4°C	250 mL NS 23°C	250 mL D5W 4°C	250 mL D5W 23°C	250 mL D5W 4°C	250 mL D5W 23°C				
2	99.22±0.48	99.71±0.61	98.10±0.43	98.29±0.54	100.00±0.00	99.57±0.61	94.84±2.40	95.27±1.08						
7	99.32±1.14	100.10±0.69	100.18±2.89	100.34±0.53	99.91±0.39	99.66±0.42	98.72±1.42	98.29±1.35						
9	100.00±0.37	100.20±0.80	99.31±0.54	100.35±1.06	100.17±0.27	100.09±0.39	100.45±1.95	99.15±1.34						
16	98.54±0.62	99.71±0.61	100.18±1.02	100.86±1.00	98.70±0.29	99.31±0.43	102.60±1.62	102.16±1.04						
21	99.71±0.96	100.49±0.58	99.66±0.85	101.55±1.54	99.39±0.39	100.09±0.61	98.29±1.35	98.72±1.42						
23	99.81±0.71	101.67±0.86	99.48±0.57	101.03±1.12	100.96±0.21	100.95±0.60	97.85±1.08	97.41±0.04						
28	99.71±0.49	101.18±0.64	98.96±0.01	102.06±1.11	99.74±0.29	100.09±0.51	97.85±1.08	97.85±1.08						
30	100.10±0.44	101.18±1.27	99.48±0.57	101.54±0.85	100.09±0.21	100.35±0.42	98.72±1.42	98.29±1.35						
35	99.81±0.30	101.96±0.30	99.48±0.57	102.23±0.41	99.83±0.27	100.69±0.63	98.29±1.35	100.01±1.64						
50	99.91±1.13	103.23±1.38	101.21±1.19	106.00±1.41	99.57±0.21	100.26±0.54	104.32±1.30	105.60±0.97						
63	100.39±1.87	105.00±0.90	101.21±0.42	106.52±0.51	99.91±0.21	101.65±0.51	101.73±1.32	102.59±0.03						

Slope ² (% change per day)	0.013	0.079	0.028	0.118	0.002	0.025	0.064	0.090
Intercept	99.41	99.33	99.10	98.94	99.90	99.63	97.95	97.48
Sy.x ³	0.44	0.53	0.72	0.76	0.55	0.45	2.32	2.24
Confidence Interval for slope	±0.016	±0.019	±0.025	±0.027	±0.020	±0.016	±0.082	±0.079
Shortest Time to Achieve 90% (95% Confidence) days ⁴	355.7	102.4	186.1	69.2	469.0	246.0	68.7	59.2
Weight Loss (gm/day)	0.022	0.055	0.024	0.055	0.013	0.030	0.015	0.030
Shortest Time to Achieve 90% after Weight Correction (95% Confidence) days ⁴	403.0	233.1	330.2	111.3	290.6	492.2	76.4	71.7

1. Each value is based on duplicate determinations of three samples. Percent Remaining is based on 100% found on Day 0.
2. Slope represents the change in concentration as determined by linear regression of percent remaining on each study day. Change in concentration is largely due to water loss.
3. Sy.x is the standard deviation of regression. This is equivalent to the inter-day variability of the analytical method.
4. Time to achieve 90% of initial concentration (T-90) based on the degradation rate and is generally regarded as the Beyond Use Date.

Analysis of variance was able to detect significant differences in percent remaining due to temperature (p<0.0004), solution type (p<0.03), study days (p<0.0005) and concentration (p<0.0001) for both sodium and phosphate. In all cases, the difference is 1% or less for sodium and approximately 0.8% or less for phosphate. The most readily apparent differences in concentration are related to temperature and bag volume (concentration) and can be directly attributed to weight loss resulting in an increase in concentration. When sodium and phosphate concentrations are corrected for water loss, analysis of variance was unable to detect significant differences in percent remaining due to temperature or concentration.

RESULTS

Table 2. Percent Remaining¹ of Phosphate During Storage

Expected Phosphate Concentration (mmol/L)	150.0		150.0		150.0		150.0		30.0		30.0		30.0		30.0	
	Observed Initial Concentration (mmol/L)	155.2±0.6	154.7±1.8	154.3±1.2	154.9±1.5	31.5±0.3	31.7±0.3	31.1±0.3	31.4±0.3							
Study Day	100 mL NS 4°C	100 mL NS 23°C	100 mL D5W 4°C	100 mL D5W 23°C	250 mL NS 4°C	250 mL NS 23°C	250 mL D5W 4°C	250 mL D5W 23°C <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>								
2	99.22±0.43	97.45±2.08	99.21±0.90	99.42±1.59	99.44±0.65	98.68±0.80	99.30±1.45	98.76±0.66								
7	99.44±1.27	99.23±0.87	98.64±3.13	99.31±1.21	97.89±0.90	98.42±1.07	98.80±1.06	98.92±0.48								
9	98.87±0.48	99.33±0.55	99.23±0.81	100.23±1.35	98.76±0.83	99.10±0.79	99.45±0.86	98.87±0.77								
16	101.44±1.08	100.76±1.87	100.02±2.01	101.77±1.50	100.45±0.63	100.46±0.86	101.11±0.24	100.41±1.15								
21	100.24±1.75	101.49±1.59	100.22±1.07	102.64±1.33	100.57±0.60	101.23±0.89	100.09±3.99	101.07±1.15								
23	100.36±2.41	101.71±0.56	101.14±0.52	102.89±0.96	100.05±0.67	100.26±1.32	101.10±0.91	100.88±0.70								
28	100.58±1.61	102.56±1.55	101.14±0.95	103.16±0.88	99.47±1.17	99.47±0.88	100.39±0.60	100.09±0.76								
30	98.28±0.97	98.82±1.44	98.10±0.50	100.04±1.21	98.08±0.51	97.92±0.86	98.54±1.70	99.02±0.73								
35	98.22±1.46	100.50±1.06	98.28±1.06	100.96±0.57	98.29±1.24	99.40±0.61	99.28±1.20	99.09±0.81								
50	99.60±1.30	101.96±0.74	99.01±0.68	102.84±1.76	98.16±1.39	98.87±1.46	99.19±0.80	99.69±0.33								
63	100.97±2.42	105.34±1.31	100.88±0.24	104.92±1.78	100.25±0.62	101.46±0.80	100.45±1.16	101.53±0.75								

Slope ² (% change per day)	0.008	0.084	0.008	0.073	-0.003	0.017	0.004	0.023
Intercept	99.59	98.77	99.47	99.80	99.35	99.21	99.72	99.33
Sy.x ³	1.06	1.36	1.11	1.18	1.05	1.11	0.89	0.90
Confidence Interval for slope	±0.037	±0.048	±0.039	±0.041	±0.037	±0.039	±0.031	±0.032
Shortest Time to Achieve 90% (95% Confidence) days ⁴	224.0	75.8	213.2	87.9	251.2	180.1	287.3	185.1
Weight Loss (gm/day)	0.022	0.055	0.024	0.055	0.013	0.030	0.015	0.030
Shortest Time to Achieve 90% after Weight Correction (95% Confidence) days ⁴	194.7	129.7	182.7	168.9	189.0	192.5	235.9	260.4

1. Each value is based on duplicate determinations of three samples. Percent Remaining is based on 100% found on Day 0.
2. Slope represents the change in concentration as determined by linear regression of percent remaining on each study day. Change in concentration is largely due to water loss.
3. Sy.x is the standard deviation of regression. This is equivalent to the inter-day variability of the analytical method.
4. Time to achieve 90% of initial concentration (T-90) based on the degradation rate and is generally regarded as the Beyond Use Date.

DISCUSSION & CONCLUSION

We are unaware of any published studies which document the chemical stability of sodium phosphate in standard IV solutions. When considering the stability of sodium phosphate it should be recognized that sodium is an element, and while there are 20 known isotopes of sodium, effectively 100% of sodium on earth exists as the stable, non-radioactive form, ²³Na. Sodium is generally regarded as stable.

Elemental phosphorus is never found as a free element. Phosphorus has a single naturally occurring isotope, but in biological systems, phosphorus is found as free phosphate ion in solution. Phosphate ion exists in dilute aqueous solutions in four forms. In strongly-acid conditions, aqueous phosphoric acid (H₃PO₄) is the primary form, although some amount of each of the other 3 forms will be present and in equilibrium with all other forms. A shift from one form to another is not considered instability. There is no indication that phosphate degrades.

During the 63-day study period PVC bags lost weight proportional to surface area and temperature. With the over-wrap removed, the weight loss was greater for 100 mL bags (1.4% at 4C; 3.4% at 23C) compared to (0.9% at 4C; 1.9% at 23C) 250 mL bags.

During the 63-day study period, after correction for weight <water> loss, confidence limits constructed about the rate of change in concentration included a rate of zero for both sodium and phosphate. This indicates that neither sodium nor phosphate was observed to degrade during the 63-day study period.

When establishing a BUD for intravenous admixtures of sodium phosphate injection, USP 797 guidelines for compounded sterile products (CSP) based on risk level, institutional compliance and storage conditions should be considered.

