

Calcium and phosphate compatibility: Revisited again

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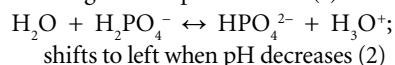
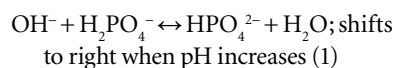
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The subject of the compatibility between calcium and phosphates was revisited in an April 1994 FDA safety alert,^{1,2} 6–16 years after the four seminal research articles appeared in 1978,³ 1980,⁴ 1982,⁵ and 1988.⁶ In the 1980s there were two case reports of nonfatal adverse events involving calcium phosphate precipitation in total parenteral nutrient (TPN) admixtures.^{7,8} A review of the main determinants of parenteral drug and admixture compatibility and stability also appeared during that decade.⁹ Soon after the April 1994 safety alert, several publications on calcium phosphate precipitation in TPN formulations appeared.^{10–18} Thus, this article is yet another revisit of calcium and phosphate compatibility with i.v. formulations.

This article discusses the chemistry and practical compatibility or solubility factors relevant to the safe administration of combination therapy with calcium gluconate and potassium or sodium phosphate injections. Patient case reports that led to adverse events and pharmaceutical and clinical factors important to calcium phosphate solubility are also presented.

pH and pK_a equilibria relevant to calcium and phosphate compatibility. The keys to understanding the chemical reactions and relative risks for calcium phosphate precipitation are as follows:

- The clinically relevant dissociation equilibria for which the pK_{a2} of phosphoric acid is 7.2 (i.e., the pH at which the concentrations or, thermodynamically, the ionic activities of HPO₄²⁻ and H₂PO₄⁻ are equal) (Table 1):



- The Henderson–Hasselbach equations^{9,19}:

$$\text{pH} = \text{pK}_a + \log \left(\frac{[\text{A}^-]}{[\text{HA}]} \right); \text{ percent ionized, } \text{A}^- = 100 / (1 + \text{antilog} [\text{pK}_a - \text{pH}]) = 100 \{ [\text{A}^-] / ([\text{A}^-] + [\text{HA}]) \} \text{ (3)}$$

$$\text{pH} = \text{pK}_a + \log \left(\frac{[\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]} \right); \text{ percent HPO}_4^{2-} = 100 / (1 + \text{antilog} [\text{pK}_a - \text{pH}]) = 100 \{ [\text{HPO}_4^{2-}] / ([\text{HPO}_4^{2-}] + [\text{H}_2\text{PO}_4^-]) \} \text{ (4)}$$

- The compatibility curves for calcium gluconate versus phosphate concentrations in clinical mixtures.^{4,5,17,18}

- The influence of other drugs and nutrients.^{4–8,10–18}

The application of knowledge about calcium and phosphate compatibility in i.v. therapy has been facilitated by four hallmark articles,^{3–6} several editions of the *Handbook on Injectable Drugs*¹⁷ since 1983, and *Trissel's Calcium and Phosphate Compatibility in Parenteral Nutrition*.¹⁸ Despite the availability of these literature sources, calcium and phosphate compatibility continues to be a clinical enigma.

Physicochemical factors. *Calcium and phosphate solubility chemistry.* The aqueous chemistry and solubility of the two phosphate anions and their calcium salts that are important to the safety of i.v. therapy are summarized in Table 1. The main facts are as follows: The lower the solution pH is below 7.2, which is the critical pK_{a2} of phosphoric acid in practice, the greater is the majority percentage of the desired H₂PO₄⁻ anion (dihydrogen or monobasic phosphate). H₂PO₄⁻, with two dissociable protons, is an acid relative to HPO₄²⁻, and HPO₄²⁻ (i.e., monohydrogen or dibasic phosphate) is a base or weaker acid relative to H₂PO₄⁻. Ca[H₂PO₄]₂ (calcium dihydrogen phosphate) is 60 times more soluble than CaHPO₄ (calcium monohydro-

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Table 1.
Chemistry and Water Solubility of Phosphates and Calcium Phosphates

Ion or Salt ^a	Names	Solubility (mg/mL) ^{5,10}
H ₂ PO ₄ ⁻	Monobasic ^b phosphate, dihydrogen phosphate	NA ^c
HPO ₄ ²⁻	Dibasic ^d phosphate, monohydrogen phosphate	NA
Ca[H ₂ PO ₄] ₂	Monobasic calcium phosphate, calcium dihydrogen phosphate	18
CaHPO ₄	Dibasic calcium phosphate, calcium monohydrogen phosphate	0.3

^aThe phosphoric acid aqueous equilibria H₃PO₄ ↔ H₂PO₄⁻ + H⁺ (for which pK_{a1} = 2.1) and HPO₄²⁻ ↔ PO₄³⁻ + H⁺ (for which pK_{a3} = 12.3¹⁹) are clinically negligible.¹⁴

^bMonobasic refers to neutralization of the -1 charge on H₂PO₄⁻ by one +1 cation (e.g., K⁺ or Na⁺, from bases [alkali] such as potassium hydroxide or sodium hydroxide or carbonate).

^cNA = not applicable.

^dDibasic refers to neutralization of the -2 charge on HPO₄²⁻ by two +1 cations (e.g., 2 K⁺ or 2 Na⁺, or one +2 cation, e.g., Ca²⁺).

gen phosphate), because CaHPO₄ is less dissociated.^{19,20} Note that, typical of most divalent cation–divalent anion salts, CaHPO₄ is minimally dissociated into its constituent ions. Consequently, most of the Ca²⁺ and HPO₄²⁻ ions cannot be solvated by dipolar water molecules via ion–dipole intermolecular forces, resulting in 0.3-mg/mL solubility in water. Ion–dipole forces generally result in greater solubility in water than do other types of solute–water intermolecular forces.^{19,20} The contrasting high solubility of the divalent cation–divalent anion, magnesium sulfate, at more than 500 mg/mL, results from dipole–dipole forces between water and the mostly nondissociated MgSO₄ ion pairs, which are dipoles. The efficient water solubility of some nonionic organic compounds (e.g., sugars) results from accepting and donating multiple intermolecular hydrogen bonds with water (i.e., one hydrogen bond for at least every four carbon atoms).²⁰

The percentages of H₂PO₄⁻ and HPO₄²⁻ decrease and increase, respectively, by 1.6% to 5.7% for each 0.1 pH unit increase over the pH range of 6.0–7.6.¹⁴ Because 1 meq of HPO₄²⁻ corresponds to 2 meq of H₂PO₄⁻, phosphate concentration

should be expressed in millimoles per liter, not in milliequivalents per liter. In the article by Schuetz and King,³ phosphates were reported in milliequivalents per liter but without specific concentrations of H₂PO₄⁻ and HPO₄²⁻. The appendix shows the calculation for milliequivalents of potassium and for millimoles of phosphates per milliliter in commercial Potassium Phosphates Injection, USP, and for milliequivalents of calcium per milliliter in commercial 10% Calcium Gluconate Injection, USP.

Before the transition to the Pharm.D. degree began achieving national momentum in the 1970s, most U.S. pharmacy schools required courses in qualitative and quantitative chemical analysis and inorganic pharmaceutical chemistry. Those courses were particularly pertinent to the solubility of calcium salts, as illustrated by the following excerpt from a monograph on CaHPO₄ in a standard pharmacy textbook from 1967: “Because this salt is almost insoluble in water, its chemical reactions are few and relatively unimportant. It is soluble in diluted hydrochloric acid.”¹⁹ That CaHPO₄ is more soluble at increasingly acidic pH represents the leftward shift in equation 2, and the “unimportance”

of CaHPO₄ reactions stated in the 1967 source ended in 1968 with the report that launched TPN,²¹ which made reactions between calcium and phosphates in i.v. formulations a matter of life and death.

Calcium and phosphate solubility for i.v. therapy. It is unlikely that any patient-specific i.v. admixture containing calcium and phosphates will exactly duplicate the compatibility results of published studies. Three common variables are (1) practitioner and device volume-measurement accuracy and precision, (2) content and pH ranges from *The United States Pharmacopeia and The National Formulary (USP)* for calcium gluconate injection (i.e., 95–105% of labeled content and pH 6.0–8.2) and for potassium and sodium phosphate injections (i.e., 95–105% of labeled content),²² and (3) other drugs and nutrients that may be included in i.v. admixtures (i.e., the variable composition of TPN formulations, which are often patient specific). Even small differences in the USP-allowed percent content ranges of calcium gluconate and potassium or sodium phosphate injections may contribute to the precipitation or nonprecipitation of CaHPO₄ in clinical practice.

The main factors that are important to ensuring total solubility or compatibility of calcium and phosphates in TPN and other i.v. therapy are as follows^{1–18}:

- The mixture should be agitated to achieve homogeneity after each ingredient is added.
- Potassium or sodium phosphate injection should be added early, and calcium gluconate injection should be added last or nearly last to the most dilute phosphate concentration possible.^{1,2,17,18}
- A 0.2-µm air-eliminating sterile inline filter should be used for non-fat-emulsion-containing i.v. admixtures, and a 1.2-µm filter should be used for fat-emulsion-containing i.v. admixtures.^{1–3,10,13,14,17,18}

- Calcium chloride injection should never be the calcium source in i.v. therapy that contains phosphate injections, because calcium chloride dissociates more extensively than calcium gluconate, resulting in more Ca^{2+} available to react with HPO_4^{2-} , thus increasing the likelihood of CaHPO_4 precipitation.^{4,5}
- The intersection of final calculated calcium and phosphate concentrations in clinical i.v. admixtures must be below the typical solubility curve (Figure 1).^{4,5,7,18}
- A single sum or product of calcium and phosphate concentrations must not be used as the sole criterion for judging compatibility, because products of calcium concentration (in milliequivalents per liter) and phosphate concentration (in millimoles per liter) vary inconsistently as calcium concentration decreases and phosphate concentration increases.^{4,5}
- The calculated concentrations of calcium and phosphates in TPN formulations must include all sources (e.g., amino acids injection) and not just the obvious calcium gluconate and potassium or sodium phosphate injections.
- The lower the final pH, the greater the percentage of H_2PO_4^- at which H_2PO_4^- forms more soluble calcium dihydrogen phosphate salt with Ca^{2+} . Higher final concentrations of dextrose and the age-essential amino acid cysteine hydrochloride and lower final i.v. fat-emulsion concentrations favor lower admixture pH.
- The higher the final amino acid concentration, the less likely CaHPO_4 is to precipitate. Some amino acids sequester Ca^{2+} (i.e., form stable soluble complexes). While most pharmacists are aware that disodium ethylenediaminetetraacetic acid (EDTA) sequesters divalent ions, including Ca^{2+} , fewer of them identify EDTA as an amino acid.¹⁴
- The rates of crystalline growth and precipitation of CaHPO_4 in clinical admixtures may be variable and low in supersaturated mixtures. For

example, in one study of a simulated TPN admixture, the measured calcium concentration declined exponentially from 22 to 7 meq/L over 14 days in 0.2- μm membrane filtrates of the original admixture.¹⁴ In another study of a simulated TPN admixture, an increase in CaHPO_4 particles larger than 5 μm was measured over 48 hours by using light obscuration, and the precipitates were confirmed as such by petrography and infrared spectroscopy.²³

Demonstration samples of calcium gluconate and potassium phosphate injections. Table 2 illustrates the beneficial effects of the acidic pH of dextrose injection and of calcium sequestration by amino acids on the compatibility of i.v. calcium and phosphates. The approximate calcium and phosphate concentrations of 28 meq/L and 24 mmol/L, respectively, were chosen to intersect well above recommended compatibility curves (Figure 1), so that visible pre-

cipitation would occur quickly and convincingly in samples with little or no content of dextrose and amino acids.¹⁸ After thorough mixing, the ingredients were added in this order: potassium phosphates, 50% dextrose injection, sterile water for injection (nonbacteriostatic), amino acids, and calcium gluconate. The sample tubes were stored at 22–24 °C and each day were exposed to ceiling fluorescent illumination for 10 hours and to darkness for 12 hours.

The typical results for the samples listed in Table 2 are presented in Table 3. Adding a few drops of 1.9% (0.05 M) disodium EDTA to sample A or D illustrates calcium sequestration by amino acids when the precipitated CaHPO_4 dissolves, and adding a few drops of 1 N hydrochloric acid to sample A or D illustrates the left-shifted equilibrium in equation 2, which favors calcium and phosphate compatibility. The change from colorless to pale yellow to yellow-amber in samples E, G, and H over 14 days

Figure 1. Composite curve for compatibility of calcium (as gluconate) with phosphates at 20–25 °C and pH 6.3 in 25% dextrose injection and 4–4.25% amino acids injection.^{4,5} The farther concentrations are below the curve, the greater the probability of nonprecipitation is, and the closer to or farther above the curve concentrations are, the greater the probability of precipitation of CaHPO_4 is.

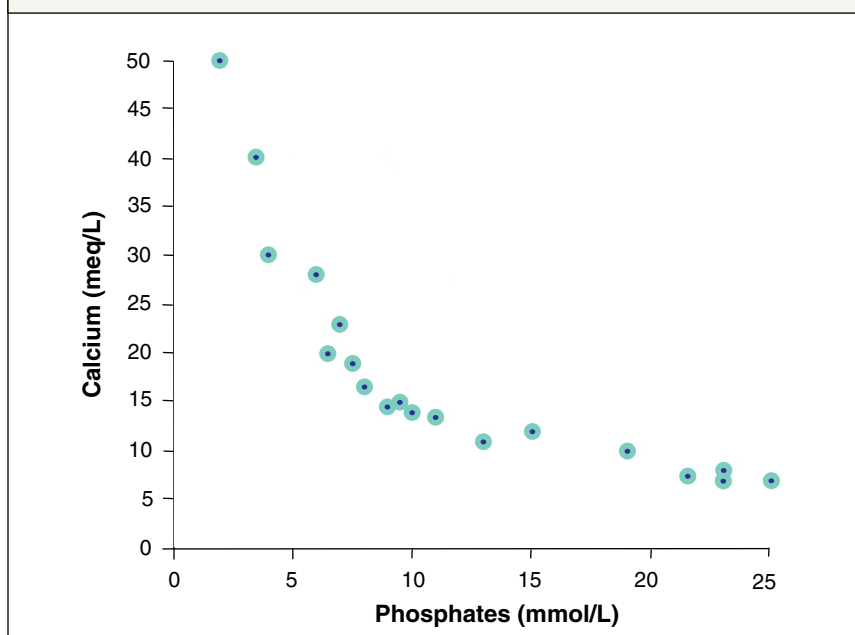


Table 2.

Mixtures of Calcium Gluconate and Potassium Phosphates Injections, USP, Used To Demonstrate Major Variables That Affect Calcium and Phosphate Compatibility

Sample ^a	Volume (mL) ^{b,c}		
	50% Dextrose Injection	10% Amino Acids Injection ^d	Deionized Water
A	0	0	9.4
B ^e	2.0	0	7.4
C ^f	5.0	0	4.4
D ^g	0	1.0	8.4
E ^h	0	4.0	5.4
F ⁱ	2.0	1.0	6.4
G ^j	4.0	2.0	3.4
H ^k	5.0	4.0	0.4

^aAll samples were prepared nonaseptically in nonsterile 15-mL clear colorless glass tubes with plastic screw caps (Fisher Scientific, catalog number 07-250-135). They totaled approximately 10.1 mL and contained the following: 0.08 mL of 3-mmol/mL Potassium Phosphates Injection, USP, and 0.6 mL of 10% Calcium Gluconate Injection, USP, which are equivalent to phosphates 23.8 mmol/L and calcium 27.6 meq/L.

^bIngredients are in-date, USP-compliant commercial injections.

^cVolumes of 0.1 mL and less were measured with a 40-μL (0.04-mL) to 200-μL (0.2-mL) digital pipette; volumes greater than 0.1–2.0 mL were measured with a 100-μL (0.1-mL) to 1000-μL (1-mL) digital pipette; and volumes greater than 2.0 mL were measured in a glass class B10-mL graduated cylinder scaled in 0.2-mL increments.

^dA crystalline amino acids product without additional electrolytes.

^eEquivalent to 10% dextrose.

^fEquivalent to 25% dextrose.

^gEquivalent to 1% amino acids.

^hEquivalent to 4% amino acids.

ⁱEquivalent to 10% dextrose and 1% amino acids.

^jEquivalent to 20% dextrose and 2% amino acids.

^kEquivalent to 25% dextrose and 4% amino acids.

illustrates the Maillard, or “brown-ing,” reaction (Figure 2).^{9,24} This is initially a covalent condensation of primary amino groups on amino acids, R-NH₂, with the acyclic aldehyde anomer of dextrose (i.e., R-NH₂ + O=CHC₅H₁₁O₅ → R-N=CC₅H₁₁O₅ + H₂O).²⁴ The ratio of the aqueous equilibrium of the acyclic aldehyde to cyclic forms of dextrose at pH 6–7 is approximately 0.0025% to 99.9975%.²⁵ Because of the small percentage of dextrose in the reactive aldehyde form at any given moment, it takes one day to one or more weeks at 20 to 30 °C for Maillard reaction products in mixtures of dextrose and amino acids to reach visible concentrations. The time lapse until the color of Maillard products becomes apparent decreases as the concentrations of dextrose and amino acids increase and increases as the concentrations decrease (e.g., sample F compared with sample H in Table 3).

Nearly all pharmacists know the importance of hemoglobin A_{1c} in diabetes management, but few know that A_{1c}, discovered in 1967, is a Maillard reaction product.²⁶

Calcium versus phosphate concentration curve. To construct one calcium phosphate solubility curve for use as a general guideline applicable to TPN (Figure 1) and perform three models of linear regression, a ruler was used to visually estimate values for 10 and 9 sets of calcium gluconate and phosphate concentrations from figure 1 by Henry et al.⁴ and lower curve of figure 5 by Eggert et al.⁵, respectively. The conditions in references 4 and 5 were amino acids, 4.25%⁴ and 4%⁵; dextrose, 25%^{4,5}; pH 6.3; and 20–25 °C.^{4,5} Lower amino acid and dextrose concentrations, which are consistent with low-osmolality and low-osmolality parenteral nutrient formulations for peripheral vein administration,

would move the curve downward and vice versa for higher concentrations of amino acids and dextrose.

The data used to construct the curves in references 4 and 5 were based on visual compatibility and not on particle-size analysis capable of discerning subvisible particulate matter. This is an important point recognizing that unaided visual identification of sparse precipitation is limited to approximately 50-μm individual particles; yet, subvisible precipitates ranging from 5 to 50 μm may occlude the microvasculature, such as in the pulmonary system.^{8,12}

The curve in Figure 1 represents a general guideline as one factor for judging compatibility, but it is not possible to predict the precise changes in such a curve for other, un-evaluated, concentrations of dextrose and amino acids. The compatibility curves for calcium versus phosphates typified by references 4 and 5 are generally elbow shaped, with a slope slightly left of vertical as calcium declines from 50 to 2 meq/L and phosphates increase from 5 to 8 mmol/L and a slope slightly below horizontal as calcium declines from 14 to 5 meq/L and phosphates increase from 8 to 23 mmol/L. For all such curves, concentration pairs beneath the curves were judged to reflect visual compatibility.^{4,5,18}

To determine the best-fit curve according to the correlation coefficient between the Figure 1 variables of calcium and phosphate concentrations, variations in the mathematical function of the concentrations were applied. The regression of the natural logarithm of calcium concentration versus the natural logarithm of phosphate concentration yielded better correlation ($r = -0.99$) than the regression of the natural logarithm of calcium concentration versus phosphate concentration and the regression of calcium concentration versus phosphate concentration. Products of calcium concentration (in milliequivalents per liter) with phos-

phate concentration (in millimoles per liter) vary inconsistently from 130 to 170⁴ and from 100 to 190⁵ as calcium concentration decreases and phosphate concentration increases. This is why a single product should not be used as a sole criterion for judging compatibility.

Case reports. The calcium and phosphate concentrations that re-

sulted in patient harm or death are reviewed below (Figure 3).

*Report by Robinson and Wright.*⁷ A right subclavian catheter became occluded after 64 days of continuous TPN therapy. The TPN admixture consisted of 500 mL of 8.5% amino acids injection and 500 mL of 50% dextrose injection in a 1000-mL formula that also contained calcium

gluconate 10 meq/L and phosphate 80 mmol/L (evenly divided between the sodium and potassium salts). This phosphate concentration greatly exceeds the right-hand limit of 25 mmol/L on the phosphate axis in Figure 3. The patient survived, probably because a 0.22- μ m inline filter was used.

*Report by Knowles et al.*⁸ A patient who had been receiving home TPN therapy for five years developed diffuse granulomatous interstitial pneumonitis due to exposure to precipitated CaHPO₄. The TPN formulation contained 4.25% amino acids injection and 5% dextrose injection; this is a low-osmolality and low-osmolality formulation that would be expected to be more susceptible to calcium and phosphate precipitation than, for example, the dextrose concentrations described by Henry et al.,⁴ Eggert et al.,⁵ and Fausel et al.¹⁴

*Report by Hill et al.*¹² This report, which prompted the FDA safety alert,^{1,2} involved four patients who had been receiving a low-osmolality TPN admixture via a peripheral vein during hospitalization at Tripler Army Medical Center in Honolulu and who developed sudden and un-

Table 3.

Appearance of Samples of Calcium Gluconate and Potassium Phosphates Injections, USP, after Standing at 22–24 °C

Sample	Visual Appearance at Interval Indicated ^{a,b}					
	10 min	1 hr	1 Day	5 Days	9 Days	14 Days
A	3 ^c	3	3 ^d	3 ^d	3 ^d	3 ^d
B	0	0	0	0	0	0
C	0	0	0	0	0	0
D	1 ^c	1	1 ^e	1 ^e	1 ^e	1 ^e
E	0	0	0	0	0	0, Y
F	0	0	0	0	Y	0, Y
G	0	0	0	0, Y	0, YA ₁	0, YA ₁
H	0	0	0, Y	0, YA ₁	0, YA ₂	0, YA ₃

^a0 = no precipitate or color change, 1 = faint turbidity from CaHPO₄ precipitate, 3 = intense turbidity from CaHPO₄ precipitate, Y = pale yellow, YA₁ = pale yellow-amber, YA₂ = darker yellow-amber than YA₁, YA₃ = darker yellow-amber than YA₂.

^bSample tubes were gently agitated at each observation time to swirl any possible scant crystalline precipitate from the bottoms. White or black fungi and mold may appear as fluffy masses after several days in dextrose-containing samples, but those are easily distinguished from precipitated CaHPO₄.

^cPrecipitation occurred instantly upon the addition of calcium gluconate injection.

^dClear supernatant over approximately 0.75 in-thick sediment of gelatinous-appearing precipitate.

^eClear supernatant over approximately 0.75 in-thick sediment of gelatinous-appearing precipitate.

Figure 2. Calcium gluconate and potassium phosphate injection samples A–H (see Tables 2 and 3) photographed at 14 days.

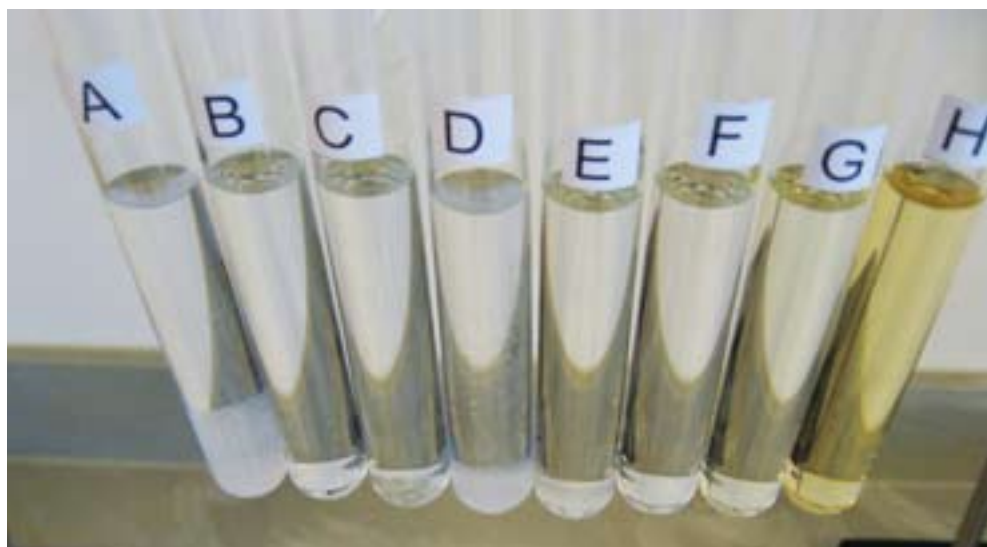
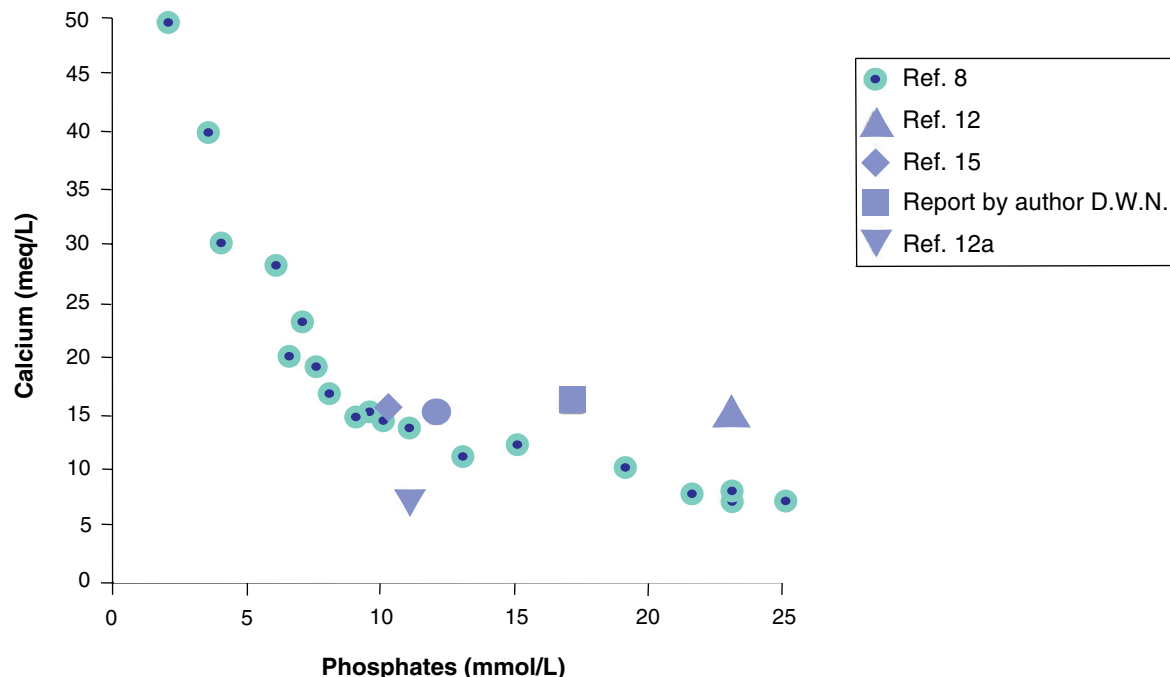


Figure 3. Calcium and phosphate concentrations that resulted in patient harm or death, superimposed over the compatibility curve shown in Figure 1. Ref. 12a represents values for the total volume of total parenteral nutrient (TPN) formulation to which calcium gluconate injection was added; Ref. 12 represents values for only 46% of the total TPN admixture volume.



explained respiratory distress, which was fatal in two cases. Postmortem examination of lung tissue identified CaHPO₄ crystals in the pulmonary microvasculature. Table 4 compares the institution’s peripheral-vein and central-vein TPN formulations and illustrates most of the important calcium and phosphate compatibility factors. The deaths were attributed to an unfavorable mixing sequence, lack of inline filtration, and a short time from compounding to administration.¹² The calcium and phosphate concentrations did not exceed the solubility limit in the final TPN admixture volume, but CaHPO₄ precipitated when calcium gluconate was added before 70% dextrose injection to only 46% of the final volume of the TPN admixture. There was not adequate time between the completion of compounding and the start of infusion for the precipitated CaHPO₄

to dissolve, nor was the formulation agitated sufficiently.

*Report by Shay et al.*¹⁵ This retrospective cohort study reviewed all hospitalized patients who received a low-osmolality and low-osmolarity formulation (peripheral-vein par-enteral nutrient [PN] formulation) containing calcium and phosphate over a 16-month period. The definition for possible calcium phosphate precipitation and harm was met if “while receiving [peripheral-vein] PN during the study period, [the patient] developed unexplained chest pain, dyspnea, or cardiopulmonary arrest of noncardiac etiology or had new, unexplained bilateral interstitial infiltrates noted on chest radiograph.” Of the 50 patients who received the therapy, 5 met this definition, and 4 of them died.

Report by author. One of the authors (D.W.N.) served as a consultant

in a lawsuit involving a baby’s death (after 2001) caused by precipitation of CaHPO₄ during an i.v. dextrose infusion. The confidential information provided indicated that (1) relevant literature sources^{4,5,17,18} were either misinterpreted or not reviewed, (2) the curve for calcium concentration versus phosphate concentration was interpreted as a downward-slanting straight line,^{4,5,17,18} (3) a compatibility chart for amounts of calcium gluconate and potassium phosphate injected was based on a final volume of x mL, but the actual volume compounded was 0.5x mL, resulting in twice the assumed concentrations of calcium and phosphates, and (4) an inline filter was not used. One physician who attempted to rescue the baby stated “Ten to 15 minutes into resuscitation, the lower 1–2 cm of the baby’s i.v. fluid bag, as well as the i.v. tubing, showed precipitation.”

Table 4.

Calcium and Phosphate Compatibility Factors in Central- and Peripheral-Vein Parenteral Nutrient Formulations at Tripler Army Medical Center

Ingredient	Content	
	Central-Vein Formulation ^a	Peripheral-Vein Formulation ¹²
Dextrose	24%	7% ^b
Freamine III with electrolytes	41 g	33 g ^c
Fat from i.v. emulsion	28 g	39 g ^d
Phosphorus ^e	14 mmol	15 mmol ^f
Calcium ^g	5 meq/L	10 meq/L ^h

^aFrom confidential documents provided to author (D.W.N.) as a consultant for a lawsuit in 1997.

^bA lower final dextrose concentration favors a higher final mixture pH, which favors a higher percentage of phosphate as HPO_4^{2-} , which favors greater formation of the least-soluble CaHPO_4 salt.

^cA lesser amino acids concentration reduces Ca^{2+} sequestration, which increases the free Ca^{2+} concentration available to react with phosphates.

^dA higher fat content favors a higher final mixture pH, from the alkaline pH of fat emulsion, which favors a higher percentage of phosphate as HPO_4^{2-} , which favors greater formation of the least-soluble CaHPO_4 salt.

^eFrom potassium phosphate injection.

^fA higher final phosphate concentration favors greater CaHPO_4 formation, which increases precipitation potential.

^gFrom calcium gluconate injection.

^hA higher final calcium concentration favors greater CaHPO_4 formation, which increases precipitation potential.

Preventing future harm. All institutions must establish calcium and phosphate mixing guidelines that are supported by peer-reviewed literature and the manufacturers' product information. The compatibility guidelines should be based on actual clinical conditions and be reviewed and approved by the pharmacy and therapeutics committee. Low-osmolality and low-osmolarity formulations, such as PN admixtures administered through a peripheral vein, are notorious for calcium and phosphate incompatibility; thus, they should be avoided when possible. A recent investigation of such compatibility for peripheral-vein PN admixtures ($\leq 3\%$ amino acids and $\leq 5\%$ dextrose) showed that the upper limit of compatibility was calcium gluconate 5 meq/L and sodium phosphates 15 mmol/L, or approximately half the parenteral equivalent of the recommended daily allowance of these minerals.²³

In the early TPN studies used to construct the curve in Figure 1,^{4,5} a limited range of macronutrient con-

centrations was employed, and only visual identification of precipitation, which can be highly variable, was performed. Recent studies employing particle detection and size measurement by light obscuration provide objective evidence of subvisible microprecipitation,²³ which can be clinically dangerous.

Careful interpretation of the calcium and phosphate compatibility literature is necessary before application to clinical practice. For example, Wong et al.²⁷ recently suggested that calcium and phosphate concentrations in TPN admixtures for neonates could be doubled to meet fetal accretion rates by using a formulation containing only monobasic potassium phosphate, KH_2PO_4 . This claim was based on the correct premise that the divalent phosphate anion, HPO_4^{2-} , is the culprit in calcium phosphate precipitation in TPN formulations. However, it did not emphasize that increasing pH (e.g., pH in TPN formulations that is much higher than pH in the KH_2PO_4 injection product) will cause the

monobasic anion, H_2PO_4^- , to convert to the dibasic anion, HPO_4^{2-} , as depicted in equation 1. In the study by Wong et al., samples were evaluated on three occasions between 0 and 27 hours after admixture preparation. Only 1 of 45 sample measurements exceeded pH 6 (i.e., 6.06) whereas most of the TPN admixtures studied by Henry et al.,⁴ Eggert et al.,⁵ and Fausel et al.¹⁴ had a pH of 6.3. Wong et al.²⁷ would have identified CaHPO_4 precipitation in more samples if the pH had been higher.

Conclusion. Understanding the chemical and practical compatibility of calcium gluconate and potassium or sodium phosphate injections is critical to ensuring the safe i.v. administration of these supplements and preventing patient harm.

References

1. Lumpkin MM, Burlington DB. FDA safety alert: hazards of precipitation associated with parenteral nutrition. Rockville, MD: Food and Drug Administration; 1994 Apr 18.
2. Food and Drug Administration. Safety alert: hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm.* 1994; 51:1427-8.
3. Schuetz DH, King JC. Compatibility and stability of electrolytes, vitamins and antibiotics in combination with 8% amino acids solution. *Am J Hosp Pharm.* 1978; 35:33-44.
4. Henry RS, Jurgens RW Jr, Sturgeon R et al. Compatibility of calcium chloride and calcium gluconate with sodium phosphate in a mixed TPN solution. *Am J Hosp Pharm.* 1980; 37:673-4.
5. Eggert LD, Rusko WJ, Mackay MW et al. Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. *Am J Hosp Pharm.* 1982; 39:49-53.
6. Lenz GT, Mikrut BA. Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing TrophAmine. *Am J Hosp Pharm.* 1988; 45:2367-71.
7. Robinson LA, Wright BT. Central venous catheter occlusion caused by body-heat-mediated calcium phosphate precipitation. *Am J Hosp Pharm.* 1982; 39:120-1.
8. Knowles JB, Cusson G, Smith M et al. Pulmonary deposition of calcium phosphate crystals as a complication of home total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1989; 13:209-13.
9. Newton DW. Introduction: physicochemical determinants of incompatibility and instability of drugs for injection and infusion. In: Trissel LA, ed. Handbook on

- injectable drugs. 3rd ed. Bethesda, MD: American Society of Hospital Pharmacists; 1983:xiii-xv.
- Driscoll DF, Newton DW, Bistran BR. Precipitation of calcium phosphate from parenteral nutrient fluids. *Am J Hosp Pharm.* 1994; 51:2834-6. Letter.
 - Maswoswe JJ, Okpara AU, Hilliard MA. An old nemesis: calcium and phosphate interaction in TPN admixtures. *Hosp Pharm.* 1995; 30:579-86.
 - Hill SF, Heldman LS, Goo ED et al. Fatal microvascular pulmonary emboli from precipitation of a total nutrient admixture solution. *JPEN J Parenter Enteral Nutr.* 1996; 20:81-7.
 - Newton DW. Rx: calcium, phosphate, and *secundum artem*. *Nutrition.* 1997; 13:390-1.
 - Fausel CA, Newton DW, Driscoll DF et al. Effect of fat emulsion and supersaturation on calcium phosphate solubility in parenteral nutrient admixtures. *Int J Pharm Compound.* 1997; 1:54-9.
 - Shay DK, Fann LM, Jarvis WR. Respiratory distress and sudden death associated with receipt of a peripheral parenteral nutrition admixture. *Infect Control Hosp Epidemiol.* 1997; 18:814-7.
 - Reedy JS, Kuhlman JE, Voytovich M. Microvascular pulmonary emboli secondary to precipitated crystals in a patient receiving total parenteral nutrition: a case report and description of the high-resolution CT findings. *Chest.* 1999; 115:892-5.
 - Trissel LA. Handbook on injectable drugs. 12th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2007:242-58.
 - Trissel LA. Trissel's calcium and phosphate compatibility in parenteral nutrition. Houston: Tripharma; 2001.
 - Soine TO, Wilson CO. Roger's inorganic pharmaceutical chemistry. 8th ed. Philadelphia: Lea & Febiger; 1967:141-2,170-2,388.
 - Allen LV Jr, Popovich NG, Ansel HC. Ansel's pharmaceutical dosage forms and delivery systems. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2005:338,341.
 - Dudrick SJ, Wilmore DW, Vars HM et al. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery.* 1968; 64:134-42.
 - The United States pharmacopeia, 30th rev., and The national formulary, 25th ed. Rockville, MD: United States Pharmacopoeial Convention; 2006:1600,2993.
 - Driscoll DF, Joy J, Silvestri AP et al. Calcium (Ca) and phosphate (P) compatibility in low osmolality parenteral nutrition (PN) mixtures. *Clin Nutr.* 2005; 24:695.
 - Newton DW, Narducci WA. Extemporaneous formulations. In: King RE, ed. Dispensing of medication. 9th ed. Chap 12. Easton, PA: Mack; 1984:258-88.
 - Murray RK, Granner DK, Mayes PA et al. Harper's biochemistry. Stamford, CT: Appleton & Lange; 1996:137-9.
 - Rahbar S. The discovery of glycated hemoglobins. In: Baynes JW, Monnier VM, Ames JM et al., eds. The Maillard reaction: chemistry at the interface of nutrition, aging, and disease. *Ann NY Acad Sci.* 2005; 1043:9-19.
 - Wong JC, McDougal AR, Tofan M et al. Doubling calcium and phosphate concentrations in neonatal parenteral nutrition solutions using monobasic potassium phosphate. *J Am Coll Nutr.* 2006; 25:70-7.

Appendix—Calculation of calcium concentration in Calcium Gluconate Injection, USP, and phosphorus and potassium concentrations in Potassium Phosphates Injection, USP

Calcium Gluconate Injection, USP

- Selected information from *The United States Pharmacopeia and the National Formulary (USP)*²²: Contains 95–105% of labeled strength of calcium gluconate. A small amount of calcium content from the gluconate salt may be replaced by calcium saccharate or other calcium salts for stabilization.
- Typical commercial product label information: strength, 10%; calcium 0.465 meq/mL; content, calcium gluconate monohydrate 98 mg/mL and calcium saccharate tetrahydrate 4.6 mg/mL.
- Chemical formulas and weights: calcium gluconate monohydrate, Ca(C₆H₁₁O₇)₂·H₂O, 448.39 g; calcium saccharate tetrahydrate, CaC₆H₈O₈·4H₂O, 320.26 g.
- Calcium gluconate monohydrate calculation

$$\frac{98 \text{ mg}}{\text{mL}} \cdot \frac{\text{g}}{1000 \text{ mg}} \cdot \frac{\text{mol}}{448.39 \text{ g}} \cdot \frac{2 \text{ eq}}{\text{mol}} \cdot \frac{1000 \text{ meq}}{\text{eq}} = \frac{0.437 \text{ meq}}{\text{mL}}$$

- Calcium saccharate tetrahydrate calculation

$$\frac{4.6 \text{ mg}}{\text{mL}} \cdot \frac{\text{g}}{1000 \text{ mg}} \cdot \frac{\text{mol}}{320.26 \text{ g}} \cdot \frac{2 \text{ eq}}{\text{mol}} \cdot \frac{1000 \text{ meq}}{\text{eq}} = \frac{0.029 \text{ meq}}{\text{mL}}$$

- Sum of answers for steps 4 and 5 is 0.466 meq/mL.
- Calcium equivalencies: 1 mmol = 2 meq (because of 2+ calcium ion valence), 1 meq = 20.04 mg, 1 mmol = 40.08 mg.

Potassium Phosphates Injection, USP

- Selected *USP* monograph information: Contains 95–105% of labeled strengths of monobasic and dibasic potassium phosphates.
- Typical commercial product label information: phosphorus, 3 mmol/mL; potassium, 4.4 meq/mL; anhydrous monobasic potassium phosphate, KH₂PO₄, 224 mg/mL; anhydrous dibasic potassium phosphate, K₂HPO₄, 236 mg/mL.
- Chemical formulas and weights: KH₂PO₄, 136.09 g; K₂HPO₄, 174.18 g.
- Phosphorus calculation^a

a. KH₂PO₄ contribution

$$\frac{0.224 \text{ g}}{\text{mL}} \cdot \frac{\text{mol}}{136.09 \text{ g}} \cdot \frac{1000 \text{ mmol}}{\text{mol}} = \frac{1.65 \text{ mmol}}{\text{mL}}$$

b. K₂HPO₄ contribution

$$\frac{0.236 \text{ g}}{\text{mL}} \cdot \frac{\text{mol}}{174.18 \text{ g}} \cdot \frac{1000 \text{ mmol}}{\text{mol}} = \frac{1.35 \text{ mmol}}{\text{mL}}$$

- Sum of answers for steps 4a and 4b is 3 mmol/mL.
- Potassium calculation

a. KH₂PO₄ contribution

$$\frac{0.224 \text{ g}}{\text{mL}} \cdot \frac{\text{mol}}{136.09 \text{ g}} \cdot \frac{\text{eq}}{\text{mol}} \cdot \frac{1000 \text{ meq}}{\text{eq}} = \frac{1.65 \text{ meq}}{\text{mL}}$$

b. K₂HPO₄ contribution

$$\frac{0.236 \text{ g}}{\text{mL}} \cdot \frac{\text{mol}}{174.18 \text{ g}} \cdot \frac{2 \text{ eq}}{\text{mol}} \cdot \frac{1000 \text{ meq}}{\text{eq}} = \frac{2.71 \text{ meq}}{\text{mL}}$$

- Sum of answers for steps 6a and 6b is 4.36 or 4.4 meq/mL.

^a1 mmol of any compound contains 1 mmol of each of its constituent atoms or ions.