

RESEARCH ARTICLE

Stability of trace elements and vitamin-containing TPN admixture of in a multi-chamber bag (Fulcaliq)

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Keywords

Multi-chamber bag
stability
parenteral nutrition
trace elements
vitamin

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Abstract

A multi-chamber for total parenteral nutrition (TPN), Fulcaliq[®], which is convenient for mixing of liquids from 3 chambers, was stability evaluated in clinical setting when exposed to trace elements up to 14 days. Branded or generic formulations of trace elements were compared in 3 groups: 1) glucose solution + trace elements, 2) a mixture of glucose solution and amino acid solution (Mixture A) + trace elements and 3) the 3 solutions (Mixture B) + trace elements. Stability was assessed visually and by means of pH measurement and UV-vis spectrophotometry. In all samples, no suspension or particles were visually identified and the pH remained within the controlled range of Fulcaliq itself. With regard to the color and absorbance, the glucose solution spiked with trace elements remained unchanged up to Day 14, Mixture A and Mixture B spiked with trace elements started to change from Day 7. The same results were observed upon spiking with a generic drug instead of a branded one as trace elements. For the glucose solution spiked with trace elements, unless not mixed with other solution(s), it is not crucial to mix the trace elements just before use, and it can be prepared and supplied weekly.

Introduction

The trace elements such as iron, copper and zinc are essential to maintain the physiological functions and activity of certain enzymes. Although trace element deficiency is considerably rare in patients with a normal diet, long-term total parenteral nutrition (TPN) therapy readily causes this deficiency unless trace elements are additionally supplied (American Society for Parenteral and Enteral Nutrition, 1996). It was reported that, in 55 patients receiving home parenteral nutrition (HPN) for more than six months, 30 (55%) patients had iron deficiency anemia. Although ten of them had iron deficiency anemia at the start of HPN, the remaining twenty patients developed iron deficiency anemia from 2 to 97 months after the start of HPN (Khaodhiar *et al*, 2002). When the required amount of iron was given at once, 25% of patients experienced adverse reactions. However, the patients well tolerated continuous administration of HPN solution spiked with a small amount of iron (Khaodhiar *et al*, 2002). It was reported that, in one case, long-term (15 months) use of TPN led to anemia and pancytopenia due to copper deficiency, which was improved within two weeks by the treatment with copper (20 $\mu\text{mol}/\text{day}$) (Wasa *et al*, 1994). Therefore, a long-term use of TPN should be accompanied by the use of trace elements regardless of the site of administration (American Society for Parenteral and Enteral Nutrition, 1993).

A multi-chamber TPN kit formulation (Fulcaliq®; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) as shown in Figure 1 consists of glucose, amino acids, and electrolyte and vitamin solutions in three separate chambers. It has been designed to avoid Maillard reaction between glucose and amino acid and is available in Japan. The partitions between chambers are designed to be readily broken just before use to mix the solutions. Trace elements have been

reported to accelerate the deterioration of vitamin-containing TPN formulation. Allwood (1984) reported that the degradation rate of vitamin C in TPN formulation increased 30- to 120-fold by trace elements including copper. This incidence, however, remains to be investigated whether trace elements affect the stability of non-mixed or mixed Fulcaliq solutions. The present study was designed to examine the stability of the glucose solution of Fulcaliq and its mixtures spiked with trace elements.

Materials and Methods

Fulcaliq No. 1, No. 2 and No. 3 (Fulcaliq®, Japan), are composed of 3 chambers, L, M and S, each of which separated by breakable partitions as shown in Figure 1.

The solution in Chamber L consists of glucose (No. 1: 120 g/700 ml, No. 2: 175 g/700 ml, No. 3: 250 g/700 ml), electrolytes (Na^+ : 50 mEq, K^+ : 30 mEq, Mg^{2+} : 10 mEq, Ca^{2+} : 8.5 mEq, Cl^- : 49 mEq, acetate $^-$: 11.9 mEq, L-lactate $^-$: 30 mEq, gluconate $^-$: 8.5 mEq, P: 250 mg, Zn: 20 μmol), vitamin B₁ (1.5 mg), vitamin B₆ (2 mg) and nicotinamide (20 mg). The solution in Chamber M consists of amino acid (branched/total free amino acid: 31.0w/v%), vitamin B₂ (2 mg/chamber), vitamin C (50 mg/chamber) and pantothenic acid (7.5 mg/chamber). The solution in Chamber S (2 ml) contains vitamin A (1,650 IU), B₁₂ (5 μg), D (5 μg), E (7.5 mg), K₁ (1 mg), folic acid (0.2 mg) and biotin (0.05 mg). The trace element formulations are Elemenmic injection® (Ajinomoto, Tokyo, Japan) as a branded drug, and Cizanarin injection® (Nissin Pharma, Yamagata, Japan), Volvix injection® (Fuji Medicine, Tokyo, Japan) and Mineramic injection® (Towa Pharmaceutical, Osaka, Japan) as generic drugs. Each formulation contains iron (35 μmol), manganese (1 μmol), zinc (60 μmol), copper (5 μmol) and iodine (1 μmol) in 2 ml.

We investigated the combinations of three kit formulations, Fulcaliq No. 1, No. 2 and No. 3, and five formulations of trace elements, Elemenmic, Cizanarin, Volvix, Mineramic and control. For Fulcaliq No. 2, only the combination with branded drug was examined, that is, a total of 12 combinations were examined. For each combination, the following three conditions were examined: 1) solution in Chamber L was spiked with trace elements, while three solutions were not mixed, 2) the mixture of solutions in Chambers L and M (Mixture A) was spiked with trace elements and 3) the mixture of all the three solutions (Mixture B) was spiked with trace elements. In all studies, each solution was spiked with 2 ml of trace element formulation. After spiking, each sample was covered with a dark-brown transparent plastic envelope supplied by the manufacturer of Fulcaliq and sampled to be analyzed immediately after mixing and after 1, 7 and 14 days. Two storage conditions i.e., room condition (480 ~ 640

Lx, 25 ~ 30°C, humidity is not controlled) and a cool and dark place (3 ~ 5°C, humidity is not controlled), were studied. The former was only tested for branded trace element formulation, Elemenmic, that is, a total of 54 combinations/conditions were studied.

The stability was evaluated by the change in visual appearance, pH and UV-vis spectrometry (Karnatz et al, 1989). Changes in the solution, such as color, cloudiness, precipitation and suspension, were evaluated by macroscopic observation of the sample placed in front of white and black backgrounds. An aliquot of 10 ml of solution was sampled at the designated time to measure pH using a pH meter (Docu-pH, Sartorius, Germany) and to analyze the UV-vis absorption spectrum (250-500 nm) using a spectral absorption photometer (UVmini-1240 UV-VIS spectrophotometer, Shimadzu, Kyoto, Japan).

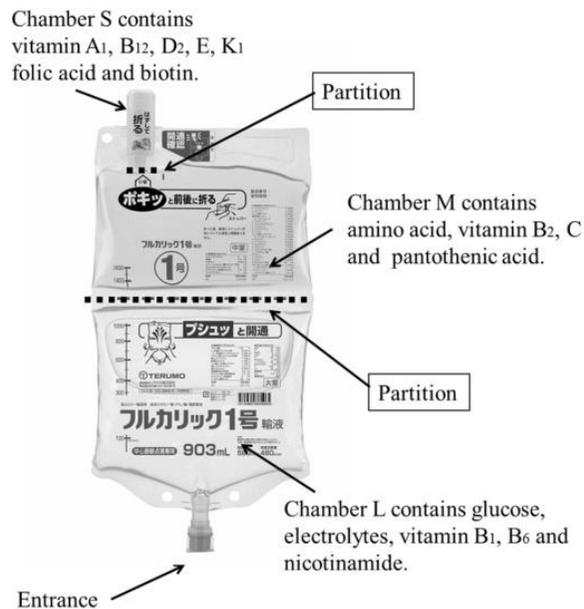


Figure 1 Appearance of Fulcaliq; Chamber L contains glucose, electrolyte, vitamins B₁, B₆ and nicotinic acid amide, Chamber M contains amino acids, vitamins B₂, C and pantothenic acid, and Chamber S contains vitamins A, B₁₂, D, E, K₁, folic acid and biotin. In use, the partition wall (dotted line) is manually opened for mixing.

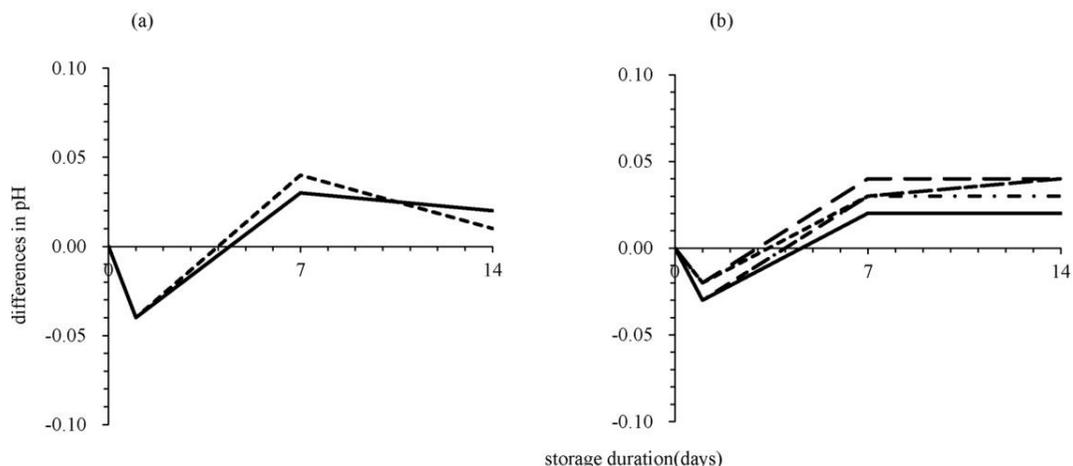


Figure 2 Differences in pH of Mixture B of Fulcaliq No. 3 alone (control) or spiked with branded formulation of trace elements, pH measured immediately after spiking. (a) Stored at room conditions (480 ~ 640 Lx, 25 ~ 30°C) with light-shield cover after spiking the branded formulation. (b) Stored in a cool dark place (3 ~ 5°C) after spiking the branded and generic ones. Solid line: Control-(a) and (b); dotted line: Elemenmic-(a) and (b); dashed line: Cizanarin-(b); long dashed line: Volvix-(b); dot dashed line: Mineramic-(b).

Results and Discussion

The solution in Chamber L spiked with trace elements was found to be macroscopically unchanged until Day 14 regardless of storage conditions and brand of trace element formulation, with a slight yellow color attributable to the trace element formulation itself. Both Mixture A and Mixture B spiked with trace elements showed no change in color on the day of and the day after mixing. However, the color became slightly brownish yellow and yellow-brown at Day 7 and Day 14, respectively, regardless of storage conditions and the brand of trace element formulation. Even without spiking trace elements, the color of Mixture A and Mixture B remained unchanged only until the day after mixing but thereafter became yellow-brown when stored under room conditions at Day 7 and Day 14. Cloudiness, precipitation and suspension were not macroscopically observed in all samples. The pH of solution in Chamber L of Fulcaliq No. 3 spiked with branded trace element formulation was unchanged after

storage under room conditions until Day 14. That spiked with branded or generic trace element formulation was also unchanged after storage in a cool and dark place (data not shown). The pH of Mixture A and Mixture B of Fulcaliq No. 1, No. 2 or No. 3 spiked with branded or generic trace element formulation remained within respective controlled pH ranges indicated by the manufacturer (e.g. Mixture A: pH 4.5 ~ 5.5, 4.8 ~ 5.8 and 4.9 ~ 5.9 for Fulcaliq No. 1, No. 2 and No. 3, respectively) until Day 14. Figure 2 shows the pH difference in Mixture B of Fulcaliq No. 3 alone and spiked with trace element formulation for 14 days. As assessed by the differences in pH, no decomposition was observed in all samples.

Figure 3 (a), (b) and (c) show the UV-vis absorption spectra of solutions in Chamber L of Fulcaliq No. 3 on the day and after 7 days in spiking of branded or generic formulation of trace elements. No significant change in spectrum was detected in the solutions immediately after

spiking the branded formulation (Figure 3 (a)), in those stored for seven days under room conditions after spiking the branded one (Fig. 3 (b)), and in those stored for seven days in a cool dark place after spiking the branded and generic ones (Figure 3 (c)). Similarly, no changes were detected at Day 1 and 14 in all of the samples above (data not shown).

Figure 3 (d), (e) and (f) show the spectra of Mixture A of Fulcaliq No. 3 spiked with

trace element formulation. An apparent increase in the absorbance at 300-400 nm was shown for Mixture A spiked with trace elements and stored at room conditions for 7 days compared to that just after spiking the branded trace element formulation (Figure 3 (e) vs. (d)). Upon storage in a cool dark place for 7 days, a similar increase in the absorbance was observed (Figure 3 (f)) but to a lesser extent.

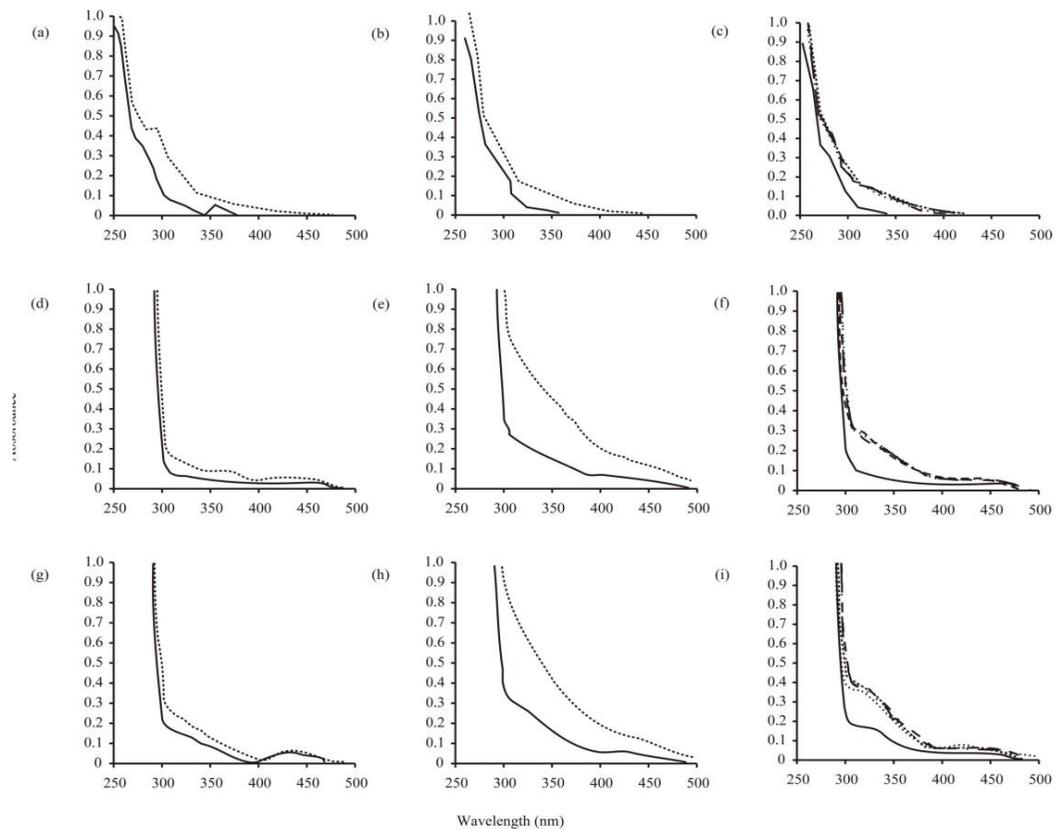


Figure 3 Absorption spectra of Fulcaliq solutions after spiking of trace elements: (a) in Chamber L immediately, (b) in Chamber L, 7 days, room conditions, light-shield cover storage, (c) in Chamber L 7 days, cool dark storage, (d) Mixture A immediately, (e) Mixture A 7 days, room conditions, light-shield cover storage (f) Mixture A 7 days storage in a cool dark place, (g) Mixture B immediately, (h) 7 days, room conditions, light-shield cover storage, (i) Mixture B 7 days, cool dark storage. Solid line: Control-(a), (b), (d), (e), (g), (h); dotted line: Elemenmic-(a), (b), (d), (e), (g), (h); dashed line: Cizanarin-(c), (f), (i); long dashed line: Volvix-(c), (f), (i); dot dash line: Mineramic-(c), (f), (i)

It should also be noted that the increase in the absorbance of solutions in Chamber L, Mixture A and Mixture B, observed just after the spiking of trace element formulation was in good agreement with the absorption spectrum of the trace element formulation itself (data not shown). The change in the spectrum of Mixture B of Fulcaliq No. 3 spiked with trace elements was similar to that observed in Mixture A of Fulcaliq No. 3 (Figure 3 (g), (h) and (i)). The results for Fulcaliq No. 1 and No. 2 were essentially identical to those shown above.

In the present study, the solution in Chamber L spiked with the branded formulation of trace elements was unchanged both macroscopically and spectrometrically after storage under room conditions for 14 days (Figure 3 (b)). So far, as assessed by indices of stability such as appearance, pH and UV-vis spectrum, the solution in Chamber L of Fulcaliq was considered to be stable for 14 days even after spiking the branded element formulation.

The stabilities of the solution in Chamber L after spiking the trace elements were equivalent between branded and generic formulations (Figure 3 (c)), suggesting that the use of generic formulation may not impair the stability of solution.

Taking these findings together, the weekly batch process to spike the trace elements is considered to be feasible practically, as long as the partition wall is not broken to mix the solutions. The pH of the solution in Chamber L was not affected by spiking and remained within a pH range indicated by the manufacturer, probably because the pH levels of the two solutions were close (4.0 to 5.0 for solution in Chamber L and pH 4.5 to 6.0 for trace element formulations), so acid-base reaction did not occur.

The change in the color of Mixture A and Mixture B without trace elements after 7 days was significantly greater in samples stored at room conditions than in those

stored in a cool dark place (Figure 3 (e), (h) vs. (f), (i)), which is consistent with the previous finding that the rate of Maillard reaction is greater under a higher temperature (Spanyar, 1976).

The increase in the absorbance of Mixture A and Mixture B observed 7 days after the addition of trace elements was larger in the samples stored under room conditions than in those stored in a cool dark place, which is consistent with the change in color observed macroscopically. Moreover, after storage for 7 days in a cool dark place, a change in UV-vis spectra was detected in Mixture A and Mixture B spiked with trace elements, but not in those without trace elements (Figure 3(d), (g) vs. (f), (i)). This increase in the absorption spectra was prominent within the range from 300 to 450 nm, which corresponds to the spectrum of Maillard reaction product with a maximum absorption wavelength of <400 nm. These results suggest that trace elements accelerate the Maillard reaction even under cool and dark conditions. Spiking the trace elements into Mixture A and Mixture B is not appropriate for 7-day storage, and may even accelerate the decomposition of potentially unstable mixtures that seem to last for 7 days.

Conclusion

All the trace element formulations investigated, that is, the branded and generic formulations, were proved not to affect the stability of the glucose solution of Fulcaliq. However, trace element formulation may accelerate the decomposition of Mixture A or Mixture B, which may remain unaffected for seven days in a cool dark place. To spike the trace elements into a multi-chamber TPN kit formulation in weekly batch process, spiking should occur into the glucose solution chamber so as not to impair the stability.

References

- Allwood MC. Factors influencing the stability of ascorbic acid in total parenteral nutrition infusions. *J Clin Hosp Pharm.* 1984;9:75-85.
- American Society for Parenteral and Enteral Nutrition. Section 2 Rationale for Adult Nutrition Support Guidelines. A.S.P.E.N. Board of Directors. *J Parenter Enteral Nutr.* 1993;17 (Suppl.): 1SA-52SA.
- American Society for Parenteral and Enteral Nutrition. Standards for Nutrition Support Physicians. A.S.P.E.N. Board of Directors. *Nutr Clin Pract.* 1996;11:235-240
- Karnatz NN, Wong J, Baaske DM, Johnson JH, Speicher ER and Herbranson DE. Stability of esmolol hydrochloride and sodium nitroprusside in intravenous admixtures. *Am J Hosp Pharm.* 1989;46:101-104.
- Khaodhiar L, Keane-Ellison M, Tawa NE, Thibault A, Burke PA and Bistran BR. Iron deficiency anemia in patients receiving home total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2002;26:114-119.
- Spanyar P. The importance of the Maillard Reaction in Food Chemistry. *Period. Polytech Chem Ng.* 1976; 20:371-37.
- Wasa M, Satani M, Tanano H, Nezu R, Takagi Y and Okada A. Copper deficiency with pancytopenia during total parenteral nutrition. *J Parenter Enteral Nutr.* 1994; 18:190-192.