

See discussions, stats, and author profiles for this publication at: <http://www.researchgate.net/publication/256102278>

Assessment of the Physicochemical Stability of All-in-One Parenteral Emulsions for Neonates According to USP Specifications

ARTICLE *in* JOURNAL OF PARENTERAL AND ENTERAL NUTRITION · AUGUST 2013

Impact Factor: 3.14 · DOI: 10.1177/0148607113499589 · Source: PubMed

CITATION

1

DOWNLOADS

35

VIEWS

86

4 AUTHORS, INCLUDING:



Sophia Hatziantoniou

University of Patras

54 PUBLICATIONS 761 CITATIONS

SEE PROFILE



Sophia L Markantonis

National and Kapodistrian University of Ath...

66 PUBLICATIONS 809 CITATIONS

SEE PROFILE

Journal of Parenteral and Enteral Nutrition

<http://pen.sagepub.com/>

Assessment of the Physicochemical Stability of All-in-One Parenteral Emulsions for Neonates According to USP Specifications

Christos Athanasiou, Sophia Hatziantoniou, Maria Skouroliakou and Sophia Markantonis-Kyroudis

JPEN J Parenter Enteral Nutr published online 23 August 2013

DOI: 10.1177/0148607113499589

The online version of this article can be found at:

<http://pen.sagepub.com/content/early/2013/08/23/0148607113499589>

Published by:



<http://www.sagepublications.com>

On behalf of:



American Society for Parenteral
and Enteral Nutrition

The American Society for Parenteral & Enteral Nutrition

Additional services and information for *Journal of Parenteral and Enteral Nutrition* can be found at:

Email Alerts: <http://pen.sagepub.com/cgi/alerts>

Subscriptions: <http://pen.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [OnlineFirst Version of Record](#) - Aug 23, 2013

[What is This?](#)

Assessment of the Physicochemical Stability of All-in-One Parenteral Emulsions for Neonates According to USP Specifications

Journal of Parenteral and Enteral
Nutrition
Volume XX Number X
Month 2013 1–6
© 2013 American Society
for Parenteral and Enteral Nutrition
DOI: 10.1177/0148607113499589
jpen.sagepub.com
hosted at
online.sagepub.com



Christos Athanasiou, MD¹; Sophia Hatziantoniou, PhD¹; Maria Skouroliakou, PhD²; and Sophia Markantonis-Kyroudis, PhD¹

Abstract

Background: The purpose of this study was to describe the methodology to assess the stability of all-in-one (AIO) parenteral nutrition admixtures, containing glucose, proteins, and lipids, to the standards of U.S. Pharmacopoeia (USP <729>). The influence of calcium and commercially available lipid emulsions and amino acid solutions were also examined. **Methods:** Four batches of 5 AIO admixtures containing calcium were compounded with commercially available lipid emulsions and amino acid solutions. Two of them contained calcium. Their stability was tested under conditions simulating clinical use. All the admixtures were assessed for criteria set by the USP <729>: (1) mean droplet diameter (MDD) and (2) percentage of volume weighted particles with diameter > 5 μm (PFAT₅). **Results:** All admixtures were within the specifications set by the USP with respect to the MDD at 0, 24, and 48 hours, but only those batches lacking calcium met the benchmarks set by the pharmacopoeia, with respect to PFAT₅, on the day of preparation. **Conclusions:** The presence of calcium destabilized the admixtures, while the use of different commercial ingredients altered the admixtures' characteristics. Only 1 batch of the AIO admixtures studied was found to be compliant with USP <729> standards. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

all-in-one parenteral emulsion; neonates; physicochemical stability, emulsions

Clinical Relevancy

All-in-one (AIO) admixtures for parenteral nutrition for neonates prepared using different commercial ingredients, with or without the presence of calcium, in conditions simulating clinical use. Their adherence with U.S. Pharmacopoeia (USP) <729> standards was tested. The findings of the study may be used as a guide for the assessment of AIO admixtures for neonates.

Introduction

Parenteral nutrition (PN) aims to provide the patient with all the essential macro and micronutrients, including amino acids, carbohydrates, lipids and electrolytes required daily. It has been argued that the use of PN admixtures with all the nutrients in the same container, reduces manipulation during administration and the risk of contamination, and may be more cost-effective.^{1,2,3} However, such AIO admixtures are extremely complex and inherently unstable.⁴⁻⁶ Due to their numerous ingredients an unequivocal prediction of their stability and safety is impossible. Moreover, FDA has published an alert for the hazards of precipitation associated with PN,⁵ since deaths have been attributed to undetected sediment. Calcium phosphate precipitation was a fairly common problem but lately, the use of organic phosphorus has partially solved this issue.^{7,8} Nevertheless every admixture extemporaneously prepared in

the hospital pharmacy must be thoroughly examined for those characteristics considered essential for their safety,⁹ for example, the size distribution of the lipid droplets, for which the USP has set certain limits.⁴

AIO admixtures for neonates are not in use since the restricted volume of fluids permitted for administration in combination with the high needs of neonates for electrolytes make these admixtures extremely concentrated and therefore unstable.^{10,11} However, according to studies conducted lately, AIO admixtures based on Medium and Long Chain Triglycerides (MCT/LCT) emulsions, like Smoflipid® 20% used in this study are considered more stable.¹²⁻¹⁴

From ¹Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Athens, Athens, Greece; and ²Department of Diabetics and Nutritional Science, Harokopio University, Athens, Greece.

Financial disclosure: none declared.

Received for publication March 28, 2013; accepted for publication July 8, 2013.

Corresponding Author:

Sophia Hatziantoniou, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Athens, Athens, Greece.
Email: shatzi@pharm.uoa.gr

Table 1. Composition by Volume (ml) of Batches C1 and S1 AIO Admixtures.

	AIO2	AIO3	AIO4	AIO5	AIO6
Amino acid solution ^a	48.2	56.4	64.5	85.4	72.1
Dextrose 50%	28.8	34.2	42	52.8	46.9
Lipid emulsion ^b	11.0	13.5	16	16.8	19.5
KCl 10%	1.9	1.8	1.8	2.1	1.8
Ca gluconate 10% ^c	5.6	7.0	8.2	11.1	9.4
MgSO ₄ ·7H ₂ O 25%	0.3	0.4	0.4	0.6	0.5
Sodium glycerophosphate anhydrous 21.6% w/v ^d	0.8	1.1	1.3	1.8	1.4
Water soluble vitamins ^e	0.0	0.0	0.0	3.1	2.6
Lipid soluble vitamins ^f	0.0	0.0	0.0	6.7	6.5
Heparin	1.5	1.7	3.6	4.4	3.8
Water for injection	37.5	35.4	28.8	25	31.6

The synthesis of admixtures AIO2-AIO6. Batch C2 and batch S2 were free of calcium. Fluid retention from automatic compounder 25 ml, lipid retention 6 ml.

^aAA2 for batch C and AA1 for batch S. These volumes refer to AA1; for AA2 the volumes used were adapted and the difference was replenished with water for injection. The total volume was equal for both batches.

^bLE2 for batch C and LE1 for batch S, respectively.

^cVolumes refer to batch C1 and batch S1. Batches C2 and S2 were free of calcium.

^dGlycophos®, Fresenius Kabi.

^eSoluvit®, Fresenius Kabi.

^fVitalipid®, Fresenius Kabi.

The aim of this study was to describe the methodology used to assess the stability of a series of 5 AIO admixtures, for neonates with gestational age of 26-28 weeks, to the standards set by the USP (USP <729>). The influence of different commercially available ingredients and the presence of calcium ions on their stability were also examined. The AIO admixtures were prepared at the maternity hospital IASO, Athens.

Clinical Relevancy Statement

Although the use of AIO admixtures for PN in adult patients is already common practice, preparing admixtures for neonates is still problematic due to stability and compatibility issues. Overall, preparing AIO bags for PN in neonates may benefit everyday clinical practice and possibly reduce costs. With a view to producing AIO admixtures that will meet neonates' special nutrition needs, we have studied a series of admixtures prepared for the first days of life of a specific subgroup of premature neonates and assessed their compliance with USP <729> standards.

Materials and Methods

Preparation of PN Admixtures

For the preparation of the AIO admixtures the following products were used:

AA1 (amino acid solution); Vamin Infant (Fresenius Kabi Hellas Sa): An electrolyte-free solution for intravenous (IV) nutrition that provides a mixture of essential and

nonessential amino acids as well as cysteine, tyrosine, histidine. The total concentration of the amino acids is 65.3 g/L, essential amino acids 3.9 g, and pH 5.2.

AA2 (amino acid solution); PRIMENE 10% (Baxter [Hellas] Ltd): An amino acid solution for IV infusion in neonates, infants, and children that provides a mixture of essential and nonessential amino acids as well as taurine and cysteine. Essential amino acids 47.5% and branched chain amino acids 24% and pH 5.5.

LE1 (lipid emulsion) Smoflipid® 20 (Fresenius Kabi Hellas Sa): An α -tocopherol-enriched lipid emulsion consisting of soybean oil as the source of essential fatty acids (30%), medium-chain triglycerides, rapidly oxidized to provide energy (30%), refined olive oil as the source of monounsaturated fatty acids, in particular oleic acid (25%), and fish oil as the source of very long-chain ω -3 fatty acids (15%). pH approximately 8.

LE2 (lipid emulsion) ClinOleic® 20% (Baxter Hellas Ltd): A sterile fat emulsion containing of a mixture of refined olive oil (approximately 80%) and refined soya oil (approximately 20%). It also contains egg lecithin (purified egg phospholipids), glycerol, sodium oleate, and water for injections. One of the active ingredients, soya oil, contains ascorbyl palmitate as an antioxidant (0.15 mg per g of oil). pH range 6.0-8.0.

The composition of the admixtures (batch 1) prepared was based on the IASO Hospital (Athens) PN protocols for neonates with a gestational age of 26-28 weeks for days 2-6 after birth (AIO2-AIO6) (Table 1). On day 1 no lipids are

administered, so no AIO admixture is prepared. All nutrients are calculated per body weight; every admixture fulfils the requirements for 1 kg body weight. To assess the influence of electrolytes on their chemical and physical stability, a separate batch of the 5 AIO admixtures (batch 2) was prepared free of calcium.

As the final stability of AIO compounded admixtures is also known to be affected by the composition of commercial lipid emulsions and commercial solutions of amino acids,^{15,16} each batch of admixtures (batch 1 and batch 2) was prepared in 2 different ways using the most common commercial formulations in Greece. The first using LE1 as the lipid emulsion in combination with AA1 as the amino acid solution (batch S) and the second using LE2 as the lipid emulsion in combination with AA2 as the amino acid solution (batch C). Overall, 4 batches of 5 AIO admixtures (S1, S2, C1, C2) were prepared and tested.

In our experience, it is much more common and convenient for a hospital's PN unit to use 1 company's products at any 1 time. Thus, in this study amino acid solutions and lipid emulsions were not cross-checked; the same combination of both nutrients (essential and semiessential amino acids and fat emulsions) was furnished by each manufacturer.

The admixtures were prepared in duplicate bags made of ethyl vinyl acetate ester, at the IASO maternity hospital, using an automated filling (MicroMacro 12 compounder; Baxa, Englewood, CO).

Methodology to Assess Stability of Admixtures

Visual inspection of samples. For visual inspection of AIO parenteral admixtures, each bag was inverted for sampling 5 times, to test the redispersability of flocculation or sedimentation. An aliquot of the emulsion was placed in a beaker to observe its surface under normal light. The appearance of large colorless or yellow droplets at the surface was considered to indicate phase separation and unacceptable emulsion stability.

Physicochemical characterization according to USP <729>. The USP has set the following limits⁴; (1) the intensity-weighted mean droplet diameter (MDD) for lipid injectable emulsions must be < 500 nm or 0.5 μm , irrespective of the concentration of the dispersed lipid phase and (2) the volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than 5 μm (PFAT₅) for a given lipid injectable emulsion, must be < 0.05%.

MDD assessment. The admixtures were assessed for 2 parameters, namely the MDD and the volume weighted percentage of droplets with diameter > 5 μm (PFAT₅). To estimate the average droplet diameter (MDD), as required by the pharmacopoeia, photon correlation spectroscopy (Zetasizer

3000HSA; Malvern, UK) was applied. Of each sample, 16 μl aliquots were diluted with water for injection (WFI) to a final volume of 3 ml. Measurements were performed at 25°C, detection wavelength 633 nm, and a fixed angle of 90°. For data analysis the Contin method (Malvern Software) was used.

PFAT₅ assessment. To estimate the "tail of large diameter," laser diffraction was applied (Mastersizer S, Malvern Instruments Ltd, Malvern, UK; fitted with a small volume sampler set at 50% of its speed capacity). A 330 mm size focal lens was used with detection range 0.5-880 μm . The Real Refractive Index was set to 1.456 and the Imaginary Refractive Index to 0.01. The background signal was adjusted after filling the stirrer with WFI. A small quantity of each admixture was removed, using a plastic syringe, and added drop-wise into the stirrer until obscuration reached 14%. For each admixture the measurement was repeated twice.

Simulation of Clinical Use Conditions

To assess the admixtures under simulated clinical conditions the AIO bags were prepared in duplicate. One of each pair of bags was used for the assessment of the size distribution of the droplets within 3 hours of preparation and then connected to a supply pump (module MPV, Fresenius Kabi) and reassessed at 24 hours. The admixture flow rate was set at 2 ml/h. The second bag was stored at 4°C for 24 hours and assessed before (24 hours at 4°C) and after its connection to a supply pump for a further 24 hours of pumping (48 hours after preparation).

Results

Visual Inspection of Samples

On the day of preparation all samples were subjected to optical observation for detection of signs of instability such as creaming, flocculation, and sedimentation. We observed the following:

1. Batches S1 and C1: Within 24 hours of their preparation, creaming was noted. For some of these admixtures creaming was not easily reversed with gentle shaking, indicating the beginning of coalescence that is an irreversible stage of instability.
2. Batches S1 and C1: Signs of precipitation were observed within a few hours of their preparation.
3. Batches S2 and C2: Optical observation did not reveal any sediment or creaming.

Of the 4 batches of AIO admixtures assessed, only S2 and C2 (ie, all 5 samples of the batch) were entirely within USP <729> limits on the day of preparation. Moreover, batch C2 remained stable and within specifications after 24 hours at room temperature and at 4°C.

Table 2. Droplet Size Distribution of AIO Admixtures (MDD) on the Preparation Day (nm).

	S1 ^a		S2		C1 ^b		C2	
	MDD ^c ± SD	PI ^d	MDD ± SD	PI	MDD ± SD	PI	MDD ± SD	PI
AIO2	300.2 ± 4.2	0.055	297.4 ± 4.0	0.072	262.9 ± 7.3	0.042	271.9 ± 0.9	0.057
AIO3	300.1 ± 2.7	0.067	298.2 ± 1.4	0.028	263.1 ± 8.4	0.037	270.7 ± 2.3	0.047
AIO4	305.3 ± 2.7	0.052	299.1 ± 2.7	0.064	267.4 ± 5.1	0.054	273.6 ± 3.7	0.030
AIO5	298.9 ± 1.5	0.107	291.3 ± 0.7	0.096	265.4 ± 4.4	0.065	268.6 ± 4.8	0.058
AIO6	298.8 ± 1.4	0.107	291.1 ± 1.1	0.086	263.9 ± 5.7	0.046	272.0 ± 3.1	0.070

The synthesis of admixtures AIO2-AIO6, as presented in Table 1. Batch C2 and batch S2 were free of calcium.

^aLE1 and AA1 for batch S.

^bLE2 and AA2 for batch C.

^cMDD: mean droplet diameter.

^dPolydispersity index (PI).

Table 3. The Conformity of AIO Admixtures With USP <729> Requirements With Respect to PFAT₅.

Admixture	Batch C1		Admixture	Batch C2	
	Day of Preparation	At 24 Hours		Day of Preparation	At 24 Hours
AIO2	A	R	AIO2	A	A
AIO3	A	R	AIO3	A	A
AIO4	R	—	AIO4	A	A
AIO5	R	—	AIO5	A	A
AIO6	R	—	AIO6	A	A

Admixture	Batch S1		Admixture	Batch S2	
	Day of Preparation	At 24 Hours		Day of Preparation	At 24 Hours
AIO2	R	—	AIO2	A	R
AIO3	R	—	AIO3	A	R
AIO4	R	—	AIO4	A	R
AIO5	R	—	AIO5	A	A
AIO6	R	—	AIO6	A	A

Bags connected to a supply pump for 24 hours at room temperature (25°C). The synthesis of admixtures AIO2-AIO6, as presented in Table 1. Batch C2 and batch S2 were free of calcium. The percentage of volume weighted particles with diameter > 5 µm. LE1 and AA1 for batch S, LE2 and AA2 for batch C. A for admixtures within acceptable limits, R for rejected admixtures, — for admixtures not assessed because they had already been rejected.

Physicochemical Characterization According to USP <729>

MDD assessment. All admixtures assessed (S1, S2, C1, C2 batches of AIO2-AIO6) were within the specifications set by U.S. Pharmacopoeia. Table 2 shows the results for each of the twenty admixtures on the preparation day. For all admixtures and both storage conditions at each time point, this parameter was within specifications.

PFAT₅ assessment. Only 2 batches, both lacking calcium, were in accordance with benchmarks set by the pharmacopoeia on the day of preparation. In addition, only 1 of them (batch C2) remained stable and within specifications for 24 hours at both room temperature and at 4°C. Detailed results for each admixture are presented in Tables 3 and 4.

Discussion and Conclusions

Although there are encouraging references to AIO parenteral admixtures for neonates,^{17,18} a hospital pharmacy is required to assess the characteristics of every formulation prepared extemporaneously and to document if it is appropriate for clinical use.

The procedures followed in our study were identical to those proposed for clinical use. Since every parenteral formulation prepared in a hospital pharmacy has to be used within 24-30 hours¹⁹ to decrease the risk of contamination, and because of the unpredictable kinetic stability of AIO parenteral admixtures (associated with their synthesis),²⁰ the characteristics of our admixtures were assessed on the day of preparation (within 3 hours) and then 24 hours after being connected to a supply pump, at room temperature. In addition to this, a second

Table 4. The Conformity of AIO Admixtures With USP <729> Requirements With Respect to PFAT₅.

Admixture	Batch C1			Batch C2		
	Day of Preparation	At 24 Hours	At 48 Hours	Day of Preparation	At 24 Hours	At 48 Hours
AIO2	A	R	—	AIO2	A	A
AIO3	A	R	—	AIO3	A	A
AIO4	R	—	—	AIO4	A	A
AIO5	R	—	—	AIO5	A	R
AIO6	R	—	—	AIO6	A	R

Admixture	Batch S1			Batch S2		
	Day of Preparation	At 24 Hours	At 48 Hours	Day of Preparation	At 24 Hours	At 48 Hours
AIO2	R	—	—	AIO2	A	R
AIO3	R	—	—	AIO3	A	R
AIO4	R	—	—	AIO4	A	R
AIO5	R	—	—	AIO5	A	R
AIO6	R	—	—	AIO6	A	R

Bags stored at 4°C for 24 hours, then connected to a supply pump for 24 hours, at 25°C. The synthesis of admixtures AIO2-AIO6, as presented in Table 1. Batch C2 and batch S2 were free of calcium. The percentage of volume weighted particles with diameter > 5 µm. LE1 and AA1 for batch S, LE2 and AA2 for batch C. A for admixtures within acceptable limits, R for rejected admixtures, — for admixtures not assessed because they had already been rejected.

bag of each admixture was assessed after storage at 4°C for 24 hours because it is often desirable to prepare a formulation, store it, and use it later or the following day.

The addition of calcium seems to have had an undesirable effect on the admixtures in 2 ways. First, it enhanced aggregation and subsequently caused the production of sediment, and second it led to an increase of PFAT₅ (both batches S1 and C1). The latter was probably due to the aggregation of lipid droplets, a phenomenon that has been cited as the cause of emulsion destabilization.²¹ In general, this effect was expected because of the extremely high concentration of calcium and was the reason why batches S2 and C2 were also prepared.

The use of ingredients of different commercial origin seems to have produced admixtures with different characteristics. Only batch C2 admixtures (containing the lipid emulsion LE2 and the amino acid solution AA2) were within acceptable limits after 24 hours at both 4°C and 25°C in contrast to batch S2. What is more, on the day of preparation batch C2 admixtures had an MDD of 271 ± 0.8 nm compared with 295 ± 1.7 nm for batch S2 ($P < .0001$, unpaired t test).

Also of interest were the findings for batch C2 (Table 4); AIO1, AIO2, and AIO3 admixtures remained within the USP <729> standards, whereas AIO5 and AIO6 did not. In our opinion, vitamin additives could possibly have affected the stability of the admixtures, since only AIO5 and AIO6, the admixtures containing vitamins (water and lipid soluble), did not comply with the USP <729> standard.

In summary, all admixtures assessed were within the specifications set by the U.S. Pharmacopoeia with respect to the MDD at all time points, but only batch C2 remained within PFAT₅ limits after 24 hours; further testing is necessary to

validate its appropriateness for administration. In all the other admixtures, the presence of calcium led to precipitation due to its incompatibility with the other components of the admixtures, regardless of the commercial ingredients used for their preparation. The formation of precipitates due to the presence of calcium has resulted in fatalities²² and should be avoided. In this context it is clear that compatibility testing of commercial products prior to the preparation of AIO admixtures is of great clinical importance.

References

1. Driscoll DF. Total nutrient admixtures: theory and practice. *Nutr Clin Pract.* 1995;10(3):114-119.
2. Alpers DH, Stenson WF, Taylor BE, et al. Parenteral nutritional therapy. In: Mitcell CW, ed. *Manual of Nutritional Therapeutics*. Philadelphia, PA: Lippincott Williams and Wilkins; 2008:373-403.
3. Wereszczynski N, Grosse PY, Pellissier D. Assessment of clinical and economic impact of all-in-one admixtures in total parenteral nutrition. *EHP.* 2001;7(4):122-127.
4. United States Pharmacopeia. *Chapter <729>. Globule Size Distribution in Lipid Emulsions*. Rockville, MD: United States Pharmacopeia; 2007.
5. Food and Drug Administration. Safety alert: hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm.* 1994;51: 1427-1428.
6. Driscoll DF, Bistran BR, Demmelair H, et al. Pharmaceutical and clinical aspects of parenteral lipid emulsions in neonatology. *Clin Nutr.* 2008;27(4):497-503.
7. Chaieb DS, Chaumeil JC, Jebnoun S, et al. Calcium and phosphate compatibility and stability studies in different neonatal parenteral nutrition mixtures. *EJHP Science.* 2006;12:35-40.
8. Ribeiro D, Lobo BW, Volpato NM, et al. Influence of the calcium concentration in the presence of organic phosphorus on the physicochemical compatibility and stability of all-in-one admixtures for neonatal use. *Nutr J.* 2009;8:51.

9. Hardy G, Puzovic M. Formulation, stability and administration of parenteral nutrition with new lipid emulsions. *Nutr Clin Pract*. 2009;24(5):616-625.
10. Driscoll DF, Nehne J, Peterss H, et al. Physicochemical stability of intravenous lipid emulsions as AIO admixtures intended for the very young. *Clin Nutr*. 2003;22(5):489-495.
11. Julie J, Silvestri AP, Franke R, et al. Calcium and phosphate compatibility in low osmolarity parenteral nutrition admixtures intended for peripheral vein administration. *JPEN J Parenter Enteral Nutr*. 2010;34(1):46-54.
12. Driscoll DF, Silvestri AP, Bistran BR. 30-hour stability of MCT/LCT-based all-in-ones (AIOs) as neonatal TPN admixtures. *Clin Nutr*. 2008;33(suppl1):170.
13. Driscoll DF, Nehne J, Peterss H, et al. The influence of medium chain triglycerides on the stability of all in one formulations. *Int J Pharm*. 2002;240(1-2):1-10.
14. Skouroliakou M, Kountouri AM, Hatziantoniou S, Koutri K, Chiou A. Physicochemical stability assessment of all-in-one parenteral emulsion for neonates containing SMOFlipid. *Eur J Hosp Pharm*. 2012;19:514-518.
15. Driscoll DF, Silvestri PA, Bistran BR. Stability of MCT LCT-based total nutrient admixtures for neonatal use over 30 hours at room temperature: applying pharmacopeial standards. *JPEN J Parenter Enteral Nutr*. 2010;34(3):305-312.
16. Silvano R, Galeotti N, Cini-Lombardini E, et al. Stability of lipid emulsions in mixtures for all-in-one parenteral nutrition. *EHP*. 1998;4(3):79-83.
17. Didier ME, Fischer S, Maki DG. Total nutrient admixtures appear safer than lipid emulsion alone as regards microbial contamination: growth properties of microbial pathogens at room temperature. *JPEN J Parenter Enteral Nutr*. 1998;2(5):291-296.
18. Rollins CJ, Elsberry VA, Pollack KA, et al. Three-in-one parenteral nutrition: a safe and economical method of nutritional support for infants. *JPEN J Parenter Enteral Nutr*. 1990;14(3):290-294.
19. Driscoll DF. Lipid injectable emulsions. *Nutr Clin Pract*. 2006;21(4):381-386.
20. Télessy IG, Balogh J, Szabó B, et al. Kinetic stability of all-in-one parenteral nutrition admixtures in the presence of high dose Ca^{2+} additive under clinical application circumstances. *Nutr J*. 2012;11:32.
21. Joy J, Silvestri AP, Franke R, et al. Calcium and phosphate compatibility in low-osmolarity parenteral nutrition admixtures intended for peripheral vein administration. *JPEN J Parenter Enteral Nutr*. 2010;34(1):46-54.
22. Hill SE, Heldman LS, Goo ED, et al. Fatal microvascular pulmonary emboli from precipitation of a total nutrient admixture solution. *JPEN J Parenter Enteral Nutr*. 1996;20:81-87.