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Finding new solutions in pediatric parenteral admixtures; how to improve quality and to deal with shortages

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Abstract

Introduction: **Pediatric parenteral nutrition enables normal growth even of preterm infants. Those children require, however, tailored parenteral nutrition and the creation of such can be challenging due to the risk of instability and shortages.**

Objective: **Prototypical parenteral admixtures were created using different calcium salts (organic and inorganic) and different lipid emulsions and tested for stability. 36 of parenteral admixtures containing two types of calcium salts: chloride or gluconolactobionate and different lipid emulsions (SMOFlipid® or Lipofundin MCT/LCT®) were under investigation.**

Methods: **Preliminary admixtures were prepared in two-chamber bags whereas lipid emulsions were placed separately in the second chamber. Pre-admixtures were stored for up to 21 days at +4ºC. Contents of the two chambers were combined at t = 0 or after 21 days of storage. Physical analysis of completed admixtures (visual inspection, microscopic observation, pH measurement and determination of the size distribution of oily droplets) was carried out after 21 days of the storage. Stability of lipid, commercial emulsions stored in ethylene vinyl acetate (EVA) bags for 42 days was also studied.**

Results: **Irrespectively of the time of storage of pre-admixtures and type of calcium salt and different lipid emulsions among 36 total parenteral admixtures only one showed signs of destabilization after preparation and one was unstable when stored for longer than 14 days. All other formulations were qualified to be stable during the study. All investigated commercial lipid emulsions were physically stable in EVA bags even when stored at room temperature.**

Conclusion: **The study proved that it was possible to store pre-admixture in EVA bags for 21 days at 4°C as**

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ENCONTRANDO NUEVAS SOLUCIONES EN LAS MEZCLAS PARENTERALES PEDIATRICAS; ¿CÓMO MEJORAR LA CALIDAD Y GESTIONAR EL DESABASTECIMIENTO?

Resumen

Introducción: **La nutrición parenteral pediátrica permite un crecimiento normal incluso en lactantes pretérmino. Sin embargo, estos niños requieren una nutrición parenteral a medida y la formulación de tal nutrición puede suponer un reto por el riesgo de inestabilidad y el desabastecimiento.**

Objetivo: **Se crearon mezclas parenterales prototípicas utilizando diferentes sales de calcio (orgánicas e inorgánicas) y diferentes emulsiones lipídicas probando su estabilidad. Se investigaron 36 mezclas parenterales que contenían dos tipos de sales de calcio (cloruro o gluconolactobionato) y diferentes emulsiones lipídicas (SMOFlipid® o Lipofundin MCT/LCT®).**

Métodos: **Se prepararon unas pre-mezclas en bolsas bicompartimentales mientras que las emulsiones lipídicas se colocaron de forma separada en la segunda cámara. Las pre-mezclas se almacenaron hasta 21 días a +4º C. Se combinaron los contenidos de ambas cámaras en t = 0 o después de 21 días de almacenamiento. El análisis físico de las mezclas completadas (inspección visual, observación microscópica, medición del pH y determinación de la distribución por tamaño de las gotitas lipídicas) se realizó a los 21 días de almacenamiento. También se estudió la estabilidad de las emulsiones lipídicas almacenadas en bolsas comerciales de acetato de etilen vinilo (AEV) durante 42 días.**

Resultados: **Independientemente del tiempo de almacenamiento de las pre-mezclas y el tipo de sal de calcio y de las diferentes emulsiones lipídicas de entre el total de 36 mezclas parenterales, sólo en una se vieron signos de desestabilización tras la preparación y una fue inestable cuando se almacenó más de 14 días. El resto de las formulaciones se consideraron estables durante el estudio. Todas las emulsiones lipídicas comerciales investigadas fueron estables físicamente en las bolsas de AEV, incluso cuando se almacenaron a temperatura ambiente.**

Conclusión: **El estudio mostró que es posible almacenar pre-mezclas en bolsas de AEV durante 21 días a 4° C. También se vio que el NAC (número de agregación crítica) y el CaxP (los productos de la multiplicación de**

well as that CAN (critical aggregation number) and CaxP (the products of multiplication of calcium and phosphate ions concentration) should not be used as reliable indicators of admixture physical stability. No influence of the type of calcium salts on stability of admixtures was observed.

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Key words: *Parenteral nutrition. Shortages of drugs. Pediatric parenteral mixtures. Physical stability. Two compartment bag. Calcium salts.*

las concentraciones de los iones calcio y fósforo) no deberían utilizarse como indicadores fiables de la estabilidad física de las mezclas. No se observó ninguna influencia del tipo de sal de calcio sobre la estabilidad de las mezclas.

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Palabras clave: *Nutrición parenteral. Desabastecimiento de medicamentos. Mezclas parenterales pediátricas. Estabilidad física. Bolsa bicompartimental. Sales de calcio.*

Abbreviations

CAN: Critical aggregation number.

CaxP: the products of multiplication of calcium and phosphate ions concentration.

EVA: Ethylene vinyl acetate.

Introduction

Pediatric parenteral nutrition concerns mostly premature babies with low birth weight, children with congenital malformation of digestive system, or children with insufficiently developed digestive system[1]. Parenteral intervention enables normal growth. The main recipients of parenteral nutrition therapy are preterm infants and children born before the 37th week of pregnancy. This group is frequently intolerant to enteral feeding due to anatomic and functional immaturity of the digestive tract[2].

Children and adults have different nutritional needs; therefore, compositions of admixtures must vary[3]. Parenteral intervention must be tailored: adapted to age, body weight, growth rate, metabolic parameters and co-existing diseases. Standards for prescribing and administering nutritional mixtures for children were prepared in 2005 by European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and European Society for Clinical Nutrition and Metabolism (ESPEN)[4].

Children, who require parenteral nutrition for more than three months and can be discharged may be fed parenterally at home (Home Parenteral Nutrition, HPN) to improve the quality of life and decrease health care costs. Proper parenteral admixtures and the catheter care are keys to success during such treatment. The first include the preparation of admixtures in the hospital pharmacy by the pharmacist, and allowing the improved screening for admixtures incompatibilities. The latter may be challenging as children formulas contain high concentrations of electrolytes in a low volume, which poses a higher risk of incompatibilities, such as calcium phosphate's precipitation[5]. Moreover, the concentrations of calcium and phosphate in TPN mixtures employed in neonatology often exceed the maximum values approved for use, expressed as the products of multiplication of calcium and phosphate ions concentration (CaxP < 72 mmol^2/l^2). During HPN organic salts, particularly calcium, are preferred (e.g. calcium gluconate or calcium gluconolactobionate)[6-8].

Another issue is the physicochemical behavior of oily droplets in all-in-one (AIO) admixtures. Instable lipid emulsion, i.e. formation of oily droplets larger than 5 μm, is potentially dangerous due to emboli formation[9].

Shelf life of parenteral nutrition mixtures, prepared in single-chamber bags, is limited and usually does not exceed 24 hours (including the time needed for their administration). As it is necessary for the patient to use TPN mixtures every day, collecting the mixtures from the hospital pharmacy is inconvenient for the patient's care givers, and a regular delivery expensive due to the cost of logistics. A two-chamber bag, which separates lipid emulsion from the other components, can be used to extend storage time. In this case, mixing the emulsion and the solutions, and the addition of vitamins is performed immediately before administration. It, however, reduces the patient's quality of life and increases the risk of contamination.

Problems described above become even bigger in case of drug shortage, particularly the lack of organic calcium salts or phosphate. In those cases it is extremely easy to break rule just to avoid delivery failure. Therefore the aim of the study was to determine whether it was possible to prepare physically stable pediatric admixtures after the replacement of organic calcium salts with inorganic calcium product. The other end-points were: to examine whether the change of lipid emulsion influence the physical stability and to assess the new type of ethylene vinyl acetate wrap, which was supposed to increase the quality of the PN admixture.

Materials and methods

Prototypical admixtures for the purpose of the study were prepared by pediatrics gastroenterologist of Nico-

laus Copernicus Pomeranian Trauma Center of Gdansk (Poland) using the routine approach. The main idea was to compare admixtures, in which only one ingredients changed each time. Such modifications included: replacement of organic calcium with inorganic one and replacement of Lipofundin LCT/MCT (B Braun, Melsungen, Germany) was with SMOFlipid (Fresenius Kabi, Bad Homburg, Germany).

Parenteral admixtures were prepared with a computer-controlled pump: Multicomp II (Fresenius Kabi, Uppsala, Sweden) in the parenteral nutrition department of the Hospital Pharmacy of Nicolaus Copernicus Pomeranian Trauma Center in Gdansk. Pre-admixtures were prepared in two-chamber ethylene vinyl acetate (EVA) bags (Dimix®, Diffuplast, Olgiate Olona, Italy). Lipid emulsion, Lipofundin MCT/LCT® 20% (B. Braun, Melsungen, Germany) or SMOFlipid® (Fresenius Kabi, Bad Homburg, Germany), was placed in the smaller chamber of the bag and the rest of ingredients were mixed in the other chamber: amino acid solutions – Aminoven 10% Infant® (Fresenius Kabi, Uppsala, Sweden) or Primene® 10% (Baxter, Lessines, Belgium); Glucose 40% solution (B. Braun Melsungen, Germany); Magnesium sulfate 20% solution (Polpharma, Starogard Gdanski, Poland); Potassium chloride solution 15% (WZF Polfa, Warsaw, Poland); Sodium chloride solution 10% (Polpharma, Starogard Gdanski, Poland); Calcium Pliva® 10% - solution of calcium gluconolactobionate containing 0.23 mmol Ca^{2+}/ml (Pliva Cracow, Cracow, Poland), or Calcium chloride WZF 10% – solution of calcium chloride injection containing 0.45 mmol Ca^{2+}/ml (WZF Polfa, Warsaw, Poland); Glycophos® – Sodium glycerophosphate concentrated solution (Fresenius Kabi, Uppsala, Sweden); Peditrace® – mixture of trace elements, concentrated solution (Fresenius Kabi, Uppsala, Sweden). Multi-vitamin products: Vitalipid N Infant® lipid emulsion (Fresenius Kabi, Uppsala, Sweden) and Soluvit N® lyophilisate for solution (Fresenius Kabi, Uppsala, Sweden) were added immediately after mixing of two chambers.

Twelve admixtures were manufactured using lipid emulsion Lipofundin MCT/LCT® (composition "A") and twenty-four of TPN admixtures were created using SMOFlipid® (composition "B" was formulated with organic calcium salt and composition "C" with inorganic calcium salt). Compositions of the prepared TPN admixtures, calculated critical aggregation number (CAN) and CaxP, as well as osmolality were presented in table I. Electrolytes' content was presented in table II (sodium ions originated from both Glycophos and sodium chloride, whereas chloride ions originated from the preparations of sodium chloride, potassium chloride, and calcium chloride).

After labeling, pre-admixtures were protected from light and stored in controlled temperature at 4 ± 1°C for 21 days. Each pre-admixture was prepared twice.

Pre-admixtures were transferred to room temperature approximately 4 hours prior to the analysis. Two chambers was mixed and vitamins (Soluvit N dissolved in Vitalipid N Infant) were added afterwards. This step was carried out under non-aseptic conditions to simulate home conditions, where complete (i.e. all the components mixed together) admixtures will be prepared by the caregivers.

Physical analysis of complete TPN admixtures

Procedure for the stability test was presented in Scheme I. Physical analysis of complete admixtures was carried out immediately after preparation (t = 0) and after 24 hours of storage at room temperature under dark conditions. Pre-admixtures were combined together at t = 0 or after 21 days of storage. Complete admixtures were subjected to psysicochemical stability analysis consisting of visual inspection, microscopic observation (light microscope with camera, B1 223A Motic, Wetzlar, Germany), pH measurement (pH meter, Orion 350, Beverly, USA, with combination electrode) and determination of the size distribution of oily droplets (laser diffractometer, MasterSizer E, Malvern Instruments, Malvern, UK). Laser diffractometer method allowed determination of the median diameter ($d_{0.5}$; the diameter of 50% of oily droplets lies below the value of this parameter) and the maximum diameter of 90% of oily droplets ($d_{0.9}$). Additionally, visual inspection and pH measurements of the aqueous phase of the pre-admixtures were performed.

Examination of the stability of submicron emulsions stored in Dimix® bags

The smaller chamber of a Dimix® bag was filled with 50 ml of one of the following lipid emulsions under aseptic conditions: ClinOleic®, SMOFlipid®, or Lipofundin MCT/LCT® (20% w/w of oily phase) and stored for 42 days. Two bags were prepared; one was kept in controlled temperature at 4 ± 1°C (in refrigerator), whereas the other at room temperature (21 ± 1ºC). Following this, physical analysis was performed: visual and microscopic observation, oily droplet size distribution, and pH measurements.

Results

CAN values, calculated with Multicomp Calculator program, were found to be in the range of 583-1103 mmol/l. Some of admixtures were characterized by CAN values that were higher than the commonly accepted maximal cut-offs (CAN ≤ 600 mmol/l). Admixtures 4A, 4B, and 4C possessed the highest CAN values (above 1000 mmol/l), whereas the smallest values of CAN (below 600 mmol/l) were found in samples 5A, 5B, and 5C.

Table I

Composition [ml] of TPN admixtures containing 20% parenteral emulsion Lipofundin LCT/MCT ("A") or SMOFlipid ("B", "C") and calcium gluconolactobionate 10% solution ("A" and "B") or calcium chloride 10 solution ("C")

Composition of admixture		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Glucose 40%		78.7	96.9	95.7	96.5	94.2	94.7	95.4	95.6	134.3	134.1	138.1	138.2
Primene 10%		78.7	-	95.7	96.5	-	110.4	127.1	127.5	-	129.4	-	79.0
Aminoven Infant 10%		-	80.8	-	-	119.9	-	-	-	129.5	-	78.9	-
Lipofundin LCT/MCT	A	31.3	39.1	39.1	39.0	46.8	47.0	54.0	54.4	54.0	54.0	54.4	54.0
SMOFlipid	B, C	31.3	39.1	39.1	39.0	46.8	47.0	54.0	54.4	54.0	54.0	54.4	54.0
Water for injection		138.3	4.7	37.1	2.2	103.5	57.0	17.3	1.6	6.2	1.1	53.5	44.2
Glycophos		2.2	2.3	2.2	2.9	2.2	2.8	2.2	2.9	2.2	2.8	2.2	2.8
10% NaCl		6.7	6.8	3.0	2.3	6.7	15.2	6.7	6.0	6.7	11.5	12.3	11.5
15% KCl		3.1	3.2	3.2	3.2	3.1	6.3	3.2	3.2	3.2	6.3	3.2	3.2
Peditrace		3.1	3.2	3.2	3.2	3.1	3.2	3.2	3.2	3.2	3.2	3.2	3.2
20% $MgSO_4$		0.8	0.8	0.8	1.2	0.8	1.2	0.8	1.2	0.8	0.8	0.8	1.2
Calcium Pliva 10%	A, B	10.9	11.2	11.1	14.0	10.9	13.7	11.1	13.9	11.0	13.7	11.0	13.7
Calcium chloride	C	5.5	5.6	5.6	7.1	5.5	6.9	5.6	7.0	5.5	6.9	5.5	6.9
Soluvit N		4.2	3.9	3.9	3.9	3.7	3.7	3.6	3.6	3.6	3.6	3.6	3.6
Vitalipid N Infant		4.2	3.9	3.9	3.9	3.7	3.7	3.6	3.6	3.6	3.6	3.6	3.6
Total volume	A, B	358.0	252.9	295.0	265.0	384.9	355.0	325.0	313.1	355.1	360.9	361.2	355.0
	C	356.8	251.2	293.4	262.0	383.2	351.9	323.1	309.8	353.2	357.7	359.3	351.8
CAN [mmol/l]	A, B	626.4	906.5	749.5	1073	582.6	867.7	699.7	924.0	636.3	779.3	651.9	832.5
	C	640.1	927.0	768.9	1102	594.8	888.9	716.4	949.7	646.3	798.4	662.0	853.0
CIP CaxP [$mmol^2/l^2$]	A, B	43.0	92.6	64.5	133.0	37.2	70.0	53.2	94.6	44.1	67.7	42.7	70.0
	C	44.1	95.6	66.0	138.7	37.6	72.0	54.4	97.8	44.6	69.4	43.3	72.0
osmolarity [mOsm/l]	A, B	839	1404	1160	1309	978	1163	1183	1237	1369	1399	1298	1303

Table II
Content of electrolytes in TPN admixtures [mmol/l]

Component of admixture	Na^+	K^+	Mg^{2+}	Ca^{2+} TPN A, B	Ca^{2+} TPN C	Cl^- TPN A, B	Cl^- TPN C	Phosphates	SO_4^{2-}
1	44.3	17.4	3.7	7.0	7.1	49.4	63.4	6.1	3.7
2	64.2	25.4	5.3	10.2	10.4	71.4	92.2	9.1	5.3
3	32.3	21.8	4.5	8.7	8.8	39.2	56.8	7.5	4.5
4	36.7	24.3	7.5	12.2	12.5	39.1	64.1	10.9	7.5
5	41.2	16.2	3.5	6.5	6.6	46.0	59.2	5.7	3.5
6	89.0	35.7	5.6	8.9	9.0	108.9	126.9	7.9	5.6
7	48.8	19.8	4.1	7.9	8.0	55.1	71.1	6.8	4.1
8	51.3	20.5	6.4	10.2	10.4	54.3	75.1	9.3	6.4
9	44.7	18.1	3.7	7.1	7.2	50.4	64.8	6.2	3.7
10	70.0	35.1	3.7	8.7	8.9	89.6	107.4	7.8	3.7
11	70.4	17.8	3.7	7.0	7.1	76.0	94.2	6.1	3.7
12	71.2	18.1	5.6	8.9	9.0	73.5	92.8	7.9	5.6

Parenteral (PN) admixtures were characterized by high value of CaxP, i.e. 37 to 139 $mmol^2/l^2$. For admixtures 4A, 4B, and 4C the value of CaxP was twice as high as recommended (CaxP ≤ 72 $mmol^2/l^2$). Figures 1 and 2 illustrate above issues.

Visual and microscopic observations

Barely noticeable creaming was visually observed in completed admixtures after 24 hours of storage at room temperature. This occurred in all admixtures despite

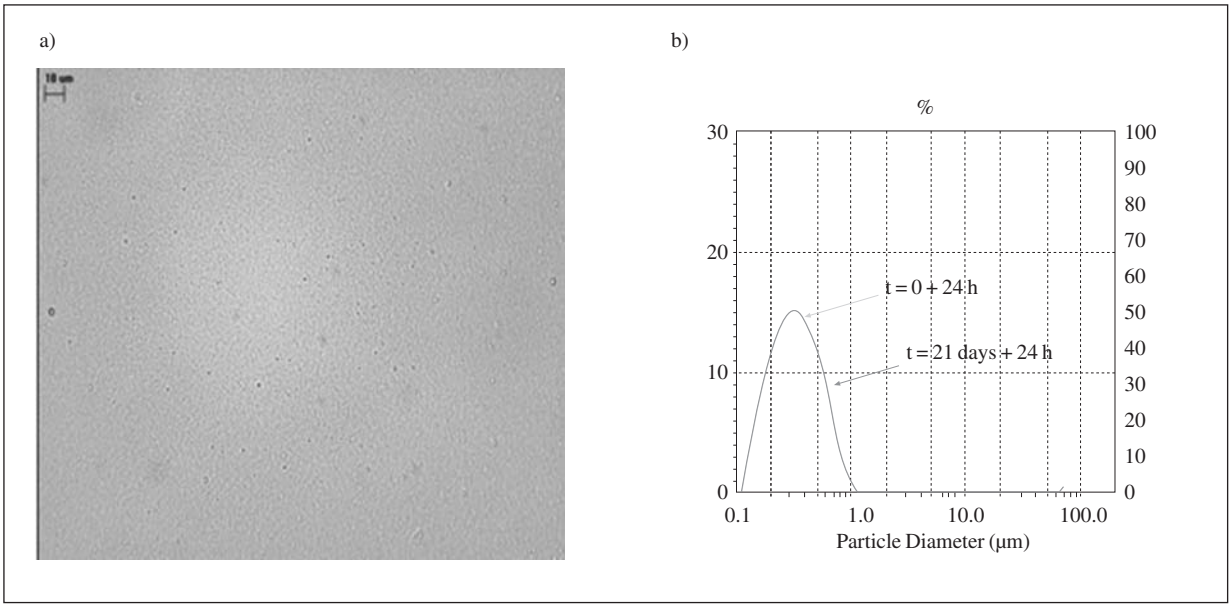


Fig. 1.—Microscopic observation at t = 0 + 24 h (a) and oily globules size analyzed at t = 0 + 24 h at t = 21 days + 24 h (b) in admixture TPN 9C.

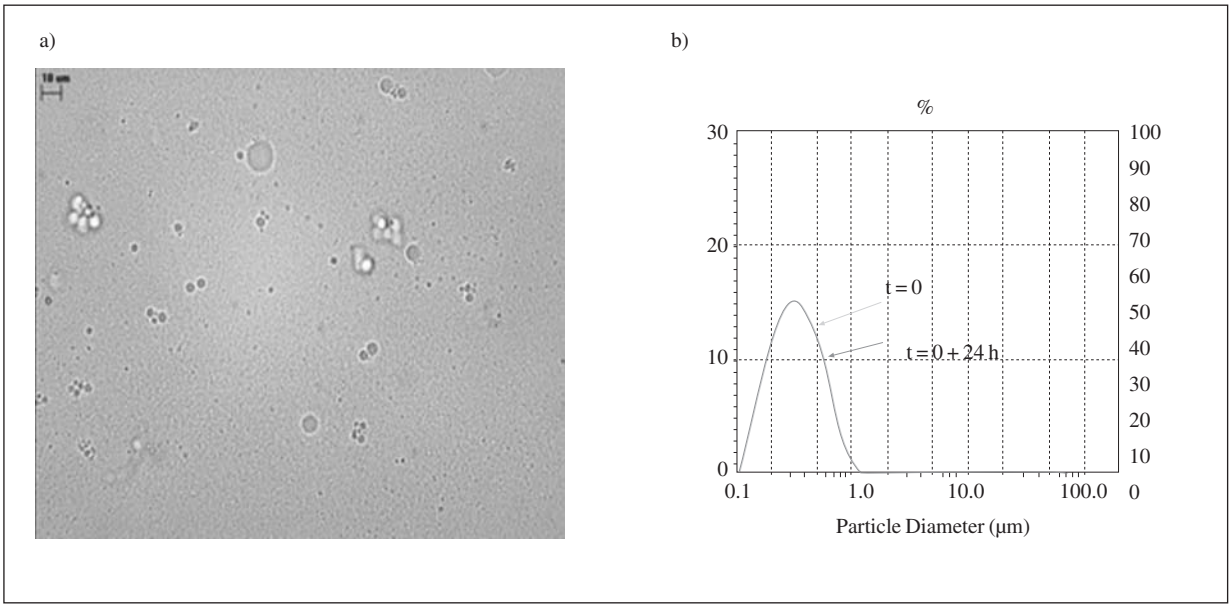


Fig. 2.—Microscopic observation of admixture TPN 1C at t = 0 + 24 h (a) and droplet size distribution at t = 0 and t = 0 + 24 h (b).

various compositions, but disappeared after short mixing.

On microscopic observation, the majority of the completed admixtures were characterized by the size of oily droplets not larger than 1 µm, considered to be safe for patients (fig. 1). Following 21 days of storage, oily droplets in TPN prepared from pre-admixture 6B had a tendency to agglomerate. However, this admixture was additionally prepared and examined after 14 days of storage at 4°C at which time no destabilization was observed. Only in one final admixture (1C), a few droplets, about 8-10 µm in size and with a tendency to agglomerate (fig. 2), were observed. As this fact was found to occur in both batches, admixture 1C was considered unstable.

Oily droplet size distribution

No oily droplets lager than 1 µm were detected in any of the admixtures (laser diffractometry method; fig. 1). The median size of oily droplets ($d_{0.5}$) in the final admixtures was determined to be 310-330 nm; 90% of oily droplets ($d_{0.9}$) were under 580-670 nm. The size of oily droplets did not change following 24-hour storage at room temperature (fig. 1). It was observed that duration of storage of pre-admixtures in two-chamber bags had no influence on droplet size distribution. (fig. 3). There were no differences between stable and unstable TPN admixtures (9C and 1C, see above) using laser diffractometry method (fig. 1 and 2).

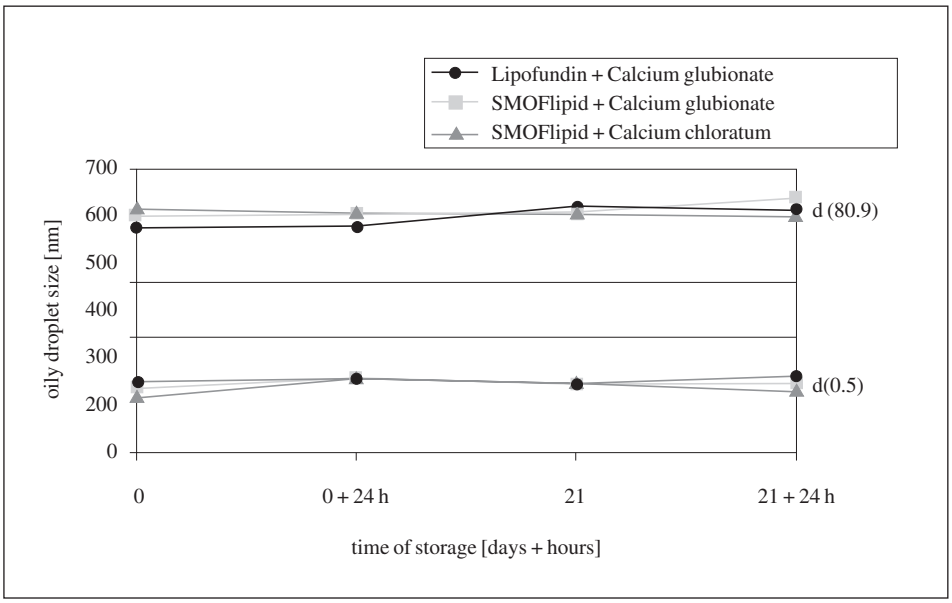


Fig. 3.—The effect of storage of TPN 1 pre-admixture for 21 days on oily deoplet size [µm].

pH measurement

The pH values of TPN admixtures were in the same narrow range as those measured before blending with lipid emulsion (5.4-6.2). These values did not change during storage (fig. 4).

Analysis of lipid emulsions in EVA bags

All lipid emulsions stored in EVA bags for 42 days at +4ºC and +21ºC were homogenous and stable. On microscopic examination, oily droplet size did not change and only a few droplets were found to be approximately 2-3 μm in size. Oily droplet size was similar for all investigated emulsions, independently of time and conditions of storage (fig. 5). The median droplet diameter ($d_{0.5}$) was in the range of 300-340 nm and the largest of oily droplets were about 540-890 nm in size. No significant changes in pH values ($p < 0.05$) of lipid emulsions stored at +4ºC and +21ºC were observed (figs. 6 and 7).

Discussion

During HPN physicians, dieticians, and nurses focus mostly on the nutritional requirements and venous

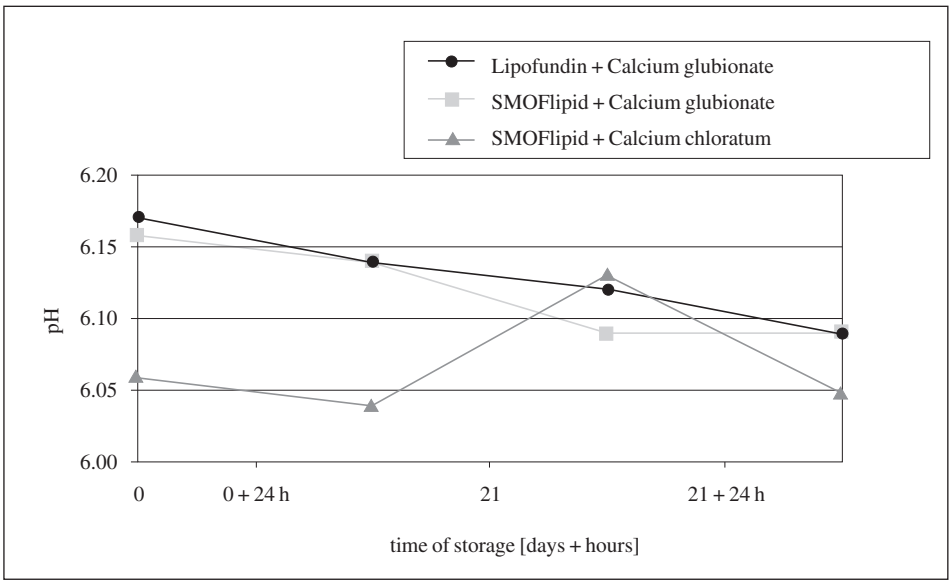


Fig. 4.—The pH values of the complete admixture (TPN 2)- the effect of various composition.

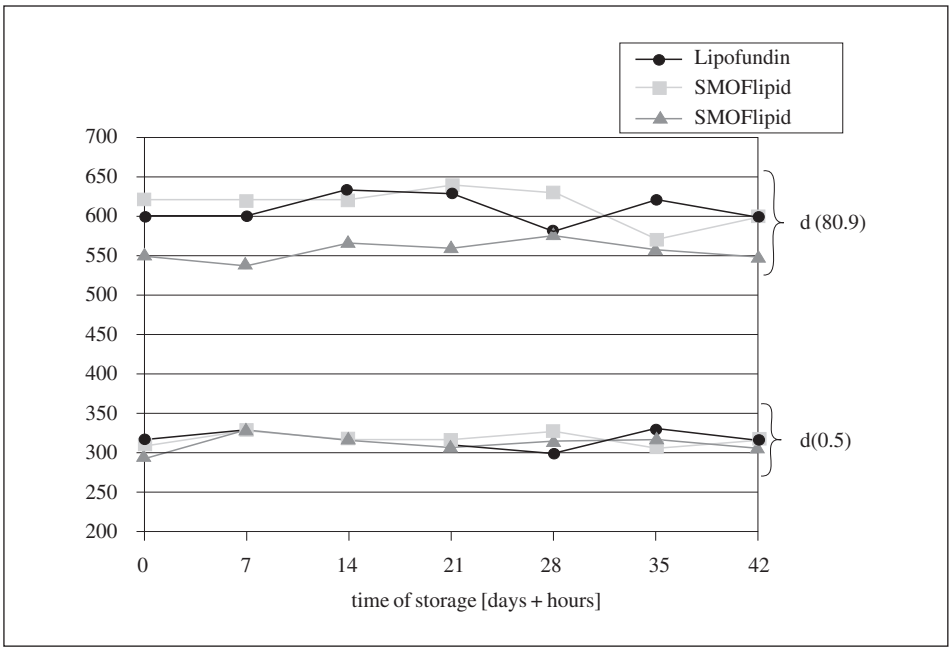


Fig. 5.—Oily droplets size distribution in lipid emulsions storage in EVA bags at room temperature during 42 days.

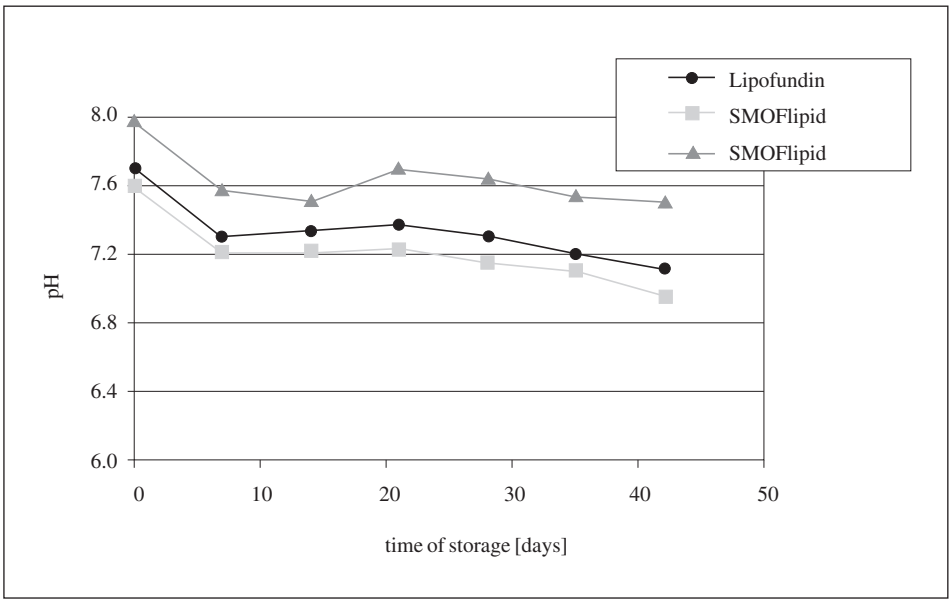


Fig. 6.—The pH values of lipid emulsions storage at 21 ± 1º C during 42 days.

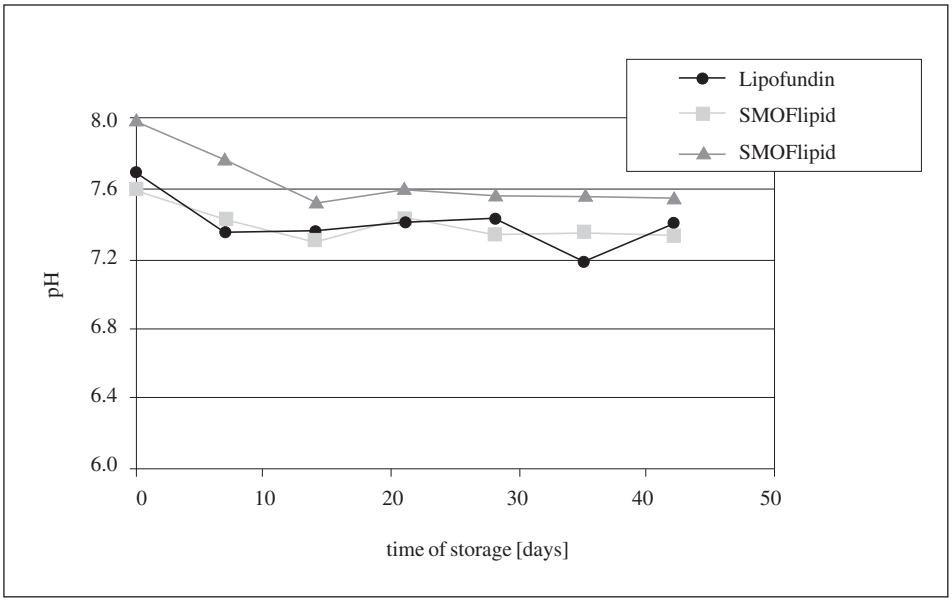


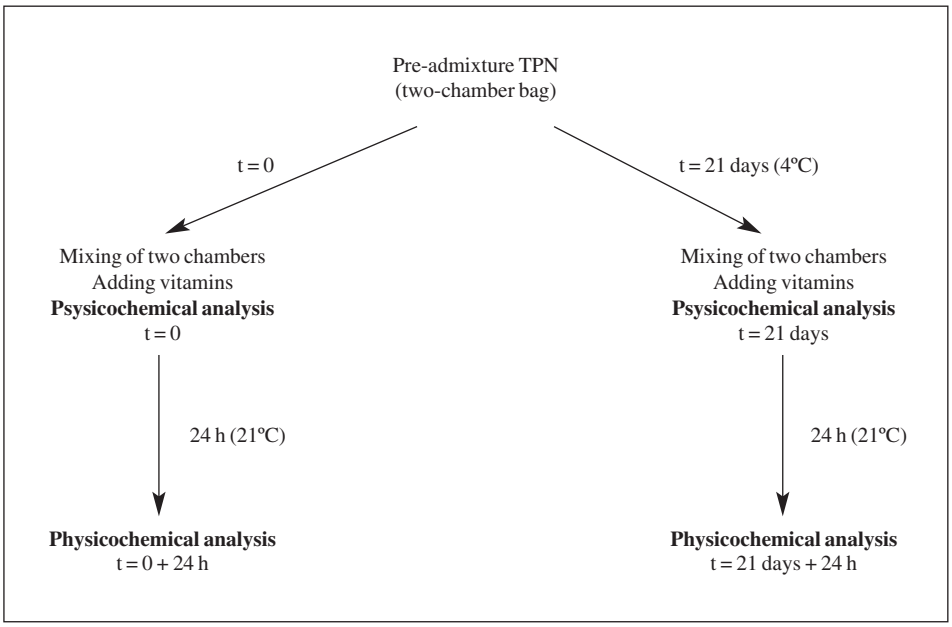
Fig. 7.—The pH values of lipid emulsions storage at 4 ± 1º C during 42 days.

access, but not the admixture itself. Hospital pharmacists, who are familiar with issues related to physical and chemical processes occurring in parenteral admixtures, should ensure patient's safety[10]. Parenteral nutrition represents a pharmaceutical challenge due to various potential incompatibilities[7].

All investigated HPN admixtures were prepared according to procedures that are routinely used at hospital pharmacies. It was interesting to notice that admixtures were characterized by nearly twice as high as physiological concentration of calcium (6.5-12.5 mmol/l Ca^{2+}) and relatively physiological concentration of magnesium ions (3.5-7.7 mmol/l Mg^{2+}). Nonstandard concentration of potassium ions (16.2-35.7 mmol/l K^{+}) resulted from the clinical needs. The values of CAN in the investigated admixtures were in the range of 583-1103 mmol/l, while CaxP was found to be between 37 and 139 $mmol^2/l^2$. Nitrogen – calorie ratio was determined to be in the range of 120-266 kcal/g N.

Barely noticeable creaming was visually observed in all completed admixtures after 24 hours of storage at room temperature; it disappeared after short mixing. Creaming was deemed to be normal and acceptable because it occurred in all admixtures despite various compositions.

The value of pH in aqueous phase of pre-admixtures and in TPN admixtures did not differ significantly and did not change during storage; therefore, all admixtures were characterized by stable pH.



Scheme 1.—Scheme of physicochemical analysis of all TPN admixtures.

On microscopic observation, all, expect one, solutions were characterized by oily droplets not larger than 1 μm in size, which are considered to be safe during intravenous administration (fig. 1). Only one completed admixture (1C) was found to be unstable due to few oily droplets, approximately 8-10 μm in size. Admixture 1C, containing calcium chloride and characterized by lower concentration of glucose, amino acids and lipids than other admixtures, was determined to be unstable on the basis of two samples. Oily droplets in admixture 6B had a tendency to agglomerate when the mixture was prepared from pre-admixtures stored for 21 days. However, no destabilization was observed in the same mixture stored for a shorter time (i.e. 14 days).

Using laser diffractometry, oily droplets larger than 1 μm in size, even in admixtures with microscopically determined large droplets or agglomerates were not observed. Laser diffractometry did not show destabilization of the completed admixtures deemed unstable (fig. 3). This result indicates that the size of oily droplets measured by laser diffractometry must always be verified by microscopic observations, especially in the case of polydispersed systems, which are submicron emulsions.

Preparing TPN admixture in a one chamber bag forces its prompt use; however, when the emulsion is separated from the other components (two-chamber bag), the duration of storage may be extended. Our study provides evidence that storing the proposed pre-admixtures in two-chamber bags for 21 days at a temperature of 4°C can be considered to be safe. Despite the high CAN (about 1000) and CaxP (90-139) values, the investigated admixtures were physically stable. This means that CAN and CaxP parameters, theoretically too high, do not limit the physical stability of TPN admixtures.

No influence of the type of calcium salts or lipid emulsion on the stability of the investigated TPN admixtures was observed. It also appeared to be safe to store lipid emulsions (Lipofundin LCT/MCT, SMOFlipid, and ClinOleic) in one of the chambers of EVA bags at +4°C as those solutions remained stable even for 42 days at a temperature of 21°C.

Conclusions

Pre-admixtures can be stored in EVA bags for 21 days at 4°C. It is possible to obtain stable TPN admixtures with high electrolyte levels. CAN and CaxP parameters may not be used as reliable indicators of admixture physical stability. No influence of the type of calcium salts on stability of admixtures was observed.

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Conflicts of Interest

The authors declare no conflict of interest.

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