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Evaluation of physical stability of all in one parenteral admixtures for pediatric home care with high electrolytes concentrations

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Abstract

Introduction: **The aim of the study was to evaluate stability of 48 total parenteral admixtures for pediatric patients who require home parenteral nutrition. Admixtures contain high amounts of electrolytes. In a clinical practice electrolytes-enrichment of the parenteral nutrition admixtures is a usual demand, especially on the neonatal/pediatric wards. The supplementation of parenteral nutrition with high concentration of electrolytes is a living problem due to decreased stability of lipid emulsions in nutrition admixtures caused by bivalent cations.**

Methods: **Preliminary admixtures were prepared in two-chamber ethylene vinyl acetate bags: amino acids, glucose and electrolytes were combined in one chamber and 20% (w/w) lipid emulsions (SMOFlipid®, Intralipid® or ClinOleic®) were placed separately in the second chamber. Organic salts of calcium and phosphates were used. Pre-admixtures were stored at +4ºC for up to 21 days after preparation. Each composition of admixtures was prepared twice, because contents of the two chambers were combined at t=0 or after 21 days of storage at +4ºC. Visual observations, globule size distribution (using optical microscopy, laser diffraction and photon correlation spectroscopy methods), pH analyses, zeta potential and surface tension were performed after combining all components together with vitamins.**

Results: **Among 48 of investigated admixtures only two were problematic and other may be stored for at least 21 days at 4°C and completed admixtures demonstrated stability for at least 24 h at room temperature.**

Conclusion: **It was possible to obtain stable admixtures despite of the high concentration of electrolytes.**

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Key words: *Pediatric parenteral nutrition. Physical stability. Lipid emulsion. High electrolytes concentration. Home parenteral nutrition.*

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EVALUACIÓN DE LA ESTABILIDAD FÍSICA DE PREPARADOS PARENTERALES "TODO EN UNO" PARA ATENCIÓN PEDIÁTRICA DOMICILIARIA CON ALTAS CONCENTRACIONES DE ELECTROLITOS

Resumen

Introducción: **El objetivo del estudio fue evaluar la estabilidad de un total de 48 preparados o mezclas parenterales para pacientes pediátricos con necesidad de nutrición parenteral domiciliaria. Los preparados contienen cantidades elevadas de electrolitos. En la práctica clínica, el enriquecimiento con electrolitos de los preparados de nutrición parenteral es una demanda habitual, especialmente en las unidades neonatales/pediátricas. El complemento de la nutrición parenteral con altas concentraciones de electrolitos es un problema corrriente debido a la menor estabilidad de las emulsiones lipídicas en preparados de nutrición provocada por cationes bivalentes.**

Métodos: **Se prepararon mezclas preliminares en bolsas de etilenvinilacetato de dos cámaras: se combinó amino ácidos, glucosa y electrolitos en una cámara y en la segunda cámara se puso por separado emulsiones lipídicas 20% (w/w) (SMOFlipid®, Intralipid® o ClinOleic®). Se utilizaron sales orgánicas de calcio y fosfatos. Se almacenaron pre-mezclas a +4ºC durante 21 días después de la preparación. Cada composición de mezcla fue preparada dos veces, dado que el contentido de las dos cámaras se combinó en t=0 o después de 21 días después del almacenamiento a +4ºC. Se realizaron observaciones visuales, distribución del tamaño globular (empleando métodos de microscopía óptica, difracción por láser y espectroscopía de correlación fotónica), análisis de pH, potencial zeta y tensión superficial después de combinar todos los componentes a la vez con vitaminas.**

Resultados: **De los 48 preparados investigados solo dos resultaron problemáticos y el resto se pudo almacenar durante al menos 21 días a 4°C y las mezclas completadas presentaron estabilidad durante al menos 24 h a temperatura ambiente.**

Conclusión: **Fue posible obtener preparados estables a pesar de la alta concentración de electrolitos.**

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Palabras clave: *Nutrición parenteral pediátrica. Estabilidad física. Emulsión lipídica. Alta concentración de electrolitos. Nutrición parenteral domiciliaria.*

Abbreviations

CAN: critical aggregation number.
CaxP: the products of multiplication of calcium and phosphate ions concentration.
EVA: ethylene vinyl acetate.
LD: laser diffractometry method.
PCS: photon correlation spectroscopy method.
PN: parenteral nutrition.
SBS: short bowel syndrome.
TPN: total parenteral nutrition.

Introduction

Home parenteral nutrition is an essential way of nutrition in case of intestinal failure, when oral or enteral nutrition is unable to meet the nutritional requirements. The main indication for home parenteral nutrition in children are primary digestive diseases (76-86%). Among digestive diseases, short bowel syndrome (SBS) of neonatal origin due to necrotizing enterocolitis, intestinal atresia, gastroschisis or long segment agangliosis is the major cause of long term parenteral nutrition support[1,2]. That is way in majority of pediatric patients parenteral nutrition (PN) is introduced in first days of life and is required for next several years[2]. Moreover, the risk of fatal complications is increased in children below 24 months of age[3].

Proper provision of macro- and micronutrients during first years of life is crucial for both biological as well as psychomotoric development of a child. The deficiency of any of nutritional components may have also long term effects on child`s health. From the clinical point of view the aim of nutritional support is to obtain optimal growth and development in terms of bone health, body composition[3-5]. In majority of cases the standard well-balanced provision of macro- and micronutrients is sufficient to achieve that goal[6].

However in cases complicated by prematurity, high output stoma, very short remnant bowel or cholestasis covering special needs by parenteral nutrition may be required[7]. Recently, the neonatal therapeutic hypothermia-associated hypomagnesemia during parenteral nutrition therapy was described in 80% of children on standard supplementation[8]. In 40% of adult patients with SBS on long term PN hypomagnesemia is present[9].

Bone mineral disease complicates prematurity. The risk increases with the duration of parenteral nutrition as well as the calcium deficiency. Therefore the proper supply with calcium is one of the important factor in preventing bone mineral disease[10].

Due to different nutritional needs for children and adults, admixtures preparing for small patients contain high electrolytes concentration in low final volume, which creates higher risk of incompatibilities. Using such admixtures in practice is only limited by performing for each of composition physical stability. Any changes such as replacing components produced by one manufacturer with products of other require re-testing. It is very important to performed physical stability issues for each admixture with a new composition.

Aim of the study

The composition of parenteral admixtures has to be tailored according to the patient` clinical situation. Therefore the aim of our study was to evaluate the physical stability of 48 pediatric all in one admixtures designed for home parenteral nutrition. All parenteral admixtures characterized by high electrolytes concentrations. Three types of lipid emulsions: SMOFlipid, Intralipid or ClinOleic were used for preparation of admixtures. This allowed comparing stability of parenteral admixtures with different types of lipid emulsions in the presence of high electrolytes concentration.

Materials and methods

Parenteral pre-admixtures were filled 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. Compositions of parenteral admixtures were prescribed by pediatricians.

Pre-admixtures were prepared in two-chamber EVA (ethylene vinyl acetate) bags (Dimix, *Diffuplast*, Olgiate Olona, Italy). Lipid emulsion SMOFlipid, Intralipid (*Fresenius Kabi*, Austria) or ClinOleic (Baxter, Lessines, Belgium) was placed in smaller chamber of the bag. In the second chamber the following components were mixed: 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 (glubionate) containing 0.23 mmol Ca^{2+}/ml (Pliva Cracow, Cracow, Poland); Glycophos – Sodium glycerophosphate concentrated solution (Fresenius Kabi, Uppsala, Sweden); Peditrace - mixture of trace elements, concentrated solution (Fresenius Kabi, Uppsala, Sweden). Multiple vitamin preparations - Vitalipid N Infant lipid emulsion (Fresenius Kabi, Uppsala, Sweden) and Soluvit N *lyophilisate* for *solution* (Fresenius Kabi, Uppsala, Sweden) were added immediately after combining the contents of the two chambers of the bags.

Sixteen of TPN admixtures were prepared using parenteral emulsion SMOFlipid and Aminoven Infant solution (signature as compositions "A"), the next sixteen of admixtures contain Intralipid and Aminoven Infant solution (signature as compositions "B") and the last sixteen admixtures contain ClinOleic and Primene (signature as compositions "C") table I. Compositions

Table I
Composition [ml] of TPN admixtures containing 20% parenteral emulsion SMOFlipid and Aminoven Infant ("A"), Intralipid and Aminoven Infant ("B") or ClinOleic and Primene ("C")

TPN	Glukose 40%	Aminoacids	Lipid emulsion	Water for injection	Glycophos	10% NaCl	15% KCl	Peditrace	20% MgSO4	Calcium glubionate	Soluvit	Vitalipid
1	94.8	86.7	32.5	5.1	3.7	4.6	5.4	2.2	4.1	18.8	2.2	2.2
2	93.3	85.3	32.0	69.0	3.6	4.5	5.3	2.1	4.0	18.6	2.1	2.1
3	82.5	66.0	22.0	16.3	2.6	4.7	4.4	2.2	2.8	14.3	2.2	2.2
4	80.0	64.0	21.3	122.5	2.6	4.5	4.3	2.1	2.7	13.9	2.1	2.1
5	96.3	66.0	22.0	0.6	2.2	6.5	5.5	2.2	2.2	14.3	2.2	2.2
6	94.8	65.0	21.7	44.0	2.2	6.4	5.4	2.2	2.2	14.1	2.2	2.2
7	93.3	64.0	21.3	107.3	2.1	6.3	5.3	2.1	2.1	13.9	2.1	2.1
8	82.5	66.0	22.0	14.1	3.7	2.1	3.3	2.2	2.8	19.1	2.2	2.2
9	81.3	65.0	21.7	57.2	3.7	2.0	3.3	2.2	2.7	18.8	2.2	2.2
10	80.0	64.0	21.3	120.3	3.6	2.0	3.2	2.1	2.7	18.6	2.1	2.1
11	82.5	66.0	22.0	19.2	2.2	3.9	3.3	2.2	2.2	14.3	2.2	2.2
12	81.3	65.0	21.7	62.2	2.2	3.8	3.3	2.2	2.2	14.1	2.2	2.2
13	80.0	64.0	21.3	125.3	2.1	3.8	3.2	2.1	2.1	13.9	2.1	2.1
14	56.3	33.8	22.5	25.0	3.8	4.8	5.6	2.3	4.2	19.6	2.3	2.3
15	55.0	33.0	22.0	68.4	3.7	4.7	5.5	2.2	4.1	19.1	2.2	2.2
16	53.3	32.0	21.3	173.0	3.6	4.5	5.3	2.1	4.0	18.6	2.1	2.1

of the prepared TPN admixtures and calculated CAN (critical aggregation number) and CaxP parameters as well as osmolarity are presented in table II. Contents of electrolytes are presented in table III (sodium ions come from both Glycophos and sodium chloride, whereas chloride ions come from the preparations of sodium chloride and potassium chloride).

Pre-admixtures after labeling were stored protected from light under controlled temperature at 4±1°C for 21 days. Each pre-admixture was prepared twice.

Pre-admixtures were transferred to room temperature about 4 h before the analysis. Next the content of two chambers was mixed together and vitamins (Soluvit N dissolved in Vitalipid N Infant) were added. To simulate home conditions in which completed admixtures will be prepared by caregivers this step was carried out under nonaseptic conditions.

Physical analysis of complete parenteral admixutres

The scheme of the physical stability test is presented in Scheme I. Analysis of the complete admixtures was carried out immediately after preparation (t=0) and after 24 h of storage at room temperature, with light protection. Activation of pre-admixtures was at t=0 or after 21 days of storage. Completed parenteral admixtures were subjected to physical stability analysis consisting of

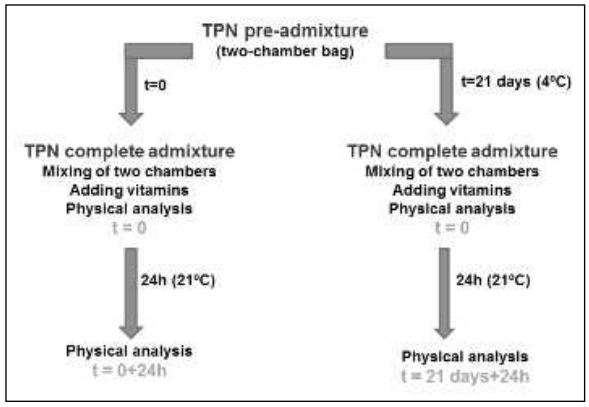
Table II
CAN and CaxP parameters, α coefficient and theoretical osmolarity of TPN admixtures

TPN	CAN [mmol/l]	CaxP [mmol²/l²]	α coefficient	Theoretical osmolarity [mOsm/L]
1	1973	268	158	1408
2	1577	171	158	1126
3	1711	199	168	1387
4	1140	91	168	925
5	1591	172	189	1565
6	1333	121	189	1303
7	1057	76	189	1042
8	2012	366	168	1356
9	1664	258	169	1131
10	1342	164	168	904
11	1551	172	168	1344
12	1299	121	169	1121
13	1030	76	168	896
14	2947	574	254	1296
15	2355	366	255	1037
16	1577	164	254	691

Table III
Concentration of electrolytes in TPN admixtures [mmol/l]

TPN	Na^+	K^+	Mg^{2+}	Ca^{2+}	PO_4^{3-}
1	58.02	41.17	13.76	14.33	14.11
2	45.37	32.93	10.94	11.56	11.18
3	58.40	39.60	11.09	12.87	11.70
4	38.14	26.70	7.38	8.63	8.07
5	68.80	49.50	8.71	12.87	9.90
6	57.77	41.16	7.38	10.75	8.38
7	46.05	32.93	5.74	8.64	6.52
8	49.30	29.70	11.09	17.19	16.65
9	40.21	25.16	9.06	14.33	14.11
10	32.36	19.88	7.38	11.55	11.18
11	48.80	29.70	8.71	12.87	9.90
12	40.77	25.15	7.38	10.75	8.38
13	33.04	19.88	5.74	8.63	6.52
14	82.64	61.37	20.25	21.48	20.82
15	68.32	49.53	16.24	17.20	16.66
16	45.37	32.93	10.94	11.56	11.18

visually inspection, microscopic observation (biologic microscope with camera B1 223A *Motic*, Wetzlar, Germany), determination of oily globules size distribution - laser diffractometer (MasterSizer E *Malvern Instruments*, Malvern, UK) and photon correlation spectroscopy (Zetasizer, *Malvern Instruments*, Malvern, UK), zeta potential (Zetasizer, *Malvern Instruments*, Malvern, UK), pH measurement (ph meter *Orion 350*, Beverly, USA, with combination electrode). Laser diffractometer



Scheme I.—Scheme of physical analysis of complete TPN admixtures.

method (LD) allows determining the *median diameter* ($d_{0.5}$ below this parameter is diameter of 50% of oily globules) and the maximum diameter of 90% of oily globules ($d_{0.9}$). Photon correlation spectroscopy method (PCS) is used to determine Z-avarage parameter. Additionally the aqueous phase of the pre-admixtures was suspected to visual inspection and pH measurements.

Results

Visual and microscopic observations

Very slight creaming after 24 h of storage at room temperature in complete admixtures despite various compositions was visually observed. Creaming was observed in all admixtures but easily disappeared after short mixing.

In microscopic observation most of the complete admixtures were characterized by size of oily globules not larger than 1 µm, which are safe for patients (Fig. 1).

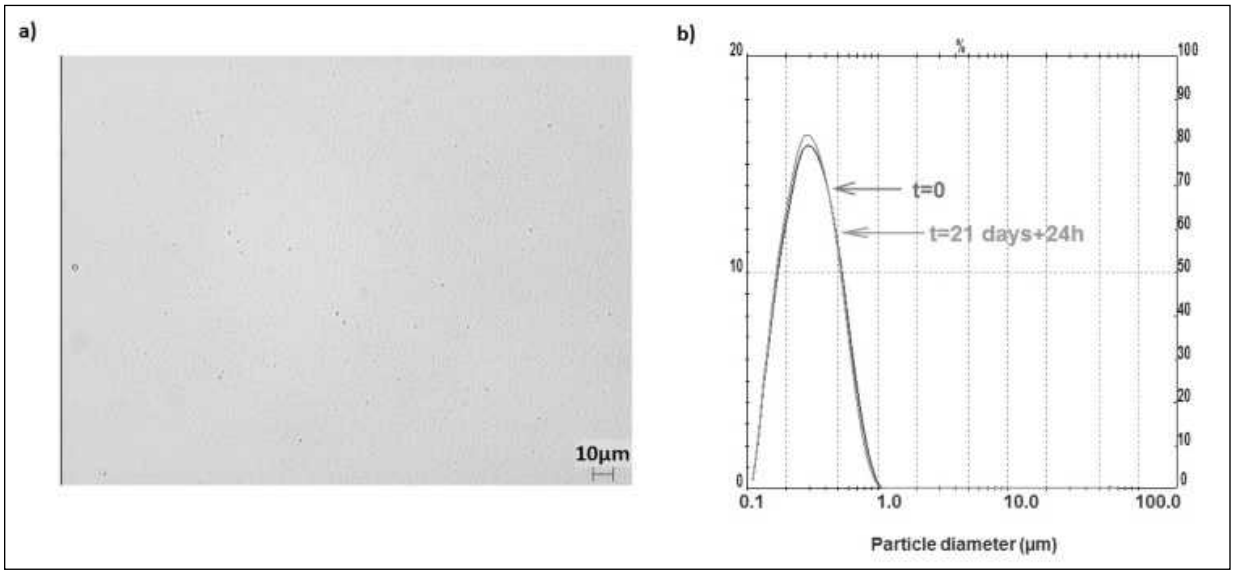


Fig. 1.—Microscopic observation (scale 10 µm) at t = 21 days+24h (a) and distribution of oily droplets of TPN admixture 14A (b).

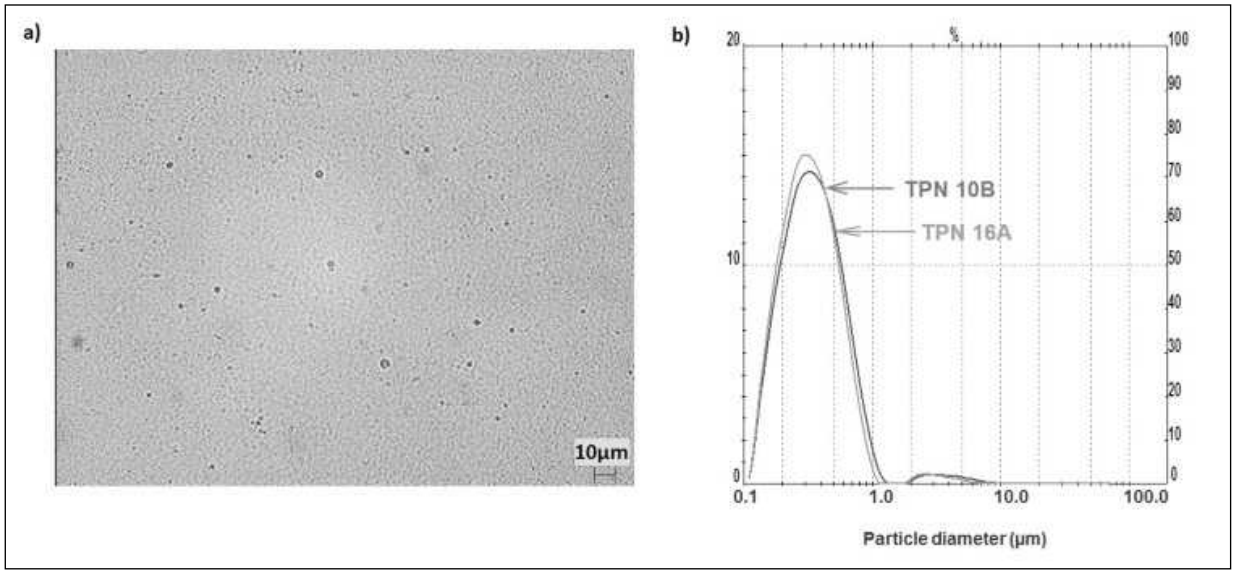


Fig. 2.—Microscopic observation (scale 10 µm)(a) and distribution of oily droplets of TPN admixtures at t = 21 days+24h (b).

Among 48 of admixtures only one was problematic. In complete admixtures prepared from pre-admixtures 15B and 16A stored for 21 days oily droplets undergo of coalescency and few globules about 5 µm in size were observed (Fig. 2). No destabilization was observed in additionally analysis when complete admixtures 15B and 16A were prepared only at t=0 and were stored 24h.

Oily droplet size distribution

a) Laser diffractometry method

Value of median ($d_{0.5}$) of oily droplets size in the complete admixtures was 320±30 nm and 90% of oily droplets ($d_{0.9}$) were under 620 ±30 nm. No oily globules lager than 1 µm were detected in any of all admixtures by using laser diffractometry method (Fig. 1).

b) Photon correlation spectroscopy

Z-avarage of oily droplets size was about 320 nm. Size of oil droplets was significant smaller for TPN admixtures containing ClinOleic as lipid emulsion (Z-avarage 250 nm) (Fig. 3).

For all of admixtures no changes (±30 nm) during storage were observed. In admixtures TPN 2B – 6B, 8B and 10B (containing SMOFlipid) decreasing, about 70 nm comparing with t=0, of oily droplets size was observed. Whereas Z-avarage of admixtures TPN 9C - 16C containing ClinOleic was increasing during storage, the highest was in TPN 6A (55 nm).

Zeta potential analysis

Zeta potential of all admixtures was in range -36 to -47 mV and did not change during the storage (±5 mV)

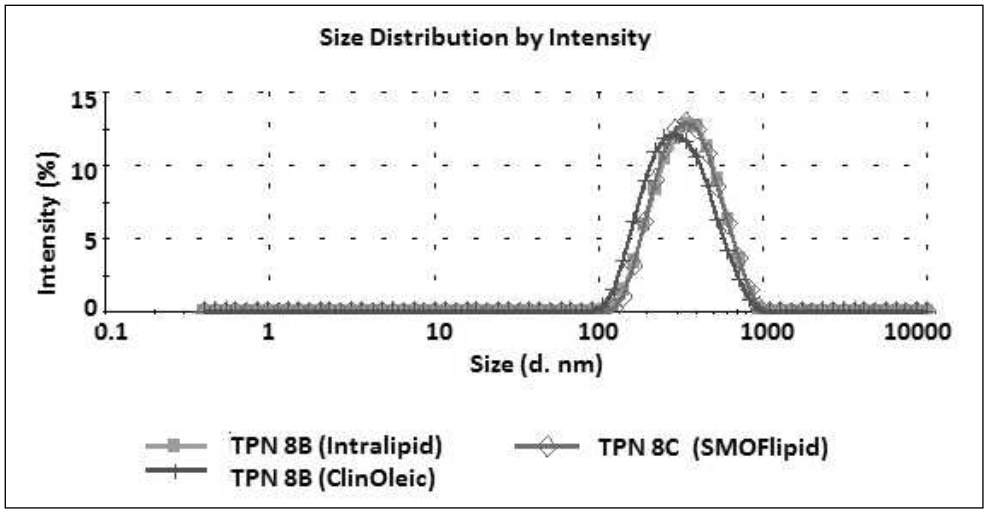


Fig. 3.—Distribution of oily droplets of TPN admixtures at t=21 days+24h.

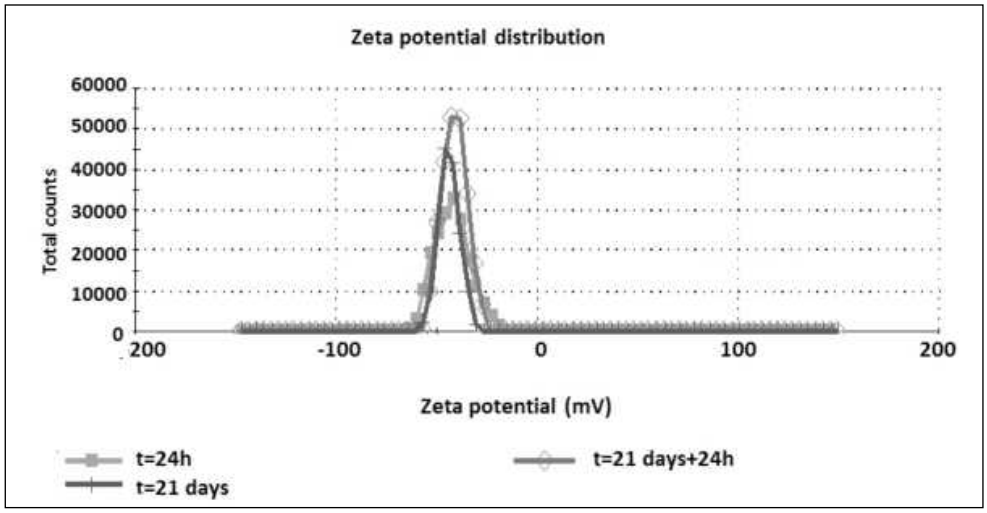


Fig. 4.—Zeta potential of admixtures TPN 14A – effect of store.

in comparing with t=0 (Fig. 4). The greatest decreasing of negative value of zeta potential (-6.8 mV) was noticed in admixture 14B, while the greatest increasing (10.4 mV) was in admixture 12C.

pH measurement

The pH values in complete TPN admixtures were in range 5.6 – 6.7. Comparing with t=0, these values did not change (±0.05 of units) during storage (Fig. 5). The greatest decreasing of pH value (0.11) was noticed for admixtures 8B and 11B at t=0+24h. The greatest increasing of pH values (0.10) was observed for admixtures 3C at t=21+24h.

Discussion

All investigated TPN admixtures were prepared with commonly using procedures in hospital pharmacy. Due to clinical needs, admixtures characterized much higher than physiological concentration of electrolytes: calcium (8-22 mmol/l Ca^{2+}), magnesium (5-20 mmol/l Mg^{2+}) and potassium (20-60 mmol/l K^{+}) ions. CAN parameter of investigated admixtures was much higher than current in range 1030 – 3000 mmol/l and CaxP was in range 76 - 574 $mmol^2/l^2$. Nitrogen – calorie ratio values was in range 158 – 255 kcal/g N. The highest CAN parameter was noticed in admixtures 14 (2947 mmol/l), whereas the smallest in admixtures 7 (1057 mmol/l).

Despite even repeatedly exceeded the limits specified parameters, most of TPN mixtures tested showed appropriate physical stability when during the analysis. These admixtures can be administered to the patient only when they are prepared with the same composition containing the same or a lower concentration of electrolytes. Of course, it is necessary to maintain identical conditions of preparing such mixtures and using the same manufacturers of packaging and type of product.

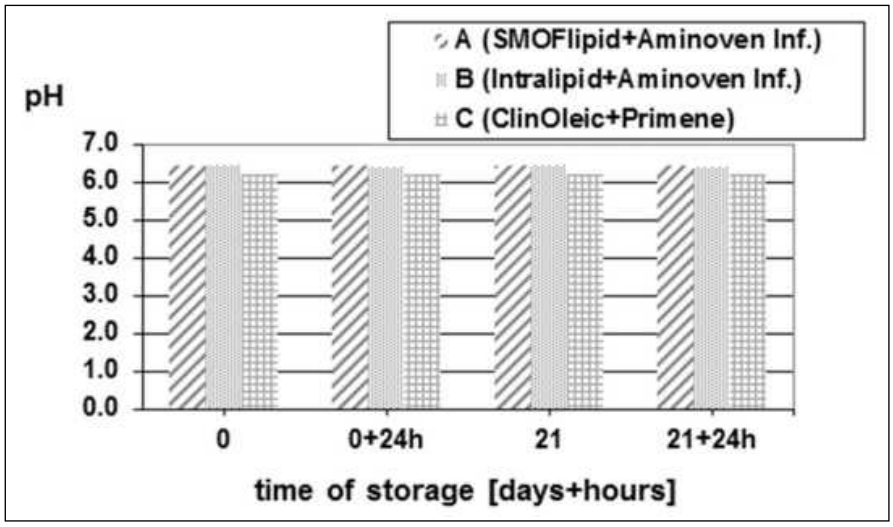


Fig. 5.—The pH values of the complete admixture TPN 14 – the effect of various lipid emulsion.

Very slight creaming after 24 h of storage at room temperature all admixtures was visually observed and it disappeared after short mixing. Creaming occurred in all admixtures despite various compositions so it was normally acceptable.

In microscopic observation all, except for two, complete admixtures were characterized by oily globules not larger than 3 μm, which are safe for patients when they are intravenously administered (Fig. 1). Only two complete admixtures (16A and 15B) in t=21 days+24h were found unstable because of few oily globules about 6 – 8 μm in size and tendency for agglomeration were observed (fig. 2). Lack of stability of these admixtures was checked in two independents studies.

Examination of the droplet size of the oil phase was carried out using a laser diffractometer. In all admixtures, except for two (Fig. 1), oily droplets larger than 1 μm were detected. Moreover, using this method no change droplet size of the oil phase during the storage of TPN admixtures up to 21 days was observed. Using LD method the presence of large droplets of oily phase observed in the optical microscope only for two unstable admixtures was confirmed. Whereas for others admixtures oily droplets in range 2-3 μm observed in the optical microscope was not confirmed. Most likely, this is due to the fact that too low a sensitivity of the device - in the whole volume of the TPN mixture containing droplets <1 μm is too small amount of large droplets of the oily phase.

PCS technique to give a more varied results mean droplet size of the oil phase, than when using laser diffraction – Z-average of oily droplet was approximately of 250 - 400 nm, whereas the laser diffraction method, the median of oily droplets was 300 - 330 nm. None of the systems tested was not noticed oily droplets larger than 1 μm using PCS method.

Based on the results, it was found that a more sensitive method for detecting the oily droplet size below 500 nm is the technique of PCS. In contrast, measurements should also be performed by laser diffraction method that allows to detect larger drops.

For such systems considered stable TPN admixtures with a negative zeta potential of 31 mV below [11]. All TPN admixtures showed a zeta potential in range -37 to -45 mV, which proves their stability. The zeta potential during storage do not undergo significant changes (Fig. 4). Fluctuations were observed in the range of ± 9 mV, the difference between the value at t=0 and t=21+24h are insignificant (about ±5 mV).

The pH values of TPN admixtures during storage did not undergo significant ($p<0.05$) changes (Fig. 5). Admixtures containing ClinOleic as fat emulsion showed a slightly lower pH (5.68 - 6.31) than the other admixtures of TPN (6.11 - 6.57).

No influence of the type of lipid emulsions and aminoacid preparations on the physical stability of the investigated TPN admixtures was observed. It also appeared to be safe to prepare TPN admixtures with high concentration of electrolytes using as well as Lipofundin LCT/MCT, SMOFlipid and ClinOleic.

Conclusions

Despite the store for 21 days and high concentrations of electrolytes pre-TPN admixture of the proposed composition provide complete TPN admixtures of appropriate quality, lasting for 24 hours. Only the admixtures kept for 21 days (15B and 16A) does not allow the stable TPN admixtures. Due to coalescence of the emulsion particles is desirable to shorten the retention time of the complete mixture of the TPN 15B and 16A to 24 h. Since the obtained stable TPN admixture having a high concentration of electrolytes (high CAN and CaxP parameters), theoretical values of these parameters cannot decide about the stability of TPN admixtures. Microscopic observation should be a part of physical analysis of TPN admixtures. Type a submicron emulsion and the preparation of amino acids does not affect the physical stability of TPN mixtures.

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Conflicts of Interest

The authors declare no conflict of interest.

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