EXPERIMENTAL INVESTIGATIONS

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Comparison of Long-Term Stability of Parenteral All-in-One Admixtures Containing New Lipid Emulsions Prepared Under Hospital Pharmacy Conditions

Michal Janů[1, 2], Helena Brodská[3], Marek Vecka[4], Ruta Masteiková[2], Eva Kotrlíková[5], Robertas Lažauskas[6], Rimantas Pečiūra[7], Jurga Bernatonienė[7]

[1]Hospital Pharmacy, General University Hospital in Prague, Czech Republic, [2]Department of Pharmaceutics, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences Brno, Czech Republic, [3]Institute of Clinical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic, [4]4th Department of Medicine – Department of Gastroenterology and Hepatology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic, [5]3rd Department of Medicine – Department of Endocrinology and Metabolism, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Czech Republic, [6]Department of Physiology, Medical Academy, Lithuanian University of Health Sciences, Lithuania, [7]Department of Pharmaceutical Technology and Social Pharmacy, Medical Academy, Lithuanian University of Health Sciences, Lithuania

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Summary. *All-in-one (AIO) admixtures for parenteral nutrition are common in hospital pharmacy practices. They are extemporaneously prepared and should be stable during preparation, storage, and administration. Lipid emulsion is a clinically important and very susceptible component of instability. The objective of study was to evaluate the long-term stability of AIO admixtures containing modern lipid emulsions.*

Material and methods. AIO admixtures with two different emulsions (SMOFlipid and Lipoplus) containing the same amount of glucose and complex amino acid solution, and variable amounts of ions were prepared. Samples were evaluated at 2, 5, 8 and 30 days after preparation. The main indicator of AIO system stability was the amount of lipid globules greater than 5 μm in diameter, which is limited by pharmacopoeia. Optical microscopy was used for particle size measurement.

Results. All prepared AIO admixtures remained stable during observation. The counts of over-limit lipid particles were within pharmacopeial limit nevertheless tended to increase in time. After 30-day storage, their value was influenced mainly by concentration of calcium ions, which at lower concentrations had a greater impact on SMOFlipid-based admixtures, whereas at the highest concentration on Lipoplus-based admixtures. The concentration of ions and osmolarity remained without changes; pH of admixtures slightly decreased.

Conclusions. Both lipid emulsions were found to be suitable for preparation AIO admixtures with different concentrations of electrolytes. The formulations were stable even if contained high concentrations of divalent ions. The comparison of emulsions revealed the superiority of Lipoplus – electrolyte concentrations and duration of storage had a greater impact on admixtures with SMOFlipid.

Introduction

All-in-one (AIO) admixtures, also known as total parenteral nutrition (TPN) or total nutrient admixtures, are parenteral nutrition (PN) formulations containing water, glucose (dextrose), amino acids, lipids, electrolytes, trace elements, and vitamins in a single container (1). Lipid emulsions belong to the main constituents of these admixtures. They are not only a valuable source of energy and essential fatty acids, but also may act as an effective modulator of the immune system (2–4) and inflammatory responses (4, 5). The evolution of parenteral lipid emulsions may be divided into three generations of products. The first generation is represented by conventional lipid emulsions based on soybean and/or safflower oil, very rich in ω-6 polyunsaturated fatty acids (PUFAs) (6). Mainly due to their side effects – they may be associated with increased rates of infection and lipid peroxidation, which can exacerbate oxidative stress (4) – new emulsions were developed. The second-generation parenteral lipid emulsions, respecting the potential disadvantageous

Correspondence to J. Bernatonienė, Department of Pharmaceutical Technology and Social Pharmacy, Medical Academy, Lithuanian University of Health Sciences, A. Mickevičiaus 9, 44307 Kaunas, Lithuania. E-mail: jurgabernatoniene@yahoo.com

Adresas susirašinėti: J. Bernatonienė, LSMU MA Vaistų technologijos ir socialinės farmacijos katedra, A. Mickevičiaus 9, 44307 Kaunas. El. paštas: jurgabernatoniene@yahoo.com

effects of the high levels of PUFAs, are represented by the physical and chemical (structured lipid emulsions) mixtures of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs), as well as the olive oil-containing lipid emulsions (6). The third-generation parenteral lipid emulsions are characterized by the inclusion of fish oil and designed according to a specific fatty acid pattern (6). Modern emulsions provide a mixture of lipids from different sources (2, 4, 7, 8).

TPN is an especially complex admixture commonly consisting of 40 and more components. Errors in PN formulation and compounding may lead to serious even lethal complications. That is why the design of PN formulation must consider the stability and compatibility of the constituents. In some cases, these considerations limit one's ability to individualize nutrient doses (9). The major stability and compatibility issues can be divided as follows: (i) physicochemical stability of the lipid emulsions; (ii) chemical instabilities due to incompatibility between amino acids and glucose in the aqueous phase of AIO mixture; (iii) precipitation of chemical components in the aqueous phase, mainly as calcium and phosphate interactions (10); and (iv) stability and compatibility of vitamins, trace elements, and added drugs (11).

Lipid emulsion is the most sensitive part of TPN. The stability of the lipid emulsion is maintained by mechanical and electrostatic repulsive forces counteracting the coalescence of small oil droplets dispersed by an emulsifying agent (9). One of the most important factors influencing physical stability of fat particles is zeta potential. Each oil droplet within the lipid emulsion is coated with a layer of phospholipids, which provides a negative surface charge (zeta potential), and this reduces the aggregation of particles, which prevents the coalescence and formation of large droplets. Each additive of AIO initially diffuses into the outer layer of the droplet, altering the surface charge. Surrounding medium pH, electrolytes, trace elements, and other additives may reduce the repulsive forces among the particles resulting in aggregation (seen as creaming), which may lead to coalescence and larger droplet formation (1).

Physical stability of the lipid emulsion in TPN formulations is influenced firstly by the ion strength of electrolytes – it has a major effect on the zeta potential of emulsion (9). Trivalent and divalent cations are more disruptive than monovalent ones (11). The critical aggregation number (CAN) is associated with cationic concentrations at which lipid particles aggregate. Calculation of the CAN is accomplished using the following formula (12):

$$CAN=a+64\times b+729\times c,$$

where a stands for monovalent, b for divalent, and c for trivalent cation molar concentrations.

This measure equals to the total amount of cations expressed as monovalent cations, and it should be less than 600 mmol/L (13). The ratio of monovalent, divalent, and trivalent cations is a practical approach for use by a compounding pharmacy.

The next factor influencing the stability of emulsion is pH of formulation. Native (concentrated) lipid emulsions are formulated at pH of 6–8 (12). Once the lipids are mixed as a TPN, the pH of admixture decreases because of other additives (glucose, amino acids, electrolytes) (14). Emulsion instability usually occurs when the pH of the admixture is less than 5.5; when pH falls below 5.0, lipid emulsion stability decreases (1). Acidic amino acids may destabilize AIO by decreasing surface potential. That is why amino acid products with pH 5.5 or lower should not be used to compound the TPN (12).

Furthermore, the quality of emulsion may be affected by the composition of oil phase particularly by the character of component oils. Emulsions consisting of LCTs only are least stable (15). TPN containing structured lipids (both medium-chain fatty acids and long-chain fatty acids are esterified to the same glycerol molecule) proved to be more stable, especially at lower storage temperatures (7). Driscoll et al. reported that MCTs when they are made as a physical oil mixture have a positive impact on the stability of AIO formulations (16, 17), which is in case of modern lipid emulsions.

The physicochemical stability of lipid emulsions is vital to their safety (7). The main indicator of the emulsion system stability is the size of fat globules – particles of internal phase of emulsion. Ideally, an intravenous emulsion has a mean droplet size similar to natural chylomicrons, i.e., approximately 0.3 μm, and a narrow range of globule size distribution (1, 7). Of particular concern is the population of large-diameter fat globules capable of occluding the microvasculature. As the internal diameter of human capillaries is 4–9 μm, fat globules with a similar diameter may cause a fat embolism (7, 14). However, it should also be taken into consideration that oil droplets are biologically degradable, and thus a small number of larger particles would seem to be tolerable (18). The U.S. Pharmacopeia (USP) has established the globule-size limits for all commercial intravenous nutritional lipids in Chapter 729 and in an accompanying monograph (19). These limits involve the mean droplet diameter (MDD) and the large-diameter tail ($PFAT_5$), expressed as the volume-weighted percent of fat greater than 5 μm (19). The number of large-diameter fat globules in any lipid emulsion should be minimized and primarily influenced by the manufacturer or final user (14).

SMOFlipid and Lipoplus belong to the third-generation parenteral lipid emulsions. Both emulsions contain 20% of oil phase. SMOFlipid is based on a physical mixture of soybean oil, MTC (coconut oil), olive oil, and fish oil (ratio, 30:30:25:15) (2, 4). Mixing four different oils optimizes the fatty acid profile and is in accordance with the current recommendations that new lipid emulsions should be composed of a reduced content of ω-6-fatty acids and counterbalanced by MCT, monounsaturated fatty acids (MUFA), and long-chain ω-3-fatty acids (2). Lipoplus contains soybean oil, MTC (coconut oil), and fish oil (ratio, 40:50:10) (4). Soybean oil provides essential fatty acids, MCT is a good source of rapidly available energy sparing larger amounts of essential fatty acids for incorporation into cell membranes, and fish-oil-derived long-chain ω-3-fatty acids influence the inflammatory reaction potential of cells (2). Olive oil in SMOFlipid has an indirect anti-inflammatory effect by replacing ω-6-fatty acids with oleic acid and is less prone to peroxidation than PUFA (2).

Clinical safety and efficacy of emulsions SMOFlipid and Lipoplus have been sufficiently evidenced in the number of clinical studies (2, 4, 20–24). Nevertheless, only few studies aimed to evaluate these emulsions in TPN admixtures from the point of stability and compatibility (16, 17, 25), and none study was carried out with the aim to compare SMOFlipid and Lipoplus in AIO formulations. Thus, the objective of the study was to evaluate the long-term stability of AIO admixtures containing these modern lipid emulsions.

Material and Methods

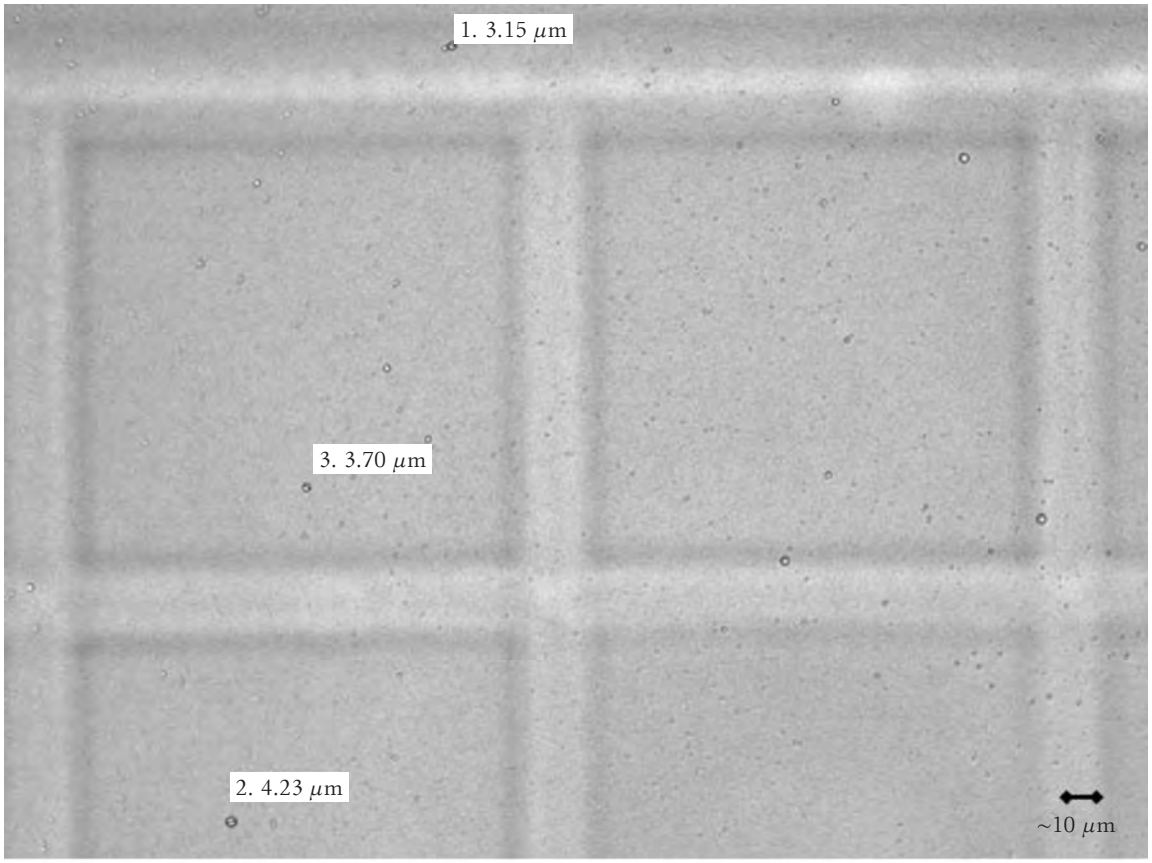
Materials. The following components of TPN admixtures were available as sterile and apyrogenic injections/infusions from the pharmaceutical industrial companies: SMOFlipid (Fresenius Kabi AB, Sweden), Lipoplus (B. Braun Melsungen AG, Germany), Neonutrin 15% (Fresenius Kabi, Czech Republic), Ardeanutrisol G 40 (Ardeapharma Inc., Czech Republic), Ardeaelytosol conc. kaliumchlorid 7.45% (Ardeapharma Inc., Czech Republic), Ardeaelytosol conc. natriumchlorid 10% (Ardeapharma Inc., Czech Republic), Calcium inj. sol. 10×10 mL/1 g Biotika (Hoechst-Biotika Ltd, Slovakia), Magnesium sulfuricum Biotika 10% (Hoechst-Biotika Ltd, Slovakia), Addamel N (Fresenius Kabi AB, Sweden). The dibasic potassium phosphate solution (Kalii dihydrogenphosphatis inf. conc. 13.6%) was prepared extemporaneously at the Hospital Pharmacy, General University Hospital in Prague.

Preparation of Admixtures. All AIO admixtures were prepared at the Hospital Pharmacy, General University Hospital in Prague. The experimental conditions simulated the real processes during the preparation of TPN in the hospital pharmacy. The formulations were prepared aseptically under clean room conditions. Defined contents of single preparations were transferred from the individual containers to the final delivery container (ethylene vinyl acetate bag) using an automated admixing device Automix® (Baxter International, Dierfield, USA). The compounding procedures followed the common guidelines for TPN preparation (26). All admixtures contained the same amount of lipid emulsion (SMOFlipid or Lipoplus), solutions of glucose, amino acids, sodium chloride, potassium chloride, and trace elements, and the varied amounts of calcium gluconate, magnesium sulphate, and dibasic potassium phosphate solutions (Table 1). The first group of admixtures with SMOFlipid included 64 formulations, where the different amounts of abovementioned electrolyte solutions were added in a 4×4×4 combinational design. To the admixtures with Lipoplus (second group, 16 formulations), the electrolytes were added in the selected combinations following the Latin square design for ANOVA analyses. The prepared admixtures were stored in a refrigerator at 2–8°C (temperature was monitored by Regucon® system). Before the evaluation of particle size, the admixtures were stored 24 hours at room temperature (23–25°C), which simulated the clinical conditions.

Visual Inspection. Macroscopic examination of all samples was made at all measurement intervals, i.e., 2 days, 5 days, 8 days, and 30 days after preparation, starting with $t=0$ hours by visual inspection. The examination inspected the infusion bags for signs of creaming (dense white layer at the surface of a mixture) or the presence of free oil, and after rigorous agitation, the occurrence of gross precipitation was monitored. The test samples were placed against a dark background, and any visual observations were recorded using the strong light.

Table 1. Composition of All-in-One Admixtures

Component	Amount, mL
Lipid emulsion:	
(1) SMOFlipid	250
(2) Lipoplus	250
Glucose 40% solution (Ardeanutrisol G 40)	500
Amino acids:	
Neonutrin 15%	500
Electrolytes:	
NaCl 10% solution	10
KCl 7.45%	10
Calcium gluconate 10% solution	10–40
$MgSO_4$ 10% solution	10–40
KH_2PO_4 13.6% solution	10–40
Trace elements:	
Addamel N (Cr, Cu, Fe, Mn, I, F, Mo, Se, Zn)	10



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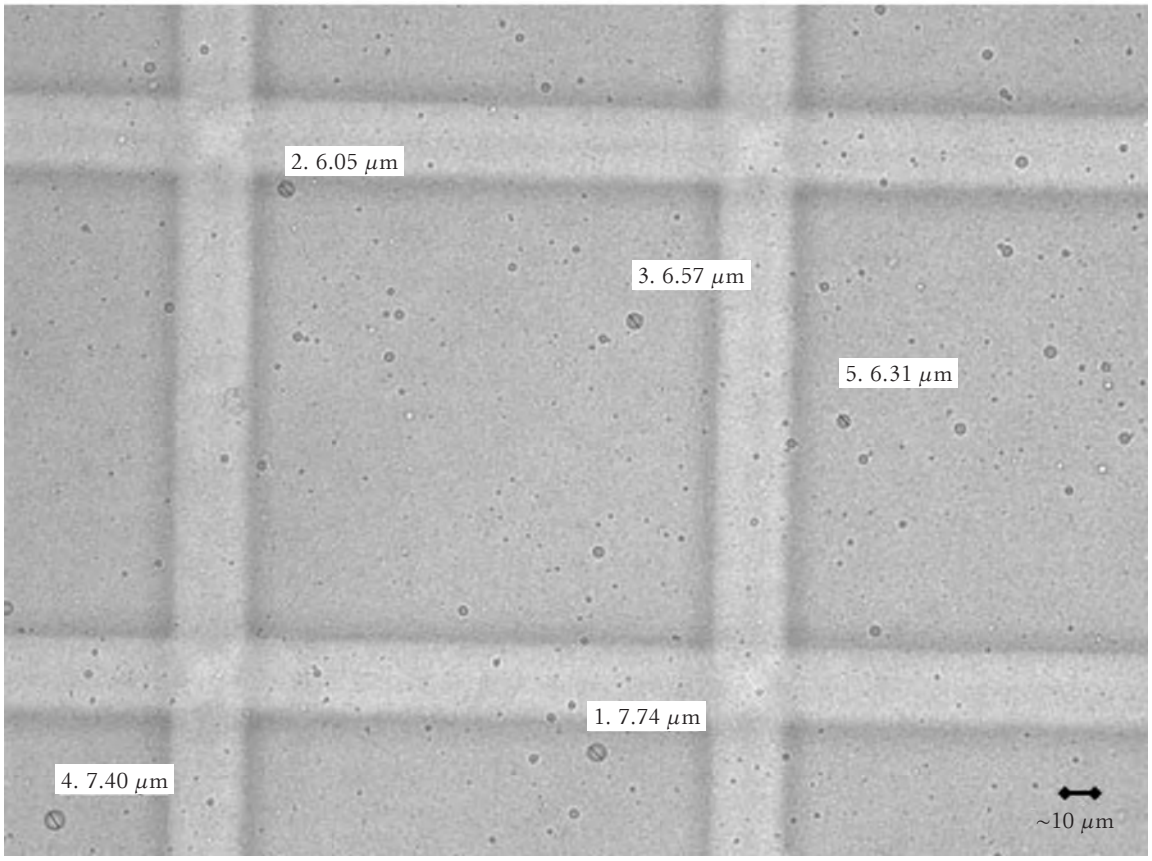

B

Fig. 1. Photographs from microscope
A, AIO admixture with Lipoplus without over-limit particles (sample 6, day 8 after preparation);
B, AIO admixture with SMOFlipid (sample 8, day 30 after preparation).

Measurement of Particle Size. The microscopic evaluation of admixtures comprised the measurement of emulsion internal phase particles size and determination of the amount of fat globules greater than 5 μm and solid particles. Each infusion bag was gently agitated before sampling to ensure the homogenity of the sample. An optical microscope (Leica Microsystems Launches Branding Campaign, Germany), which was equipped with camera and computer software for image analysis transmitted on the monitor, was used. A counting chamber Fast read with a defined reading volume of 1 μL (Biosigma S.r.l., Italy) served for the precise quantification of over-limit particles. The preparations were observed under passing light, and the measurements were performed under 400-fold magnification. A counting chamber was divided into 50 squares, which enabled to count and measure all lipid globules greater than 5 μm or solid particles. The photographs from microscope (Fig. 1) illustrate the measurements. The data were expressed as the mean of triplicate sample measurement.

Evaluation of pH, Osmolarity, and Ion Content. Measurements were made after the preparation of admixtures and at the end of observation, i.e., after 30-day storage. pH values were measured using an InoLab® Level 2 pH/mV meter (Wissenchaftlich Technische Werkstatten, Wilheim, Germany). Osmolarity was calculated based on osmolality values obtained by an Advanced® Model 2020 osmometer (Advanced Instruments Inc., Two Technology Way, USA). Analysis of the ion content was carried out at the Department of Clinical Biochemistry, Institute of Clinical Biochemistry and Laboratory Diagnostics, Charles University in Prague, in accordance with routine procedures.

Microbiological Evaluation. The proof of sterility was performed after 30-day storage according to the Ph. Eur. Ed. 6, chap. 2.6.1., at the Department of Medical Microbiology, Institute of Immunology and Microbiology, Charles University in Prague.

Statistical Analysis. Experimental data (transformed to natural logarithms where appropriate) were subjected to the analysis of variance (ANOVA) and ANOVA with the Latin square design. The calculations were done with the help of STATISTICA® for Windows software (Statsoft s.r.o., Prague, Czech Republic). The nonparametric correlations (Spearman) were calculated with the help of the same software, and for the trend analyses, the Page test for ordered alternatives was applied. *P* values less than 0.05 were considered significant.

Results

All AIO admixtures showed the homogenous distribution of lipid emulsion at all the time points of observation, i.e., they appeared to be "milky" white and opaque with a nonreflective surface, and there was also no evidence of precipitation.

Microscopic evaluation of TPN admixtures proved the sufficient quality of formulations containing SMOFlipid or Lipoplus during the storage. The amount of over-limit particles in 1 μL was found within a range of 0–425 particles in all the samples. Fig. 2 demonstrates the changes of this parameter in 16 selected samples at the different points of observation. Samples had the same composition except the type of emulsion. Fig. 3 illustrates the amount of ions in the corresponding samples.

The relationship of the over-limit particle count with the initial value (on day 2) tended to weaken over time (more pronounced in the SMOFlipid samples) (Tables 2 and 3). The strongest correlation between the over-limit particle count and concentrations of selected ions was observed in case of Ca^{2+} for the Lipoplus samples as well as between the over-limit particle count and CAN (Table 3).

The ANOVA analysis revealed the influence of lipid emulsion type on quality after 30-day storage (ANOVA; $P=0.0010$) was as well as the presence of interaction between the type of lipid emulsion and concentration of calcium ions (ANOVA; $P=0.0355$). Post hoc analyses indicate that the certain concentrations of calcium ions (4.5 and 6.8 mmol/L, samples 5–12 in Figs. 2 and 3) could increase the amount of over-limit particles in the SMOFlipid type of emulsion on day 30 in comparison with the other concentrations (2.3 and 9.0 mmol/L). The same conclusion cannot be drawn for the data points on days 5 and 8 as the amount of over-limit particles in sample 12 was highest among all the Lipoplus emulsion samples, and this count was higher as compared with the analogous samples with SMOFlipid.

The concentrations of electrolytes in AIO admixtures remained without changes during the storage. After preparation, osmolarity was within the range of 1358–1416 mosmol/L for TPN with SMOFlipid and 1364–1422 mosmol/L for admixtures with Lipoplus. These values did not differ significantly from theoretically calculated and remained at the same level after 30-day storage.

pH values of AIO admixtures ranged from 5.85 to 6.33 for SMOFlipid and from 5.71 to 6.26 for Lipoplus after preparation. During the storage, these values tended to decrease and after 30-day storage decreased to 5.48–6.01 (SMOFlipid) and 5.57–6.08 (Lipoplus).

The sterility test performed after 30-day storage proved that none of AIO admixtures contained tested microorganisms, i.e., they were sterile.

Discussion

The significance of nutrition in the hospital setting cannot be underestimated. AIO admixtures

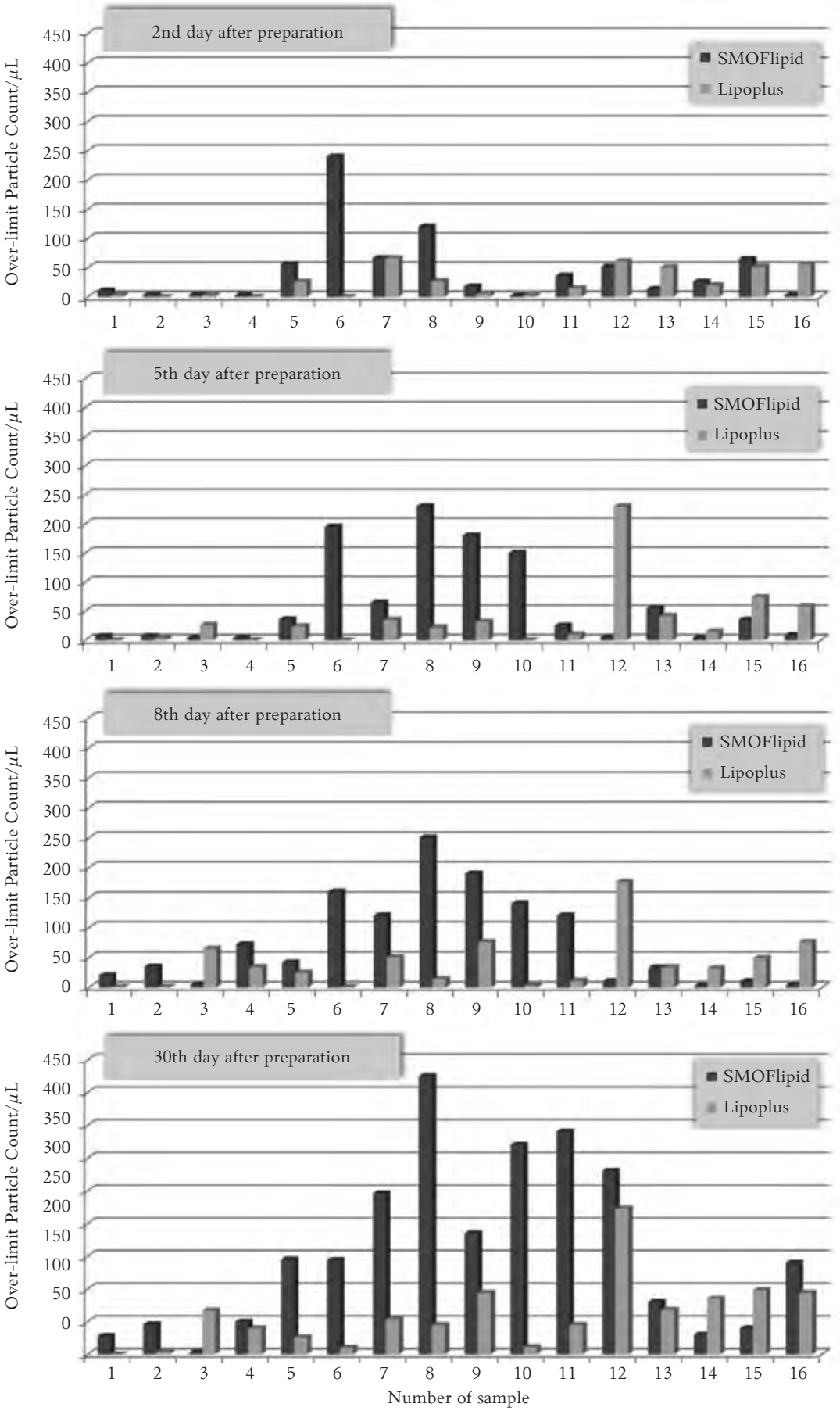

Fig. 2. The over-limit particles count in selected AIO admixtures during the storage

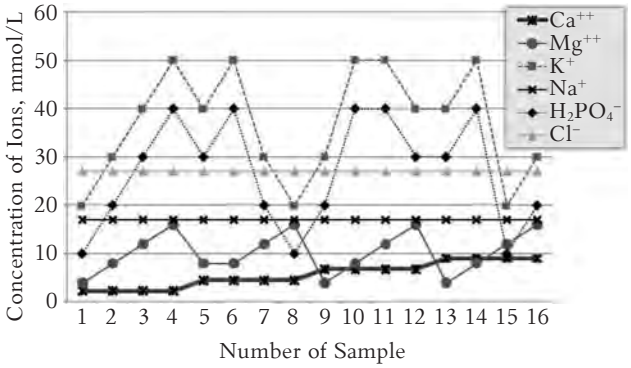

Fig. 3. Concentration of different ions in selected AIO admixtures

provide safe, effective, and low-risk PN for practically all indications and applications (26). Nevertheless, total complete admixtures, which are true ready-to-use PN, are not commercially available yet due to physicochemical instabilities. Industrially prepared multichamber bags, with established standard compositions, often are an attractive method of providing PN (14). They are beneficial in the short-term PN treatment of hospitalized adults (26). Individual compounding, which takes into account the specific needs of selected groups of patients, e.g., infants (especially preterm born) and children, critically ill patients, patients who reveive long-term home PN, etc., is, however, still required. Smolkin et al. reported that very low birth weight infants who received individualized PN showed a significantly greater weight gain, had shorter durations of exclusive PN, and needed fewer electrolyte corrections in comparison with infants who received standard PN (27). However, the adaptation of AIO admixtures to meet individual patient's requirements and at the same time to possess the criteria of microbiological and physicochemical quality and stability is not simple and requires specialized pharmaceutical knowledge. That is why the pharmacist is commonly a member of hospital nutrition team.

As mentioned above, lipid emulsion has a key position in AIO system from the aspect of stability. Therefore, an evaluation of the quality of TPN admixtures must primarily focus on the emulsion stability. The particle size diameter best characterizes the emulsion stability. Both the mean particle size diameter and percent of fat greater than 5 μm are vital for the parenteral infusions. The upper pharmacopeial limit (USP) for the mean droplet size is 500 nm, and the volume-weighted percent of fat greater than 5 μm ($PFAT_5$) must be less than 0.05% (7, 14). Although these limits refer to commercial, injectable lipid emulsions, regardless of the final concentration of lipids in the dispersed phase (14), the same values may be applied to extemporaneously compounded TPN admixtures at evaluation of their quality and stability too.

Different methods may be used for the measurement of particles size (28), e.g., laser light scattering, photon correlation spectroscopy, electrical zone sensing, light obscuration, etc. The USP chapter 729 mentions dynamic light scattering (for mean droplet diameter) and light obscuration (for large-diameter tail of droplet-size distribution) (14). These methods offer precise and reliable results, however, require an expensive apparatus, which is often unavailable in the common hospital pharmacy or at the hospital department. Optical (light) microscopy is an easily available method. Naturally, this method has some limitations. Firstly, it makes impossible the measurement of submicron particles, thereby the determination of mean droplet diameter in parenteral emulsions. Secondly, the shortcom-

Table 2. Relationship Between Over-Limit Particle Count and Selected Parameters in Admixtures With SMOFlipid Emulsion

	Day 5 count/μL	Day 8 count/μL	Day 30 count/μL	K^+ mmol/L	Ca^{2+} mmol/L	Mg^{2+} mmol/L	$Ca^{2+} + Mg^{2+}$ mmol/L	CAN mmol/L
Day 2 count/μL	0.529***	0.356**	0.187	0.085	–0.162	–0.044	–0.135	–0.121
Day 5 count/μL		0.728***	0.451***	0.089	–0.180	–0.084	–0.171	–0.157
Day 8 count/μL			0.438***	0.096	–0.190	–0.165	–0.265*	–0.252*
Day 30 count/μL				0.089	–0.036	0.426***	0.338**	0.349**

Spearman rank order correlation coefficient (n=64).
***P<0.001, **P<0.01, *P<0.05; CAN, critical aggregation number.

Table 3. Relationship Between Over-Limit Particle Count and Selected Parameters in Admixtures With Lipoplus Emulsion

	Day 5 count/μL	Day 8 count/μL	Day 30 count/μL	K^+ mmol/L	Ca^{2+} mmol/L	Mg^{2+} mmol/L	$Ca^{2+} + Mg^{2+}$ mmol/L	CAN mmol/L
Day 2 count/μL	0.856***	0.626**	0.702***	–0.393	0.572*	0.337	0.582*	0.570*
Day 5 count/μL		0.821***	0.868***	–0.401	0.556*	0.281	0.489	0.479
Day 8 count/μL			0.880***	–0.153	0.378	0.402	0.504	0.496
Day 30 count/μL				–0.140	0.692**	0.336	0.631**	0.627**

Spearman rank order correlation coefficient (n=16).
***P<0.001, **P<0.01, *P<0.05; CAN, critical aggregation number.

ing of microscopic techniques is the poor statistics obtained for a given measurement (7), because the sample analyzed includes a small amount of preparation (e.g., one drop, 1 μL). Morever, measurements are burdened by some factor of subjectivity. Driscoll et al. applied differential interference contrast light microscopy as a comparative evaluation to the methods proposed in the USP chapter 729 (29). Nevertheless, in the case of measurement of over-limit particles for a longer time interval, optical microscopy may offer sufficient information for evaluation of emulsion stability, particularly if the formulation studies are carried out. That is why the stability of AIO admixtures in our experiment was observed for a period of one month although in general the expiration of TPN admixtures is a few days (26). Our assumption was that if the amount of over-limit particles remains within limits and without greater fluctuations for all the time of observation, it is possible that the composition of AIO admixture is stable and safe for application. This assumption also relies on the statement of Gonyon et al. that the most precise method of determination of the lipid emulsion stability with respect to globule size requires a size-frequency analysis as a function of time (30).

Observing that the stability of lipid emulsion is influenced firstly by the ion strength of electrolytes, four concentrations of three ions were used: Ca^{2+}, Mg^{2+}, and K^{+} (Fig. 3). The levels of Na^{+} and Cl^{-} were kept constant, and $H_2PO_4^{-}$ level corresponded to K^{+}. The critical aggregation number (CAN) was within the range of 364–1247 mmol/L for all the samples. However, the most of admixtures studied had a CAN value near the critical level of 600 mmol/L or greater in order to evaluate modern emulsions also under extreme conditions.

In this study, Neonutrin 15% as a complex amino acid solution was used (Table 4). This nutritive solution of Czech origin showed a good tolerance and safety with a minimal risk of adverse effects (31, 32). The possibility to deliver high amounts of amino acids in case the reduced volume of intravenous liquid is required is considered as one of its benefits. Neonutrin 15% is suitable for preparation of TPN; however, the evaluation of compatibility with other components including lipid emulsion is necessary.

Native (commercial) lipid emulsions are very concentrated formulations (i.e., contain 10%–30% w/v of fat) and may contain 4 000–4 000 000 fat globules that are $\geqslant$5 μm in diameter per mL; nevertheless, not all of them meet pharmacopeial requirements (14). According to Driscoll, stable injectable lipid emulsions, which meet the USP chapter 729 limits for the larger-diameter tail, i.e., $PFAT_5$<0.05%, contain approximately between 10^4 and 10^5 over-limit particles per mL (7); for TPN admixtures, this amount was approximately 10^4 in most cases (7, 14). AIO admixtures in our experiment did not exceed this level, although the over-limit particle count was increasing in both types of tested lipid emulsions (Page test for trend, P=0.0001 for SMOFlipid and P=0.0003 for Lipoplus). Formulations with Lipoplus contained fewer large particles than those with SMOFlipid (Fig. 2). The amount of over-limit particles per μL in samples with Lipoplus was between 0 and 223, and besides sample 12, which averted from the line, was between 0 and 98 for all the time of observation, which conform to 10^4 per mL and accord with the results of Driscoll (7, 14) for stable TPN. Samples 6 and 10 contained from 0 to 4 large particles up to day 8 after preparation, and samples 1 and 2 maintained this amount up to day 30. Admixtures with SMOFlipid contained between 3 and 425 over-limit particles, and none sample was without them. As Fig. 2 and 3 show, the certain concentrations of calcium ions (4.5 and 6.8 mmol/L – samples 5–12) had the greatest impact on high fat globule amount in formulations with SMOFlipid. It is consistent with literature data (1, 12) that AIO admixtures with the lowest calcium concentration were most stable (2.3 mmol/L, samples 1–4). Surprisingly, the stability was higher at the highest concentration of calcium ions (9.0 mmol/L, samples 13–16): both the admixtures with SMOFlipid and Lipoplus contained 10^4

Table 4. Composition of Neonutrin 15%

Component	Value
Isoleucine, g	7.5
Leucine, g	12.0
Lysine monohydrate, g	12.15
Methionine, g	5.25
Phenylalanine, g	9.75
Threonine, g	6.6
Tryptophan, g	3.3
Valine, g	10.5
Histidine, g	5.25
Acetylcysteine, g	1.8
Cystine, g	0.4
Glycyltyrosine dihydrate, g (amount to 2.97 g of tyrosine and 1.23 g of glycine)	4.5
Tyrosine, g	0.3
Alanine, g	9.0
Arginine, g	13.5
Aspartic acid, g	5.25
Asparagine monohydrate, g	6.0
Glutamic acid, g	15.0
Glycine, g	8.25
Proline, g	9.0
Serine, g	6.0
Water for injection	addition to 1000 mL
Total amount of amino acids, g/L	148.7
Total nitrogen, g/L	22.3
Energetic value, kJ/L (kcal/L)	2552 (622)
Theoretic osmolarity, mosmol/L	approximately 1144
pH	6.0–7.2

over-limit particles per mL up to day 8, admixtures with Lipoplus even up to the end of observation, although as a whole this concentration influenced formulations with Lipoplus more strongly (P=0.0355). A certain possible explanation has been mentioned by Chaumeil and Brossard, who found that the critical concentration of calcium in parenteral mixtures is between about 3.5 and 7 mmol/L (33). Nevertheless, in our study, this explanation may be applied only to the admixtures with SMOFlipid, because it was not possible to confirm this factor in case of formulations containing Lipoplus, except sample 12. Most probably, a high CAN value (1146 mmol/L) could have a certain impact – it was the second highest; however, in the presence of the highest CAN (1236 mmol/L), the amount of over-limit particles in admixtures Lipoplus remained low during all the time of observation (sample 16, Fig. 2) as well as in the case of other exceeding CAN values, e.g., 1050 mmol/L (sample 15), 1034 mmol/L (sample 8), or 973 mmol/L (sample 11). Higher CAN values had a greater impact on admixtures with SMOFlipid: at day 30 of storage, the amount of over-limit particles per μL in formulations with CAN of <600 mmol/L (n=19) and CAN of >600 mmol/L (n=45) was 96.4±74.3 and 160.7±109.3, respectively (t test for unequal variances, P=0.0493). For these reasons, SMOFlipid, as a safe component, should be used for the preparation of TPN with lower CAN and divalent cation levels. In spite of promising results with extreme divalent ion concentrations, additional data confirming the suitability of SMOFlipid as well as Lipoplus for AIO admixtures are required and it will be the aim of our futher studies.

After preparation, pH of admixtures was between 5.71 and 6.33 for all preparations, which is consistent with literature data (14). During the storage, these values decreased to 5.48–6.08. Admixtures with SMOFlipid showed a slightly greater downtrend of pH values (Fig. 4), which may be indicative of lower stability as compared with Lipoplus.

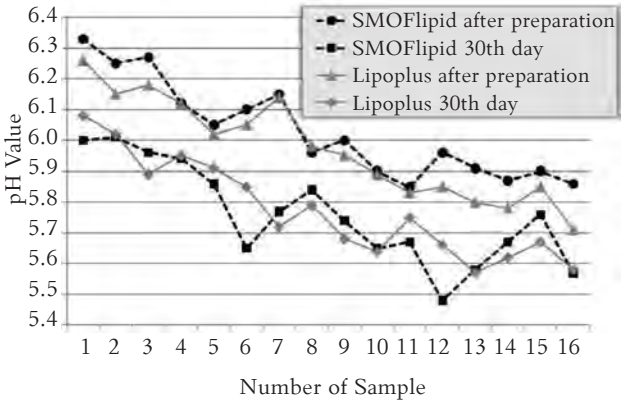

Fig. 4. Variations in pH of AIO admixtures during the 30-day storage

Conclusions

Our study confirmed the suitability of modern lipid emulsions SMOFlipid and Lipoplus for the preparation of stabile AIO admixtures. The findings that the formulations were stable in spite of high concentrations of electrolytes have an important practical consequence for the TPN preparation for critically ill patients as well as for pediatric and neonatology patients, where the special concentrations of different ions (especially calcium) in a reduced volume of preparation are often required. Despite both the emulsions showed satisfactory results, their comparison revealed the superiority of Lipoplus to SMOFlipid.

Statement of Conflict of Interest

The authors state no conflict of interest.

Ligoninės vaistinėje pagamintų parenterinių mišinių *all-in-one* su naujomis lipidų emulsijomis ilgalaikio stabilumo palyginimas

Michal Janů[1, 2], Helena Brodská[3], Marek Vecka[4], Ruta Masteiková[2], Eva Kotrlíková[5], Robertas Lažauskas[6], Rimantas Pečiūra[7], Jurga Bernatonienė[7]

[1]Bendrosios universiteto ligoninės Prahoje Ligoninės vaistinė, Čekija, [2]Brno Veterinarijos ir farmacijos mokslų universiteto Farmacijos fakulteto Vaistų technologijos katedra, Čekija, [3]Prahos Karlo universiteto 1-ojo medicinos fakulteto Klinikinės biochemijos ir laboratorinės diagnostikos institutas ir Bendroji universiteto ligoninė Prahoje, Čekija, [4]Prahos Karlo universiteto 1-ojo medicinos fakulteto 4-asis medicinos institutas – Gastroenterologijos ir hepatologijos katedra ir Bendroji universiteto ligoninė Prahoje, Čekija, [5]Prahos Karlo universiteto 1-ojo medicinos fakulteto 3-iasis medicinos institutas – Endokrinologijos ir metabolizmo katedra ir Bendroji universiteto ligoninė Prahoje, Čekija, [6]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Fiziologijos katedra, Lietuva, [7]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Vaistų technologijos ir socialinės farmacijos katedra, Lietuva

Raktažodžiai: parenterinis maitinimas, *all-in-one*, lipidų emulsija, stabilumas.

Santrauka. Parenterinės mitybos mišiniai *all-in-one* (AIO) įprasti ligoninės vaistinės praktikoje. Jie yra gaminami ekstemporaliai ir turi išlikti stabilūs gamybos, laikymo ir vartojimo metu. Lipidų emulsija yra kliniškai svarbus ir didelę įtaką nestabilumui turintis komponentas.

Tyrimo tikslas. Įvertinti mišinių AIO, savo sudėtyje turinčių modernių lipidų emulsiją, stabilumą.

Tyrimo medžiaga ir metodai. Pagaminti parenterinės mitybos AIO mišiniai savo sudėtyje turintys dvi skirtingas emulsijas (SMOFlipid ir Lipolus) su tuo pačiu kiekiu gliukozės ir kompleksinio aminorūgščių tirpalo bei įvairiomis jonų koncentracijomis. Mėginiai buvo vertinti po jų pagaminimo praėjus 2, 5, 8 ir 30 dienų. Pagrindinis rodmuo, vertinant AIO sistemos stabilumą, buvo farmakopėjoje reglamentuotas lipidų lašelių, didesnių nei 5 μm diametro, kiekis. Dalelių dydis buvo matuojamas optiniu mikroskopu.

Rezultatai. Visi paruošti AIO mišiniai visą tyrimo laikotarpį buvo stabilūs. Didesnių lipidų lašelių skaičius, tenkinęs farmakopėjoje esančius rodmenis, vis dėlto tendencingai didėjo. Po 30 dienų stebėsenos, jų reikšmėms daugiausia įtakos turėjo kalcio jonų koncentracija, mažesnė jų koncentracija didesnę įtaką turėjo SMOFlipid, o didžiausia koncentracija – Lipoplus tipo mišiniams. Jonų koncentracija ir osmolingumas preparatuose išliko nepakitęs, pH reikšmė mišiniuose nežymiai sumažėjo.

Išvados. Nustatyta, kad abi emulsijos yra tinkamos AIO mišiniams su skirtingos koncentracijos elektrolitais ruošti. Pagaminti pavyzdžiai, turintys netgi didelę dvivalenčių jonų koncentraciją, buvo stabilūs. Emulsijų palyginimas parodė Lipoplus privalumą, nes mišiniams su SMOFlipid saugojimo metu daugiau įtakos turėjo elektrolitai.

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