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Article

Existence of advanced glycation / lipoxidation end-products in parenteral nutrition solutions and effects of infusion conditions on their levels

Nurettin Kahramansoy[1*], Mustafa Çelebier[2]

[1]Department of Surgery, Faculty of Medicine, Abant İzzet Baysal University, Bolu, TÜRKİYE,
[2]Department of Analytical Chemistry, Faculty of Pharmacy, Hacettepe University, Ankara, TÜRKİYE

Infusion solutions must be stable from the production stage until the infusion stage. Some infusion fluids contain degradation products, known as advanced glycation end products (AGEs); however, it is unknown whether AGEs exist in parenteral nutrition solutions. We aimed to investigate this question and test the effect of infusion conditions on AGE formation in parenteral nutrition solution. Nine parenteral nutrition solutions were supplied by the pharmacy with which we collaborated. To simulate the infusion conditions, the solutions were held in a patient room with standard lighting and temperature for 24 hours. Samples were taken at the beginning (group A) and the end (24th hour, group B) of the infusion period. The degradation products were 3-deoxyglucosone, pentosidine, N-carboxymethyl lysine, and 4-hydroxynonenal, which we investigated by high-performance liquid chromatography-mass spectrometry (LC-MS) and Q-TOF LC/MS methods. Two of four degradation products, 4-hydroxynonenal and N-carboxymethyl lysine, were detected in all samples, and Group B had higher levels of both compounds compared to Group A, who showed that the quantities of these compounds increased in room conditions over time. The increase was significant for 4-hydroxynonenal ($p=0.03$), but not for N-carboxymethyl lysine ($p=0.23$). Moreover, we detected in the parenteral nutrition solutions a compound that could have been 4-hydroxy-2-butynal or furanone.

Keywords: Degradation products. Parenteral nutrition solution. Advanced glycation end-products. N-carboxymethyl lysine. 4-hydroxynonenal.

INTRODUCTION

Infusion solutions must maintain stability from the start of the production process through to the transport, storage, and infusion stages. During the production process, irradiation and the heat generated may cause oxidation and lipid peroxidation (Bryland *et al.*, 2010; Tovsen *et al.*, 2015; Steger, Mühlebach, 1997). Suboptimal handling conditions (e.g., temperature, daylight, long storage period) also affect stability (Hoff, Michaelson, 2009; Turmezei *et al.*, 2015; Thomovsky *et al.*, 2008). Furthermore, the composition of the infusion solutions affects the stability of the product, especially in the parenteral nutrition solution (PNS) (Allwood, Kearney, 1998; Jalabert *et al.*, 2011). There must be (an) optimum ratio(s) and compatibility between the compounds in an infusion bag (Allwood, Kearney, 1998; Jalabert *et al.*, 2011). Such destabilizing factors cause degradation products that are toxic to the body to emerge in infusion solutions containing dextrose and peritoneal dialysis solutions (Bryland *et al.*, 2010; Kawanishi *et al.*, 2013). These products are generally defined as glucose degradation products (GDPs), advanced glycation end-products (AGEs), and advanced lipoxidation end-products (ALEs), some of which are 3-deoxyglucosone (DG) and Nε-(1-Carboxymethyl)-L-lysine (CML) (Bryland *et al.*, 2010; Kawanishi *et al.*, 2013).

Major sources of GDPs, AGEs, and ALEs are heat-processed foods and in vivo degradations (Poulsen *et*

***Correspondence:** N. KAHRAMANSOY. Department of Surgery. İzmir Bozyaka Education and Research Hospital. Post Code: 35170, Karabağlar, İzmir, TÜRKİYE. Phone: +90 533 8108137. Fax**:** +90 232 2614444. E-mail: nurkahramansoy@gmail.com. ORCID: https://orcid.org/0000-0001-8990-5073

al., 2013). However, infusional therapy in a patient is another source of a number of degradation products (Bryland *et al.*, 2010). They have been identified in many cellular and systemic pathological processes of diabetes, atherosclerosis, chronic degenerative diseases, Alzheimer's dementia, Parkinson's disease, and cancer (Ajith, Vinodkumar, 2016). With regard to the acute effects of AGEs, AGEs potentiate the proinflammatory response, which results in ischemia/reperfusion injury and apoptosis (Watanabe *et al.*, 2020; Yang *et al.*, 2019). GDPs impair neutrophil functions and anti-microbial efficacy by suppressing cytokine secretion according to the molecular variety of GDP (Bryland *et al.*, 2010). A prospective study of critically ill patients reported a positive correlation between serum CML levels and elevated bilirubin levels and a negative correlation with serum CRP levels. Fortunately, no correlation was found between serum CML levels and the mortality of critically ill patients (Meertens *et al.*, 2016).

4-Hydroxynonenal (HNE) is a lipid peroxidation product (ALEs) and is present in blood circulation and tissues in various concentrations. It has proapoptotic and apoptotic effects and enhances oxidative stress (Shoeb *et al.*, 2014; Timucin, Basaga, 2017). Its effect appears to be concentration-related because at low concentrations it induces cell proliferation, while at higher concentrations it causes cell death or a precancerous state and cancer (Guéraud, 2017; Yang *et al.*, 2003).

High levels of AGEs and ALEs are probably more life-threatening in patients with acute diseases than in those with chronic ones. Therefore, limiting the accumulation of AGEs and ALEs in acute care patients (e.g., patients with sepsis) seems to be important (Christaki, Lazaridis, Opal, 2012). However, few studies report that low GDP levels in solutions or low AGE levels in circulation lead to less inflammation (Kawanishi *et al.*, 2013; Christaki, Lazaridis, Opal, 2012; Choi *et al.*, 2008).

Considering the above, we thought that PNS, which is composed of dextrose, lipids, and amino acids, may also contain a large number of GDPs, AGEs, and ALEs. To our knowledge, there is only one report on the presence of HNE in PNS (Schröter *et al.*, 2021). However, no publication has been found about AGEs or ALEs in PNS and whether infusion conditions affect the quantities of AGEs or ALEs. We have, therefore, investigated these two issues in this study and the results reported in this study are the first of their kind in the literature.

MATERIAL AND METHODS

We supplied nine PNS packages from the hospital pharmacy store. The solutions were held in a patient wardroom under room conditions with standard ambient lighting for a total of 24 hours. The administration line was connected to an infusion pump, and the PNS was set to flow at 1.0 ml/min. Infusion conditions were simulated. The PNSs were emptied from each bag via IV fluid administration lines to mimic the administration to the patients. Samples were taken in glass bottles at the beginning (Group A) and at the end (24th hour - Group B) of the infusion period. Then, the samples were stored at -20°C until analysis.

The PNS bags were three-chambered and transparent and contained a total volume of 1540 ml of dextrose (150 gram-gr), lipids (60 gr), and amino acids (51 gr) for central infusion (Kabiven, Fresenius Kabi, Uppsala, Sweden). Each component was located in a separate chamber. The seals between the chambers were broken to mix the components before infusion.

The AGEs and ALEs investigated in PNS were DG, pentosidine, CML, and HNE (Figure 1). The degradation products analyzed were DG for dextrose, HNE for lipid, pentosidine and CML for amino acids and lipids, as described in the Maillard reaction (Bryland *et al.*, 2010; Henning, Glomb, 2016). Reference standards of DG (*CAS 4084-27-9*), CML (*CAS 5746-04-3*), and HNE (*CAS 75899-68-2*) were supplied from Santa Cruz Biotechnology Inc. (Texas, U.S.A.) and the reference standard of pentosidine (*CAS 124505-87-9*) was supplied from Cayman Chemical (Michigan, U.S.A.).

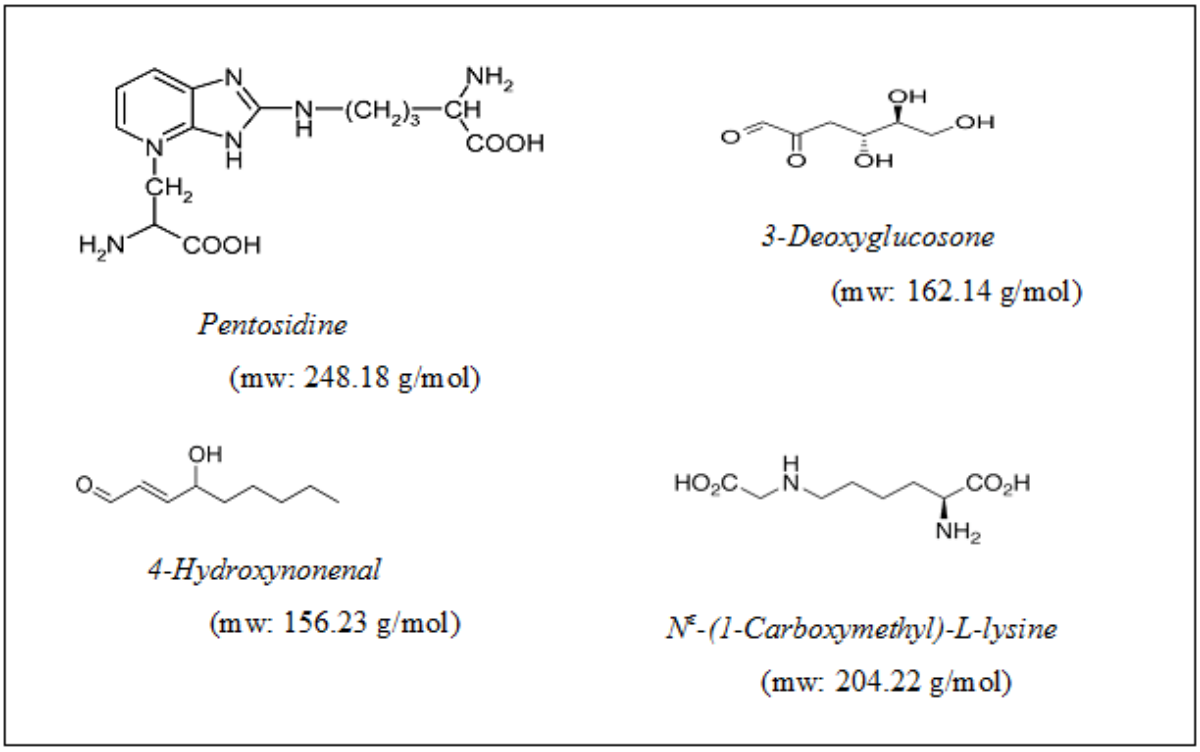

FIGURE 1 - Molecular characteristics of the degradation products investigated

We used liquid chromatography-mass spectrometry (LC-MS/MS) (Shimadzu Nexera, Tokyo, Japan) and Quadrupole time-of-flight liquid chromatography-mass spectrometry (Q-TOF LC/MS) (Agilent 6530, CA, U.S.A.) methods to identify the degradation products in the matrix. Chromatographic techniques were performed in two parts: targeted analyses for pentosidine, DG, CML, and HNE in the LC-MS/MS analyzer and untargeted analyses for any unknown compound in the Q-TOF LC/MS analyzer.

Preparation of Reference Standard for Targeted Degradation Products – AGEs

Reference standards of pentosidine, CML, and HNE were dissolved in a 50: 50% v/v methanol: water mixture and DG was dissolved in methanol by adding the solvent into the original flacons. We obtained 1000 parts per million (ppm), 1000 ppm, 10,000 ppm, and 1000 ppm solutions, respectively. These solutions were diluted between 0.1 and 1 ppm (0.1, 0.2, 0.4, 0.6, 1.0 ppm) with the mobile phase before being injected into the LC-MS/MS analyzer. A Merck SeQuant ZIC-HILIC (150x4.6 mm, 5 µm) column was used in a gradient elution mode (starting with 60% organic phase and ending with 10% at the 32nd minute) using water: acetonitrile, both including 0.1% formic acid.

Preparation of the PNS Samples

The samples were centrifuged at 14,000 rpm for 40 minutes at 20°C using an ultrafiltration tube (Amicon Ultra, 0.5 mL < 3 kDa) in a volume of 500 µL. After centrifugation, molecules less than 3 kDa in weight were collected by filtration. The collected solutions were diluted with the appropriate mobile phase for the targeted degradation products before being injected into the LC-MS/MS analyzer.

Analyses of Untargeted Degradation Products.

The samples were analyzed using a Waters XSelect HSS C18 (4.6 mm X 100 mm, 3.5 µm) column in a gradient elution mode (starting with 10% organic

phase and ending with 90% at the 25th minute) using water: acetonitrile, both including 0.1% formic acid. Ultrafiltrates were diluted with 50% acetonitrile. The XCMS software program was used in LC-MS-based metabolomics analysis to detect and identify metabolites and assess differences between metabolite masses (Smith *et al*., 2006). We used this program to process chromatograms from the Q-TOF LC/MS analyzer. In our study, compounds detected with quantities varying by ≥ 1.2 times between the two groups were considered to have statistical significance (Mihaleva *et al*., 2008).

Statistical Analysis

The data obtained for the two groups were compared using the paired T-test. Statistically, $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

The positive ionization mode peaks of pentosidine, DG, CML, and HNE were identified in the standard solutions at a 1 ppm concentration.

Detected Targeted Degradation Products

DG and pentosidine were not detected in the PNS samples of either group. However, the samples of both groups were found to contain two degradation products: CML and HNE. The mean peak values of CML and HNE were different between the two groups (Figures 2 and 3). A comparison of the quantities of CML and HNE in the PNS samples is presented in Table I. The difference was not statistically significant for CML (p=0.23) but was significant for HNE (p=0.03).

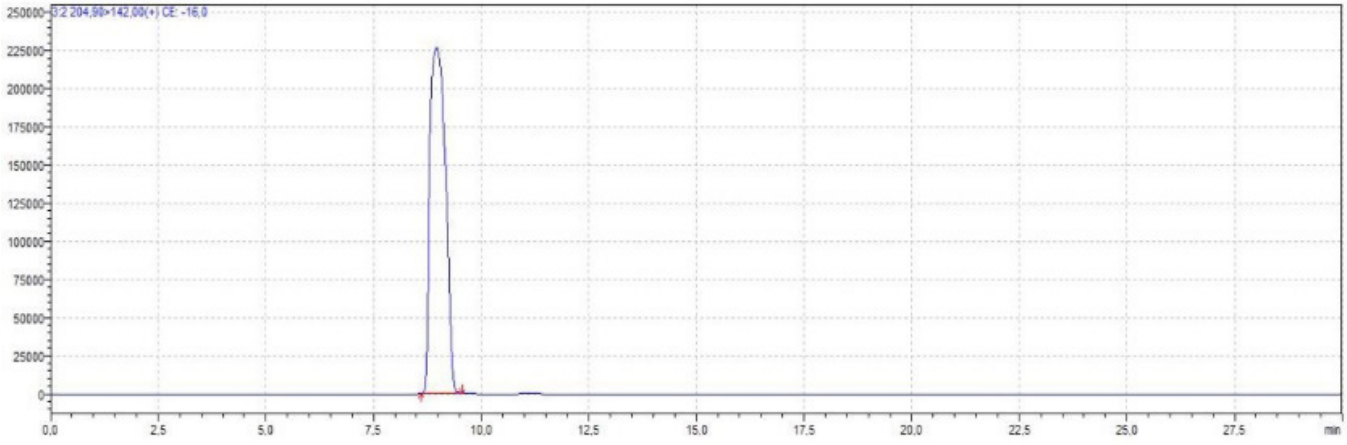

FIGURE 2 - Chromatogram of N-Carboxymethyl lysine in the PNS shows a peak at 8.0 minutes.

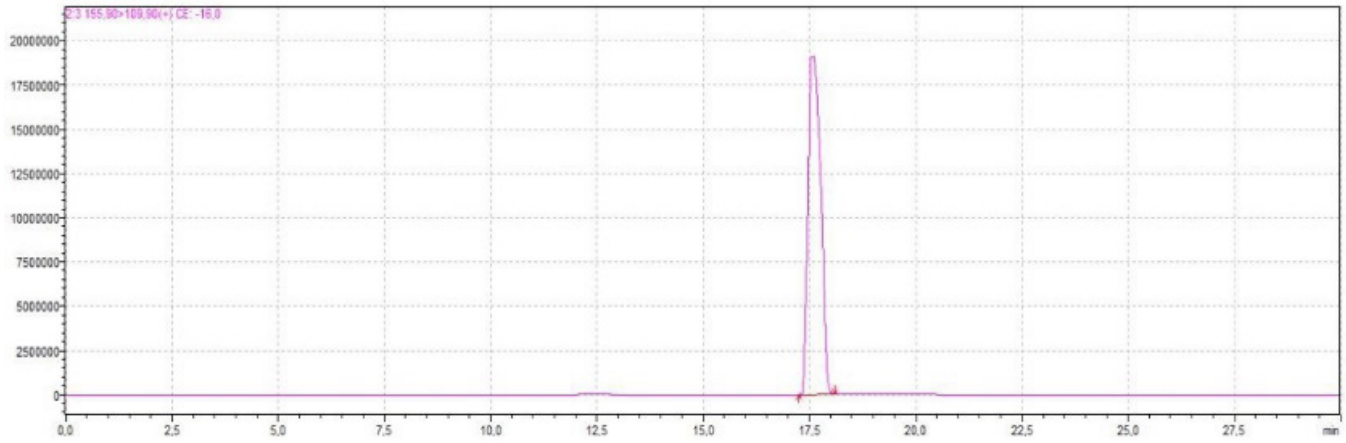

FIGURE 3 - Chromatogram of 4-Hydroxynonenal in the PNS shows a peak at 17.6 minutes.

TABLE I - CML and HNE levels (as μM) in groups and comparisons of means. SD: Standard deviation. P-value < 0.05 is considered to be significant

CML		HNE	
Group A	**Group B**	**Group A**	**Group B**
0.028	0.029	13.133	14.083
0.032	0.037	14.716	18.476
0.037	0.037	15.539	18.295
0.027	0.027	13.599	13.473
0.031	0.031	14.351	15.185
0.033	0.036	16.851	17.580
0.031	0.031	14.324	14.945
0.034	0.035	15.550	16.722
0.038	0.040	17.455	19.161
Mean: 0.032	***Mean***: 0.034	***Mean***: 15.058	***Mean***: 16.436
SD: 0.004	***SD***: 0.004	***SD***: 1.433	***SD***: 2.078
p=0.23		***p=0.03***	

Detected Untargeted Degradation Products

An injection of the sample to show the base peak chromatogram (BPC) is given in Figure 4. Profiles were determined based on the mass of each compound that remained in the ultrafiltration. Twenty-five compounds were profiled, the majority of which were amino acids, and 2 compounds were found to have an increase of ≥ 1.2-fold between groups A and B (Figure 4, Table II). A METLIN data bank search regarding the mass-to-charge ratio (m/z) values showed that one of the compounds was a type of phthalate (Figure 5). The second compound was 4-hydroxy-2-butynal (4-HB), a different degradation product, or 2(3H)-furanone with the same m/z value. (Figure 6). We did not perform a further investigation on this compound.

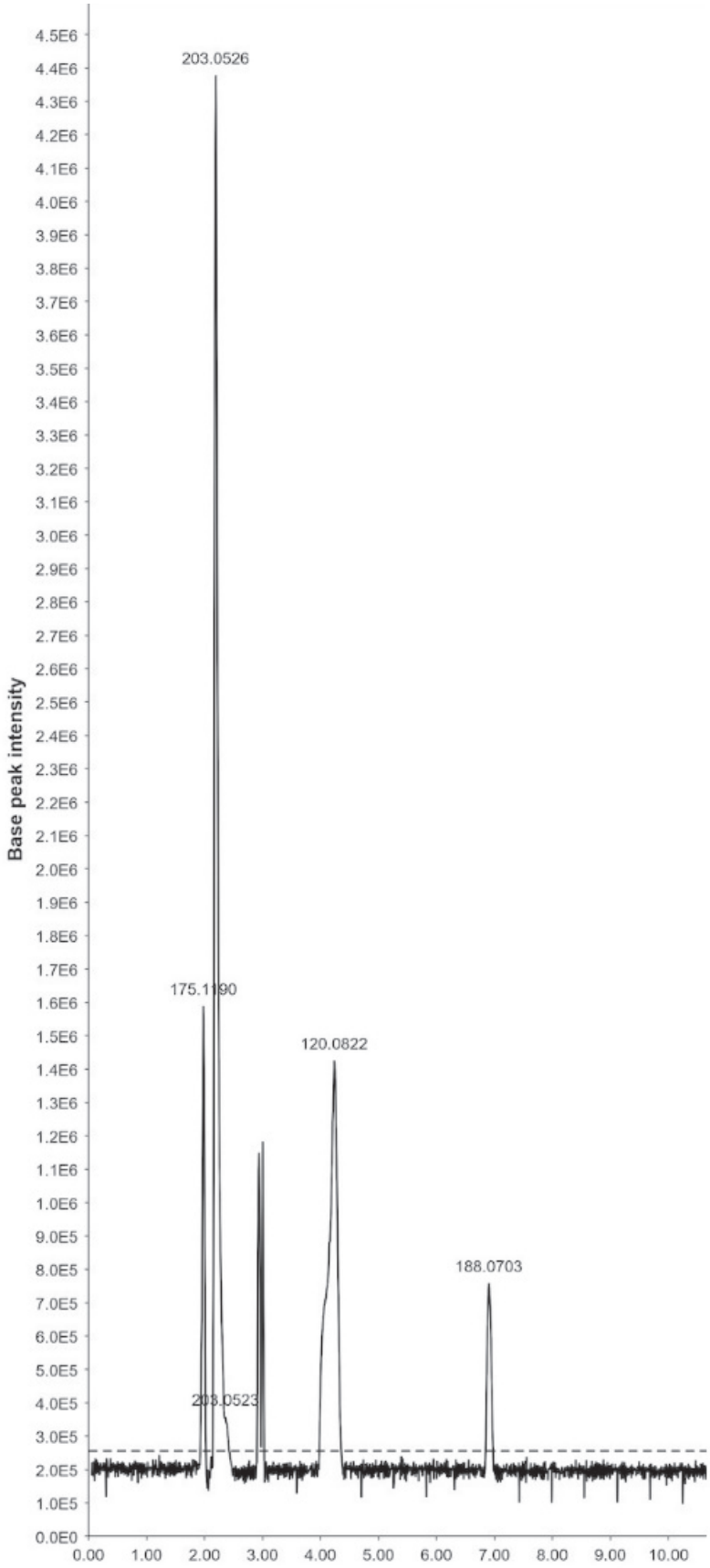

FIGURE 4 - A sample BPC of our analysis to show the untargeted analysis.

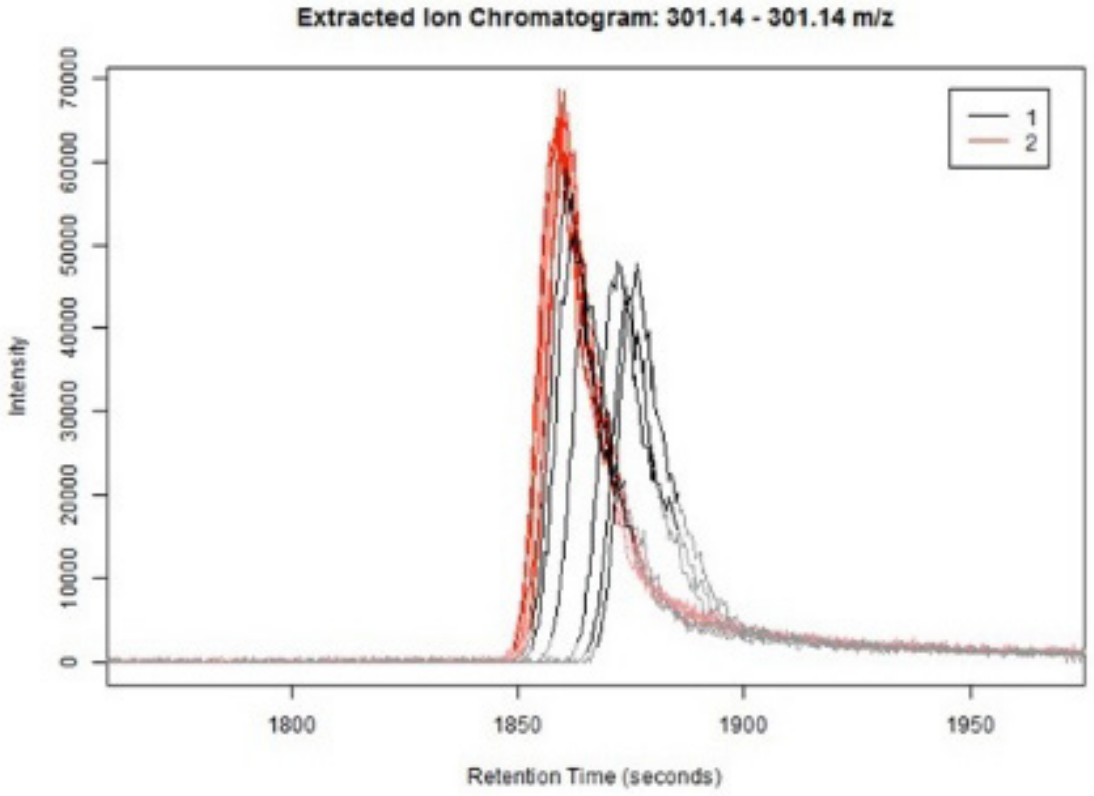

FIGURE 5 - Extracted ion chromatogram of phthalates in the PNS shows two different peaks between 1850 and 1900 seconds.

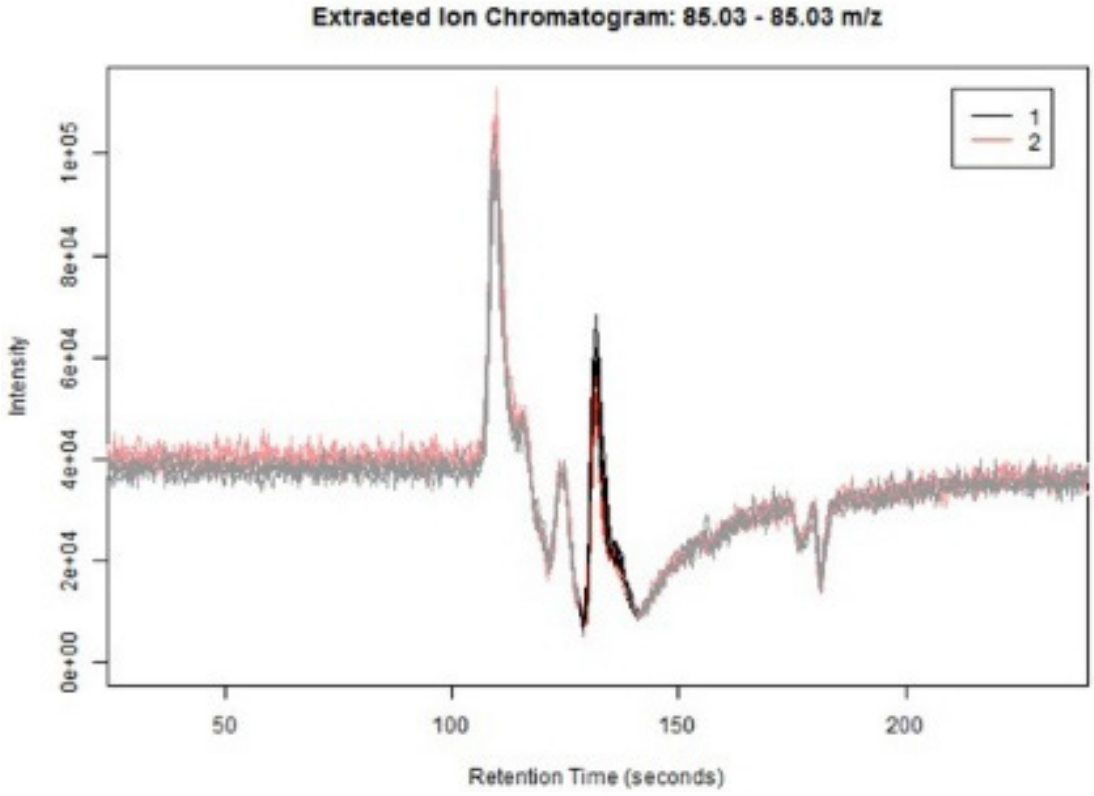

FIGURE 6 - Extracted ion chromatogram of 4-Hydroxy-2-butynal or 2(3H)-Furanone in the PNS shows two different peaks between 100 and 140 seconds.

TABLE II - The characteristics of a type of phthalate and 4-Hydroxy-2-butynal (or furanone). *Mass spectroscopy indicates that the compounds are not mass but mass/charge (m/z)

Compound	Quantity ratio	m/z*	Retention time (min)
Phthalate	1.45	301.1406	31.02
4-Hydroxy-2-butynal (or furaon)	1.21	85.0288	2.20

First of all, we should note that there is only one recently published report that is similar to our study. As a result, we have had to discuss our results in an indirect manner. The stability of compounds in PNS may be impaired during the manufacturing process, under suboptimal conditions of transport, storage, or infusion. The compatibility of the solution with the bag and drugs added to the bag may also affect the stability of the PNS. It has been reported that UVA irradiation and the heat generated during the manufacturing process may cause oxidation and lipid peroxidation (Bryland *et al*., 2010; Tovsen *et al*., 2015; Steger, Mühlebach, 1997). The pH of the PNS is lowered slightly by degradation secondary to UVA irradiation but significantly by concomitant lipid peroxidation (Tovsen *et al*., 2015; Steger, Mühlebach, 1997). Fortunately, there are substances with antioxidant features, such as vitamins and trace elements, that can protect the PNS from degradation (Tovsen *et al*., 2015; Hoff, Michaelson, 2009). However, this protection is controversial in some studies (Jalabert *et al*., 2011).

Storage conditions (e.g., temperature, light exposure, or storage duration) also affect the kinetic stability of PNS (Hoff, Michaelson, 2009; Turmezei *et al*., 2015; Thomovsky *et al*., 2008). The mean oil droplet particle size and the zeta potential of the lipid are reported to be best at 2-8°C storage temperature. The current stability of the PNS is maintained for up to ten days (Turmezei *et al*., 2015). However, in several studies it has been shown to be maintained at optimal stability for 3-4 days (Thomovsky *et al*., 2008; Jalabert *et al*., 2011). Vitamins may also be affected (or destabilized) by storage temperature (for example, ascorbic acid in the PNS may denature rapidly within 24 hours at 25°C or within 72 hours at 2–8°C) (Turmezei *et al*., 2015).

Plastic containers of the PNS are in the form of multilayer films and are generally composed of polypropylamine-polyamide or ethyl vinyl acetate. These containers have an affinity for lipid globules and interact especially with triglycerides. The interaction of lipids with plastic containers is more evident than with glass containers (Driscoll *et al*., 2007; Gonyon *et al*., 2013). In addition, peroxide formation in the PNS has been reported to be significant in plastic containers over time compared to in glass containers. The composition of the containers used also affects the pH of the PNS. It has been reported that the decrease of pH in PNS occurs more in polypropylamine-polyamide containers than in ethyl vinyl acetate containers (Steger, Mühlebach, 1997). The chemical composition of the containers can also facilitate the release of compound dissolutions into the solutions (Schröter *et al*., 2021). We also found phthalate (without typing) in the PNS that lends support to the same suggestion.

PNS seems to be photosensitive. Peroxide formation in the PNS is increased if the container and infusion set are transparent and exposed to light or phototherapy. Hoff and colleagues (2009) stated that the use of a colored infusion bag and infusion set prevented the photodegradation of PNS compounds and inhibited the formation of peroxide. If the PNS is stored under exposure to light for less than 72 hours, the state of the lipid emulsion will not change. However, if PNS is stored under exposure to light for more than 72 hours, light may increase peroxidation and may cause malondialdehyde formation (Jalabert *et al*., 2011). A colored or lightproof container is also recommended to protect vitamins (especially vitamins A and E, which degrade rapidly) from photodegradation (Allwood, Martin, 2000). However, the relationship between vitamins and PNS in terms of vitamin degradation and lipid peroxidation is a contentious issue (Jalabert *et al*., 2011).

Another factor affecting the stability of the PNS is the handling position. It is reported that lipids in the PNS remain stable for 48 hours at room temperature, and intermittent agitation does not affect the size of the lipid particles. However, continuous agitation of the PNS causes a visible oil layer in the container and administration set by the 72nd hour (Thomovsky *et al.*, 2008).

We detected CML and HNE in the PNS among the investigated AGEs: DG, pentosidine, CML, and HNE. In addition, we determined that the amounts of CML and HNE increased from the beginning to the end of the infusion within 24 hours under room conditions, and that the increase of HNE was significant. Similar to our results, Bryland and colleagues (2010) reported GDPs were detected in glucose-containing infusion fluids, and serum CML levels in patients were found to increase significantly in time due to infusion. A recent study by Schröter and colleagues (2021) reported that there was HNE in saline solutions, indicating that it was a leachable compound released from polyvinyl chloride of the administration sets (container + line). Therefore, the origin of NHE may not be the PNS or may be the PNS and the container as well. This issue needs to be clarified in new studies.

In our study, we also determined two different compounds (a type of phthalate and 4-HB or furanone) in the PNS that increased over time. Phthalates are known to be toxic and are generally added to plastics to obtain flexibility. These compounds decompose from the plastic container of the PNS and mix into the solution. Phthalates have been detected in the plasma of infants and children (Kambia *et al.*, 2013). The second compound found in the PNS was 4-HB or furanone, with the same m/z values. The exact determination of this compound is beyond the scope of this study and needs further investigation.

Considering the above, there may be even more different degradation products in PNS. Therefore, it is considered that more applications to maintain the stability of the PNS from the beginning of the manufacturing process to the end of the infusion process (e.g., using light-proof, colored, or low-volume containers and using more stable compounds for production of less flexible containers) are required.

CONCLUSION

Two types of degradation products, CML and HNE, were detected in the PNS, and levels of both were found to be higher at the end of the infusion time under standard ambient lighting and room conditions, with a significant increase in the level of HNE. We also determined two different compounds (a type of phthalate and 4-HB or furanone) in the PNS that increased over time, suggesting that there may be further different degradation products in existence.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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