R-PCT-17

KSA ***Institut für Labormedizin***

Stability of lipids in parenteral nutrition products admixed with nano-iron medicinal drugs

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GSASA BASEL KONGRESS CONGRES 2024

BACKGROUND

Iron deficiency refractory to oral treatment often requires parenteral therapy, usually intravenous (IV) infusion. **IV iron** must be administered separately, either **directly** by **slow injection** into the vein **or,** more conveniently and safely, **as** an **infusion diluted** appropriately **with 0.9% NaCl or 5% glucose**. In **specific situations**, **co-administration** with parenteral nutrition (**PN**) or other IV fluids **might be an attractive alternative when IV-line access is limited**. **However**, evaluating **stability** can be challenging, and there is **limited research on** the **compatibility** of these complex formulations with potentially **highly reactive free iron**. Various nano-colloidal IV iron products are available and commonly used for the treatment of iron deficiency. It is essential to ensure the stability of the nanoparticulate complex to avoid release of ionic iron, which adds oxidizing potential in the parenteral products and eventually to the increased inflammation state of patients. The arising **toxic products**, mainly generated from the essential polyunsaturated fatty acid **oxidation** present in the PN, **malondialdehyde (MDA), 4-hydroxy-2-hexenal (HHE), and 4-hydroxy-2-nonenal (HNE)**, substantially **impair the quality of PN admixtures** and represent a **safety issue.**

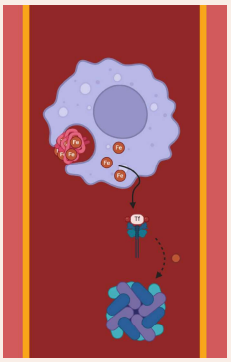


Fig. 1 (Left): Macrophages responsible for phagocytosis of nano-iron complexes are involved in the in vivo uptake mechanism. The iron is then released into the bloodstream, where it is taken up by transferrin and distributed as needed or stored in various compartments of the human body, such as ferritin.

Fig. 2 (Above): The stability of the nano-iron complex in different solutions is not guaranteed. The main problem with stability is the release of iron cations (Fe^{3+}), which are highly reactive. LPO occurs easily from polyunsaturated fatty acids present in the Parenteral Nutrition (PN).

AIM

Establish a reliable and sensitive **method for the measurement of lipidperoxidation** (LPO) in All-in-one (AiO) **PN after the admixing of nano-iron** drug products.

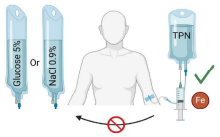
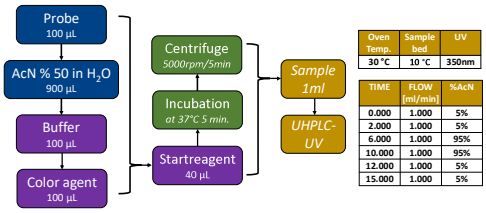


Fig. 3 (Left): Nano-iron administration is currently permitted by infusion of glucose 5% and NaCl 0.9%. Perhaps in the future PN could be an alternative for combined administration.

METHOD

Quantitative analyses: **UHPLC-UV** with **Luna C8(2)** column in gradient mode (H_2O:**AcN** 95% to 5%)**.** Qualitative analysis: **3D-field ultraviolet-visible spectrum.** Pure standards were used and Smofkabiven®-EF was used as PN standard**. Derivatizing chemical**: 3-methyl-2-benzothiazo-linone-hydrazone (**MBTH**) *(Source: Oxalate kit)*



RESULTS

The target substances were identified by **retention time** (Fig. 4) and the method was optimized for **highest signal** (Fig. 5). The use of MBTH permitted a reduction of the **incubation** period to **5 min**., thereby facilitating more frequent data sample analysis (total sample preparation + incubation: 12 min.). The method demonstrated **consistent retention times**, a **robust correlation** between **area and volume**, **high sensitivity** (detection limit **<50 µg/ml**), and **specificity**, with no apparent spectral or chromatographic interferences, see Fig.4 and 5.

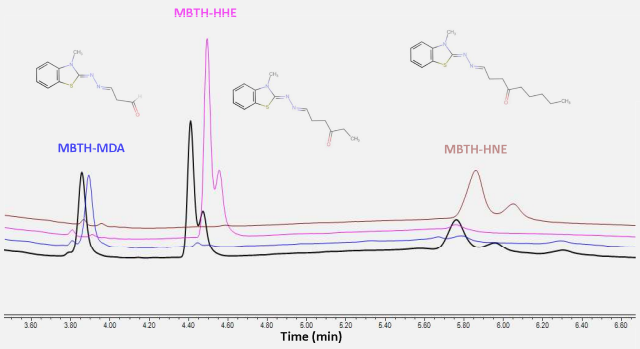
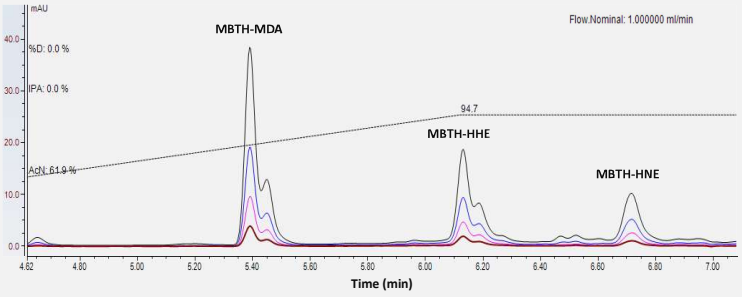


Fig. 4: Example of a combined UHPLC-UV graph (350nm) . The black line is the mixture of the 3 toxic component. This emulates the oxidized environment to exclude interference and to ensure that the peaks are resolved from our target substances.



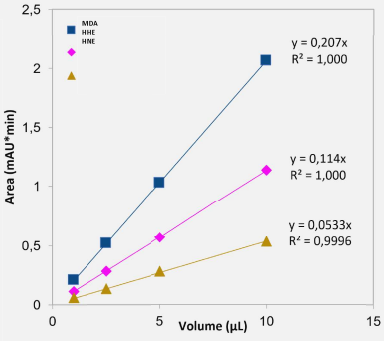


Fig. 5: Graph of the optimized UHPLC-UV (350 nm) method with varying injection volumes (1-10 µL). The right-hand side of the figure presents the area versus volume correlation and the retention time data. The R^2 value is notably high, and the retention time is well-conserved with a relative standard deviation of less close to 0% across all three substances.

Ret. Time min	MDA	HHE	HNE
Average	5,328	6,01	6,549
Relative Standard Deviation	0,04%	0,00%	0,03%

CONCLUSION

Iron plays a vital role in the treatment of severely ill and frequently iron-deficient patients on PN and with often limited venous line access. Particularly when potentially supplemented in PN, the **integrity and stability** of all components is crucial to achieve the highest benefit for the patient in terms of safety and efficacy. We present a **sensitive UHPLC-UV method** to **quantify LPO**, a potentially limiting **safety and quality factor of PN**, especially when admixing widely used **nano-iron drugs** and the inherent risk of reactive labile iron, which is prone to triggering LPO. In the next step, we will validate the method and investigate the impact of various commonly used iron products in different concentrations on the lipid stability including LPO in AiO PN admixtures.

CONTACT INFORMATION

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