



Stability of hydrophilic vitamins mixtures in the presence of electrolytes and trace elements for parenteral nutrition: A nuclear magnetic resonance spectroscopy investigation



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ABSTRACT

In total parenteral nutrition (TPN), especially in the case of preterm infants, simultaneous administration of vitamins and trace elements is still a problematic issue: guidelines put in evidence the lack of specific documentation. In this work NMR spectroscopy was applied to the study of vitamins (pyridoxine hydrochloride, thiamine nitrate, riboflavin-5'-phosphate and nicotinamide) stability in presence of salts and trace elements. Vitamins in D₂O were first analyzed by ¹H NMR spectroscopy in absence of salts and trace elements; changes in chemical shifts or in diffusion coefficients, measured by NMR DOSY technique, were analyzed. The effects of salts and trace elements on single vitamins and on their admixtures were then investigated by performing quantitative analyses during 48 h. Selected vitamins are subject to intermolecular interactions. No degradative effects were observed in presence of salts and trace elements. Only riboflavin-5'-phosphate is subject to precipitation in presence of divalent cations; however, at low concentration and in presence of other vitamins this effect was not observed. Solutions analyzed, in the condition of this study, are stable for at least 48 h and vitamins and trace elements can be administered together in TPN.

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1. Introduction

Total parenteral nutrition (TPN) is a needful feeding mode in the case of very low birth-weight premature infants [1–3]. All-in-one (AIO) admixtures are nowadays considered the best infusion system for the administration of TPN [4,5]: all substrates are admixed in a single container and simultaneously administered through one intravenous line. This method, besides reduction in costs and practical advantages for clinicians and nursing staff, allows to reduce the number of manipulation and so contamination risk, and the fact that only one intravenous line is required leads to reduced risk of infection and makes this method particularly safe especially for premature infants [4,5].

However, problems of compatibility and stability can occur when so different compounds are mixed together [6–16], in particular in AIO admixtures addressed to premature infants, considering

the low final volume that can be administered [6]. Vitamins are considered the least stable components of the admixture; it is generally recommended not to add vitamins and trace elements to the same admixture [5]. Oxidation of ascorbic acid, the least stable among the water-soluble vitamins, has been widely investigated and the role of catalyst of some bivalent ions, especially copper, has been established [12,13,16]. Ascorbic acid is also involved in reduction of selenite ion to elemental selenium that could precipitate [16]. However, guidelines highlight the lack of specific documentation [5] on the compatibility of trace elements with other vitamins and suggest the administration of vitamins and trace elements on alternated 12 h every day [11] or by two separated intravenous applications [5]. Nevertheless, especially for neonates, the need of a continuous administration of all the nutrients, and the complexity to use two intravenous lines are also claimed: a general accepted compromise is to add vitamins and trace elements to the admixture immediately before the administration to minimize interactions and eventual degradation [10]. In any case, vitamins stability should be proved at least during infusion period; furthermore, a higher stability would allow the preparation of complete AIO admixtures in hospital pharmacies [4].

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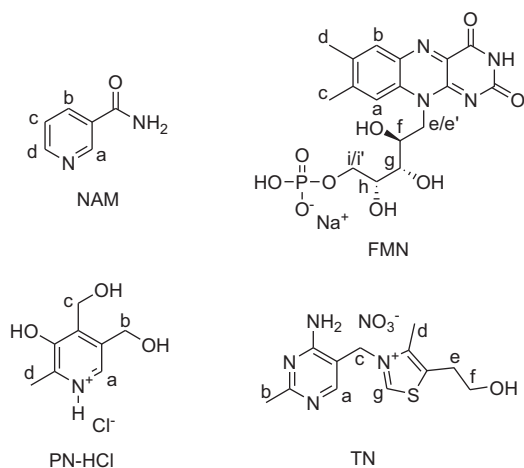


Fig. 1. Structure of vitamins with numbering scheme for NMR analysis.

Considering the clinical relevance of this issue, nuclear magnetic resonance (NMR) spectroscopy was applied to the study of vitamins stability in presence of salts and trace elements up to 48 h, in experimental conditions mimicking pharmaceutical formulations, as a non-invasive analytical procedure. The investigation focused on water-soluble vitamins, in particular pyridoxine hydrochloride (PN-HCl), thiamine nitrate (TN), riboflavin-5'-phosphate (FMN) and nicotinamide (NAM) (Fig. 1). Among the several NMR parameters, translational diffusion coefficients were exploited, which are remarkably responsive to phenomena of intermolecular aggregation, together with chemical shifts as local parameters, well reflecting structural changes due to eventual degradation processes.

2. Materials and methods

2.1. Materials

Nicotinamide, pyridoxine hydrochloride, thiamine nitrate, riboflavin-5'-phosphate, zinc chloride, copper chloride, manganese chloride tetrahydrated and phosphate buffer were purchased from Sigma-Aldrich (St. Louis, USA). Deuterated solvents, deuterium oxide and dimethyl sulfoxide, were purchased from Deutero GmbH (Kastellaun, Germany). Calcium gluconate (Polichimica, Bologna, Italy), magnesium sulfate (Fagron, Bologna, Italy), Esafosfina® (Biomedica Foscama, Ferentino (FR), Italy) and Peditrace® (Frese-nius Kabi, Isola della Scala (VR), Italy) were commercially available.

2.2. NMR measurements

NMR measurements were performed on a Varian Inova spectrometer (Agilent Technologies, Santa Clara, USA) operating at 600 MHz for ^1H nuclei. The temperature was controlled to $\pm 0.1^\circ\text{C}$. DOSY (Diffusion Ordered Spectroscopy) experiments were carried out by using a stimulated echo sequence with self-compensating gradient schemes, a spectral width of 8000 Hz and 64 K data points. Gradient strength was varied in 20 steps (16 transients each), while values of the diffusion delay and the gradient pulse duration were optimized to obtain an approximately 90–95% decrease in the resonance intensity at the largest gradient amplitude. The baselines of all arrayed spectra were corrected prior to processing the data. The data were processed with the DOSY macro (involving the determination of the resonance heights of all the signals above a pre-established threshold and the fitting of the decay curve for each resonance to a Gaussian function) to obtain pseudo two

dimensional spectra with NMR chemical shifts along one axis and calculated diffusion coefficients along the other.

2.2.1. ^1H NMR characterization of vitamins

Nicotinamide (15 mM, 600 MHz, D_2O , 25°C) δ (ppm): 8.79 (1H, H_a , dd, $J_{a-b} = 2.2$ Hz, $J_{a-c} = 0.8$ Hz), 8.57 (1H, H_d , dd, $J_{d-c} = 5.0$ Hz, $J_{d-b} = 1.7$ Hz), 8.10 (1H, H_b , ddd, $J_{b-c} = 8.0$ Hz, $J_{b-a} = 2.2$ Hz, $J_{b-d} = 1.7$ Hz), 7.45 (1H, H_c , ddd, $J_{c-b} = 8.0$ Hz, $J_{c-d} = 5.0$ Hz, $J_{c-a} = 0.8$ Hz).

Pyridoxine hydrochloride (15 mM, 600 MHz, D_2O , 25°C) δ (ppm): 8.01 (1H, H_a , s), 4.87 (2H, H_c , s), 4.67 (2H, H_b , s), 2.50 (3H, H_d , s).

Thiamine nitrate (15 mM, 600 MHz, D_2O , 25°C) δ (ppm): 7.91 (1H, H_a , s), 5.31 (2H, H_c , s), 3.74 (2H, H_f , t, $J_{f-e} = 6.0$ Hz), 3.04 (2H, H_e , t, $J_{e-f} = 6.0$ Hz), 2.42 (3H, H_d , s), 2.35 (3H, H_b , s).

Thiamine nitrate (15 mM, 600 MHz, DMSO, 25°C) δ (ppm): 9.46 (1H, H_g , s), 8.06 (1H, H_a , s), 7.13 (2H, NH_2 , br s), 5.33 (2H, H_c , s), 5.23 (1H, OH, t, $J_{\text{OH}-f} = 4.9$ Hz), 3.65 (2H, H_f , dt, $J_{f-e} = 5.5$ Hz, $J_{f-\text{OH}} = 4.9$ Hz), 3.04 (2H, H_e , t, $J_{e-f} = 5.5$ Hz), 2.51 (3H, H_d , s), 2.37 (3H, H_b , s).

Riboflavin-5'-phosphate (15 mM, 600 MHz, D_2O , 25°C) δ (ppm): 7.65 (1H, H_a , s), 7.50 (1H, H_b , s), 4.92 (1H, H_e , dd, $J_{e-e'} = 14.8$ Hz, $J_{e-f} = 7.4$ Hz), 4.57 (1H, $\text{H}_{e'}$, dd, $J_{e'-e} = 14.8$ Hz, $J_{e'-f} = 2.3$ Hz), 4.25 (1H, H_f , ddd, $J_{f-e} = 7.4$, $J_{f-g} = 4.9$ Hz, $J_{f-e'} = 2.3$ Hz), 3.98 (1H, H_i , m), 3.93 (1H, $\text{H}_{i'}$, m), 3.92 (1H, H_h , m), 3.87 (1H, H_g , dd, $J_{g-h} = 7.0$ Hz, $J_{g-f} = 4.9$ Hz), 2.38 (3H, H_c , s), 2.25 (3H, H_d , s).

3. Results and discussion

Pure vitamins (Fig. 1) were first analyzed by ^1H NMR without salts and trace elements in D_2O solutions, i.e. in the administration conditions, and compared to binary, ternary and quaternary solutions (15 mM) in order to investigate if any interaction takes place when they are mixed together.

Changes in chemical shifts can be caused by proton transfer phenomena, which can be evaluated by comparison with buffered solutions (pH 7.4, phosphate buffer). Alternatively, intermolecular interactions between vitamins could occur, as well as self-aggregation phenomena which are well reflected in diffusion coefficient (D) changes.

Translational diffusion coefficient, measured by using the NMR DOSY technique [17–19], is a size-dependent parameter, directly related to hydrodynamic radius r_H (Eq. (1)):

$$D = \frac{kT}{6\pi\eta r_H} \quad (1)$$

where k is the Boltzmann constant, T the absolute temperature, and η the solution viscosity. In the fast exchange conditions of equilibrium between free and bound species (Eq. (2)),



observed parameter (D_{obs}) is the weighted average of its value in bound (D_b) and free (D_f) states (Eq. (3))

$$D_{\text{obs}} = x_b D_b + (1 - x_b) D_f \quad (3)$$

where x_b is the molar fraction of bound species. Thus, in the analysis of multicomponent solutions, a decrease of diffusion coefficient of one component is indicative of an aggregation phenomenon.

Only negligible chemical shifts variations of each vitamin were measured in the binary mixtures with the exception of mixtures containing PN-HCl, where relevant low-frequencies shifts up to -0.30 ppm of pyridoxine protons were detected, in particular in the presence of thiamine and for the nucleus in ortho to the positively charged nitrogen atom (Table 1, Fig. 1). However, co-presence of vitamins in binary, ternary and quaternary mixtures leaves nearly unchanged the diffusion coefficient of each component, allowing us to rule out the occurrence of significant intermolecular interactions.

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