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Research article

Stability of vitamin A, E, C and thiamine during storage of different powdered enteral formulas

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ABSTRACT

In this study, two different kinds of commercial enteral formulas were selected to evaluate the changes of vitamin A, E, C and thiamine during the different storage conditions of different temperature and relative humidity (60 ± 1 °C, 60 ± 5% for 5 and 10 days; 37 ± 1 °C, 75 ± 5% for 1, 2, 3, 5 and 6 months; 25 ± 1 °C, 60 ± 5% for 3, 6, 9, 12, 18 and 24 months). The results showed that as the temperature or time increased, the content of vitamin A, E and thiamine was gradually decreased whilst the level of vitamin C remained stable. The vitamins exhibited more stability at the storage of 25 ± 1 °C, RH 60 ± 5%. Vitamin A and thiamine decreased more in the polymeric formula (EFA) than that in the oligomeric formula (EFB), while, vitamin E decreased less in EFA than that in EFB. The kinetics of vitamin A, E and thiamine degradation during storage followed first order kinetic equations. Furthermore, the final levels of vitamins were higher than the minimum level recommended by legislation.

1. Introduction

Over the past few decades, the consumption of enteral formulas (EFs) for hospitalized, critically ill and home enteral patients has dramatically increased. EFs are used to provide exclusive or partial nutritional and support for individuals with limited, impaired, or disturbed capacity of taking, digestion absorb, metabolize excrete ordinary food or certain nutrients contained food (Delompre et al., 2019; Hurt et al., 2019; Reis et al., 2018). The composition of commercial formulas for adults are different from those for children in the contents of protein (amino acids, peptides, or intact protein), carbohydrates (glucose polymers, maltodextrins, disaccharides, or oligosaccharides), fat (partially digested mono or diglycerides), as well as the micronutrients (Brown et al., 2015; Cámara-Martos and Iturbide-Casas, 2019; Iturbide-Casas et al., 2019).

EFs are designed and manufactured contain amounts of vitamins, including water-soluble and fat-soluble vitamins, to provide enough micronutrients as individuals obtain 1500–1800 calories per day (Fabiani et al., 2020). The formulas have been defined by the Chinese government as foods for special medical purposes according to National Food Safety Standards of General Rules of Foods for Special Medical Purpose (FSMP), are suitable for the population with the age of over one years old (China, 2013). The general rules established the limits of vitamins, which can be added to meet nutritional requirements and guarantee the stability of the product. It is usual for manufacturers to add a higher quantity of vitamins in the EFs than that indicated on the formulas' label, in case of the vitamins lost during processing and storage (Dhakal and He, 2020). In fact, EFs are usually not be consumed immediately after manufactured. They are frequently be stored in the uncontrolled conditions throughout the whole supply chain (Juana and Vidal-Valverde, 2001).

The stability of vitamins may be affected by various factors such as the type of packaging and condition of storage (e.g., exposure to oxygen, light, humidity, and temperatures) (Edelmann et al., 2016). Vitamins A and E exhibit stability in nitrogen atmospheres and cool places without light. They are especially sensitive to oxidation by air in the presence of light. Vitamin C is sensitive to heat, oxygen and light. Thiamine (vitamins B_1) is stable below pH = 5.5 but may be destroyed rapidly in the conditions of above pH = 7.0 regardless of the temperature (Chávez-Servín et al., 2008; Juana and Vidal-Valverde, 2001). Studies have reported water-soluble and fat-soluble vitamins contents and their stability during storage of liquid and powdered EFs. Juana et al. evaluated the stability of thiamine and vitamin E and A of two different liquid EFs after storage for 3, 6 and 9 months at 4, 20 and 30 °C (Juana and Vidal-Valverde, 2001). Frias et al. showed that two commercially powdered EFs gradually lose vitamin A, E, and thiamine contents at 30 °C for up to 6 months with a water activity (A_w) of 0.44 (Frias et al., 2009). Fávaro et al. observed

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vitamin A content being lost in 15 samples of liquid EFs during 3–6, 9 and 12 months of in closed containers, protected from light and at room temperature (22–30 °C) (Fávaro et al., 2011). Baéz et al. evaluated the effect of storage temperature (22, 37 and 45 °C) and time (105 days) on the chemical changes of main micro- and macro-components of a powdered milk formula, the results showed that vitamins A and C content in formula also gradually decreased (Baéz et al., 2012). Wang et al. studied nutrients content in a powdered EF stored at 25 °C after 720 days and discovered that compared with macronutrients and minerals, the attenuation degree of vitamin was higher, the attenuation rates of vitamin A, vitamin C and thiamine were all exceeded 20% (Wang et al., 2021). In general, the authors observed a reduction in the vitamin content of different products, and the magnitude of this reduction seemed to depend on the storage conditions.

However, until now there exists a lack of information about the stability of the vitamins in different EFs and different batches of the same EF kept in different conditions. Manufacturers recommend a shelf-life of 24 months under sealed original packaging at room temperature, although changes in these micronutrients depend on the storage conditions and changes of these vitamins content in the EFs could be crucial for patients and reflected in the daily intake consumed. Thus, it is necessary to determine the real vitamins contents of the products after processing as well as the storage at different conditions, considering the factors of temperature, relative humidity and time, to ensure the actual intake of vitamins and the accuracy of the label statements.

The main aims of this work were: first, to survey the vitamin A, vitamin E, vitamin C and thiamine contents in two different commercial powder enteral formulas comparing with the label statements; second, to evaluate the stability of the aforementioned micronutrients during the shelf-life of the product under different storage conditions; and, third, to study the compliance of those vitamin contents with the Chinese legislation and provide a reference for the development and application of EFs.

2. Materials and methods

2.1. Samples of commercial enteral formulas

Two commercial powder enteral formulas, which were polymeric formula (EFA) and oligomeric formula (EFB), containing different protein source and content with the detail information listed at Table S1, were selected for use to carry out storage trials at different storage conditions.

2.2. Standards and chemicals

Methanol and n-butyl alcohol (HPLC grade) was purchased from Merck (Darmstadt, Germany). The ultra-pure water was obtained from an in-house MilliQ system (EMD Millipore, Billerica, MA, USA). All vitamin standards were obtained from Sigma-Aldrich (Saint Quentin-Fallavier, France). The concentrations of vitamin A, vitamin E, vitamin C and thiamine working solutions were 0.5–10, 10–200, 0.3–3.0 and 0.1–3.0 μg/mL, respectively. All the working solutions were kept at −20 °C until used and the other reagents used were of analytical grade.

2.3. Storage conditions

Samples of these two enteral formulas were freshly prepared in three different batches by the industry and immediately submitted to storage studies (samples EFA 1–3 and EFB 1–3). The samples studied here were packed in tinned containers flushed with a nitrogen-modified atmosphere N_2/CO_2.

Based on previous studies, the product was kept at 60 ± 1 °C, relative humidity (RH) 60 ± 5% for over 10 days, or 37 ± 1 °C, RH 75 ± 5% for over 6 months, although the content of micronutrients meets the Chinese legislation, the product sensory is still unacceptable (Bordoloi et al., 2020; Frias et al., 2009; Hemery et al., 2020; Wang et al., 2021). To evaluate the changes of vitamins during the storage of EFA and EFB, the products were divided into three groups and kept under the following conditions:

(1) High temperature test: samples of EFA 1 and EFB 1 were stored at 60 ± 1 °C RH 60 ± 5% for 5 and 10 days.
(2) Accelerated test: samples of EFA 1–3 and EFB 1–3 were stored at 37 ± 1 °C, RH 75 ± 5% for 1, 2, 3, 5 and 6 months.
(3) Normal temperature test: samples of EFA 1–3 and EFB 1–3 were stored at 25 ± 1 °C, RH 60 ± 5% for 3, 6, 9, 12, 18 and 24 months.

In our study, 25 ± 1 °C, RH 60 ± 5% simulated the usual ambient condition in markets and food stores, 37 ± 1 °C, RH 75 ± 5% was a condition which could be reached under extreme conditions in stores without air condition in the summer, while, 60 °C was another condition which can be reached under extreme conditions during the transportation in the summer. During the experimental period, the samples were stored under sealed original packaging in constant temperature and constant humidity box. The vitamin contents of control samples (time 0) were determined after collection immediately.

2.4. Determination of vitamin A and E

Vitamin A and E were measured according to previous studies (China, 2016a; Wen et al., 2020). The standard used for vitamins A was retinol purchased from Sigma. The standard used for vitamins E were α-tocopherol, β-tocopherol, γ-tocopherol and δ-tocopherol, which were purchased from Sigma, respectively. After saponified, tocopherols and retinols were extracted with diethyl ether/petroleum ether (200:200, v/v). Then the solution was washed and condensed, following by making up the volume with methanol and filtrating through a 0.22 μm nylon syringe filter after shaking thoroughly. Then the sample was waiting to inject into the high performance liquid chromatography (HPLC) system (Agilent, NYSE.A, Palo Alto, California, USA), which consisted of an Agilent 1260 System Quaternary pump and a ultraviolet detector. The column was a Shimsen VD C30 column, 250 × 4.6 mm, particle diameter 3 μm. The mobile phase was operated in gradient elution (eluent A: water, eluent B: methanol) and the procedure was as follows: 0–13 min, 4% A and 96% B; 13–20 min, 100% B; 20–24 min, 100% B; 24–24.5 min, 4% A and 96 % B; 24.5–30 min, 4% A and 96% B. The sample was separated at 0.8 mL/min flow rate with 10 μL injection volumes and the column temperature was 20 °C. The optimum wavelength selected for the detection of vitamin A (λ = 325 nm) and E (λ = 294 nm).

2.5. Determination of vitamin C

Vitamin C was measured according to previous documents and national standards (China, 2010; Doseděl et al., 2021). Ascorbic acid was used for the calibration of the standard curve for vitamin C. Vitamin C standard was purchased from Sigma. About 5 g of sample was dissolved with metaphosphate/acetic acid solution and subsequently determined by fluorospectro photometer (Shimadzu, Japan). The optimum wavelength selected for detection of vitamin C (λex = 350 nm, λem = 430 nm) and the concentration of sample was calculated by the standard curve of vitamin C.

2.6. Determination of thiamine

Thiamine was measured based on previous documents and national standards (China, 2016b; Zeeb et al., 2010). The standard used for thiamine was thiamine hydrochloride purchased from Sigma. Thiamine was extracted with acid hydrolysis and then derivatized with potassium ferricyanide. Then the sample was made up the volume with n-butyl alcohol and filtrated through a 0.45 μm nylon syringe filter after shaking thoroughly and ready to inject into the HPLC system (Agilent, NYSE.A,

Palo Alto, California, USA). The system consisted of an Agilent 1260 System Quaternary pump and a fluorescence detector. The column was an Agilent 5 TC C18 column, 250 × 4.6 mm, particle diameter 5 μm. The mobile phase consisted of methanol/sodium acetate solution (35:65, v/v), and was pumped at a flow rate of 0.8 mL/min. The column temperature was 30 °C and the injection volume was 20 μL. The optimum wavelength for the detection of thiamine was set as: λex = 375 nm, λem = 435 nm.

2.7. Statistical analysis

Chromatographic data were acquired and analyzed with OpenLAB ChemStation (Agilent, NYSE.A, Palo Alto, California, USA). Data of others were presented as mean ± standard deviation SD (n = 3) and obtained using software of SPSS 22.0 (SPSS Inc., Chicago IL, USA) and Origin 8.0 (Origin Lab, Hampton, AK, USA). $p \leq 0.05$ was regarded as statistically significant.

3. Results and discussion

3.1. The contents of vitamin A, E, C and thiamine in fresh samples

The content of vitamin A, vitamin E (α-tocopherol, γ-tocopherol, δ-tocopherol), vitamin C and thiamine of two different commercial enteral formulas (EFA and EFB) was presented in Table 1. The formulas were freshly prepared three different batches by the industry and immediately submitted to storage studies. In EFA, the vitamin A content ranged from 391.1–407.4 μg RE/100 g, the vitamin E content, which contain the tocopherol acetate added to the EFs and tocopherols derived from the vegetable oils used for EFs manufacturing, was between 8.26–8.54 mg α-TE/100g. Here, the α-tocopherol was the main component, whilst γ-tocopherol and δ-tocopherol only contributed to vitamin E content at 10% and 1%, respectively. β-tocopherol was not detected in EFA. The vitamin C content was between 89.9–90.9 mg/100 g while the thiamine content was between 1.16–1.22 mg/100 g. In EFB, the vitamin A content ranged from 459.2–467.5 μg RE/100g, the vitamin E content was between 9.76–9.90 mg α-TE/100 g (β-tocopherol was also not detected in EFB), the vitamin C content was between 98.6–99.5 mg/100 g and the thiamine content was between 1.25–1.29 mg/100 g. There was no significant difference in our data between the three batches for EFA and EFB, respectively, whilst the initial vitamin content of EFB was higher than EFA. To be noted, the detection data in our study was higher than those reported on the label of each formula.

3.2. Change of vitamin A content during storage

The vitamins content in EFA 1 and EFB 1, quantified in samples during 0, 5 and 10 days of storage at 60 ± 1 °C, RH 60 ± 5% was shown in Table 2. The changes of vitamins in EFA 1–3 and EFB 1–3 after storage at 37 ± 1 °C, RH 75 ± 5% for 0, 1, 2, 3, 5 and 6 months could be found in Table 3A & Table 3B. The changes of vitamins in EFA 1–3 and EFB 1–3 after storage at 25 ± 1 °C, RH 60 ± 5% for 0, 3,6, 9,12, 18 and 24 months could be observed in Table 4A & Table 4B. Figure 1a, 1b, 1c, 1d indicated the effect of storage on vitamin retention in EFA and EFB during different storage condition.

The most common additive is vitamin A in the form of retinol acetate or retinol palmitate in the products of EFs, because those molecules are more stable and less susceptible to oxidation than their respective analogues from vegetable oils (Frias et al., 2009). In this study, the vitamin A content in EFA 1 and EFB 1 showed significant different when stored at 60 ± 1 °C, RH 60 ± 5% for 5 and 10 days. The decrease of 26% and 23% were observed after 5 days, respectively. When the storage was prolonged to 10 days, important decreases of 35% and 29% were observed in different formulas (Table 2). The same effects appeared when the formulas were kept at 37 ± 1 °C with RH 75 ± 5% for EFA 1–3 and EFB 1–3 after 1, 2, 3, 5 and 6 months. When the samples were stored, the vitamin A content underwent significant ($p \leq 0.05$) decrease of 9–14% in EFA and 9–12% in EFB after 2 months. When the period of storage was extended to 3 and 6 months, gradual decline of vitamin A content were observed, and reductions of 14–21%, 32–34% in EFA and 15–16%, 18–23% for EFB, respectively (Tables 3A & 3B, Figure 1a). It was found that model reductions in vitamin A content were observed at assigned shelf-life periods of time when these two formulas were stored at 25 °C with RH 60 ± 5% after 3, 6, 9, 12, 18 and 24 months. The reductions of 11–16% for EFA and 12% for EFB were observed after 24 months, respectively (Table 4A & 4B, Figure 1a).

Juana et al. studied that vitamin A content in two samples of liquid enteral formulas submitted to different storage times (3, 6 and 9 months) and different temperatures (4, 20 and 30 °C). After 6 months at 30 °C, they were appreciable about 75% and dramatic loss (99%) happened after storage for 9 months at 30 °C (Juana and Vidal-Valverde, 2001). Frias et al. evaluated the effect of A_w on vitamin A activity in two commercial powdered formulas stored after opening the packet. A gradual decrease of activity was observed under conditions of 30 °C and A_w of 0.44 and, after 6 months, only 58–68% remained. Without A_w control (atmospheric conditions), reductions of vitamin A activity were 6%, 16% and 29% after 3, 4 and 6 months, respectively (Frias et al., 2009). Fávaro et al. analyzed vitamin A content in 15 samples of enteral feeding formulas were nutritionally complete and/or recommended for different diseases, during 3–6, 9 and 12 months of storage in closed containers, protected from light and at room temperature (22–30 °C). The content of vitamin A did not decrease during both storage period (Fávaro et al., 2011). Baéz et al. evaluated vitamin A content in a powdered milk formula stored (in a chamber with thermal thermostat) at 22, 37 and 45 °C for 105 days immediately after production. At the end of the study, the loss of vitamin A was 34.01% at 37 °C (Baéz et al., 2012). Wang et al. studied the vitamin A content in a powdered formula stored at 37 °C, RH 75 ± 5% for 180 days and 60 °C, RH 60 ± 5% for 10 days, the results showed that the attenuation rates of the vitamin A was 26.6% and 19.8% (Wang et al., 2021).

Traditionally, the degradation kinetics of vitamins during food processing and storage has been determined by periodically monitoring its

Table 1. Vitamin content in enteral formula A and B.

Enteral Formula	Vitamin A (μg RE/100 g)	α -Tocopherol (mg α-TE/100 g)	γ-Tocopherol (mg/100 g)	δ-Tocopherol (mg/100 g)	Vitamin E (mg α-TE/100 g)	Vitamin C (mg/100 g)	Vitamin B_1 (mg/100 g)
A1	407.4 ± 21.8[a]	8.15 ± 0.23[a]	3.89 ± 0.02[a]	0.82 ± 0.00[a]	8.54 ± 0.23[a]	90.8 ± 3.46[a]	1.16 ± 0.06[a]
A2	397.7 ± 11.2[a]	7.89 ± 0.16[a]	3.61 ± 0.09[b]	0.85 ± 0.01[b]	8.26 ± 0.15[a]	90.9 ± 1.77[a]	1.22 ± 0.06[a]
A3	391.1 ± 17.4[a]	8.05 ± 0.01[a]	3.93 ± 0.15[a]	0.83 ± 0.01[a]	8.45 ± 0.01[a]	89.9 ± 1.81[a]	1.16 ± 0.01[a]
B1	462.3 ± 25.4[a]	9.61 ± 0.25[a]	2.90 ± 0.15[a]	0.61 ± 0.01[a]	9.90 ± 0.23[a]	98.9 ± 1.00[a]	1.29 ± 0.02[a]
B2	459.2 ± 17.0[a]	9.48 ± 0.28[a]	2.91 ± 0.37[a]	0.60 ± 0.01[a]	9.76 ± 0.32[a]	99.5 ± 0.50[a]	1.25 ± 0.01[a]
B3	467.5 ± 12.6[a]	9.47 ± 0.15[a]	3.10 ± 0.07[a]	0.82 ± 0.04[b]	9.79 ± 0.15[a]	98.6 ± 1.30[a]	1.27 ± 0.04[a]

Values are in dry matter and they are the mean of three determinations±standard deviation. Values in the same column for each vitamin with the different superscript are significantly different ($p \leq 0.05$). Enteral formula A stands for polymeric formula, enteral formula B stands for oligomeric formula. The significance calculated is for each enteral formula.

Table 2. Changes in vitamin content of enteral formula A1 and B1 after storage at 60 ± 1 °C, RH 60 ± 5%.

Storage Condition (60 ± 1 °C, RH 60 ± 5%)		Vitamin A (μg RE/100 g)	α -Tocopherol (mg α-TE/100 g)	γ-Tocopherol (mg/100 g)	δ-Tocopherol (mg/100 g)	Vitamin E (mg α-TE/100 g)	Vitamin C (mg/100 g)	Vitamin B_1 (mg/100 g)
A1	control	407.4 ± 21.8^{a}	8.15 ± 0.23^{a}	3.89 ± 0.02^{a}	0.82 ± 0.00^{a}	8.54 ± 0.23^{a}	90.8 ± 3.46^{a}	1.16 ± 0.06^{a}
	5 days	301.4 ± 17.4^{b}	7.19 ± 0.19^{b}	3.58 ± 0.12^{b}	0.97 ± 0.02^{a}	7.56 ± 0.19^{b}	88.0 ± 0.76^{a}	1.00 ± 0.02^{b}
	10 days	264.3 ± 9.5^{c}	7.11 ± 0.43^{b}	3.19 ± 0.02^{c}	0.94 ± 0.03^{a}	7.44 ± 0.43^{b}	90.7 ± 0.29^{a}	0.90 ± 0.03^{b}
B1	control	462.3 ± 25.5^{a}	9.61 ± 0.24^{a}	2.90 ± 0.15^{a}	0.61 ± 0.04^{a}	9.90 ± 0.23^{a}	98.9 ± 1.00^{a}	1.29 ± 0.02^{a}
	5 days	358.1 ± 10.8^{b}	8.81 ± 0.07^{b}	2.28 ± 0.11^{b}	0.65 ± 0.02^{a}	9.05 ± 0.08^{b}	97.8 ± 1.80^{a}	1.22 ± 0.03^{a}
	10 days	326.7 ± 14.1^{b}	8.32 ± 0.17^{c}	2.43 ± 0.03^{b}	0.71 ± 0.01^{b}	8.57 ± 0.17^{c}	98.7 ± 0.71^{a}	0.98 ± 0.04^{b}

Values are in dry matter and they are the mean of three determinations±standard deviation. Values in the same column for each vitamin with the different superscript are significantly different ($p \leq 0.05$). Enteral formula A stands for polymeric formula, enteral formula B stands for oligomeric formula. "RH" stands for relative humidity.

Table 3A. Changes in vitamin content of enteral formula A after storage at 37 ± 1 °C, RH 75 ± 5%.

Storage Condition (37 ± 1 °C, RH 75 ± 5%)		Vitamin A (μg RE/100 g)	α -Tocopherol (mg α-TE/100 g)	γ-Tocopherol (mg/100 g)	δ-Tocopherol (mg/100 g)	Vitamin E (mg α-TE/100 g)	Vitamin C (mg/100 g)	Vitamin B_1 (mg/100 g)
A1	control	407.4 ± 21.8^{a}	8.15 ± 0.23^{a}	3.89 ± 0.02^{a}	0.82 ± 0.00^{a}	8.54 ± 0.23^{a}	90.8 ± 3.46^{a}	1.16 ± 0.06^{a}
	1 month	401.7 ± 26.8^{a}	7.69 ± 0.17^{ab}	3.69 ± 0.11^{b}	1.05 ± 0.01^{b}	8.07 ± 0.16^{b}	89.9 ± 2.78^{a}	1.05 ± 0.01^{b}
	2 months	349.7 ± 6.4^{b}	7.47 ± 0.38^{b}	3.00 ± 0.15^{c}	0.77 ± 0.03^{c}	7.78 ± 0.40^{bc}	89.7 ± 1.21^{a}	0.95 ± 0.01^{c}
	3 months	333.2 ± 4.4^{b}	7.51 ± 0.16^{c}	3.45 ± 0.01^{de}	0.91 ± 0.02^{d}	7.86 ± 0.15^{bc}	88.4 ± 2.94^{a}	0.96 ± 0.02^{c}
	5 months	290.9 ± 0.8^{c}	7.36 ± 0.33^{b}	3.27 ± 0.16^{e}	0.95 ± 0.03^{de}	7.70 ± 0.035^{bc}	89.1 ± 3.81^{a}	0.94 ± 0.04^{c}
	6 months	268.2 ± 18.1^{c}	7.19 ± 0.19^{c}	3.58 ± 0.12^{d}	0.97 ± 0.02^{e}	7.56 ± 0.19^{c}	88.1 ± 2.25^{a}	0.94 ± 0.04^{c}
A2	control	397.7 ± 11.2^{a}	7.89 ± 0.16^{a}	3.61 ± 0.09^{a}	0.85 ± 0.01^{a}	8.26 ± 0.15^{a}	90.9 ± 1.77^{a}	1.22 ± 0.06^{a}
	1 month	387.5 ± 21.9^{a}	7.62 ± 0.05^{ab}	3.55 ± 0.11^{a}	0.99 ± 0.02^{b}	7.98 ± 0.06^{ab}	90.2 ± 1.50^{a}	1.04 ± 0.04^{b}
	2 months	354.6 ± 18.5^{b}	7.62 ± 0.14^{ab}	2.77 ± 0.10^{b}	1.00 ± 0.01^{b}	7.91 ± 0.14^{b}	89.6 ± 1.41^{a}	1.01 ± 0.01^{bd}
	3 months	340.6 ± 9.1^{b}	7.47 ± 0.21^{bc}	3.45 ± 0.12^{a}	0.77 ± 0.03^{c}	7.82 ± 0.22^{bc}	89.6 ± 0.36^{a}	0.94 ± 0.04^{c}
	5 months	289.9 ± 17.4^{c}	7.24 ± 0.12^{c}	2.88 ± 0.11^{b}	0.90 ± 0.02^{d}	7.54 ± 0.13^{c}	89.5 ± 3.70^{a}	0.96 ± 0.01^{cd}
	6 months	266.5 ± 13.3^{c}	7.24 ± 0.16^{c}	2.32 ± 0.01^{c}	0.90 ± 0.01^{d}	7.48 ± 0.26^{cd}	89.3 ± 2.88^{a}	0.96 ± 0.02^{cd}
A3	control	391.1 ± 17.4^{a}	8.05 ± 0.01^{a}	3.93 ± 0.15^{a}	0.83 ± 0.01^{a}	8.45 ± 0.01^{a}	89.9 ± 1.81^{a}	1.16 ± 0.01^{a}
	1 month	375.3 ± 11.3^{ab}	7.51 ± 0.16^{b}	2.71 ± 0.07^{b}	0.98 ± 0.02^{b}	7.79 ± 0.17^{b}	89.3 ± 4.02^{a}	1.07 ± 0.00^{b}
	2 months	357.3 ± 16.3^{b}	7.51 ± 0.25^{b}	3.70 ± 0.05^{c}	0.99 ± 0.01^{b}	7.89 ± 0.25^{b}	88.7 ± 2.33^{a}	0.98 ± 0.05^{c}
	3 months	308.2 ± 18.1^{c}	7.44 ± 0.27^{bc}	2.81 ± 0.01^{b}	0.76 ± 0.02^{c}	7.73 ± 0.26^{bc}	89.2 ± 0.90^{a}	0.92 ± 0.05^{d}
	5 months	268.0 ± 4.4^{d}	7.14 ± 0.07^{c}	2.42 ± 0.04^{d}	0.88 ± 0.01^{d}	7.39 ± 0.08^{c}	88.1 ± 4.80^{a}	0.91 ± 0.02^{d}
	6 months	265.3 ± 5.9^{d}	7.14 ± 0.23^{c}	2.82 ± 0.00^{b}	0.89 ± 0.01^{d}	7.42 ± 0.23^{c}	88.1 ± 4.19^{a}	0.91 ± 0.05^{d}

Values are in dry matter and they are the mean of three determinations±standard deviation. Values in the same column for each vitamin with the different superscript are significantly different ($p \leq 0.05$) for every batch. Enteral formula A stands for polymeric formula. "RH" stands for relative humidity.

decreasing concentration at several constant temperatures (Peleg et al., 2016). The first-order kinetics model for vitamin A degradation determined in this study in agreement with the other studies (Albalá-Hurtado et al., 2000; Baéz et al., 2012; Yan et al., 2010). The rate constants obtained showed that vitamin A degradation was temperature dependent (Table 5). In this case, for vitamin A, activation energy was a measure of temperature sensitivity to reactions responsible for the degradation. The Arrhenius equation showed 125.29 kJ/mol and 122.94 kJ/mol of activation energy for EFA and EFB, respectively, which was similar to the value 100.41 kJ/mol as Yan et al. (2010) reported, and are more than 51.96 kJ/mol reported by Baéz et al. (2012). These results suggested that vitamin A stability were similar in both enteral formulas, however the initial content of vitamin A in EFA was lower than that in EFB, the decrease of vitamin A in EFA was slightly faster than that did in EFB during storage. On the other hand, it reported that vitamin A destruction follows a zero-order (Jiang et al., 2021). The degradation of vitamin A and its esters (acetate, palmitate) is mainly derived from isomerization and oxidation by the action of light, oxygen and acids. As reported, retinol of samples stored at pH 4–5 could produce a trans-cis isomerization and subsequent loss of vitamin activity (Ren and Yan, 2009). Packer et al. suggested that an autoxidation process took place during processing and the storage of retinol-containing foods (Packer et al., 1981). Under UV light, the photo-oxidation occurred of vitamin A, and produce the mixture of retinal and epoxy derivatives. However, vitamin A could produce an hydrovitamin A and some fragments, which derived from the cleavage of the side-chain double bonds. The vitamin A could produce epoxides, peroxides and cleavage products, while the palmitate could mainly product the cleavage fragments. The photosensitized processes considered to be initiated by singlet oxygen (Crank & Pardijanto, 1995).

3.3. Change of vitamin E content during storage

In this study, the changes in vitamin E content were the total tocopherol changes (supplemented with α-tocopherol acetate in EFs and tocopherols in vegetable oils used for formula manufacturing). The vitamin E content also showed a significant decreased ($p \leq 0.05$) between the samples stored for 5 days (11% in EFA 1 and 13% in EFB 1) and samples stored for 10 days (10% in EFA 1 and 14% in EFB 1) under the condition of 60 ± 1 °C, RH 60 ± 5% (Table 2). Besides, the vitamin E content in the samples of EFA 1–3 and EFB 1–3 also showed a slight significant decrease ($p \leq 0.05$) of 6–10% after kept at 37 °C with RH 75 ± 5% for 1 month. As the period of storage extended to 2, 3, 5 and 6 months, the gradual decreases in vitamin E content were observed, and the reduction of 5–8%, 9–12% in EFA 1–3 and 11–14%, 14–18% in EFB 1–3 were obtained after stored for 3 and 6 months, respectively (Table 3A & Table 3B, Figure 1b. There was a slight significant decreased ($p \leq 0.05$) of the vitamin E content in EFA 1–3 between samples stored for 3 months (3–6%) and 6 months (7–10%) under the condition of 25 °C, RH 60 ± 5%. After 24 months, the reduction of 13–15% for EFA 1–3 and 16–18%

Table 3B. Changes in vitamin content of enteral formula B after storage at 37 ± 1 °C, RH 75 ± 5%.

Storage Condition (37 ± 1 °C, RH 75 ± 5%)		Vitamin A (μg RE/100 g)	α -Tocopherol (mg α-TE/100 g)	γ-Tocopherol (mg/100 g)	δ-Tocopherol (mg/100 g)	Vitamin E (mg α-TE/100 g)	Vitamin C (mg/100 g)	Vitamin B_1 (mg/100 g)
B1	control	462.3 ± 25.4^{a}	9.61 ± 0.25^{a}	2.90 ± 0.15^{a}	0.61 ± 0.01^{a}	9.90 ± 0.23^{a}	98.9 ± 1.00^{a}	1.29 ± 0.02^{a}
	1 month	436.3 ± 19.2 ^{ab}	8.60 ± 0.17^{b}	2.53 ± 0.15^{b}	0.60 ± 0.03^{a}	8.86 ± 0.19^{b}	98.0 ± 2.39^{a}	1.27 ± 0.05 ^{ab}
	2 months	422.4 ± 11.7^{b}	8.51 ± 0.25^{b}	1.80 ± 0.08^{c}	0.62 ± 0.01^{a}	8.69 ± 0.25^{b}	94.6 ± 1.56^{a}	1.21 ± 0.04 ^{ab}
	3 months	386.5 ± 9.2^{c}	8.53 ± 0.16^{b}	1.76 ± 0.02^{c}	0.39 ± 0.00^{b}	8.71 ± 0.16^{b}	95.1 ± 5.69^{a}	1.20 ± 0.01 ^{ab}
	5 months	384.5 ± 8.9^{c}	8.38 ± 0.21^{b}	2.57 ± 0.16^{b}	0.60 ± 0.02^{a}	8.64 ± 0.23^{b}	94.6 ± 2.54^{a}	1.13 ± 0.06^{c}
	6 months	377.2 ± 23.1^{c}	8.29 ± 0.04^{b}	2.34 ± 0.08^{d}	0.37 ± 0.01^{b}	8.56 ± 0.04^{b}	94.3 ± 1.34^{a}	1.06 ± 0.05^{c}
B2	control	459.2 ± 17.0^{a}	9.48 ± 0.28^{a}	2.91 ± 0.37^{a}	0.60 ± 0.01^{a}	9.76 ± 0.32^{a}	99.5 ± 0.50^{a}	1.25 ± 0.01^{a}
	1 month	445.5 ± 26.9^{a}	8.90 ± 0.20^{b}	2.93 ± 0.13^{a}	0.63 ± 0.03^{a}	9.20 ± 0.21^{b}	99.3 ± 2.20^{a}	1.22 ± 0.05^{a}
	2 months	407.3 ± 15.3^{b}	8.71 ± 0.25^{b}	2.01 ± 0.09^{b}	0.62 ± 0.02^{a}	8.92 ± 0.25^{b}	96.5 ± 5.13^{a}	1.21 ± 0.05^{a}
	3 months	391.3 ± 4.99^{bc}	8.20 ± 0.17^{c}	2.29 ± 0.05^{b}	0.58 ± 0.01^{b}	8.43 ± 0.17^{c}	96.3 ± 1.58^{a}	1.19 ± 0.05^{a}
	5 months	379.0 ± 19.0^{bc}	8.21 ± 0.36^{c}	2.05 ± 0.10^{b}	0.36 ± 0.02^{c}	8.42 ± 0.35^{c}	96.5 ± 3.86^{a}	1.09 ± 0.02^{b}
	6 months	367.9 ± 22.3^{c}	7.84 ± 0.26^{c}	1.81 ± 0.01^{b}	0.36 ± 0.02^{b}	8.02 ± 0.26^{c}	95.2 ± 2.00^{a}	1.05 ± 0.00^{b}
B3	control	467.5 ± 12.6^{a}	9.47 ± 0.15^{a}	3.10 ± 0.07^{a}	0.82 ± 0.04^{a}	9.79 ± 0.15^{a}	98.6 ± 1.30^{a}	1.27 ± 0.04^{a}
	1 month	456.3 ± 24.6^{a}	8.59 ± 0.24^{b}	2.25 ± 0.14^{b}	0.57 ± 0.02^{b}	8.82 ± 0.25^{b}	98.0 ± 5.84^{a}	1.25 ± 0.04^{a}
	2 months	409.0 ± 23.5^{b}	8.53 ± 0.23^{b}	2.64 ± 0.03^{c}	0.81 ± 0.03^{a}	8.80 ± 0.23^{bc}	95.7 ± 3.17^{a}	1.20 ± 0.04^{ab}
	3 months	397.0 ± 23.4^{b}	8.31 ± 0.19^{bc}	1.84 ± 0.00^{d}	0.84 ± 0.01^{a}	8.57 ± 0.07^{bcd}	96.4 ± 5.86^{a}	1.21 ± 0.04^{ab}
	5 months	386.5 ± 2.1^{bc}	8.30 ± 0.06^{bc}	2.58 ± 0.11^{c}	0.80 ± 0.04^{a}	8.50 ± 1.89^{cd}	95.2 ± 0.89^{a}	1.16 ± 0.07^{bc}
	6 months	357.8 ± 11.1^{c}	8.14 ± 0.08^{c}	2.12 ± 0.05^{b}	0.56 ± 0.01^{b}	8.36 ± 0.08^{d}	95.3 ± 5.81^{a}	1.10 ± 0.00^{c}

Values are in dry matter and they are the mean of three determinations±standard deviation. Values in the same column for each vitamin with the different superscript are significantly different ($p \leq 0.05$) for every batch. Enteral formula B stands for oligomeric formula. "RH" stands for relative humidity.

for EFB 1–3 could be observed, respectively (Table 4A & Table 4B, Figure 1b).

Different effects have been observed in vitamin E contents after storage of enteral formulas under different conditions. Albalá-Hurtado et al. found that the storage of liquid and powder infant milk formulas for 12 months at 37 °C did not affect the vitamin E content (Albalá-Hurtado et al., 2000). Juana et al. observed a slight reduction in vitamin E happened when the two samples of liquid enteral formulas were kept at 20 or 30 °C for 3 months. However, when the samples were kept at 30 °C for 9 months, a decrease of 51–55% was found (Juana and Vidal-Valverde, 2001). Miquel et al. observed that four milk-based infant formulas kept at 37 °C for 17 months underwent vitamin E reductions of 50% (Miquel et al., 2004). Frias et al. found the vitamin E content in two powder enteral formulas opening the bag decreased by 59–60% after storage at 30 °C with $A_w = 0.44$ for 6 months, and reductions of 30% were obtained after 6 months at 30 °C without controlled A_w (Frias et al., 2009). Wang et al. studied the vitamin E content in a powdered formula stored at 37 °C, RH 75 ± 5% for 180 days and 60 °C, RH 60 ± 5% for 10

Table 4A. Changes in vitamin content of enteral formula A after storage at 25 ± 1 °C, RH 60 ± 5%.

Storage Condition (25 ± 1 °C, RH 60 ± 5%)		Vitamin A (μg RE/100 g)	α -Tocopherol (mg α-TE/100 g)	γ-Tocopherol (mg/100 g)	δ-Tocopherol (mg/100 g)	Vitamin E (mg α-TE/100 g)	Vitamin C (mg/100 g)	Vitamin B_1 (mg/100 g)
A1	control	407.4 ± 21.8^{a}	8.15 ± 0.23^{a}	3.89 ± 0.02^{a}	0.82 ± 0.00^{a}	8.54 ± 0.23^{a}	90.8 ± 3.46^{a}	1.16 ± 0.06^{a}
	3 months	369.6 ± 22.3^{b}	7.68 ± 0.30^{ab}	2.72 ± 0.05^{b}	0.59 ± 0.02^{b}	8.13 ± 0.25^{ab}	90.7 ± 1.53^{a}	1.04 ± 0.01^{b}
	6 months	345.2 ± 14.5^{bc}	7.39 ± 0.11^{b}	1.97 ± 0.07^{c}	0.63 ± 0.01^{c}	7.91 ± 0.09^{bc}	88.5 ± 4.06^{a}	0.96 ± 0.02^{c}
	9 months	346.4 ± 15.1^{bc}	7.39 ± 0.07^{b}	1.71 ± 0.07^{d}	0.75 ± 0.01^{d}	7.57 ± 0.07^{c}	89.7 ± 4.37^{a}	0.94 ± 0.03^{c}
	12 months	342 ± 5.7^{c}	7.33 ± 0.68^{b}	1.77 ± 0.04^{d}	0.81 ± 0.01^{e}	7.52 ± 0.67^{c}	89.5 ± 1.68^{a}	0.93 ± 0.04^{c}
	18 months	354.5 ± 11.9^{bc}	7.29 ± 0.12^{b}	1.81 ± 0.10^{d}	0.60 ± 0.01^{b}	7.48 ± 0.12^{c}	88.7 ± 4.03^{a}	0.93 ± 0.03^{c}
	24 months	342.7 ± 7.7^{bc}	7.28 ± 0.25^{b}	1.75 ± 0.07^{d}	0.60 ± 0.01^{b}	7.47 ± 0.25^{c}	88.4 ± 1.74^{a}	0.91 ± 0.01^{c}
A2	control	397.7 ± 11.2^{a}	7.89 ± 0.16^{a}	3.61 ± 0.09^{a}	0.85 ± 0.01^{a}	8.26 ± 0.15^{a}	90.9 ± 1.77^{a}	1.22 ± 0.06^{a}
	3 months	358.8 ± 10.2^{b}	7.70 ± 0.20^{ab}	1.94 ± 0.10^{b}	0.61 ± 0.01^{bc}	7.90 ± 0.19^{ab}	89.7 ± 0.80^{a}	1.01 ± 0.04^{b}
	6 months	355.4 ± 10.4^{b}	7.35 ± 0.41^{bc}	1.59 ± 0.14^{c}	0.67 ± 0.07^{b}	7.52 ± 0.41^{bc}	90.0 ± 2.01^{a}	1.02 ± 0.06^{b}
	9 months	352.4 ± 17.0^{b}	7.24 ± 0.16^{cd}	1.52 ± 0.15^{c}	0.63 ± 0.05^{bc}	7.40 ± 0.18^{c}	89.1 ± 4.01^{a}	1.00 ± 0.03^{b}
	12 months	350.0 ± 8.7^{b}	7.19 ± 0.26^{cd}	1.57 ± 0.19^{cd}	0.64 ± 0.01^{bc}	7.35 ± 0.27^{c}	89.7 ± 0.92^{a}	1.01 ± 0.02^{b}
	18 months	349.3 ± 2.5^{b}	6.95 ± 0.11^{d}	1.75 ± 0.05^{d}	0.61 ± 0.02^{c}	7.13 ± 0.11^{c}	90.0 ± 2.58^{a}	1.01 ± 0.05^{b}
	24 months	353.1 ± 7.2^{b}	6.96 ± 0.06^{d}	1.96 ± 0.71^{d}	0.66 ± 0.03^{bc}	7.14 ± 0.06^{c}	89.4 ± 1.77^{a}	1.01 ± 0.02^{b}
A3	control	391.1 ± 17.4^{a}	8.05 ± 0.01^{a}	3.93 ± 0.15^{a}	0.83 ± 0.01^{a}	8.45 ± 0.01^{a}	89.9 ± 1.81^{a}	1.16 ± 0.01^{a}
	3 months	366.9 ± 13.9^{b}	7.76 ± 0.46^{a}	2.49 ± 0.22^{b}	0.57 ± 0.01^{b}	8.02 ± 0.47^{ab}	89.1 ± 3.47^{a}	1.03 ± 0.01^{b}
	6 months	352.1 ± 11.2^{b}	7.31 ± 0.23^{b}	2.71 ± 0.04^{c}	0.66 ± 0.01^{c}	7.59 ± 0.23^{bc}	89.1 ± 2.38^{a}	0.98 ± 0.00^{c}
	9 months	348.0 ± 19.6^{b}	7.25 ± 0.12^{b}	2.74 ± 0.04^{d}	0.71 ± 0.03^{d}	7.48 ± 0.12^{c}	88.9 ± 2.17^{a}	0.97 ± 0.06^{c}
	12 months	344.4 ± 6.1^{b}	7.26 ± 0.11^{b}	2.12 ± 0.10^{d}	0.81 ± 0.01^{a}	7.48 ± 0.10^{c}	88.5 ± 3.13^{a}	0.97 ± 0.00^{c}
	18 months	341.7 ± 0.6^{b}	7.05 ± 0.32^{b}	1.80 ± 0.02^{e}	0.57 ± 0.03^{b}	7.24 ± 0.32^{c}	88.8 ± 2.61^{a}	0.99 ± 0.02^{c}
	24 months	341.4 ± 5.4^{b}	6.96 ± 0.27^{b}	1.73 ± 0.05^{e}	0.57 ± 0.04^{b}	7.14 ± 0.27^{c}	88.5 ± 2.23^{a}	0.97 ± 0.01^{c}

Values are in dry matter and they are the mean of three determinations±standard deviation. Values in the same column for each vitamin with the different superscript are significantly different ($p \leq 0.05$) for every batch. Enteral formula A stands for polymeric formula. "RH" stands for relative humidity.

Table 4B. Changes in vitamin content of enteral formula B after storage at 25 ± 1 °C, RH 60 ± 5%.

Storage Condition (25 ± 1 °C, RH 60 ± 5%)		Vitamin A (μg RE/100 g)	α -Tocopherol (mg α-TE/100 g)	γ-Tocopherol (mg/100 g)	δ-Tocopherol (mg/100 g)	Vitamin E (mg α-TE/100 g)	Vitamin C (mg/100 g)	Vitamin B_1 (mg/100 g)
B1	control	462.3 ± 25.4^{a}	9.61 ± 0.25^{a}	2.90 ± 0.15^{a}	0.61 ± 0.01^{a}	9.90 ± 0.23^{a}	98.9 ± 1.00^{a}	1.29 ± 0.02^{a}
	3 months	452.8 ± 19.5^{ab}	9.47 ± 0.12^{a}	1.60 ± 0.09^{b}	0.40 ± 0.01^{b}	9.63 ± 0.13^{b}	98.4 ± 1.31^{ab}	1.20 ± 0.06^{b}
	6 months	443.9 ± 2.6^{abc}	9.20 ± 0.11^{b}	1.23 ± 0.06^{c}	0.29 ± 0.00^{c}	9.32 ± 0.11^{c}	95.0 ± 3.40^{b}	1.17 ± 0.03^{b}
	9 months	443 ± 25.3^{abc}	8.68 ± 0.14^{c}	1.55 ± 0.07^{b}	0.29 ± 0.02^{c}	8.84 ± 0.14^{d}	$99.3 \pm 2.55a$	1.16 ± 0.06^{b}
	12 months	425.3 ± 4.5^{bcd}	8.52 ± 0.17^{c}	1.58 ± 0.03^{b}	0.55 ± 0.01^{d}	8.68 ± 0.18^{d}	97.9 ± 1.26^{ab}	1.18 ± 0.03^{b}
	18 months	421.9 ± 16.2^{cd}	8.09 ± 0.14^{d}	1.27 ± 0.02^{c}	0.26 ± 0.01^{e}	8.22 ± 0.14^{e}	96.5 ± 3.31^{ab}	1.17 ± 0.03^{b}
	24 months	407.1 ± 3.9^{d}	8.11 ± 0.08^{d}	1.27 ± 0.02^{c}	0.26 ± 0.00^{e}	8.24 ± 0.09^{e}	95.6 ± 0.69^{ab}	1.15 ± 0.04^{b}
B2	control	459.2 ± 17.0^{a}	9.48 ± 0.28^{a}	2.91 ± 0.37^{a}	0.60 ± 0.01^{a}	9.76 ± 0.32^{a}	99.5 ± 0.50^{a}	1.25 ± 0.01^{a}
	3 months	433.4 ± 10.2^{b}	9.19 ± 0.18^{b}	1.70 ± 0.08^{b}	0.42 ± 0.01^{b}	9.36 ± 0.18^{b}	98.6 ± 2.13^{a}	1.17 ± 0.07^{b}
	6 months	426.4 ± 14.9^{b}	9.09 ± 0.06^{bc}	1.35 ± 0.01^{c}	0.29 ± 0.01^{c}	9.23 ± 0.06^{b}	95.3 ± 2.03^{a}	1.15 ± 0.05^{bc}
	9 months	425.4 ± 3.1^{b}	8.87 ± 0.18^{c}	1.95 ± 0.07^{b}	0.27 ± 0.01^{d}	9.07 ± 0.18^{b}	95.9 ± 4.80^{a}	1.16 ± 0.06^{bc}
	12 months	419.6 ± 9.2^{bc}	8.48 ± 0.12^{d}	1.71 ± 0.04^{b}	0.55 ± 0.01^{e}	8.66 ± 0.12^{c}	99.6 ± 1.12^{a}	1.14 ± 0.03^{bc}
	18 months	407.2 ± 15.4^{c}	8.04 ± 0.07^{e}	1.26 ± 0.02^{c}	0.26 ± 0.01^{d}	8.16 ± 0.07^{d}	98.3 ± 2.73^{a}	1.15 ± 0.01^{bc}
	24 months	405.6 ± 4.6^{c}	8.06 ± 0.10^{e}	1.25 ± 0.05^{c}	0.26 ± 0.00^{d}	8.19 ± 0.10^{d}	97.2 ± 1.55^{a}	1.11 ± 0.05^{c}
B3	control	467.5 ± 12.6^{a}	9.47 ± 0.15^{a}	3.10 ± 0.07^{a}	0.82 ± 0.04^{a}	9.79 ± 0.15^{a}	98.6 ± 1.30^{ab}	1.27 ± 0.04^{a}
	3 months	455.3 ± 2.4^{ab}	9.07 ± 0.31^{ab}	1.49 ± 0.04^{b}	0.55 ± 0.01^{b}	9.23 ± 0.32^{b}	99.3 ± 1.13^{ab}	1.18 ± 0.07^{b}
	6 months	442.9 ± 18.6^{abc}	8.90 ± 0.07^{bc}	1.15 ± 0.06^{c}	0.45 ± 0.01^{c}	9.02 ± 0.07^{bc}	95.3 ± 1.75^{a}	1.19 ± 0.02^{ab}
	9 months	430.5 ± 13.0^{bcd}	8.57 ± 0.39^{cd}	1.83 ± 0.12^{d}	0.40 ± 0.01^{d}	8.76 ± 0.39^{c}	98.1 ± 1.89^{ab}	1.12 ± 0.02^{b}
	12 months	425.9 ± 22.9^{cd}	8.41 ± 0.22^{d}	1.50 ± 0.04^{b}	0.71 ± 0.03^{e}	8.56 ± 0.23^{c}	99.8 ± 5.05^{b}	1.17 ± 0.05^{b}
	18 months	417.4 ± 25.7^{cd}	7.95 ± 0.37^{e}	1.25 ± 0.09^{c}	0.28 ± 0.01^{f}	8.08 ± 0.38^{d}	99.2 ± 1.61^{ab}	1.15 ± 0.06^{b}
	24 months	409.5 ± 6.3^{d}	7.87 ± 0.08^{e}	1.22 ± 0.05^{c}	0.27 ± 0.01^{f}	7.99 ± 0.08^{d}	97.8 ± 1.42^{ab}	1.15 ± 0.04^{b}

Values are in dry matter and they are the mean of three determinations±standard deviation. Values in the same column for each vitamin with the different superscript are significantly different ($p \leq 0.05$) for every batch. Enteral formula B stands for oligomeric formula. "RH" stands for relative humidity.

days, the results showed that the attenuation rates of the vitamin E were 22.5% and 4.7% (Wang et al., 2021).

From the results in Table 5, rate constants showed that the vitamin E degradation also followed a first-order kinetics model, which was temperature dependent. Using the Arrhenius Law, the activation energies were 102.7 kJ/mol for EFA and 93.51 kJ/mol for EFB, which were more than 13.15 kJ/mol Jiang et al. reported (Jiang et al., 2021). The results indicated that the vitamin E in EFA was more stable than in EFB. The α-tocopherol form of vitamin E is highly unstable and can be easily oxidized during processing and storage (Gawrysiak-Witulska et al., 2009). The stability of tocopherols can be affected by environmental factors such as light, oxygen and temperature, including food-related factors such as moisture content, water activity, lipid oxidation, alkaline media and small amounts of transition metals. Tocopherol can react with peroxide radicals to generate peroxide and a tocopherol radical, tocopherol radicals are not active, which can be produced dimeric tocopherol or trimeric tocopherol. These substances are further oxidized to produce tocopherol oxides (tocopheryl-quinone, tocopherol hydroquinone). The synthetic esterified forms of α-tocopherols are less susceptible to oxidation than α-tocopherols (Moffatt et al., 1987).

3.4. Change of vitamin C content during storage

EFs are usually fortified with vitamin C in the form of sodium ascorbate because sodium ascorbate is more stable than ascorbic acid. Vitamin C showed good stability in relation to storage, the contents in EFA and EFB throughout storage at all test conditions only showed a slight decrease, which was not statistically significant (Tables 2, 3, and 4, Figure 1c). The results did not agree with those reported in a previous study of the stability of vitamin C in different formulas (Baéz et al., 2012; Wang et al., 2021). Baéz et al. evaluated vitamin C content in a powdered milk formula stored (in a chamber with thermal thermostat) at 22, 37 and 45 °C for 105 days immediately after production. At the end of the study, the loss of vitamin C was 19.98% at 37 °C (Baéz et al., 2012). Wang et al. studied the vitamin C content in a powdered formula stored at 37 °C, RH 75 ± 5% for 180 days and 25 °C, RH 60 ± 5% for 720 days, the results showed that the attenuation rates of the vitamin C were 30.7% and 21.7% (Wang et al., 2021).

The results of this study are not consistent with previous report. Like most vitamins of interest, the kinetics of vitamin C degradation during storage follow a first order kinetic equation. Jiang et al. reported the activation energy for vitamin C degradation was 74.67 kJ/mol (Jiang et al., 2021). Baéz et al. and Burdurlu et al. studied the value 51.96 and 56 kJ/mol (Baéz et al., 2012; Burdurlu et al., 2006), respectively. Degradation of vitamin C proceeds both aerobic and anaerobic pathways and depends upon many factors such as oxygen, heat, light, storage temperature and storage time. Oxidation of vitamin C occurs mainly during the processing, whereas, anaerobic degradation of vitamin C mainly appears during storage. It was reported that several decomposition reactive products (furans and their derivatives) occur via the degradation of vitamin C. These compounds may combine with amino acids, result in formation of brown pigments. Hydoxymethylfurfural (HMF) is one of the decomposition products of vitamin C, which suggested that a precursor of brown pigments. It is used to evaluate severity of heating and applied to fruit juices during processing for quality control (Hande Selen Burdurlu et al., 2006; Liu et al. 2013).

3.5. Change of thiamine content during storage

The EFA and EFB were supplemented with thiamine hydrochloride. When the EFA 1 and EFB 1 formulas were stored at 60 ± 1 °C with RH 60 ± 5%, the thiamine content in EFA 1 underwent a significant decreased ($p \leq 0.05$) of 14% after 5 days, whilst a significantly reduction ($p \leq 0.05$) of 24% was obtained only after 10 days in EFB 1 (Table 2). When EFA 1-3and EFB 1–3 were kept at 37 ± 1 °C with RH 75 ± 5% for after 1, 2, 3, 5 and 6 months, the thiamine content in EFA 1–3 underwent a significant decreased ($p \leq 0.05$) of 8–15% after 1 month. When the period of storage was extended to 3 and 6 months, the decreases in thiamine content were observed and reductions of 17–23% and 19–22%, whilst the thiamine content in EFB 1–3 suffered a slight and not significant decrease of 5–7% after 3 months. When the period of storage was prolonged to 6 months, an important reduction of 14–18% was observed (Table 3A & Table 3B,

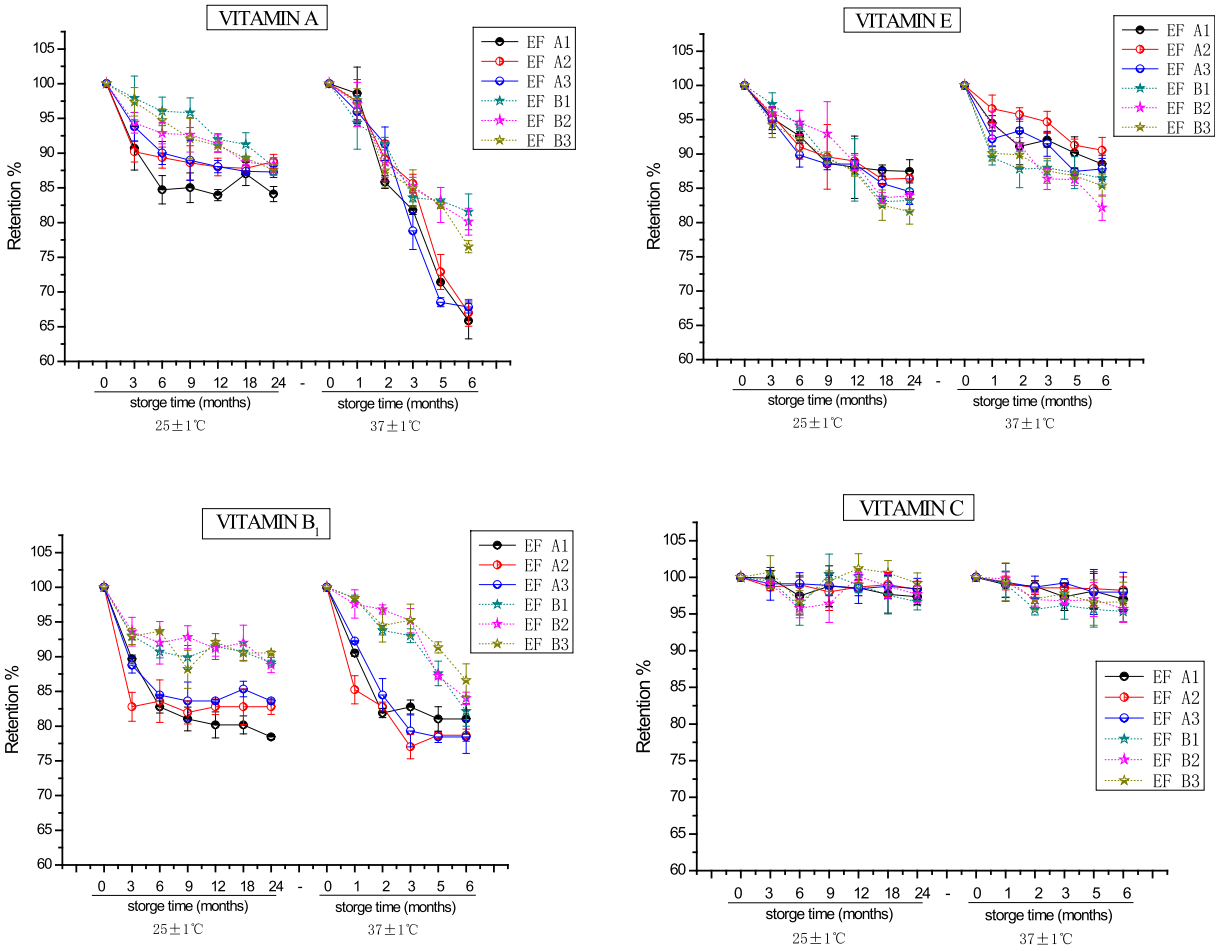

Figure 1. Effect of storage conditions on the vitamin retention of enteral formulas. (a) Effect of storage conditions on the vitamin A retention of enteral formulas; (b) Effect of storage conditions on the vitamin E retention of enteral formulas; (c) Effect of storage conditions on the vitamin B1 retention of enteral formulas; (d) Effect of storage conditions on the vitamin C retention of enteral formulas. Enteral formula A1-3 stands for three different batches of polymeric formula, enteral formula B1-3 stands for three different batches of oligomeric formula.

Figure 1d). When the formulas were kept at 25 °C with RH 75 ± 5%, the thiamine content underwent significant decrease ($p \leq 0.05$) of 10–17% and 6–7% for EFA and EFB after 3 months, respectively. When the period of storage was extended to 6, 12 and 24 months, gradual decreases in the thiamine content were observed, and reductions of 16–22% for EFA and 7–9% for EFB after 24 months, respectively (Table 4A & Table 4B, Figure 1d).

Similar results were reported by Juana et al. who observed noticeable losses (20–23%) in thiamine when enteral feeding formulas were kept at 30 °C after 6 months (Juana and Vidal-Valverde, 2001). However, Albalá-Hurtado et al. found that thiamine content remained unchanged when the powder and liquid infant milk formulas were kept at 37 °C for 12 months (Albalá-Hurtado et al., 2000). Frias et al. evaluated the thiamine content decreased by 52% and 70%, when two powdered enteral formulas opening the bag were stored at 30 °C with or without $A_w = 0.44$ after 6 months, respectively (Frias et al., 2009). Wang et al. studied the thiamine content in a powdered formula stored at 37 °C, RH 75 ± 5% for 180 days and at 25 °C, RH 60 ± 5% for 720 days, the results showed that the attenuation rates of the thiamine were 10.3% and 24.3%, respectively (Wang et al., 2021).

Thiamine's degradation during thermal processing and storage of foods is known to follow first order kinetics with associated activation energies in the range of 33–124 kJ/mol, where the rate constant's temperature-dependence can be described by the Arrhenius equation (Ramaswamy et al., 1990). From the results in Table 5, rate constants showed that the thiamine degradation also followed a first-order kinetics model, which was temperature dependent. Using the Arrhenius Law, the activation energy were 105.98 kJ/mol for EFA and 123.48 kJ/mol for

Table 5. Results of kinetics parameters.

	Indicators	60 ± 1 °C		37 ± 1 °C		25 ± 1 °C		Ea, (kJ/mol)
		K	R^2	K	R^2	K	R^2	
EF A	Vitamin A	0.043	0.9511	0.002	0.9812	0.0002	0.4307	125.29
	Vitamin E	0.014	0.8357	0.0005	0.7803	0.0002	0.7275	102.77
	Vitamin B_1	0.025	0.9905	0.001	0.6636	0.0003	0.6457	105.98
EF B	Vitamin A	0.035	0.9311	0.001	0.8793	0.0002	0.9628	122.94
	Vitamin E	0.014	0.9805	0.0006	0.545	0.0003	0.9184	93.51
	Vitamin B_1	0.02	0.6892	0.001	0.9658	0.0001	0.5055	123.48

Table 6A. Daily vitamin intake ratio of powder enteral formula A* vs. Chinese RNI for women and men.

EF A storage conditions	Vitamin A EF A/RNI	Vitamin A EF A/UL	Vitamin A EF A/Label	Vitamin E EF A/RNI	Vitamin E EF A/UL	Vitamin E EF A/Label	Vitamin B_1 EF A/RNI	Vitamin B_1 EF A/Label	Vitamin C EF A/RNI	Vitamin C EF A/UL	Vitamin C EF A/Label
	men/women			men/women			men/women		men/women		
control	1.79/2.05	0.48	1.42	2.16	0.04	1.17	3.03/3.54	1.48	3.26	0.16	1.29
Storage at (37 ± 1 °C, RH 75 ± 5%)											
3 months	1.47/1.68	0.39	1.17	2.01	0.04	1.08	2.42/2.82	1.18	3.21	0.16	1.27
6 months	1.20/1.37	0.32	0.95	1.93	0.04	1.04	2.41/2.81	1.17	3.19	0.16	1.26
Storage at (25 ± 1 °C, RH 60 ± 5%)											
3 months	1.64/1.88	0.44	1.30	2.06	0.04	1.17	2.64/3.08	1.28	3.23	0.16	1.28
6 months	1.58/1.80	0.42	1.25	1.97	0.04	1.11	2.54/2.96	1.23	3.21	0.16	1.27
12 months	1.55/1.78	0.41	1.23	1.92	0.04	1.07	2.49/2.91	1.21	3.21	0.16	1.27
24 months	1.56/1.78	0.41	1.23	1.86	0.04	1.03	2.48/2.89	1.20	3.20	0.16	1.27

Daily intake of enteral formula (1500 Kcal). Enteral formula A stands for polymeric formula. "RH" stands for relative humidity. "RNI" stands for recommended nutrient intake. "UL" stands for upper level of intake.

EFB, respectively. The results showed that the thiamine in EFA was less stable than that in EFB. Thiamine is one of the least stable vitamins. The structure of thiamine consists of substituted pyrimidine and thiazole rings linked by a methylene bridge. Under acidic conditions (pH = 6), the thiamine free base becomes protonated, which is susceptible to hydrolytic cleavage to yield 2-methyl-4-amino-5-hydroxymethyl pyrimidine and 4-methyl-5-hydroxyethyl thiazole. In strong acidic solutions, thiamine degrades to form oxythiamin by the replacement of the primary amino group on the pyrimidine ring by a hydroxyl group. Under alkaline conditions (pH > 7), thiamine is converted into the neutral pseudobase, which is further converted into the thiol form and then into a variety of sulfur-containing lower-molecular-weight compounds. The degradation of thiamine can occur both during thermal processing and product storage (Pachapurkar and Bell, 2005).

From the above data, we found that the stability of vitamins except vitamin C were higher when stored at 25 °C with RH 60 ± 5%. As the samples were always protected from daylight under sealed original packaging (tinned using modified atmosphere-nitrogen), the observed losses in vitamin content during storage should not be related to light and oxygen effect and could be possible linked to some other factor such as the storage temperature, storage time and different kinds of formulas. As the storage temperature or the storage time increased, the content of vitamins in two formulas was decreased. Under the same conditions, the decrease of vitamin A and thiamine in the EFA samples was faster than they did in the EFB samples, while, the decrease of vitamin E in EFA was lower than that did in EFB. In addition, the sensory of all samples were decreased during the entire storage. However, sensory degradation changed at the different temperatures during the storage. The samples stored at lower temperatures showed a better state than that at higher temperature. Good sensory for overall impression was considered as the borderline of acceptability equivalent to slight off odor and off taste development. Fresh enteral formulas were milk white and had a slight vanilla and milk smell, which developed into yellowish-brown color and a rancidity odor during the storage. When the samples were kept at 60 ± 1 °C, relative humidity (RH) 60 ± 5% for over 10 days, or 37 ± 1 °C, RH 75 ± 5% for over 6 months, although the content of micronutrients meets the Chinese legislation, the observed the sensory of samples were not acceptable. These results were consistent with previous studies (Bordoloi et al., 2020; Frias et al., 2009; Hemery et al., 2020; Wang et al., 2021).

3.6. Daily vitamin intake ratio of EFs

Table 6A & Table 6B showed the ratio for vitamin levels delivered from the enteral formulas that were freshly prepared and after storage versus their Chinese recommended nutrient intake, assuming that the daily intake of enteral formula is 1500 kcal, and values of Chinese recommended nutrient intake (RNI) (vitamin A of 700 μg RE/d for women and 800 μg RE/d for men, vitamin E of 14 mg α-TE/d for both women and men, vitamin C of 100 mg/d for both women and men, and for thiamine of 1.2 mg/d for women and 1.4 mg/d for men) and upper level of intake (UL) (vitamin A of 3000 μg RE/d, vitamin E of 700 mg α-TE/d, and for vitamin C of 2000 mg/d) (Zhai et al., 2005; Ren et al., 2019).

The two formulas satisfied the vitamin requirements in different ways. Formula B provided only slightly higher vitamin content than formula A. The freshly prepared formulas studied here provided large amount of vitamins, exceeding several times the RNI, but still far bellow UL. When they were stored at different storage conditions, decreases in

Table 6B. Daily vitamin intake ratio of powder enteral formula B* vs. Chinese RNI for women and men.

EF B storage conditions	Vitamin A EF B/RNI	Vitamin A EF B/UL	Vitamin A EF B/Label	Vitamin E EF B/RNI	Vitamin E EF B/UL	Vitamin E EF B/Label	Vitamin B_1 EF B/RNI	Vitamin B_1 EF B/Label	Vitamin C EF B/RNI	Vitamin C EF B/UL	Vitamin C EF B/Label
	men/women			men/women			men/women		men/women		
control	2.08/2.38	0.56	1.32	2.52	0.05	1.23	3.27/3.81	1.41	3.56	0.18	1.38
Storage at (37 ± 1 °C, RH 75 ± 5%)											
3 months	1.76/2.01	0.47	1.12	2.20	0.04	1.07	3.09/3.60	1.41	3.45	0.17	1.33
6 months	1.65/1.89	0.44	1.05	2.14	0.04	1.04	2.75/3.21	1.26	3.42	0.17	1.32
Storage at (25 ± 1 °C, RH 60 ± 5%)											
3 months	2.01/2.30	0.54	1.28	2.42	0.05	1.18	3.04/3.55	1.39	3.56	0.18	1.37
6 months	1.97/2.25	0.53	1.25	2.36	0.05	1.15	3.01/3.51	1.38	3.43	0.17	1.32
12 months	1.91/2.18	0.51	1.21	2.22	0.04	1.08	2.99/3.49	1.37	3.57	0.18	1.38
24 months	1.83/2.10	0.49	1.16	2.09	0.04	1.02	2.92/3.41	1.34	3.49	0.17	1.35

Daily intake of enteral formula (1500 Kcal). Enteral formula B stands for oligomeric formula. "RH" stands for relative humidity. "RNI" stands for recommended nutrient intake. "UL" stands for upper level of intake.

vitamin intakes were observed in most of the conditions (Amiri et al., 2019; Caritá et al., 2021; Xu et al., 2021). Whilst, taking into consideration of the least favorable conditions (37 °C with RH 75 ± 5% for 6 months), the formulas still contained sufficient vitamins to meet the RNI and the label states. For EFs, when stored at 37 ± 1 °C, RH 75 ± 5% after 6 months of storage, 1.20–1.37-fold and 1.65–1.89-fold of the RNI and 0.95-fold and 1.05-fold of the label states for vitamin A, 1.93-fold and 2.14-fold of the RNI and 1.04-fold of the label states for vitamin E, 3.19-fold and 3.42-fold of the RNI and 1.26-fold and 1.37-fold of the label states for vitamin C, 2.41–2.81-fold and 2.75–3.21-fold of the RNI and 1.17-fold and 1.26-fold of the label states for thiamine respectively. This observation can be attributed to manufacturers wishing to ensure that at the end of the shelf-life of the formula, vitamin contents are at least as high as the label states.

It is evident from this study that losses of vitamin A, E and thiamine during storage were observed in the EFs, the vitamin C values found remained nearly unchanged during storage of the studied vitamins. The temperature and period of the storage play important roles in the vitamin content of the EFs under sealed original packaging. These results justified the finding that over-fortification in the EFs with vitamins is necessary to ensure that those vitamins meet the content stated on the labels. They should be taken into consideration by manufacturers to recommend the storage conditions when establishing the shelf-life in which RNI and the label states can be satisfied.

4. Conclusion

The two different kinds of commercially-used enteral formulas with different protein source and content (total protein and peptides, respectively) were stored in different storage conditions with different temperature and relative humidity up to 24 months. The content of vitamin A, E (α-, β-, γ-, and δ-tocopherol), C and thiamine was determined in the initial samples and stored samples. As the temperature or time increased in the period of storage, the content of vitamin A, E and thiamine was gradually decreased, while, the level of vitamin C remained stable. The stability of vitamins was higher as stored at 25 ± 1 °C, 60 ± 5%. Under the same conditions, vitamin A and thiamine in the EFA decreased more than they did in the EFB, while vitamin E in EFA decreased less than that in EFB. The kinetics of vitamin A, E and thiamine degradation during storage followed first order kinetic equations. Vitamins overfortification was more than that needed to compensate for their losses during storage. Furthermore, the final levels of vitamins were higher than the minimum level recommended by legislation.

Declarations

Author contribution statement

Yang, Hong: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xu, Li Li: Analyzed and interpreted the data; Wrote the paper.

Hou, Ling: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Xu, Tong Cheng: Conceived and designed the experiments; Analyzed and interpreted the data.

Ye, Shu Hong: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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