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Variability in Quality Attributes of Commercial Alpha-Lipoic Acid Dietary Supplements: Evidence from Pharmacopoeial Testing

Milana Vuković[1], Mladena Lalić-Popović[1,2*], Nemanja Todorović[1], Jelena Čanji Panić[1], Dunja Veskovic[3,4], Ivana Smiljanić[5], and Jelena Jovičić-Bata[1]

[1]*Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia.*
[2]*Centre for Medical and Pharmaceutical Investigations and Quality Control (CEMPhIC), Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia.*
[3]*Department of Dermatovenereology, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia.*
[4]*Clinic for Dermatology, Clinical Center of Vojvodina, Novi Sad, Serbia.*
[5]*Clinic for Plastic and Reconstructive Surgery, Clinical Center of Vojvodina, Novi Sad, Serbia.*

e-mail: mladena.lalic-popovic@mf.uns.ac.rs

ABSTRACT

Introduction: Alpha-lipoic acid (ALA) is a bioactive compound marketed as a dietary supplement (DS) worldwide. **Methods**: This study assessed the quality of nine commercial ALA DS formulations (seven hard capsules, two gastro-resistant capsules) from the Serbian market using *European Pharmacopoeia* tests for solid dosage forms: uniformity of mass (2.9.5), content determination by UV–Vis spectrophotometry, disintegration (2.9.1), and dissolution (2.9.3) in 0.5% sodium lauryl sulfate medium at 37 °C (United States Pharmacopeia apparatus 1 [basket], 900 mL, 100 rpm). **Results**: Measured ALA content ranged from 77.79% to 120.39% of the declared amount, with notable intrabatch variability in some products. Five formulations failed at least one test: two failed uniformity of mass (C, D), two failed content uniformity (B, D), one did not disintegrate within 30 min (H), and three failed dissolution criteria (B, F, H). Our findings reveal an inconsistent quality of ALA DS. **Conclusion**: There is a need for a transparent and credible quality signal that would inform consumers, guide clinicians, and motivate manufacturers to meet higher standards and more consistent product performance.

KEYWORDS: alpha-lipoic acid (ALA), dietary supplements, dissolution testing, UV–vis spectrophotometry

INTRODUCTION

Alpha-lipoic acid (ALA), also known as thioctic acid, is a naturally occurring antioxidant globally marketed for its potential health benefits in metabolic disorders and oxidative stress-related conditions (*1–4*). In Serbia, as well as in other European countries, ALA is registered both as a drug and a dietary supplement (DS), even at the same doses (*5*). In contrast, in the USA, ALA is marketed solely as a DS and is not approved as a prescription or over-the-counter drug (*4*).

In most jurisdictions, DS are regulated as a category of food (*6*), with regulatory oversight focused primarily on safety and labeling rather than on efficacy or pharmaceutical quality. These products can be registered and marketed without prior demonstration of therapeutic efficacy or formal quality control testing (*7*). As a result, the responsibility for ensuring quality, such as content uniformity, disintegration, and dissolution, lies primarily with the manufacturer, and pharmacopoeial standards are not matched by the regulations (*7, 8*).

According to the USP, a high-quality DS is one that, besides being safe (free from harmful levels of contaminants) and labelled accurately, contains the listed ingredients in the declared potency and amounts, ensures bioavailability, and is manufactured according to established current Good Manufacturing Practices (cGMP) (*8*). However, adherence to USP standards is voluntary, and the U.S. Food and Drug Administration (FDA) does not require DS to meet USP quality benchmarks (*7, 9, 10*). Instead, the United States Pharmacopeia (USP) provides a third-party

*Corresponding author

verification program as a tool for manufacturers to ensure DS quality (*10*).

Multiple studies have documented discrepancies between declared and actual active ingredient content in commercially available DS raising concerns about their quality, safety, and efficacy (*4*, *11–15*). ALA, in particular, presents formulation challenges due to its poor water solubility, instability in gastric acid, and extensive hepatic metabolism, resulting in an estimated oral bioavailability of only 30% (*16*). Therefore, the pharmaceutical and technological characteristics of ALA dosage forms can significantly affect its bioavailability and, consequently, its clinical effects (*7*).

The quality control of DS is important because they easily cross international borders in today's increasingly globalized marketplace (*17*). The global use of DS is on the rise and with the lack of mandatory quality testing in most regulatory systems, there is a pressing need for independent, evidence-based assessments of their quality (*18–20*).

The aim of the study was to investigate the quality of commercially available DS containing ALA by evaluating mass and content uniformity, disintegration time, and dissolution profiles, using analytical methods and regulatory acceptance criteria for solid dosage forms prescribed by the *European Pharmacopoeia*, *11th edition* (EP).

METHODS

The experimental part of the research was conducted in the laboratories of the Department of Pharmacy, Faculty of Medicine, University of Novi Sad. A total of nine formulations of DS containing ALA (randomly labeled A–I) were analyzed in the study, including two gastro-resistant capsule formulations (B and I) and seven hard capsule formulations. The investigated DS were purchased from local pharmacies in Novi Sad, Serbia, and some samples were donated by the manufacturers. All samples were stored in their original packaging, in a dry and dark place at room temperature (20–25 °C).

Uniformity of Mass

Uniformity of mass was conducted according to *EP* 2.9.5. Uniformity of mass of single-dose preparations (*21*). For each sample, 20 randomly selected units were weighed using an analytical balance (Radwag, Radom, Poland). The samples were considered to comply with the specification if not more than two of the individual masses deviated from the average mass by more than the permitted percentage deviation: ± 10% for capsules with an average mass of less than 300 mg, and ± 7.5% for capsules with an average mass of 300 mg or more. No units were allowed to deviate by more than twice the specified percentage (*21*).

Determination and Uniformity of Content

The content of ALA was determined by a previously published method (*22*). The stock standard solution of ALA was prepared by dissolving ALA standard (Farmalabor, Canosa di Puglia, Italy) in methanol (Lach-Ner, Neratovice, Czech Republic) at a concentration of 30 mg/mL. Seven working standard solutions were prepared by diluting the stock solution to obtain concentrations ranging from 0.046875 to 3 mg/mL. The absorbance of each solution was measured, and the calibration curve exhibited linearity within the observed concentration range (R^2 = 0.9975).

For each tested product, 10 randomly selected units were extracted with 10 mL of methanol (Lach-Ner, Neratovice, Czech Republic) using an ultrasonic bath (Velleman, VTUSC2, Gavere, Belgium) for 16 minutes without heating. The extracts were centrifuged at room temperature for 5 minutes at 4000 rpm (SL 16R Thermo Fisher Scientific, Osterode am Harz, Germany). Depending on the declared ALA dose per dosage unit, the solutions were further diluted: 10-fold for 100 mg and 150 mg ALA products, 20-fold for 200 mg and 300 mg ALA products, and 40-fold for 600 mg ALA products.

The absorbance of the prepared solutions was measured using a single-beam UV-Vis spectrophotometer (8453 G1103A, Agilent Technologies, Santa Clara, CA, USA) at 333 nm (*22*). Quartz cuvettes with a 1 cm path length were used for all UV-Vis measurements. The ALA content was determined for 10 individual dosage units, and the mean value and standard deviation were calculated.

The formulation was considered to comply with the pharmacopoeial requirement if not more than one out of 10 units deviated from the average content by more than ± 15%, and none deviated by more than ± 25% (*21*).

Disintegration Testing

The disintegration testing of capsules was performed according to the EP 2.9.1. using a standard disintegration apparatus (Erweka ZT3, Langen, Germany). Test A was conducted on six units per sample. The immersion fluid was distilled water, maintained at 37 ± 2 °C. Disintegration was monitored visually, and the disintegration time was recorded as the time when the last unit disintegrated completely.

According to the general monographs of the EP, the disintegration time limit for hard capsules was 30 minutes (*21*).

Dissolution Testing

The dissolution rate of ALA from the tested formulations was determined using USP apparatus 1 as described in EP 2.9.3 (*21*).

Compliance with pharmacopoeial criteria was evaluated according to EP 2.9.3 and 5.17.1. A formulation met the acceptance criteria at stage S1 if all six units released at least 80% of the determined amount of ALA within 45 minutes. To eliminate variability caused by deviations between the declared and the actual content of the active substance, dissolution results were calculated based on the determined content of each formulation.

Calibration

The calibration curve was constructed using ALA standard (Farmalabor, Canosa di Puglia, Italy). The initial UV-Vis absorption spectrum of the standard ALA solution was recorded in the range of 200–400 nm, with a maximum absorption observed at 334 nm. For calibration, the stock solution was prepared by dissolving ALA in 0.5% (w/v) sodium lauryl sulfate (SLS) solution at a concentration of 1 mg/mL. Serial dilutions were made to obtain working standard solutions with concentrations ranging from 0.0625 to 1 mg/mL. The calibration curve exhibited linearity across the entire concentration range with a correlation coefficient $R^2 = 0.9989$.

Dissolution Procedure

The dissolution medium was prepared by dissolving SLS (Lach-Ner, Neratovice, Czech Republic) in purified water obtained by laboratory distillation (AC–L8, Optic Ivymen System, J.P. Selecta, Barcelona, Spain) to a final concentration of 0.5% (w/v). This medium was selected due to the known low water solubility of ALA to ensure complete and reproducible dissolution suitable for quantitative analysis.

Dissolution testing was performed using a dissolution tester (DT 600, ERWEKA GmbH, Langen, Germany) with USP apparatus 1 (basket) and a volume of 900 mL of dissolution medium, maintained at 37 ± 0.5 °C, with a stirring speed of 100 rpm for all formulations.

Sampling was performed using an autosampler equipped with cannula filters of 10 µm porosity (ERWEKA GmbH, Langen, Germany), enabling immediate and consistent filtration of samples to eliminate undissolved particles prior to spectrophotometric analysis. Aliquots of 5 mL were withdrawn at time points of 5, 15, 25, 35, 45, and 60 minutes, with immediate replacement by the same volume of fresh, preheated medium. The amount of dissolved ALA was determined by UV-Vis spectrophotometry at 334 nm. Dissolution testing was conducted on six dosage units for each tested product.

A full analytical method validation was not performed. However, the UV–vis method applied for dissolution sample analysis was based on a previously published procedure for ALA determination and was considered fit for purpose for comparative dissolution testing (*7*).

RESULTS

Uniformity of Mass and Content

Out of the nine ALA DS, formulation C failed the uniformity of mass test, as 8 out of 20 capsules deviated from the average mass by more than ± 7.5%. Formulation D failed the test due to 11 individual capsules deviating from the average mass by more than ± 10%.

According to test B for uniformity of content of single-dose preparations (EP 2.9.6), formulations B and D failed to comply with the acceptance criteria, as more than three individual dosage units fell outside the limits of 85–115% of the average content. All other formulations (A, C, E, F, G, H, and I) complied with the specified acceptance criteria. These results are presented in Table 1.

Disintegration and Dissolution Test

All disintegration times are shown in Figure 1. Only one formulation (H) failed to disintegrate within 30 minutes.

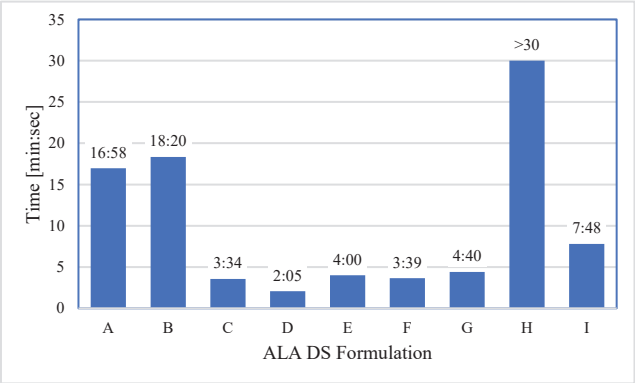

Figure 1. Disintegration times for the alpha-lipoic acid dietary supplement (ALA DS) formulations in distilled water at 37 °C.

The dissolution profiles of the nine tested DS formulations containing ALA are presented in Figure 2. According to the EP dissolution criteria for conventional-release dosage forms, formulations B, F, and H did not meet the acceptance criteria (*21*). Marked differences in dissolution behavior were observed among the tested formulations.

Table 1. Uniformity of Mass and Content for ALA DS Formulations

Formulation	Lot No.	Expiry Date	Declared Content (mg)	Measured Content (mg)	
				Mean ± SD	% of Declared
A	L0724061	7/27	300	240.97 ± 17.49	80.32 ± 5.83
B	0124501	1/26	600	490.69 ± 46.89	81.78 ± 7.81
C	300067	8/26	300	277.11 ± 25.55	92.37 ± 8.52
D	C47S460724	7/27	200	192.66 ± 25.27	96.33 ± 12.64
E	046426	8/27	100	111.55 ± 2.80	111.55 ± 2.80
F	0403	5/27	300	361.18 ± 39.06	120.39 ± 13.02
G	0081024	10/26	300	290.14 ± 13.11	96.71 ± 4.37
H	0324115	3/27	300	311.80 ± 25.19	103.93 ± 8.40
I	1023012	10/25	150	116.68 ± 10.19	77.79 ± 13.59

ALA DS: Alpha-lipoic acid dietary supplement.

The highest dissolution was observed in formulation A (123.97%), and formulation H reached only 7.15%.

Standard deviation values for dissolution profiles varied considerably among formulations and across time points, reflecting intra-formulation variability in dissolution behavior. Formulations A and B exhibited particularly high SD values at early time points (e.g., SD up to 29.24% for formulation A at 25 minutes and 16.00% at 5 minutes), suggesting inconsistent initial release kinetics within the tested units. In contrast, formulations such as E, G, and H generally demonstrated lower SD values across most sampling points, indicating more consistent dissolution performance.

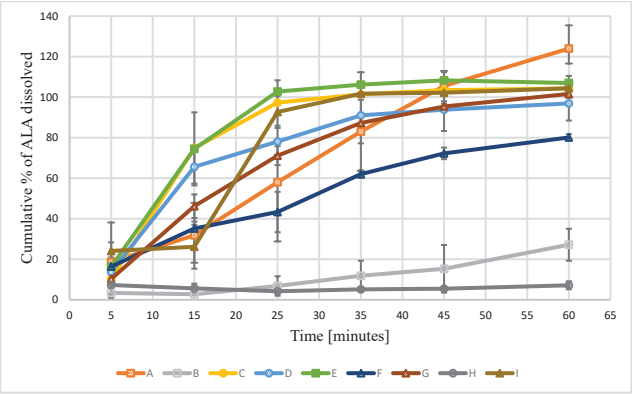

Figure 2. Dissolution profiles of commercial alpha-lipoic acid (ALA) formulations at 37 °C in 0.5% sodium lauryl sulphate medium. Values represent mean ± SD (n = 6).

DISCUSSION

Generally, although various analytical methods for ALA, such as high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), UV-Vis spectrophotometry, capillary electrophoresis, and electrochemical detection have been developed, relatively few studies have applied these techniques to analyze commercially available ALA DS (*12*, *14*, *23–26*).

As highlighted by Durazzo et al., the dissemination of such findings remains an area in need of further improvement and attention (*17*). Despite analytical methods being transferable internationally through standardized scientific channels, reports concerning the actual quality of DS are rarely communicated globally, limiting transparency and consumer awareness (*17*).

In the present study, mass and content uniformity testing identified inconsistencies, with three of nine formulations failing to meet mass uniformity, content uniformity, or both. Variability in ALA content (77.79% ± 13.59%–120.39% ± 13.02%) is consistent with Ravanic et al., who reported a wide range (53–100%), whereas Lalić-Popović et al. reported 98–107%, and Sitton et al. also observed 98% relative to label claims (*12*, *14*, *26*). Both consumers and health professionals expect that DS contain the ingredients and amounts listed on their labels (*17*). Thus, variability in average ALA content indicates a potentially misleading declaration, which may compromise consumer trust and underscores the need for stricter quality control and regulatory enforcement in the DS market.

In addition to the average content, variability between individual units within the same batch is a critical quality parameter. High intrabatch variability can lead to uneven therapeutic effects or suboptimal outcomes. In this study, formulations D, F, and I exhibited relatively high standard deviations (12.64%–13.59%), indicating notable intrabatch variability.

Capsule content uniformity depends on several key formulation and processing factors, including filler-binders, compatibility between the active pharmaceutical

ingredient (API) and excipients, and the particle size compatibility among all components (*29*). Significant particle size differences can cause segregation and uneven distribution. Although segregation is less likely when the API constitutes a large portion of the capsule fill weight, particle size compatibility with added excipients remains vital to maintain uniformity. In the current study, all analyzed formulations contained 150–600 mg of API per capsule, indicating that the API constituted a substantial proportion of the total fill weight. Proper blending techniques and flow optimization are therefore essential to ensure consistent capsule mass and content. Additionally, attention must be paid to possible chemical incompatibilities between excipients and the API, particularly under high-speed filling conditions where heat may promote undesired interactions (*29*).

The efficacy of a DS is determined not only by the amount of the active ingredient but also by the formulation's performance and design. DS formulation can influence the fraction absorbed, delivery to the target within a defined period, and, ultimately, the benefits it may provide to the users (*17*).

ALA, a compound with low solubility and high permeability, is classified as a Biopharmaceutics Classification System (BCS) class II substance. For compounds in this class, dissolution testing is the most appropriate and informative tool, as dissolution is the rate-limiting step in their absorption (*14*, *29*, *30*). Without appropriate disintegration or dissolution rates, ALA will not be available at the absorption site and thus will not be absorbed despite its good permeability.

The results of this study showed that disintegration outcomes varied, with one hard capsule (formulation H) failing to disintegrate within the 30-minute limit. The exact formulation did not pass the dissolution test, indicating that poor disintegration substantially impairs dissolution and downstream bioavailability. Besides formulation H, two more formulations (B and F) failed to meet dissolution criteria. These observations are consistent with Lalić-Popović et al., who reported that at a speed of 100 rpm, two out of five ALA DS dissolved 80% of their content within 45 minutes (*14*).

Among the nine analyzed DS, two pairs demonstrated similar dissolution profiles. This finding indicates that, despite the general variability in formulation and manufacturing practices across products, certain formulations may share comparable technological. However, given the overall heterogeneity of the remaining products, these matching profiles appear more coincidental than the result of standardized formulation practices across manufacturers.

Although in vitro disintegration and dissolution tests do not directly predict absorption or bioavailability (unless such a link has been experimentally established for a specific product), they remain important tools for assuring DS quality and consistency. Products that fail these tests may not properly disintegrate or release their active ingredients, leading to reduced or absent absorption and, consequently, failure to achieve the expected health benefits (*17*).

In the United States, FDA oversight focuses on safety, but monitoring the rapidly growing number of DS on the market exceeds available resources. At the same time, consumers and clinicians can consult the Dietary Supplement Label Database (DSLD) and look for evidence of third-party testing to verify label accuracy and performance (*31*, *32*). For example, the USP Verified Mark indicates a DS has passed USP's voluntary, third-party verification program, confirming identity, strength, purity, performance, and cGMP-compliant manufacturing (*33*).

Limitations

DS included in this study were purchased on the Serbian market, but most of these products are widely available internationally, and the findings are therefore informative for evaluating DS quality and consistency beyond the local context. However, a relatively small number of products and a one-batch-per-product design may limit the results of our study.

CONCLUSION

The findings of our study reveal heterogeneity in some of the critical quality attributes: mass uniformity, content uniformity, disintegration, and dissolution across commercial ALA DS. Out of nine tested formulations, five did not pass one or more pharmacopoeial tests for solid dosage forms, revealing variability in product quality, consistency, and performance. For the DS industry, this underscores the importance of formulation characteristics and process control to ensure ALA DS quality.

While stronger statutory control and harmonized enforcement would be the most direct route to improving DS quality, achieving such reforms is slow, politically complex, and in some settings not feasible in the near term. Establishing an independent third-party verification program in Europe could be one way to provide a quality signal for consumers and clinicians, as well as to motivate manufacturers to meet higher standards.

DISCLOSURES

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