CHEMICAL SCIENCES

DEVELOPMENT OF AN EXPRESS METHODOLOGY FOR ASSESSING THE QUALITY OF ALPHA-LIPOIC ACID BEFORE DISSOLUTION AND FILTRATION USING THE METHOD *NIR*

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Abstract

Alpha-lipoic acid (ALA, thioctic acid), a diethyl compound that is enzymatically synthesized in the mitochondria from octanoic acid, an essential naturally occurring dithiol compound, has become a common ingredient in many pharmaceutical products and nutritional supplements used in disease-dependent pathologies. oxidative stress. It performs the functions of a cofactor for mitochondrial ketoacid dehydrogenases, which determines its important role in the energy metabolism occurring in mitochondria. The bioavailability of ALA when taken orally is limited by pharmacokinetic features that reduce its therapeutic effectiveness (reduced solubility, insufficient stability in the stomach and breakdown in the liver, doubled by drug retardations).

The purpose of the research was to develop an express method for quality control of alphalipoic acid based on the indicator - ability to dissolve and filter. It is important to provide a drug with in vitro dissolution comparable to Rapid Lifetime Determination (RLD) is a mathematical method for extremely rapid lifetime estimation in exponential decays that allows the compound to reach a target level to provide the optimal claimed antioxidant activity of ALA at the cellular level. even for food supplements. The NIR method can be used to control the relevant properties of the material, to provide certain chemical and physical information. This information can be obtained quickly, with virtually no sample preparation, which is an advantage over many other methods.

Keywords: alpha-lipoic acid; dissolution rate; quality target product profile.

Introduction

Alpha-lipoic acid (ALA, thioctic acid) is a powerful natural lipophilic antioxidant that has the ability to inactivate free radicals and increase the activity of the body's antioxidant systems, restoring the intracellular level of glutathione and vitamin E [1-4]. The most common form of LA in medicinal preparations is a racemic mixture of R-(natural) and S-(synthetic) isomers. S-lipoic acid (S-LA) does not occur in nature and is a by-product of the chemical synthesis of LA, while R-lipoic acid (R-LA) has been shown by several studies to be the biologically active form compared to the S-form. Thus, it was shown that R-LA itself functions as a cofactor for mitochondrial enzymes involved in energy production. Despite all its potential advantages, the R-form is highly unstable in isolation and readily polymerizes in the presence of air, heat, and light. Thus, during thermal drying or cleaning with the use of ethanol, the so-called impurity B can be formed, which according to its physical characteristics is a sticky and insoluble substance [5, 6]. Also, during encapsulation due to the processes of friction, compression and temperature, polymerization is initiated, which calls into question the preservation of bioactivity of LA.

A stabilized form of LA can be obtained by complexing it with N-methylglucamine to form a meglumine salt. The resulting salt is not only water-soluble, but also causes a change in such physical properties as the melting point, boiling point, or sublimation of the complexes in comparison with the temperature parameters of free LA. The solubilizer in LA preparations is polyethylene glycol (macrogol). It forms reversible complexes with active substances, increasing their solubility. Polyethylene glycol molecules have high hydrophilicity, the high content of hydrogen atoms even in one molecule allows it to bond with 2-3 water molecules.

Table 1.

Samples for research NIR spectra

Name	Sample series	Sample name
alpha-lipoic acid	1940001121	S1
	1840002888	S2
	1840003693	S3
	1940001067	S4
	1940000850	S5
	1940000831-1	S61
	1940000831-2	S62
	1840003648	S7
	1940000269	S8
	19400001121	S9

A similar effect entails the formation of a "water cloud" around the modified molecule, due to which the hydrodynamic radius increases.

The purpose of the study was to find out the possibility of developing an express method for quality control of AFI according to the indicator - the ability to dissolve and filter. Taking into account the technical characteristics of obtaining water-soluble LA, we also had the question of studying the possibility of developing a NIR method for assessing the quality of API based on the indicator - the ability to dissolve and filter. This method is used both for individual components (active and auxiliary substances) and for final products, it is used for qualitative and quantitative determination. The NIR method can be used to control the relevant properties of the material, to provide certain chemical and physical information. This information can be obtained quickly, with virtually no sample preparation, which is an advantage over many other methods.

Samples for research, equipment and materials

NIR Analysis of α-lipoic acid using a chemometric approach using the PCA method was carried out. The study of α-lipoic acid of different series, which are listed in Table 1, was used for the study. Sample measurements occurred through transparent plastic bags that had samples.

The following equipment was used for the research:

MicroNIR onsite-W IR spectrometer (manufacturer VIAVI Solutions, USA) with a light source - two built-in vacuum tungsten lamps and a detector - a 128-pixel InGaAs photodiode; with a sapphire window with an outer diameter of 30 mm, a USB cable for connecting to a PC.

MicroNIR Onsite-W parameters:

- Range of wavelengths 950 – 1650 nm (10,526 – 6060 cm^{-1}).
- Measurement time of one sample 0,25 - 0,5 sec.

Results & Discussion

Fig. 1 shows the NIR spectra of this substance without processing and the spectrum of a transparent polyethylene bag is superimposed.

To interpret the obtained spectra, such types of processing as the second derivative and Standard Normal Variate (SNV) were applied. The NIR spectra of this substance after treatment are shown in Fig. 2.

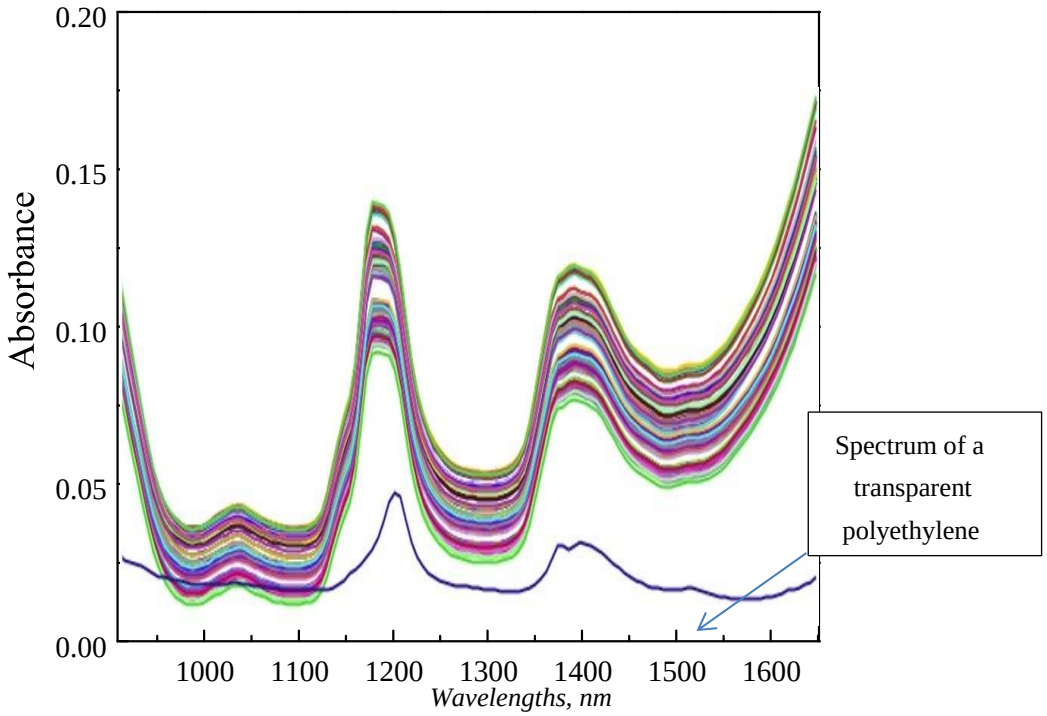

Figure 1: NIR spectra of α-lipoic acid before processing

From Fig. 2. we see slight differences in the spectra of alpha-lipoic acid series. After the NIR analysis, this set of spectra was analyzed by the PCA method. The scatter diagram of the values of the main components for α-lipoic acid is presented in Fig. 3.

From the scatter diagram of the values of the main components, we can see that the series S2, S9, S3 are isolated relative to other series. Individual groups of such series as S4 and S5, S7 and S8 and series S61, S62 with different selection dates can be separated from other series, but the distance of these groups is small relative to the spread of individual series. In general, the remoteness of these mixtures is not significant, so the second derivative was used to interpret the obtained data. Such a spread of series may depend not so much on chemical characteristics, but more on various physical properties, such as particle size. The nature of the package will have little effect on the spread of the series, since the package does not absorb in the range of wavelengths where we observe differences in the spectra.

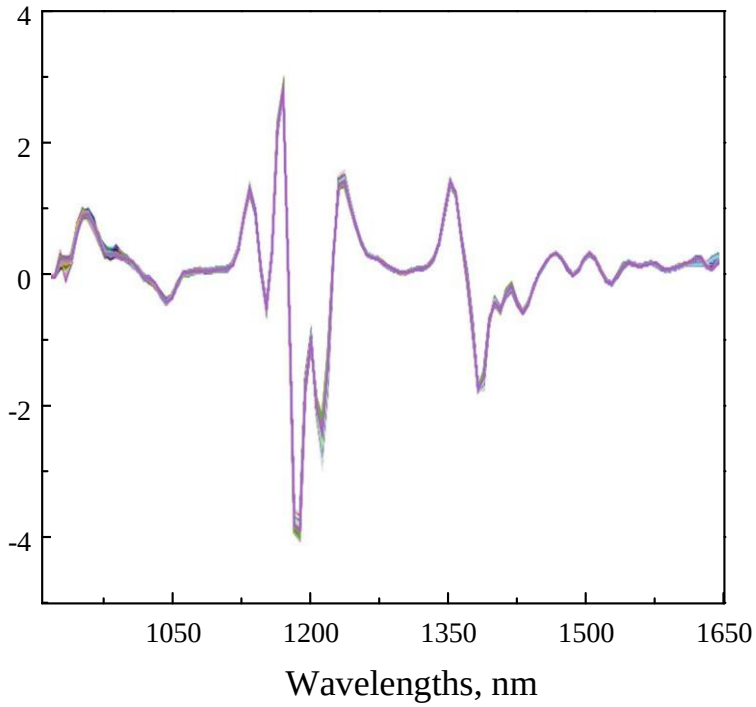

Figure 2. NIR спектри α-ліпоєвої кислоти після обробки

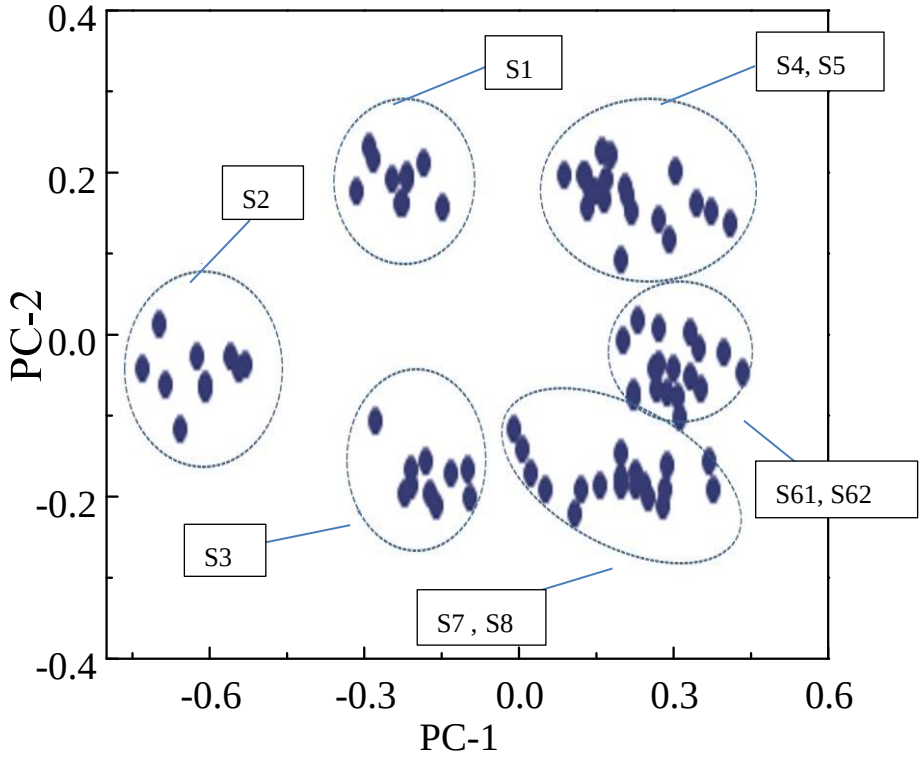

Figure 3. Scatter diagram of the values of the main components of alpha-lipoic acid

In the further analysis, we assumed the possibility of filtering alpha-lipoic acid substances, but we would like to note that the presented conclusions are assumptions on our part.

Information was provided on the filtration properties of alpha-lipoic acid of various series, the data are presented in Table 2

On the basis of the results obtained from the diagram of the scatter values of the main components and the information provided in Table 2, we tried to assume the possibility of filtration for the substances of those series that were not filtered.

Table 2.

Information on the filtration of alpha-lipoic acid of different series

№ п\п	Sample series	Place of selection	Status	Property
1	S1	Production laboratory	The substance is planned for industrial use	Filtration of the drug with the substance of this batch was not carried out
2	S2	Composition of finished products	The substance was previously used in production	Filtration of the drug solution took place without delay
3	S3	Composition of finished products	The substance was previously used in production	Filtration of the drug solution took a long time
4	S4	Production laboratory	The substance is planned for industrial use	Filtration of the drug with the substance of this batch was not carried out
5	S5	From current production	The substance is currently used in production	Filtration of the drug solution takes a long time
6	S61	From the laboratory (separate container)	The substance is used for research	Filtration of the drug with the substance from this container was not carried out
7	S62	From current production (separate container)	The substance is currently used in production	Filtration of the drug solution takes a long time
8	S7	Composition of finished products	The substance was previously used in production	The drug solution was filtered without delay
9	S8	Composition of finished products	The substance was previously used in production	Filtration of the drug solution took a long time

The information from Fig. 3 is not enough to assume the filtering properties, since the processing included the application of the second derivative. The second derivative, as a processing method, can eliminate certain effects, but on the other hand, there is a possibility of losing variables that can carry information about filtering properties. Therefore, the first derivative and SNV were applied to the NIR spectra. The scatter diagram of the values of the main components for alpha-lipoic acid is presented in Fig. 4

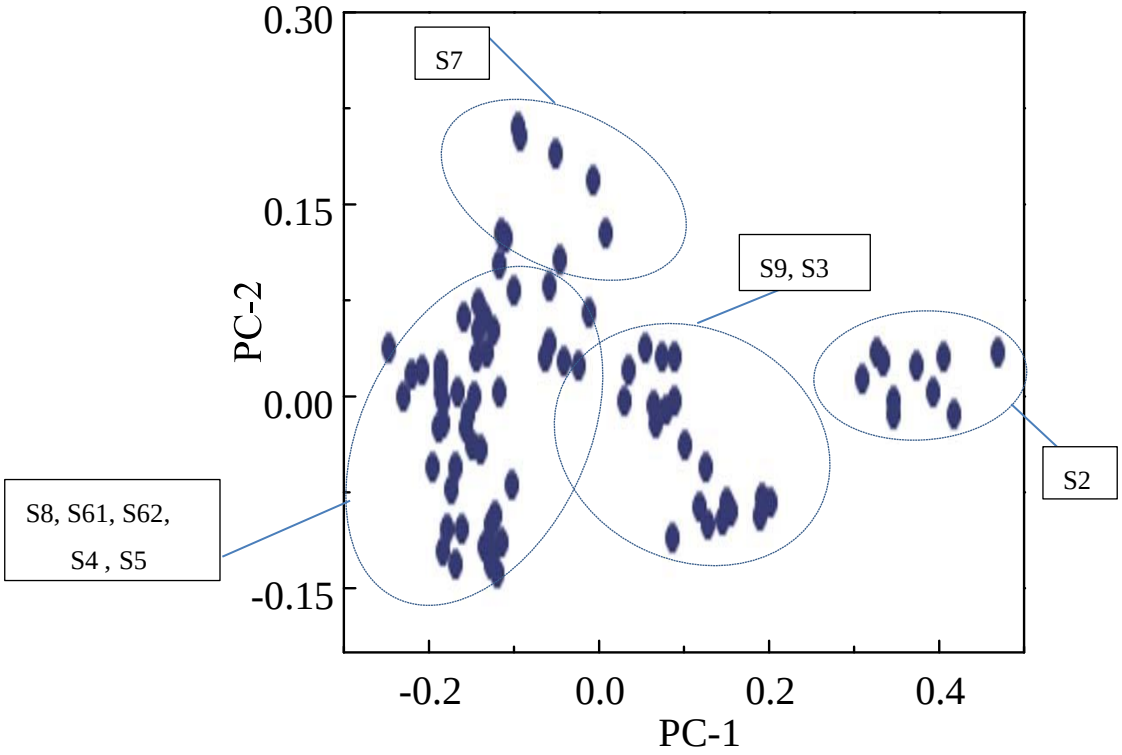

Figure 4 Scatter diagram of the values of the main components for alpha-lipoic acid

From Fig. 4, we can see that the S1 series and the S3 series are in the aggregate, so we can assume that they will have the same filtering ability. Since we know that the S3 series takes a long time to filter, it is likely that the S1 series takes a long time to filter.

The S4 series is grouped with the S8, S62 and S5 series. According to the data in table 2, it is known that the filtering for these three series is long, so we can assume that the filtering of the S4 series will also take a long time.

From the scatterplot of the principal component values, we can see that the S7 series is relatively isolated from the other series. Such an arrangement can confirm a different filtering property, since according to the data from Table 2, it is known that the filtering of S7 takes place without delay, and the filtering of such series as S8, S62, S5 takes a long time.

From Fig. 4, we can see that the S61 and S62 series are together, so we can talk about the similarity of their properties, so the filtering of the S61 series will take a long time.

But we would like to point out once again that the presented conclusions are an assumption, since the isolation of the population points on the scatter diagram of the values of the main components is very small. To verify the correctness of the assumptions, additional information is needed regarding the filtering ability of the S61, S4, S1 series AFIs.

Conclusions

The NIR spectra of alpha-lipoic acid of different series were recorded, followed by data processing by the PCA method. Series S2, S9, S3 are shown to be isolated relative to other series, while other series are found in certain assemblages. Based on the data of the PCA method, assumptions were made about the filtering properties of certain series. As can be seen from the analysis of the obtained data, the NIR method is not sensitive enough for API quality control, which prevents the development of a reliable method for predicting the solubility and filtration characteristics of alpha-lipoic acid. Assuming that the filtration problem may be due to polymerization of the acid, an important aspect is the concentration of the polymer, which can affect the rate of filtration and the formation of sediment during dissolution. The concentration of polyethylene glycol, which acts as an auxiliary substance, is also unknown. Polyethylene glycol molecules are much larger than LA molecules, which can also cause filter clogging. Therefore, at this stage it is impossible to talk about clear conclusions, therefore it makes sense to conduct an additional study by the method of Raman spectroscopy, including the study of Raman spectra of alpha-lipoic acid impurities. Raman spectroscopy provides key information about the structure of a molecule. As a result of the analysis, it is possible to determine the nature of the substance, as well as study intramolecular interactions. Raman spectroscopy can be used to analyze such physical properties as crystallinity, phase

transitions, and polymorphic states. Thus, Raman spectroscopy provides us with additional information that may help in elucidating the filtering properties of alpha-lipoic acid.

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