CHEMICAL SCIENCES

EVALUATION OF THE NIR METHOD FOR IN-LINE MONITORING OF THE MIXING HOMOGENEITY PROCESS OF BISOPROLOL FUMARATE.

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Abstract

Determining the homogeneity of mixing of the active pharmaceutical ingredient (API) (bisoprolol fumarate) is an important process control in the production of solid dosage forms. This article presented the results of tests based on near-infrared (NIR) wavelengths. The method is based on the calculation of net analyte signal (NAS) models, which are very easy to develop, are API specific and do not require additional benchmark analysis. Using the well-mixed batch as the "gold standard" batch, control charts were developed and used to monitor the uniformity of other batches using NIR. The methods were rapid, easy to use, non-destructive, and provided statistical tests of homogeneity. It has been shown that at each stage of mixing, isolation of both the active substance relative to the excipients and the resulting intermediate and final mixtures relative to the active and excipients is achieved. The sensitivity of the method is determined by the minimum amount of substance that can be detected by this method.

Keywords: Powder homogeneity; Near-infrared spectroscopy; bisoprolol fumarate.

Introduction

Traditional pharmaceutical analysis is usually performed at the expense of ongoing laboratory testing for quality control. However, assessing the quality of technological materials and finished products takes a lot of time and requires a large number of preparation stages. Homogeneity is usually determined by taking a small sample of the powder from the mixer with an absorber probe and sending the samples to a quality control laboratory remote from the process line, for example, for quality control by high pressure liquid chromatography (HPLC) analysis. The active pharmaceutical ingredient (API) content of the samples and the relative standard deviation of the API ingredient content between samples are then determined and compared to the specified values to decide whether the batch is of good quality and sufficiently uniform [1]. Therefore, near-infrared (NIR)-based spectroscopic methods have been proposed [2–9], which are non-destructive, fast, and require few resources. Over the years, there has been significant improvement in the management of pharmaceutical development, production and quality assurance processes. In the provision of the Food and Drug Administration, which describes the regulatory framework for the analytical technology of the process, one of the working principles is the control of quality indicators in real time [10]. Combined process measurements and other test data collected during the manufacturing process can demonstrate that each batch meets established regulatory quality characteristics. According to the European Medicines Agency, the NIR method can be used to control relevant material properties, for example to control the homogeneity of a mixture. The NIR method has many advantages compared to pharmacopoeial methods, providing not only chemical, but also physical information. This high-quality information can be obtained rapidly with virtually no sample preparation, in stark contrast to many pharmacopoeial methods. The technique can be applied for both quantitative and qualitative applications and can be used throughout the entire process from starting materials (active and excipients), through intermediate products to final products. The technique can be applied in laboratory or process conditions, to individual components or to the matrix as a whole.

The purpose of NIR method validation, as with any analytical procedure, is to demonstrate that the method is fit for purpose. Method validation can be planned at the development stage. This allows you to take into account certain aspects and parameters of the calibration model that is developed and tested for specific pharmaceutical compounds and drugs. The procedure involves the use of various chemometric (mathematical and statistical) approaches with appropriate validation. Calibration models already developed for the NIR method are stored and applied electronically as part of the respective instrument / software package, they are not always transferable to other instruments. Therefore, it is currently relevant to develop a calibration model based on the availability of specific drugs/samples and use the developed model to predict the properties of an unknown sample, taking into account the results obtained using an analytical device. The purpose of the study was to find out the possibility of using the NIR method for in-line control of the homogeneity of the mixing process of bisoprolol fumarate.

Stages of assessing the possibility of developing an NIR method for in-line control of the mixing homogeneity process. In order to implement the NIR method for in-line control of the mixing homogeneity process, it was necessary to conduct an evaluation of the method, the main stages of which were:

1. Record the spectra of all substances, intermediate and final mixtures.

2. Analysis of spectral data and assessment of the complexity of mixing homogeneity control.

3. Evaluation of suitability and optimization of the chemometric model.

4. Presentation of the interim report on the first stage of the evaluation of the NIR method.

Research samples, equipment and materials.

Samples of the active substance and auxiliary substances of different series and manufacturers were used for the study, as indicated in Table 1. Intermediate mixtures and the final mixture for the preparation of tablet mass were also investigated, as indicated in Table 2. All substances and intermediate mixtures used in the mixing process will be called components in the future

Table 1

Active substance	
Name	Information about the active substance
	Manufacturer company
Bisoprolol fumarate	MOEHS Catalana, S.L., Spain
Excipients	
Lactose monohydrate	DFE Pharma, Germany
	ALPAVIT Kaserei hampignon Hofmeister, Germany
	Molkerei MEGGLE Wasserburg, Germany
Microcrystalline cellulose	Itacel Farmoquimiva Ltda, Brazil
	JRS Pharma, Germany
Calcium hydrogen phosphate anhydrous	Chemische Fabric Budenheim KG Germany
Crospovidone	ISP Chemicals LLC, CIIIA
	Shanghai Yuking Water Soluble Material Tech Co., LTD, China
Silicon dioxide colloidal anhydrous	Evonik Resource Efficiency, Germany
FCF Lake Sunset Yellow dye	Sensient Colors UK Ltd, Great Britain
Magnesium stearate	NPF Trialon, Ukraine

Table 2.

Name	Information on the mixture		Measurement IR spectra Yes / No
	Composition of the mixture after mixing	Series	
Mix A	Lactose monohydrate (Part I), FCF Lake sunset yellow dye	-	No
Mix B	Bisoprolol fumarate, silicon dioxide colloidal anhydrous Microcrystalline cellulose, Mix A	1.1	Yes
		1.2	Yes
Mixture C before dusting	Calcium hydrogen phosphate anhydrous, Lactose monohydrate (II part), Crospovidone, Mixture B	2.1	Yes
		2.2	Yes
Mixture C' after powdering (final)	Mixture C for powdering, magnesium stearate	3.1	Yes
		3.2	Yes

Table 3 shows the composition and content of the active substance and excipients in one tablet and per batch of Bisoprolol Fumarate.

Table 3

The name of the raw material	Content of components for one tablet		Mass of components per series, kg
	mg	%	
Active substance:			
Bisoprolol fumarate in recalculation on 100% dry matter of wine	5,00	5,00	3,18*
Excipients:			
Lactose monohydrate	10,00	10,00	6,35
Microcrystalline cellulose	15,00	15,00	9,52
Calcium hydrogen phosphate anhydrous	65,98	65,98	41,90**
Crospovidone	1,00	1,00	0,635
Silicon dioxide colloidal anhydrous	2,00	2,00	1,27
FCF Lake Sunset Yellow dye	0,02	0,02	0,013
Magnesium stearate	1,00	1,00	0,635
Together:	100,00	100,00	63,503

Note: * - technical weight can be changed;

** - adjustment of loading is carried out at the expense of anhydrous calcium hydrogen phosphate.

Equipment and materials

The following equipment and auxiliary materials were used to conduct the research:

1) MicroNIR PAT-U Bleach spectrometer (manufactured by 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.

2) MicroNIR Pro software.

3) Glass laboratory box with an inner diameter of 33 mm, a height of 31 mm.

MicroNIR PAT-U parameters:

- Wavelength range 950 – 1650 nm (10.526 – 6060 cm-1).

- The measurement time of one sample is 0.25 - 0.5 seconds.

Development of a chemometric research model.

After the development of the NIR method, an important step was to verify the reliability of its results for everyday use, therefore, in the pharmaceutical industry, NIRS is used in combination with chemometric methods of analysis.

The method of principal components (Principal Components Analysis, PCA) is one of the main ways to reduce the dimensionality of data, losing the least amount of information. PCA is used to reduce the dimensionality of the description, extract meaningful information, analyze correspondences, and visualize data. The most important application of PCA is to reduce the number of variables and represent a multidimensional table of data in a low-dimensional space.

When studying data by the PCA method, special attention is paid to the scatter diagrams of the main components. They carry information useful for understanding how the data is related. On the scatter diagram, each sample is represented by a point in the coordinates of the principal components. The relative proximity of two points indicates the similarity of their spectra, while the relatively distant location of the points indicates the difference. From a principal component scatterplot, you can determine whether isolated areas correspond to regions of pure or homogeneous components, and also see the proximity of the components relative to the data scatter region.

Measurement procedure

The test sample is placed in the laboratory bag using a laboratory spoon and compressed as much as possible so that the thickness of the sample layer in the bag is at least 15 mm. The spectrometer with a sapphire window is placed on a tripod vertically down, as shown in fig.1.

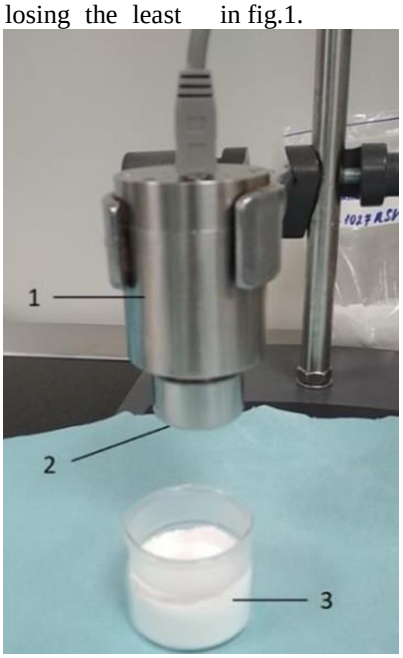

Fig. 1. Installation for measuring the spectra of the studied samples using the MicroNIR PAT-U infrared spectrometer,where 1 is a MicroNIR PAT-U BIL spectrometer, 2 is a sapphire window, and 3 is a box with the sample under study.

The sample prepared for research is brought to the spectrometer so that the sample touches the sapphire window. The spectra of each component, intermediate mixtures and the final mixture are measured over the entire range of wavelengths. Each sample was analyzed 10 times, completely repeating the sample preparation scheme and analysis conditions.

Analysis of the received data

NIR spectra of all components with basic treatment are presented in fig.2. On the basis of fig.2, specific characteristic ranges of bands for bisoprolol fumarate were established: visually 1120-1270 nm, 1340-1400 nm, 1640-1690 nm.

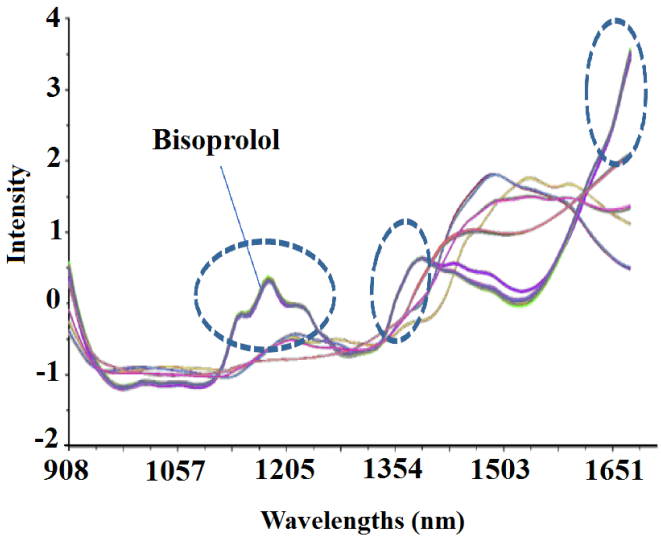

Fig. 2. NIR spectra of the active substance and excipients after processing

To evaluate the effectiveness of determining the homogeneity of mixing, this set of components was investigated by the PCA method. The scatter diagram of the values of the main components for the active substance, auxiliary substances and mixtures at all stages of mixing is presented in fig. 3.

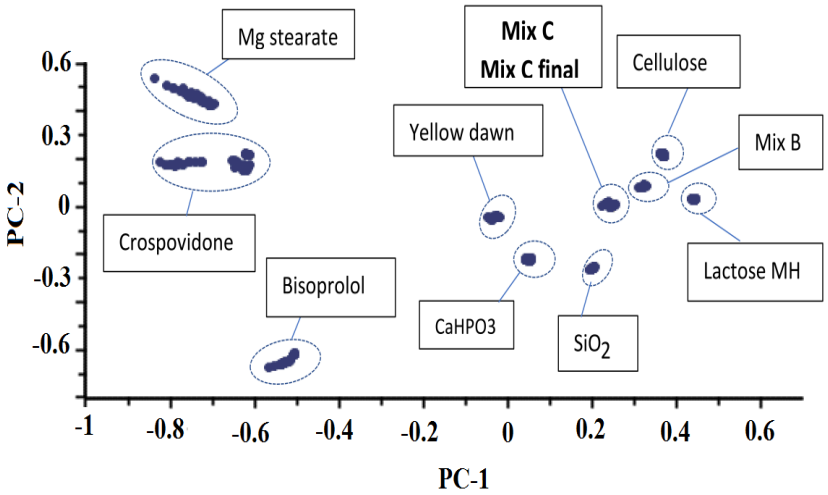

Fig. 3. Scatter diagram of the values of the main components for the active substance, excipients and mixtures

As can be seen from fig. 3, the site of the active substance is isolated from other components. At this stage, we can confirm that the method allows to determine the active substance, therefore, the specificity of the method has been proven. We can also see the isolation of mixture B and C relative to the components, but it is difficult to talk about the isolation of mixture C before powdering and after powdering. Therefore, the task arises to find out the sensitivity of the formation of mixture C after pulverization relative to the mixtures that were formed before that at the previous stages.

Consider the spectra of individual components and mixtures as separate stages. NIR spectra of the active substance without treatment are shown in fig.4.

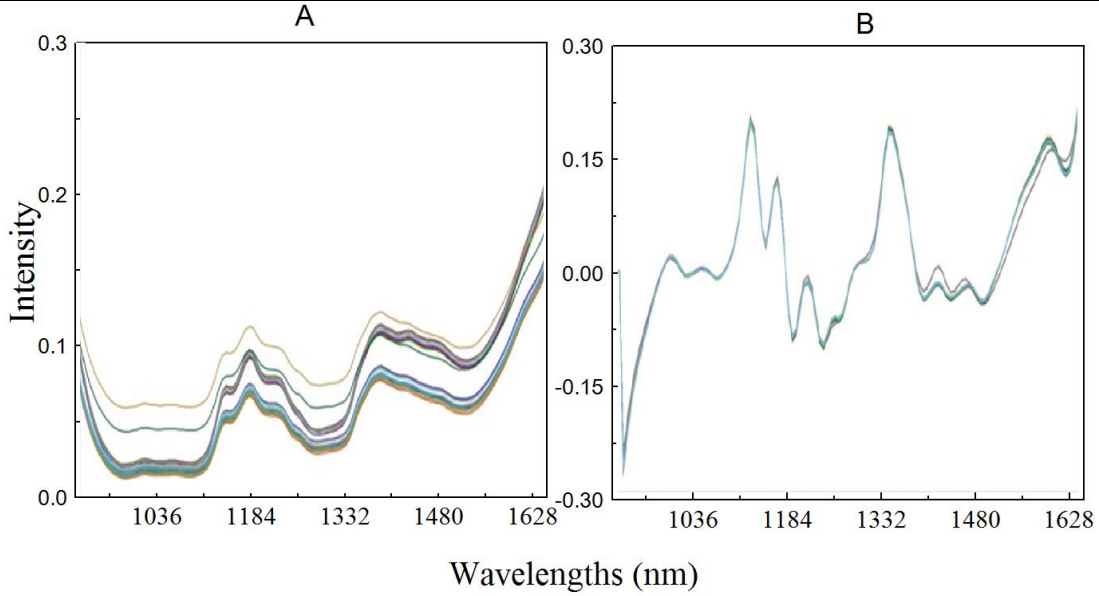

Fig. 4. NIR spectrum of the active substance bisoprolol fumarate A-before treatment B-after treatment

To interpret the obtained spectra, such types of processing as Standard Normal Variate (SNV) and the first derivative were applied. SNV is used to reduce data scatter. In fact, SNV is a normal distribution with a mathematical expectation of $\mu = 0$ and a standard deviation of $\sigma = 1$, that is, the application of the normalization function of the center and the scaling of each individual spectrum. The first derivative, as a processing method, minimizes unwanted geometric effects.

Similarly, the spectra of such auxiliary substances as microcrystalline cellulose (fig. 5), colloidal anhydrous silicon dioxide (fig. 6), lactose monohydrate (fig. 7), FCF Lake sunset yellow dye (fig. 8) and the final mixture were obtained and processed B (fig. 9).

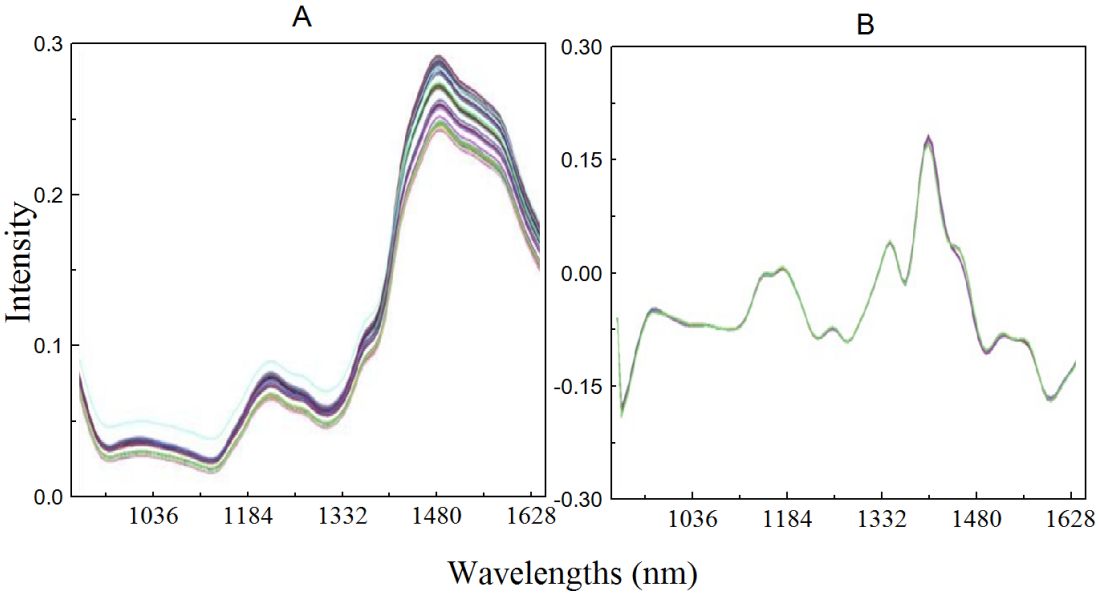

Fig. 5. NIR spectrum of microcrystalline cellulose excipient A-before processing, B-after processing.

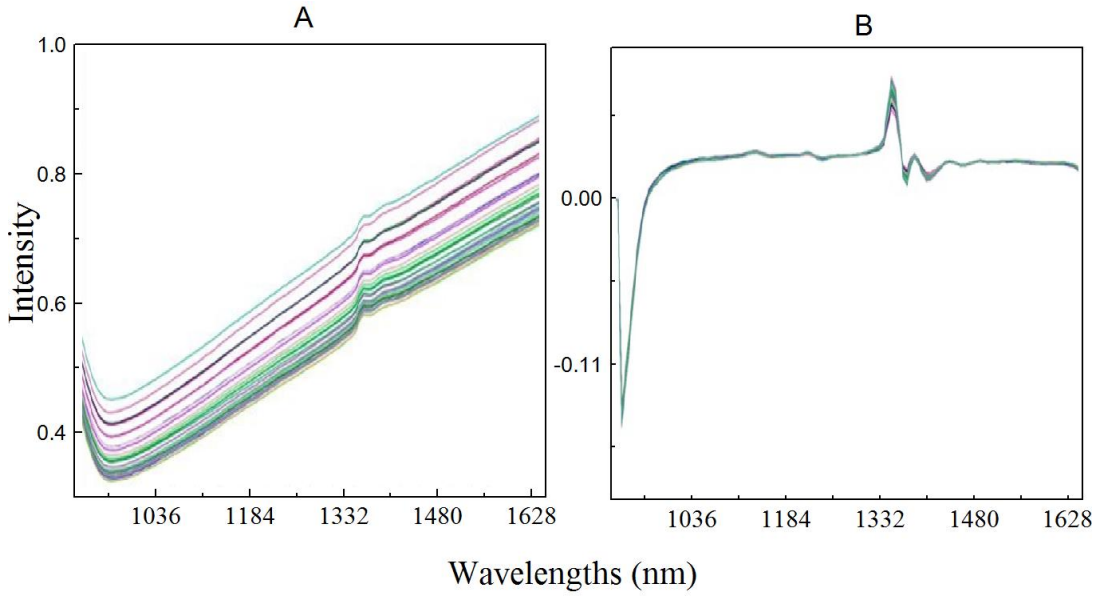

Fig. 6.

NIR спектр допоміжної речовини кремній діоксиду колоїдного безводногоA-до обробки, B-після обробки.

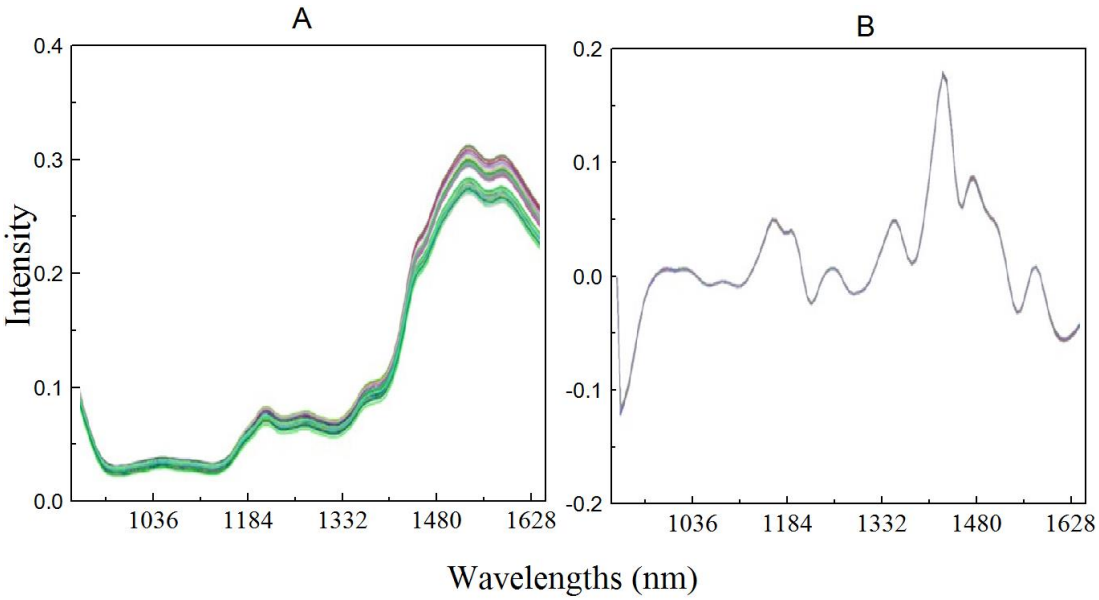

Fig. 7. NIR spectrum of excipient lactose monohydrate A-before processing, B-after processing.

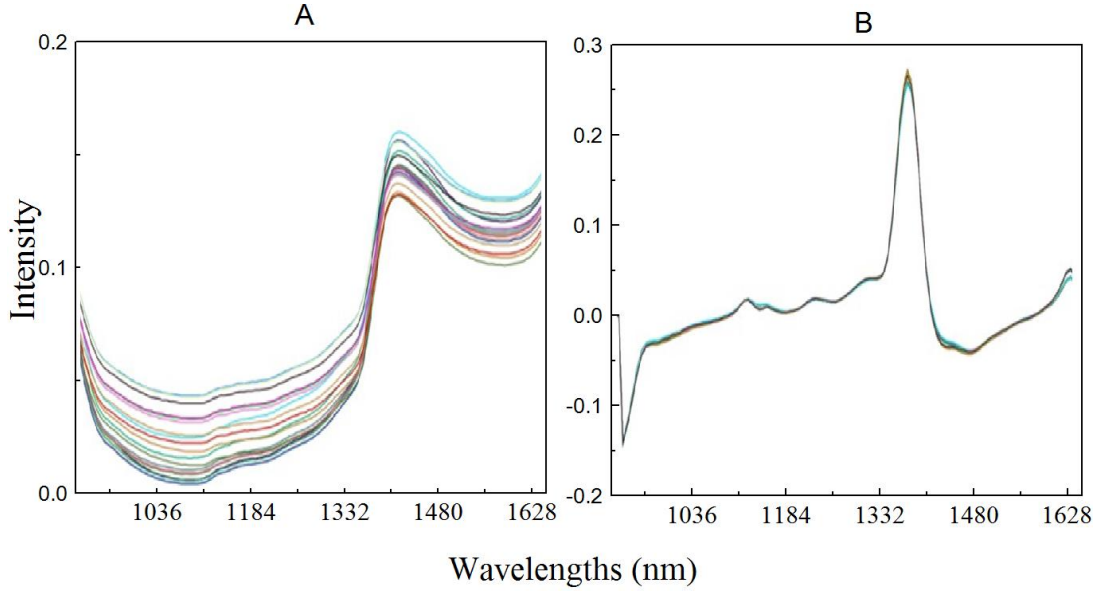

Fig. 8. NIR spectrum of the excipient dye Yellow Sunset FCF Lake A-before processing, B-after processing.

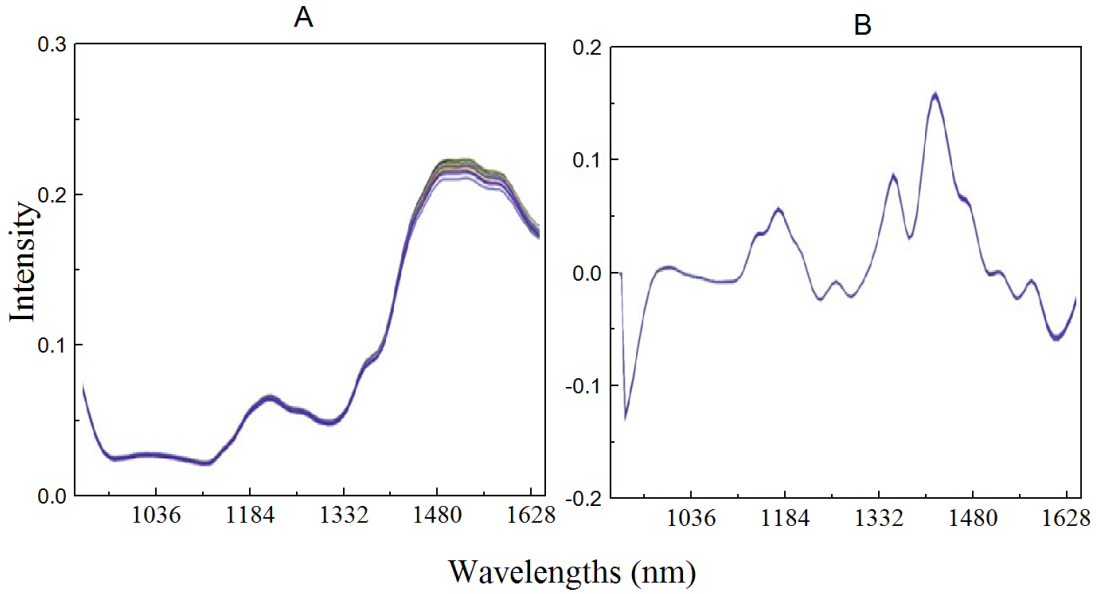

Fig. 9. NIR spectrum of mixture B A-before treatment, B-after treatment.

The PCA method was used to assess the effectiveness of determining the mixing homogeneity of the resulting mixture B. The NIR spectrum of the active and auxiliary substances that make up mixture B, before and after processing, is presented in fig.10.

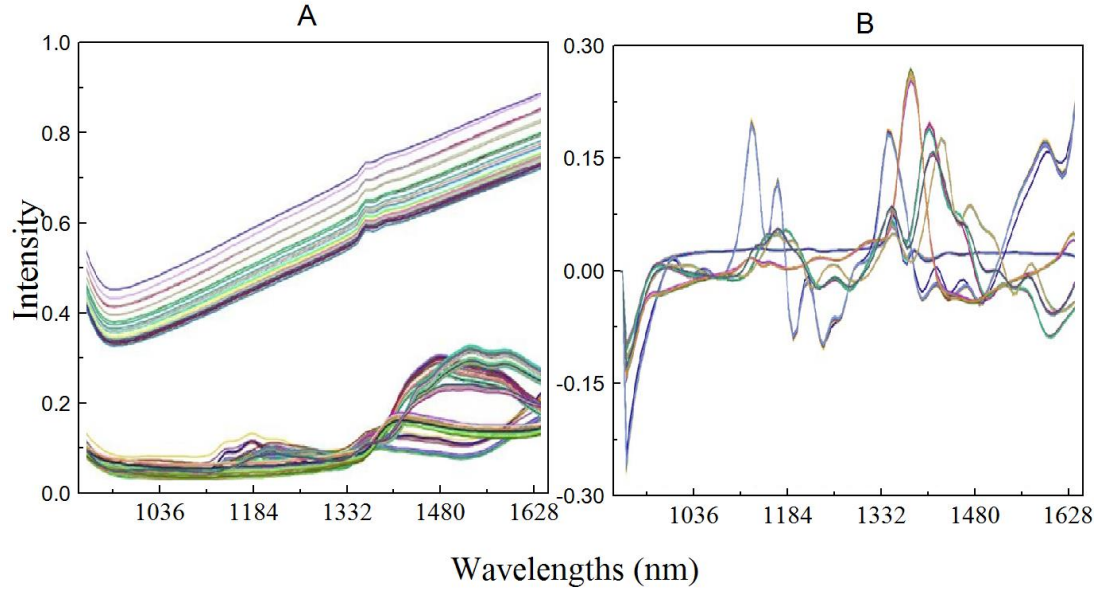

Fig. 10. NIR spectrum of active and auxiliary substances (mixture B) A-before processing, B-after processing.

The scatter diagram of the values of the main components for the active substance and auxiliary substances that make up the mixture B is presented in fig.11.

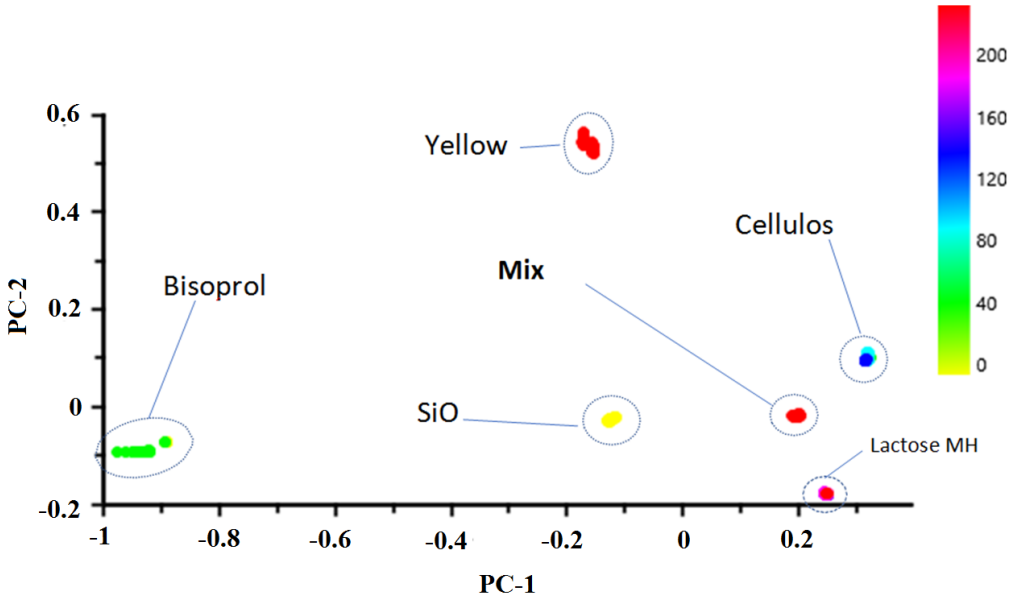

Fig. 11. Scatter diagram of the values of the main components of mixture B

From the scatter diagram of the values of the main components of mixture B, we can see that all components are isolated from each other.

Similarly, the NIR spectra of other excipients, which together with mixture B form mixture C, were recorded in the future. The spectra of such auxiliary substances as calcium hydrogen phosphate anhydrous (fig. 12), crospovidone (fig. 13), lactose monohydrate were obtained and processed. (fig.14), mixture B as a component (fig.15) and mixture C as the final mixture obtained (fig.16).

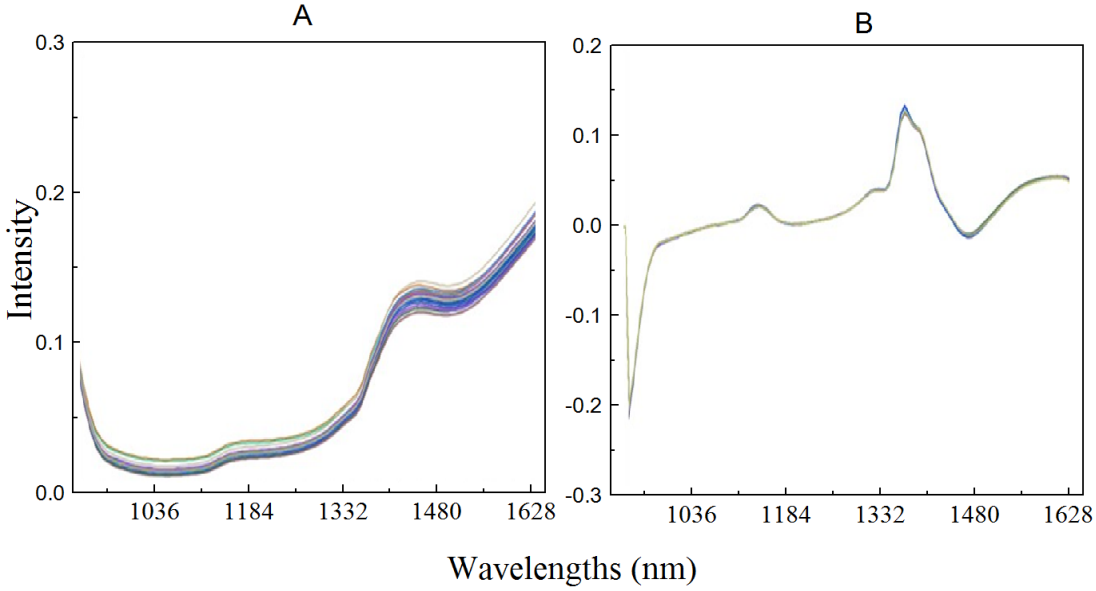

Fig. 12.
NIR spectrum of the excipient calcium hydrogen phosphate anhydrous A-before processing, B-after processing.

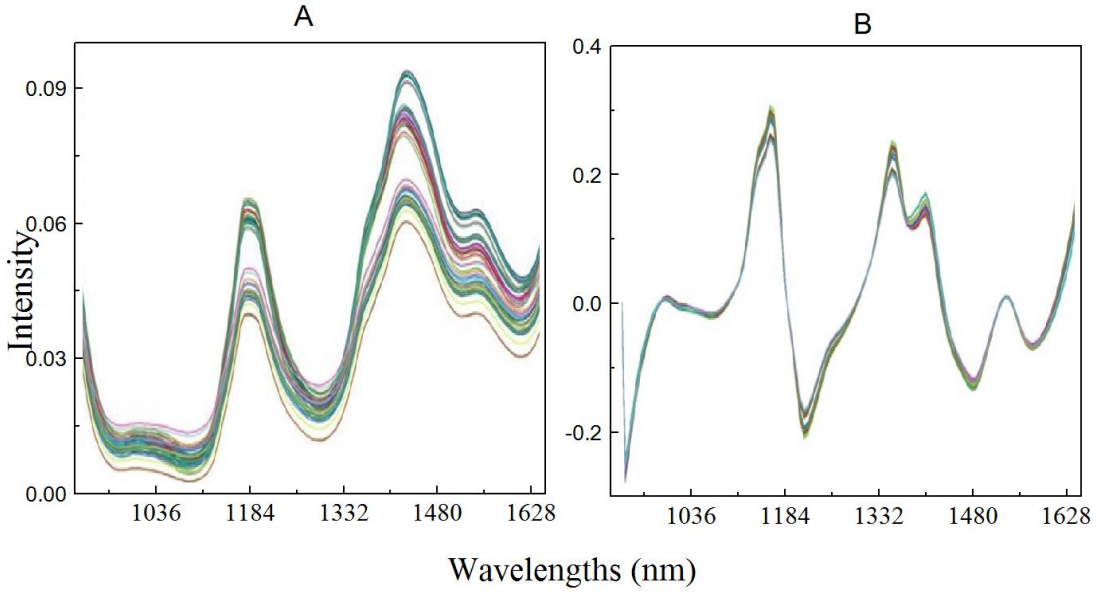

Fig. 13. NIR spectrum of crospovidone excipient A-before processing, B-after processing.

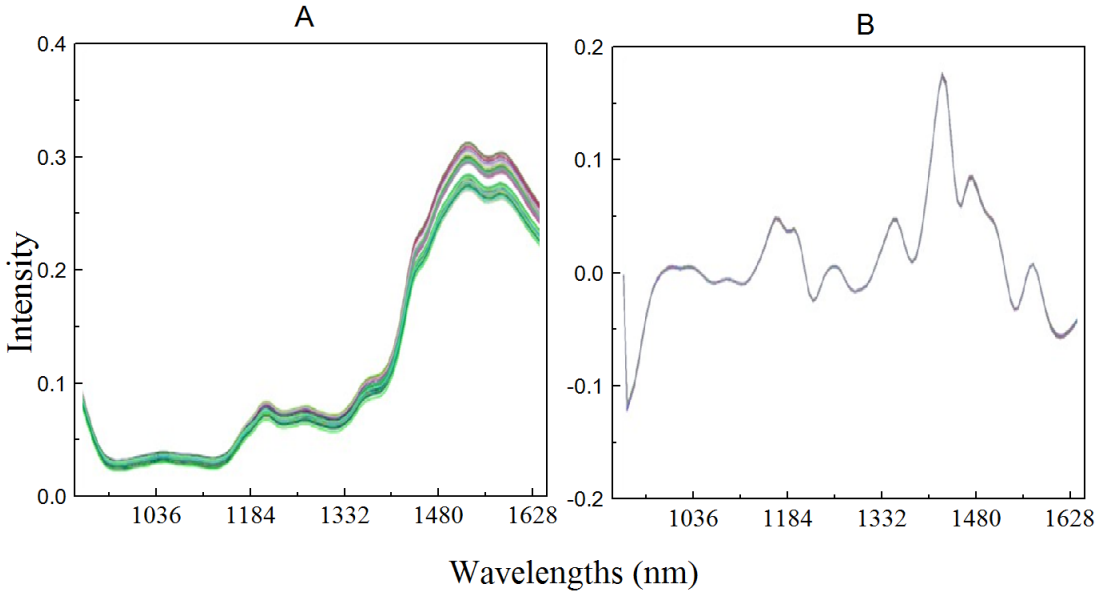

Fig. 14. NIR spectrum of excipient lactose monohydrate A-before processing, B-after processing.

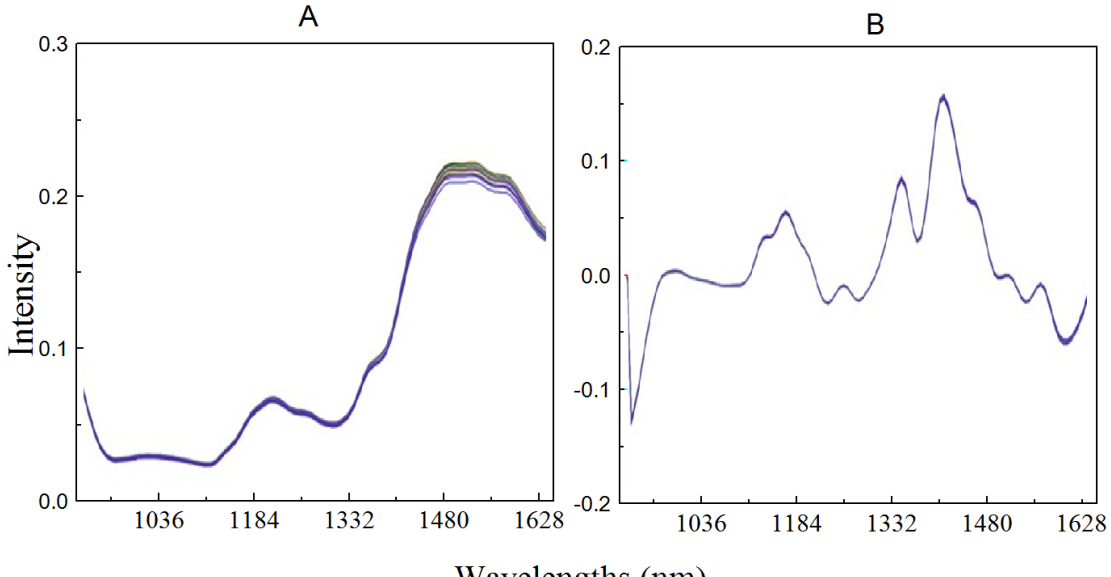

Fig. 15. NIR спектр суміші В А-до обробки, В-після обробки.

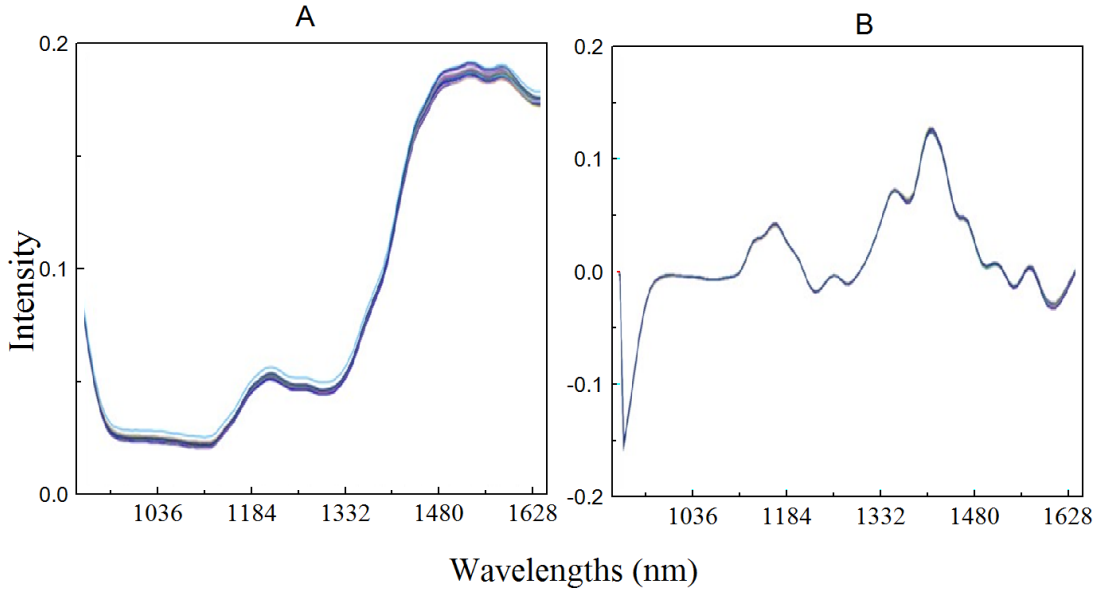

Fig. 16. NIR spectrum of mixture C A-before processing, B-after processing.

The PCA method was used to assess the effectiveness of determining the mixing homogeneity of the resulting mixture C. The NIR spectrum of mixture C, consisting of mixture B and added auxiliary substances, before and after treatment is presented in fig.17.

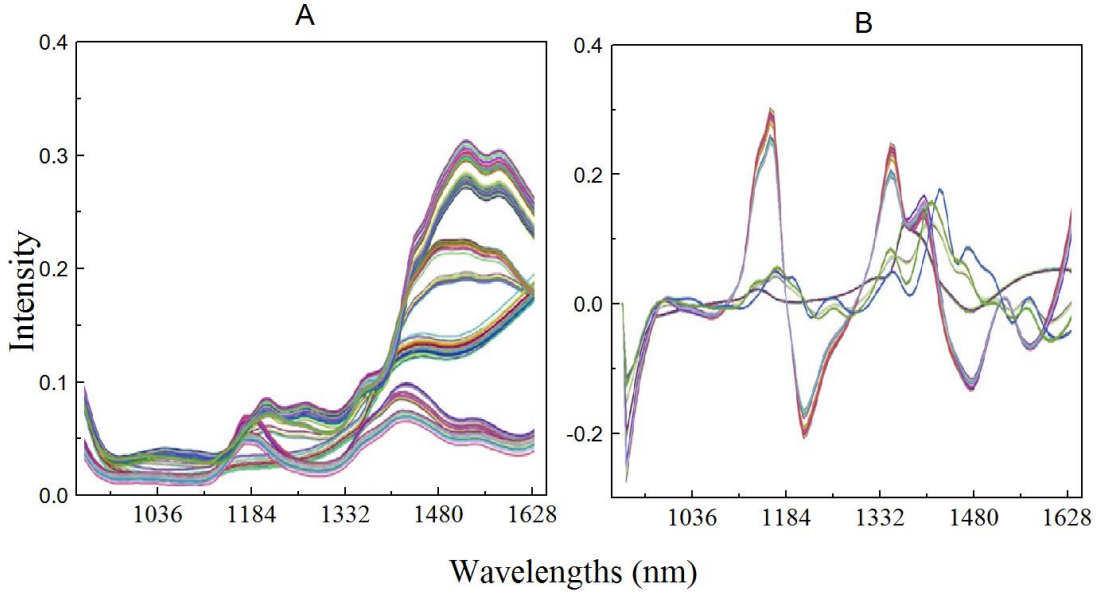

Fig. 17. NIR spectrum of active and auxiliary substances (mixture C) A- before treatment, B- after treatment.

The scatter diagram of the values of the main components for all components that make up mixture C is presented in fig.18.

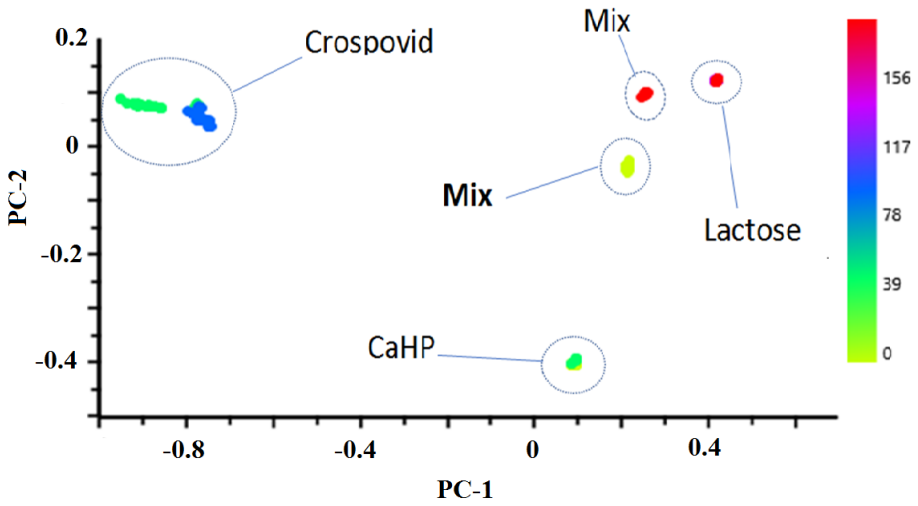

Fig. 18. Scatter diagram of the values of the main components of mixture C

From the scatter diagram of the values of the main components of mixture C, we can see that all components are isolated from each other.

At the last stage, the spectra of the excipient magnesium stearate (fig. 19), mixture C (fig. 20) and final mixture C' (fig. 21) were obtained.

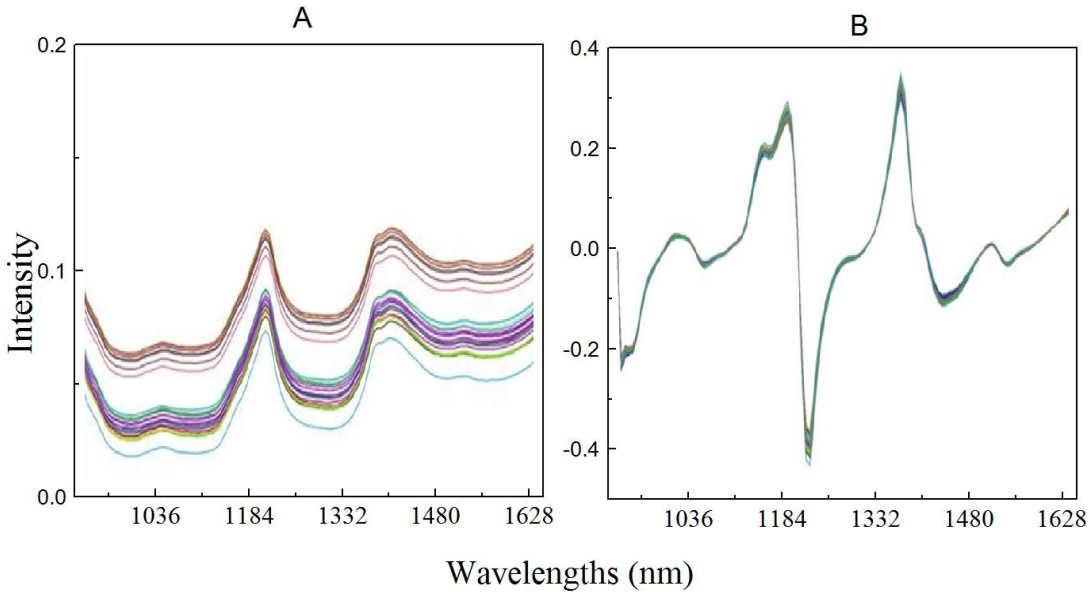

Fig. 19. NIR spectrum of excipient magnesium stearate A-before processing, B-after processing.

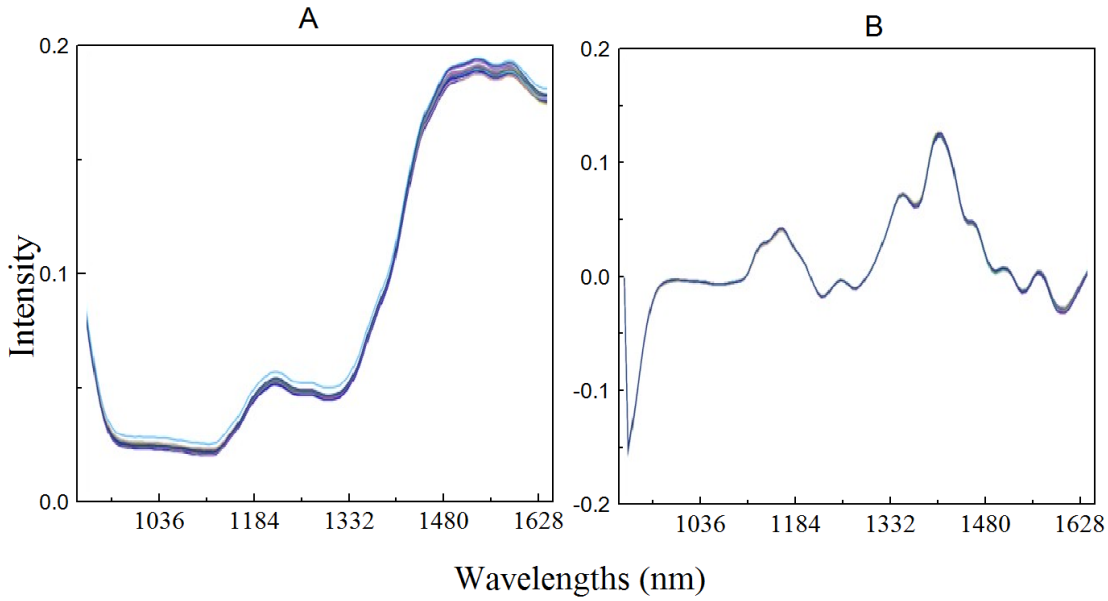

Fig. 20. NIR spectrum of mixture C (before powdering) A-before processing, B-after processing.

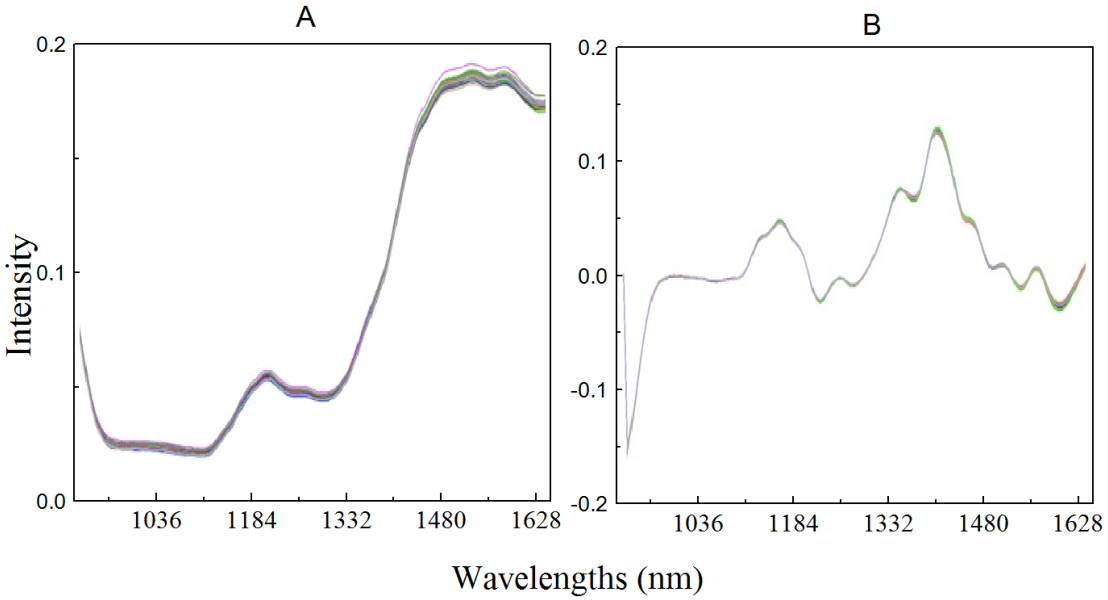

Fig. 21. NIR spectrum of mixture C (after powdering) A-before processing, B-after processing.

The PCA method was used to assess the effectiveness of determining the mixing homogeneity of the resulting C mixture after pulverization. The NIR spectrum of the final mixture C, which consists of the mixture C before powdering and the excipient magnesium stearate, before and after processing is presented in fig. 22.

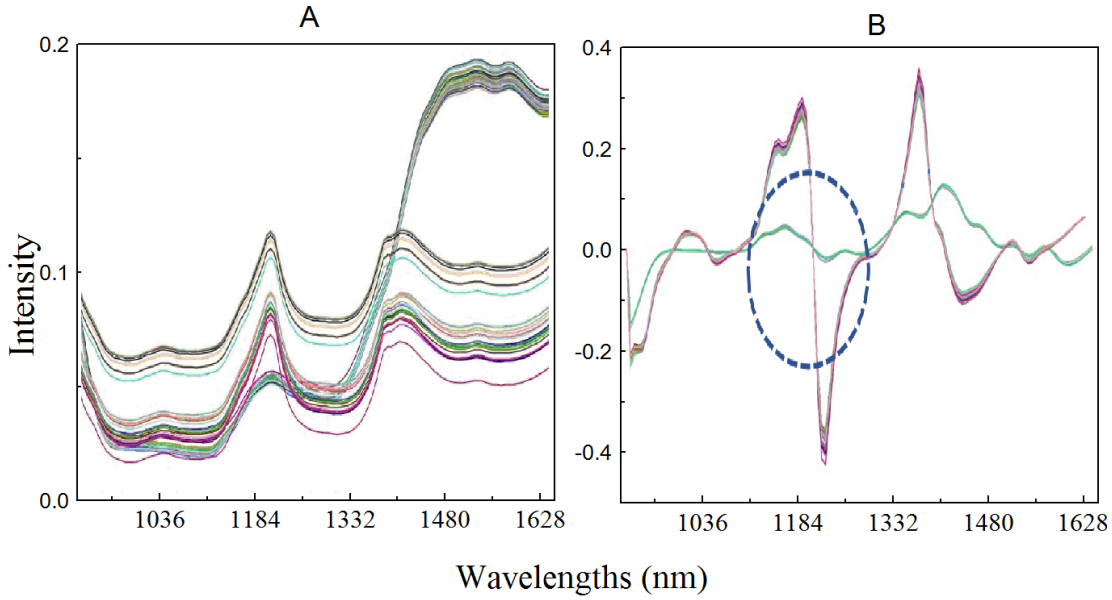

Fig. 22. NIR spectrum of mixture C before powdering and excipient magnesium stearate (mixture C' final) A-before processing, B-after processing.

When increasing the scale of fig.22 of the obtained spectrum of the mixture after processing, it is possible to notice a slight difference in the characteristic area of mixture C before powdering and mixture C after powdering. The scatter diagram of the values of the main components for the final mixture C is presented in fig.23.

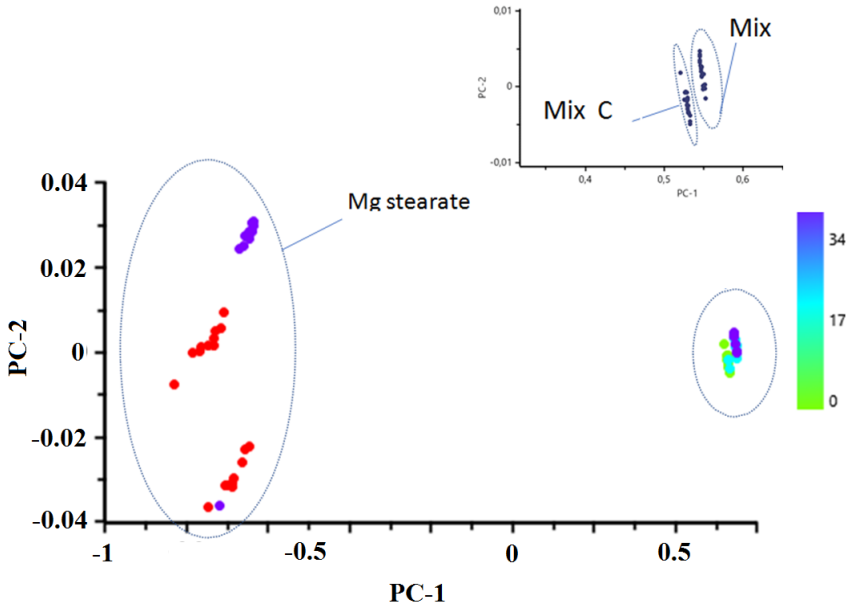

Fig. 23. Scatter diagram of the values of the main components of the final composition of the mixture C'

From the scatter diagram of the values of the main components of mixture C, we observe that the excipient magnesium stearate is isolated from the final mixture C'. When scaling the scatter diagram of mixture C and mixture C' finite, we see that they are isolated relative to each other, but the distance of the scatter is small, unlike the scatter of the components in the previous stages. A further task follows from this: to investigate how the scatter diagram of the values of the main components of the final composition of the mixture will behave if the components of other series and manufacturers are used, that is, whether the isolation of the separation of components will be preserved at the final stage.

Conclusions

An assessment of the possibility of implementing the NIR method for the current control of the homogeneity of the mixing process was carried out, which involved the use of a chemometric approach using the PCA method. The NIR spectra of active and auxiliary substances, intermediate and final mixture of bisoprolol fumarate were studied. It is shown that at each of the stages of mixing, the separation of both the active substance relative to auxiliary substances and the obtained intermediate and final mixtures relative to active and auxiliary substances is achieved. In the future, it is possible to carry out chemometric quality control of homogeneous mixing with variation of components of other

series and manufacturers to increase the amount of data. There is also a question about the sensitivity of determining the active substance. The sensitivity of the method is determined by the minimum amount of substance that can be detected by this method. In the future, the BIR spectra of model mixtures with different concentrations of the active substance and the analysis of spectral data will be investigated.

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