A project of a precision installer for measuring the inhomogeneous density of the solution has been developed. This module is one of the key components of an automated program-controlled complex created for the encapsulation of cell transport systems.

An analysis of existing methods for determining the values of viscosity and density shifts shows that optical measurement methods are the most appropriate for designing the precision installer due to their simplicity and reliability.

Implementation of optical measurement is also due to the need to ensure sterility of analyzed material, as well as non-destructive testing of liquid.

Using the ultrasound method requires immersion in liquid of transmitting element and receiver, which violates the principle of sterility. According to the results of measurements, it was found that the method of recording optical radiation can determine density distribution in the cuvette volume after centrifugation with a high degree of accuracy. The exact positioning of the needle for the selection of liquid has been achieved. A measuring optical module has been developed to determine the inhomogeneous density of the liquid.

Accurate positioning of the carousel at given points by mounting permanent neodymium magnets in the base of cuvette compartments has been achieved.

The simplification of measuring configuration by the exclusion of dispersive elements, filters and the monochromator significantly reduces the cost of measuring equipment and makes it easy to implement for solving such problems.

The introduction of modern digital technologies into the project makes it possible to process signal packets from positioning sensors and through individual channels, which is especially important for automating measurement and positioning processes, taking into account sterility.

Keywords: precision installer, optical module, inhomogeneous density of the solution, automation

1. Introduction

The implementation of engineering and technological solutions to production problems by automating time-consuming and labor-intensive manual work of personnel is a very topical issue in the proper organization of business.

The industrial production of cell transport systems is based on the use of centralized or stationary automated devices that allow procedures for the encapsulation of therapeutic substances.

The creation of transport systems for the targeted delivery of substances is the aspiration of scientific organizations around the world [1] and is of great interest in the pharmaceutical, cosmetic and food industries. The main challenges for successful industrialization are the scalability of production, process validation and quality control of manufactured products [2].

The conducted studies on the basis of PI "National Laboratory Astana" have shown the possibility of applying a biotechnological approach for the creation of cellular transport systems for targeted drug delivery.

However, in the process of creating cell transport systems, an obvious limiting challenge is the time-consuming drug loading process.
Difficulties of loading are associated with maintaining strictly sterile conditions for the preparation of cell transport systems, which is carried out manually. The routine method of preparing pharmacocytes takes 2–2.5 hours of the doctor’s working time.

The automation of the technology for obtaining a transport system provides the optimization of the introduction into practice of an innovative method of cellular bioengineering for targeted drug delivery.

Automating the drug loading process eliminates the problem of sterility impairment, strictly standardizes the preparation of cell transport systems and relieves the doctor’s working time from the laborious process.

Hypo-osmotic pre-swelling and hypotonic dialysis techniques are the most suitable procedures for automation, providing greater convenience for creating personalized and automated equipment compared to other methods of encapsulating cell transport systems.

The development of a prototype of an automated software-controlled complex for the encapsulation of certain substances in cellular transport systems is in progress.

However, this encapsulation process using cell transport systems needs to be optimized in terms of the feasibility of accurately measuring the heterogeneous density of the applied drug or substance solution.

In the automation of measuring functions in various technological processes, various measurement methods are widely used. In connection with the development of the technical and digital processor base, many measurement methods are being improved, simplifying the automation process. For this purpose, many existing measurement methods and tools are subject to processing and handling.

Optical methods for studying substances are based on the ability of these substances to generate optical radiation or interact with it. A separate place is occupied by methods for measuring the optical density of a liquid. The development of technologies in the field of development of various microelements and matrices in the electronics industry expands the scope of measurements of the optical density of a liquid. A set of technical solutions in the direction of improving the parameters of measurement automation inevitably leads to the improvement and development of instruments and devices in this area. The main emphasis in such automation is aimed at reducing the measurement time, reducing the time for changing the sample or measurement environment, etc. So, today there are still many unsolved problems in this area, which is an urgent task for finding a suitable solution.

Therefore, studies that are devoted to technical solutions in the direction of improving the parameters of automation of measuring the inhomogeneous density of a solution are of scientific relevance.

2. Literature review and problem statement

Density measurement is carried out both for the identification of liquids, and for the purposes of quality control and process control, as well as for performing accounting operations for the quantity of raw materials, fuels, reagents and prepared products [3]. Float, mass and hydrostatic densitometers are easy to operate, but almost impossible to automate [4]. The operation of radiotrace densitometers is based on determining the attenuation of a radiation beam as a result of its absorption or scattering by a liquid layer, which is related to the density of the medium. Their advantage is the absence of contact with the test liquid, and the disadvantage is the necessity to protect personnel.

Many years of experience have shown that the use of ultrasonic transducers as primary sensors for monitoring the quality of technical fluids is quite effective in many industries [5]. The physical basis for the industrial application of ultrasonic methods for measuring the characteristics of liquid media is the functional dependence both on the properties of the liquid itself and on such parameters of ultrasonic waves propagating in liquids as transmission velocity, attenuation coefficient, longitudinal and shear acoustic impedances. Currently, measurements of the speed of sound are mainly used [6]. The technical difficulties in measuring viscosity and density shifts using existing ultrasonic methods are caused by very small numerical values of the shear and longitudinal impedances of liquids compared to solids, which leads to large measurement errors [7].

At the same time, automatic ultrasonic measurements of the most demanded liquid parameters, such as viscosity and density shears, are associated with the solution of a number of physical and technical problems [8]. All these parameters that characterize ultrasonic waves in a liquid depend not only on one characteristic of the liquid, but on several characteristics [9]. Therefore, the solution to the problem of determining the values of viscosity and density shears of a liquid refers to multi-parameter measurements. Therefore, automatic devices designed to measure liquid parameters must be multichannel, and additional requirements are put forward for the electronic and acoustic compatibility of each channel [10]. In addition, for successful practical implementation, these instruments must provide measurements of viscosity and density with errors not exceeding the errors of measuring these parameters by traditional methods. A very promising direction for solving these challenges is the use of ultrasonic normal waves [11].

To implement this direction of automatic measurements of the parameters of technological fluids directly in the production process and assess their quality based on ultrasonic measurements, a complex of theoretical and experimental studies is needed. It is necessary to carry out experimental studies of the relationship between the viscosity and density of a liquid and the measured parameters of normal waves in thin plates [12]. It is also necessary to research and develop special designs of waveguides for ultrasonic viscometers and densitometers in order to optimize them depending on the conditions of use, to study the metrological characteristics of ultrasonic viscometers and densitometers [13].

In connection with the abovementioned, after a thorough analysis of the existing methods of ultrasonic measurements, the authors of the project made a preference for optical measurement methods. Simplicity and reliability, as well as the factor of non-destructive testing of a liquid medium, have made a convincing preference in favor of optical measurement methods.

The science of methods of photometry of optical radiation fluxes depending on the wavelength is called spectrophotometry [14]. It includes photometry, spectrometry and metrology. The design and operation of spectrometers, like all electronic devices, were strongly influenced by technological advances in the second half of the 20th century. Apparently, the development of charge-coupled devices (CCDs) in the early 1970s was of the greatest importance. Initially, they were invented for storing data, but it soon became clear that they were very promising as devices for obtaining images. Essentially, such a device electronically imitates photographic film. A charge-coupled device consists of individual photosensitive elements between which an electric charge can be transferred. Light falling on an array
of such elements creates a charge distribution that matches the image. This image is then electronically transferred to another location, such as a monitor, and reconstructed. Initially, CCDs were used to replace photographic plates in telescopes. The first such device was installed on the Kitt Peak National Observatory’s 1-meter telescope in 1979. Today, CCDs have made it possible to create affordable digital video cameras. Soon after the successful application of CCDs to astronomical applications, it was discovered that they could greatly improve the performance of spectrometers. To do this, the exit slit and the detector were replaced by a CCD matrix. Now it was no longer necessary to measure the intensity of light sequentially at each wavelength. The number of wavelengths that can be observed simultaneously is determined by the number of elements in the matrix. The matrix generates an output signal from which it is possible to reconstruct the intensity of light falling on each element of the array. This output signal can be sent to a monitor or printer for visualization. The instrument gives instantaneous response across the entire spectral range at once, and it is no longer necessary to scan the spectrum in different directions to measure the intensity at individual wavelengths.

Measurements of photometric parameters such as directional transmittance or specular reflection are relatively simple. These measurements are based on the fact that a sample is introduced into the flux of directed radiation and the flux transmitted through it or reflected from it, respectively, is compared to the directed flux in the absence of the sample. Spectrometry includes a variety of spectral instruments that are part of the spectrophotometer [15].

In general, the spectrophotometer includes: a source of optical radiation, a device for selecting the necessary spectral intervals, in the form of a monochromator or a set of light filters, a photodetector, and a signal registration system [16].

The registration system can be single-channel or multi-channel. A single-channel registration system is usually built on the basis of a monochromator in which scanning is performed by rotating a diffraction grating or prism. In a multichannel recording system, scanning is not used, but discrete series of wavelengths in polychromators or sections of a continuous spectrum in spectrographs are simultaneously recorded [17].

In all modern commercial spectrophotometers, the monochromator is placed between the light source and the sample in order to minimize the photochemical effect of the probing radiation [18].

All the measurement methods listed above and their implementation turned out to be insufficient for solving many problems related to the automation of measuring the inhomogeneous density of a liquid.

To find the most suitable method to obtain optimal results of accurately measuring the heterogeneous density of the active liquid, additional technological solutions need to be developed.

3. The aim and objectives of the study

The aim of the study is to design a precision liquid sampling setter, a built-in measurement module for intermediate measurements. Based on the data of the measurements made, to ensure accurate positioning of the needle and the selection of liquid of a certain density layer formed by technological devices of precision mechanics and the force of the centrifuge.

The following objectives have been set to achieve the aim:

- to develop precision mechanics units for positioning the sampling needle;
- to develop a measuring optical module to determine the inhomogeneous density of a liquid;
- to process a package of signals from positioning sensors, including data from CCD matrices, to automate the positioning process, taking into account sterility.

4. Materials and methods

The methodology for conducting engineering and experimental work to create a prototype model of a new technology has been carried out using the international standard for 3D visualization and design work. Siemens Digital Industries Software has been used for product lifecycle management. The compact and accurate JT files have been used throughout the entire product development life cycle to communicate critical design information. In particular, the following systems were used: Design and implementation of HMI/姚/MMI SCADA complexes. Development of digital and analog electronics using the Proteus 8.1 design environment. Developer of a SCADA complex (MALOKS) with a program for data collection and control, mechatronics (actuators). Siemens Step 7, HMI/姚/MMI SCADA Industrial Automation, Automation of measuring systems, creation of new device prototypes, including for scientific applications.

To solve the tasks set, the following materials and elements have been used at this level of the project:

1. CCD linear matrix.
2. Miniature linear guides and linear bearings.
3. Stepper motors.
4. Special reduction gears.
5. Optical rotation sensors.
6. End sensors.
7. Threaded shafts, with threaded seat seals of the moving part.
8. Power drivers for motor control.
9. Mounting flanges and other mounting fittings.
10. Other components and modules.

In this paper, two methods are compared for solving the tasks set, these are the ultrasonic method and the optical method for measuring the heterogeneous density of a medium.

The state of the liquid medium is assessed by comparing its current physical, chemical and other parameters with their specified values. Despite the availability of various methods for measuring these parameters, the requirement to maintain the operability and metrological characteristics of measuring instruments narrow the possibilities of their use directly in the technological process. The need for automatic measurements at high temperatures, corrosiveness and/or toxicity of test objects significantly narrow the range of types of primary converters. This is especially important for the control of biological liquids without causing destructive effects on the object.

5. Results of the design of the precision liquid sampling setter, built-in measurement module for intermediate measurements

5.1. Development of the precision mechanics units for positioning the sampling needle

The software and hardware complex being developed for automatic loading of cell transport systems with a drug mixture solution includes a module for measuring and analyzing the inhomogeneous density of the solution.
To determine the homogeneity of the density of a liquid medium, the module includes devices that are part of the cuvette holder. The complexity of measuring these parameters is due to the rotation of the cuvettes at a high speed of 1500–7500 rpm during the centrifuge process. For this purpose, elements of precision mechanics are introduced into this module. These elements of precision mechanics move the U-shaped pairs of photosensors at the moment of termination of rotation. The receiver and transmitter of optical radiation are assembled into separate functional modules and represent a set of photocells/photodiodes and emitters/luminodiodes, respectively. They are located vertically on the same line and their active part faces in one direction (Fig. 1).

The nature of the spectra is explained by the absorption bands. In this case, the measured optical density turns out to be less than the true density, as shown in (1):

$$D_{\text{meas}} = \frac{I_0 + i}{I + i} \quad D = \frac{I_0}{I}, \quad D_{\text{meas}} < D$$

where $D_{\text{meas}}$ is the measured optical density, $D$ is the true density, $i$ is the fraction of scattered light, $I_0$ is the intensity of the light flux, falling on the object, $I$ is the intensity of the light flux, transmitted through the object.

Scattering of light in the volume and on the surface of the testing samples, as well as their photoluminescence, introduces additional distortions into the observed absorption spectra. Scattering of light by the sample leads to a distortion of the shape of the spectra and to an incorrect determination of the optical density.

The nature of the spectra is explained by the absorption of light, which is associated with the excitation of the elec-
Transmission of electrons, more precisely, with the transition of electrons in the valence shells of atoms in a molecule between molecular levels or with the transition of an electron from the highest occupied molecular orbital (HOMO) to the lowest vacant molecular orbital (LUMO). The energy of such transitions is 1.77–6.2 eV, which corresponds to wavelengths of 700–200 nm.

The absorption of electromagnetic radiation in the ultraviolet, visible and infrared regions of the spectrum is quantitatively described by the Bouguer-Lambert-Beer law, as follows (2):

$$I = I_0 \cdot 10^{-\varepsilon n},$$

where $I_0$ is the intensity of the incident monochromatic light flux, $I$ is the intensity of the monochromatic light flux passing through the absorbing layer, $c$ is the concentration of the absorbing substance, $\varepsilon$ is the thickness of the absorbing layer, $n$ is the molar absorption index.

To measure the degree of absorption of electromagnetic radiation, devices have been designed that make it possible to determine not the intensity of the electromagnetic flux, but its weakening due to the absorption of the analyzed substance. To characterize the degree of absorption of the electromagnetic radiation beam, such photometric quantities as transmission and optical density are introduced.

Consider the situation when a beam of monochromatic light with intensity $I_0$ falls on a cuvette with a solution of the test substance, as shown in Fig. 2. If light is absorbed in the sample, then as a result the light intensity will decrease to the value $I$. The ratio of these quantities is called transmission [19].

$$T = \frac{I}{I_0},$$

where $T$ is transmission, $I$ is the intensity of the light flux passing through the layer of absorbing substance, $I_0$ is the intensity of the falling on light flux.

Sometimes, instead of $T$, the absorption coefficient $(1-T)$ is used (4), which is equal to:

$$1-T = \frac{(I_0-I)\cdot 100}{I_0},$$

where $In$ is the amount of light absorbed per unit of time. An increase in the concentration of the absorbing substance or the thickness of the cuvette with the solution will obviously lead to an increase in the absorption of light, that is the value $(1-T)$, and a decrease in the transmission of the sample $T$.

To measure the absorption coefficient, devices have been designed that make it possible to determine not the intensity of the electromagnetic flux, but its weakening due to the absorption of the analyzed substance. To characterize the degree of absorption of the electromagnetic radiation beam, such photometric quantities as transmission and optical density are introduced.

Transmission is the ratio of the intensity of the light flux passing through the layer of absorbing substance to the intensity of the falling on light flux, as shown in (3):

$$T = \frac{I}{I_0}.$$
The dependence of the transmission spectrum on the density of a liquid glycerin solution with a different dose of gelatin admixture is shown in Fig. 3. Measurements were carried out after centrifugation of the glycerin solution with gelatin admixture at 4,900 rpm for 2 min. Graphs of the transmission spectrum of a liquid glycerin solution with gelatin admixture are shown in Fig. 3, a: A – concentration with 15% gelatin admixture, B – concentration with 10% gelatin admixture, C – concentration with 5% gelatin admixture.

The dependence of the transmission spectrum of a liquid glycerin solution without gelatin admixture after centrifugation at 4,900 rpm for 2 minutes is shown in Fig. 3, b.

5.3. Processing of the signal package of positioning sensors and data of charge-coupled devices

Prior to the start of measurements, these modules are pre-calibrated by the level of the dark current and by the maximum radiation of the transmitting optical element.

The location of the cuvettes in the module of the intelligent centrifugation system can be seen in Fig. 4.

After a successful measurement of the density distribution over the entire volume of the liquid, the received data is processed by the built-in processor from each measurement channel.

Fig. 3. Graphs of dependence of intensity on density distribution in centrifugation: a – glycerin with an admixture of gelatin; b – glycerin without impurities. Intensity values are shown by ordinate, density values are shown by abscissa

Fig. 4. General scheme of the intelligent centrifugation system of the software and hardware complex
According to the obtained measurement results on the density distribution in the corresponding volume, the power electronics of the control of the hardware-software complex receives a command to capture and select a liquid of a certain density by immersing the needle by a certain value corresponding to the given distributed liquid density. Thus, it was possible to automate the process of selection, loading and aspiration of the active liquid, for dosage and distribution into sealed sterile containers, due to the introduction of measuring the inhomogeneous density of the liquid. According to the results of measurements, regarding the density distribution in a liquid medium, it was found that the chosen method of recording optical radiation can determine the density distribution in the cuvette volume after centrifugation with a high degree of accuracy. An important factor is the simplification of the measuring configuration by the exclusion of dispersive elements, filters, and the monochromator body itself, which significantly reduces the cost of measuring equipment and makes it easy to implement for solving such problems.

6. Discussion of the results of project development of a precision installer

The introduction of new technologies in the field of optical measurements and automation of technological processes, as well as the use of digital control systems and digital signal processing (DSP), opens up unlimited opportunities for developers to design and build different software and hardware systems. However, the encapsulation process using cell transport systems needs to be optimized in terms of the feasibility of accurately measuring the heterogeneous density of the applied drug or substance solution.

This project provides the design of the precision liquid sampling setter, a built-in measurement module for intermediate measurements, as shown in Fig. 1. The rotation chamber of the centrifuge carousel at the moment of rotation does not contain measuring U-shaped modules, they are located in special shafts of the chamber, closed by a cover.

After the carousel is completely stopped and fastened in accordance with the position of the permanent magnets, the measuring U-shaped modules are transferred from the bottom up, covering the entire cuvette compartment. The location of the cuvettes in the module of the intelligent centrifugation system can be seen in Fig. 4.

After that, scanning takes place through a vertical optically transparent window. The data is sent to the DSP module for further processing. If the position of the carousel is not set correctly, an error signal will be sent to the data collection module and further control will be blocked until this problem is corrected.

In addition to the use of the optical measurement method in this project, an alternative application of the ultrasonic method has been tested. The main conditions of the project are to ensure the sterility of the analyzed biological material.

When using the ultrasonic method, a necessary condition for the physical impact on the measurement medium is immersion in the liquid of both the transmitting element and the receiver, which violates the principle of sterility. Taking into consideration the peculiarities of the biological object of study, the authors of the project chose the optical method for further use. The optical method allows a successful measurement of the density distribution over the entire volume of the liquid and ensures sterility.

According to the results of measurements, regarding the density distribution in a liquid medium, it was found that the chosen method of recording optical radiation can determine the density distribution in the cuvette volume after centrifugation with a high degree of accuracy. An important factor is the simplification of the measuring configuration by the exclusion of dispersive elements, filters, and the monochromator body itself, which significantly reduces the cost of measuring equipment and makes it easy to implement for solving such problems.

To solve the tasks, a number of existing technologies were applied, for example, the use of linear monorails in complex with bearings, made it possible to achieve accurate and smooth movement of the needle holder carriage. Because of the linear bearings and longitudinal monorails installed in the mechanism, the positioning accuracy has been achieved with an indicator of 0.3 mm on the X-axis, 0.35 mm on the Y-axis, 0.32 mm on the Z-axis.

The inclusion of linear matrices in the measuring system made it possible to measure the inhomogeneous distribution of the optical density of the active liquid. According to the indicators of layers of different densities, the possibility of sampling with an accuracy of +0.42 mm has been achieved. The installation accuracy of the cuvette holders is 0.75 mm.

Magnetic bearing points made it possible to stop the cell compartments at the calculated location where the shafts of the measuring U-shaped modules are precisely located. The use of digital technologies has helped to solve the problem of controlling and processing data received from sensors and CCD cameras equipped with low-noise amplifiers.

Because of the technical complexity of achieving sterility of the active liquid, it is possible to solve the issue of compliance with sterility only through closed processes, using isolators or isolating technologies. Sterility indicators have been achieved and maintained during the processing of the active fluid through the introduction of isolating technologies.

Thus, in this study, the development of a project of a precision installation for measuring the inhomogeneous density of the solution was achieved. The precise positioning of the needle for the selection of the liquid formed by the technological devices of precision mechanics and the effort of the centrifuge was achieved.

The use of modern technologies and materials, as well as proven and well-studied measurement methods made it possible to solve the tasks and achieve the project goals.

7. Conclusions

1. A mechanism for transferring the sampling needle has been developed, taking into account the distribution of the density of the active liquid. All mechanical units for the movement of the sampling needle have been selected and adjusted, end position sensors and a differential sensor for the movement of the sampling needle have been collected. Because of the linear bearings and longitudinal monorails installed in the mechanism, the positioning accuracy has been achieved with an indicator of 0.3 mm on the X-axis, 0.35 mm on the Y-axis, 0.32 mm on the Z-axis.

2. A measuring optical module has been developed to determine the inhomogeneous density of a liquid. A technology has been developed for moving U-shaped modules from the waiting shafts in the direction from the bottom up to the cu-
Cuvette holders. Accurate positioning of the carousel at given points, by mounting permanent neodymium magnets in the base of the cuvette compartments, has been also achieved. According to the indicators of layers of different densities, the possibility of sampling with an accuracy of +0.42 mm has been achieved. The installation accuracy of the cuvette holders is 0.75 mm.

3. The introduction of elements of modern digital technologies into the project makes it possible to process signal packets from positioning sensors and through individual channels. Processing of the data from four CCD matrices through all separate four parallel measurement channels is especially important for automating the measurement and positioning process, taking into account sterility. The main goal of the considered project has been successfully achieved and the set tasks have been performed. It is possible to solve the issue of compliance with sterility only through closed processes, using isolators or isolating technologies. Sterility indicators have been achieved and maintained during the processing of the active fluid through the introduction of isolating technologies.

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