

Method of evaluation of process of red blood cell sedimentation based on photometry of droplet samples

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Received: 3 December 2015 / Accepted: 2 July 2016 / Published online: 11 July 2016
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Abstract The paper focuses on research aimed at creating and testing a new approach to evaluate the processes of aggregation and sedimentation of red blood cells for purpose of its use in clinical laboratory diagnostics. The proposed method is based on photometric analysis of blood sample formed as a sessile drop. The results of clinical approbation of this method are given in the paper. Analysis of the processes occurring in the sample in the form of sessile drop during the process of blood cells sedimentation is described. The results of experimental studies to evaluate the effect of the droplet sample focusing properties on light radiation transmittance are presented. It is shown that this method significantly reduces the sample volume and provides sufficiently high sensitivity to the studied processes.

Keywords Aggregation · Photometry · Erythrocyte sedimentation rate · Blood

1 Introduction

Medical laboratory practice deals with the study of dispersed media and evaluation of process dynamics. One of the main objects of research is multi-component heterogeneous dispersion medium, blood. The most vivid example of the process accompanied by a significant change of the medium dispersion is aggregation of red blood cells that

can be assessed by direct methods as well as indirectly by cell sedimentation rate.

Evaluation of the erythrocyte sedimentation rate (ESR) is one of the most frequently performed blood tests to diagnose inflammatory processes in an organism and to monitor a disease course and the therapy [17]. Despite its relative simplicity, the methods of ESR study should be automated to obtain more accurate data, to minimize the possibility of human error and to improve the performance of laboratories. The existing automated methods used to study ESR reduce the analysis time up to 10–15 min (a standard method takes 1 h), increase the sensitivity and reduce the operator's error by means of automated optical reader systems [6, 9].

However, one of the objectives in terms of optimization the ESR analysis is the problem of reducing the sample volume required for the study. The Westergren method requires a 2-ml venous blood sample. The Pachenkov's micromethod used in Russia requires about 0.2 ml of capillary blood. However, to obtain the necessary amount of blood, it is to be squeezed out of a finger under considerable physical effort on vessels. Therefore, there is a possibility of mechanical damage to cells, change of sample properties, and as a result, an increase in the probability of obtaining an erroneous result. In case of performing this analysis in pediatrics, the problem of minimizing the volume of the test sample becomes even more relevant.

One of the problems concerning minimization of the amount of blood for the ESR analysis is related to the established traditions and standards which have been used in clinical practice. To measure the sedimentation rate according to the standard method, sedimentation rate is measured by placing blood samples in a transparent tube of a specified diameter and height, and after an hour the distance of the cell–plasma interface from the initial level

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is determined [8]. This technique of the ESR analysis provides reduction of the amount of blood through the change in the height and diameter of the tube. However, if the tube diameter is reduced, near-wall effects exert a significant impact on the sedimentation process [19]. At the stage of cell aggregate formation this impact is insignificant, but at the stage of aggregate sedimentation it can compromise the physiology of the process and significantly retards it. Therefore, this parameter of the measuring tube is limited. The choice of the tube height can be related to the notion of the dynamical scale of the measured ESR parameter which distinguishes a number of boundary conditions: low-, medium- and high-ESR value. A reduced height of the tube leads to compression of the dynamic range and less accurate recording of the test parameter. In some devices, the analysis time is reduced through the tilt of the measuring tubes, centrifugation and other procedures. However, these effects violate the natural sedimentation process and can cause erroneous results. Therefore, new methods should provide minimal intervention in the research process.

From the above, it can be concluded that methodological and technical solutions which use “classical” approach to assessment of cell sedimentation do not provide effective minimization of the sample volume and the analysis time.

From our point of view, an interesting direction in analytical researches that allows eliminating the above-mentioned difficulties is development of “open” cuvette where the volume and form of the studied area are defined by forces of surface tension of liquid and interfacial interactions with a substrate, i.e., experiments are conducted with samples in the form of drops. It allows reducing sample volumes to several microliters or even hundreds of nanoliters. Additionally, there is an opportunity to assess not only of optical properties of the medium but also energy characteristics of the sample that change during chemical and physicochemical transformations of the substance.

It should be noted that application of drops for chemical and physical measurements has been known for a long time. For example, the method of hanging drops to measure the surface tension of liquids has been used for more than a century and a half. Physicochemical methods of analysis based on drop techniques are still relevant.

The analysis of literature has shown that analytical techniques based on measurements of droplet sample parameters are rapidly developing and cover different areas and several interdisciplinary fields of science: surface and interfacial surface tension, spectroscopy, analytical chemistry instrumentation and electrochemistry, etc. [11, 12]. A fairly complete analysis of drop technique application for the period up to 2000 year is provided in the review by Miller and Synovec [13]. This review contains 112 papers and reveals different aspects of analytical measurements based on droplet techniques. In particular, it considers the use of

drops as a component of the detector (sensor) and provides the analysis of fundamental studies of chemical and physical phenomena related to drops. In addition, it reports the advances in the field of microfluidic sample handling and agent transfer instrumentation and discusses technological issues related to droplet chemical analyzers.

We also study a question of application of droplet samples for carrying out clinical laboratory tests. The analysis and results of approbation of our proposed method for the study of the ESR are presented in this article.

2 Materials and methods

It is important to note that the study of liquids using drops is mainly based on assessment of their geometrical parameters via systems of photograph and video recording of the drop lateral projection with the following data processing. The assessment of optical properties of the sample is typically not performed. In most of the known developments which are based on assessment of the sample energy characteristics via photometry methods, hanging drops are most frequently used test objects. However, the equipment for hanging drops is very complicated as it requires precise pressure control in the system. In addition, despite the small volume of drops, the volume of the sample will still be significantly large to fill the entire hydrodynamic system. Moreover, only sufficiently transparent liquids can be analyzed in this system. However, cloudy heterogeneous media of the biological liquids limits the use of many of these techniques. In addition, droplet methods are limited in medical laboratory studies due to the lack of easy-to-use equipment and appropriate techniques developed for the specific types of medical analysis.

Considering all this, we offer the method of photometry when the investigated sample is in the form of a sessile drop with the predetermined diameter of its base on a transparent hydrophobic cuvette, coaxially disposed between the source and the receiver of optical radiation (Fig. 1) [2]. The design of the transparent hydrophobic cuvette made of PMMA (poly (methyl 2-methylpropenoate) prevents the drop from spreading and retains its shape. The volume of droplet sample (5–30 μl) depends on the cuvette size and determined by the aim of investigation. The optical receiver detects radiation that has passed through the drop.

The block diagram of the setup for conducting the research is presented in Fig. 2. The setup performs simultaneous measurement of the optical properties of the sample and records the shape of the lateral projection of the drop to study the dynamics of the photocurrent and relate it to changes in the drop shape and to the processes occurring in it.

As can be seen from Fig. 2, the experimental setup includes several functional blocks. The primary information

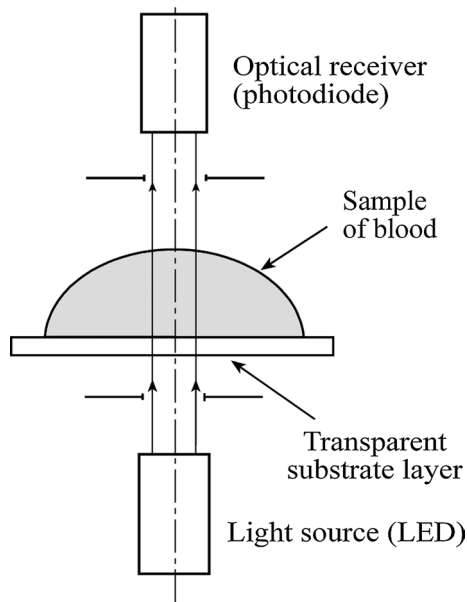


Fig. 1 Scheme of the method of droplet sample photometry

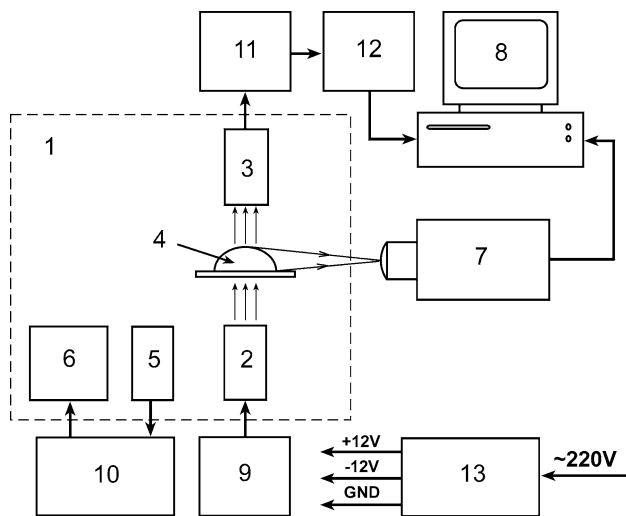


Fig. 2 Block diagram of the setup to conduct the study. The setup consists of the following blocks: 1 measuring chamber of the primary transducer, 2 radiation source, 3 radiation receiver, 4 droplet sample, 5 temperature sensor, 6 heating element, 7 video camera, 8 personal computer, 9 constant current source of the radiation source, 10 thermostat, 11 amplifying device, 12 recording device and 13 power source

on changes in the transparency and focal length of the droplet blood samples is obtained during scanning it by light radiation. Sample (4), source (2) and radiation receiver (3) are placed in the measuring chamber of primary transducer (1) where the temperature and humidity are maintained stable. We used the NIR LED (wavelength is 805 nm) as radiation source with diameter of parallel light beam from 1 to

3.5 mm (depending on the aim of investigation). The radiation detector was a photodiode with a spectral response matching the wavelength of the source.

The radiation source is powered by constant current source (9) that provides the required output power characteristics of the probing radiation, the most important of which is the stability of the power of emitted light radiation in time. It should be noted that translucence of blood layer with 2 mm thickness requires a radiation source with a power at least 10 mW. Since the measuring chamber of primary transducer is isolated from external illumination, the continuous operation mode of LED was used. After passing through the cuvette with the test sample, the radiation reaches the photodiode located coaxially with the radiation source and the droplet sample. Due to low transparency of many biological fluids, the electrical signals from the photodiode are typically of a small value; therefore, they are to be pre-amplified by analog device—operational amplifier (11). This cascade of the photodiode and the amplifier will be referred to as photoelectric converter (PEC). The signal from the photocurrent amplifier enters the computer through interface device (12). We used the National Instruments USB 6009 as an interface device with sampling rate 48 kHz. This frequency is enough for digitization a slowly changing signal (signal from the photodiode). The program for device operation and data storage was written using LabVIEW 2010 (National Instruments Corporation, Austin, TX).

To maintain the predetermined temperature in the measuring chamber of the primary transducer, analogue electronic devices include thermoregulation block (10) that controls the voltage of resistive heating element (6). The thermal stabilization system provides precise maintenance of the predetermined temperature in the chamber of the primary transducer at the level of ± 0.1 °C of the temperature set point with external temperature changes in the range from +10 to +35 °C. Setting of a certain temperature is required to provide identical optimal process conditions in the test samples and to stabilize the parameters of the radiation source and optical receiver as their output characteristics are very sensitive to changes in the external temperature.

To obtain information on the drop lateral projection, the setup is provided with digital video camera (7). The camera lens is built into the side wall of the chamber of the primary transducer and focused on the droplet sample. We used CCD-camera (DiGiVi CM-CH2-W5). The sensitivity of the camera is sufficiently high that results in significant reduction of the amount of front illumination of the drops to obtain its contour. In addition, this type of video camera has good sensitivity in the near-infrared range. It provides the possibility to visualize the light flux scattered by the droplet sample using the source of radiation with

wavelength in the near-infrared range. The setup design allows positioning of the camera in the place of the photodetector and record the scattering pattern of the radiation passing through the droplet sample. A more detailed description of the experimental setup is provided in the RF patent on utility model [1].

3 Results

3.1 Drop photometry for ESR evaluation

Some experiments were conducted to evaluate the possibility of using the method of droplet sample photometry for determining ESR. The objective was to compare dynamics of changes in the intensity of the light passing through the drop of blood during the process of aggregation and sedimentation of red blood cells, with ESR values of analyzed samples obtained by the standard technique accepted in clinical practice.

Blood of patients undergoing treatment in a regional clinical hospital of Tomsk (Tomsk, Russia) was used in our experiments. It was necessary to have the blood samples with different values of ESR. To provide a wide range of ESR values, groups of patients with inflammatory diseases have been chosen. Samples of venous blood from 37 patients of the pulmonology department were investigated. Most of the patients had a diagnosis of acute pneumonia (73 %), other patients had bronchial asthma in the period of an aggravation and chronic obstructive pulmonary disease. Patients who were taken to a hospital and patients who had already undergone treatment were investigated.

Blood sampling was carried out in the morning before meal. Blood was stabilized with 3.8 % sodium citrate. For each blood sample, the measurement of the ESR value by Pachekov's micromethod and measurement of optical properties of these samples formed as sessile drops were made. Photometry within 10 min of droplet samples was carried out on the setup described above. Blood before formation of drops was carefully mixed. Photometry was conducted immediately after placing the drops on the cuvette (with the use of micropipette). The volume of droplet samples was 20 μ l, base diameter—5.3 mm. Diameter of the light probing beam was 1.5 mm. The photodetector had an aperture of 1 mm and was placed at distance of 2 mm from the drop surface.

Figure 3 shows the curves of changes of PEC output voltage ($U_{\text{out PEC}}$) during photometry of droplet blood samples. The change in the intensity of the light passing through the sample was estimated by the value of the

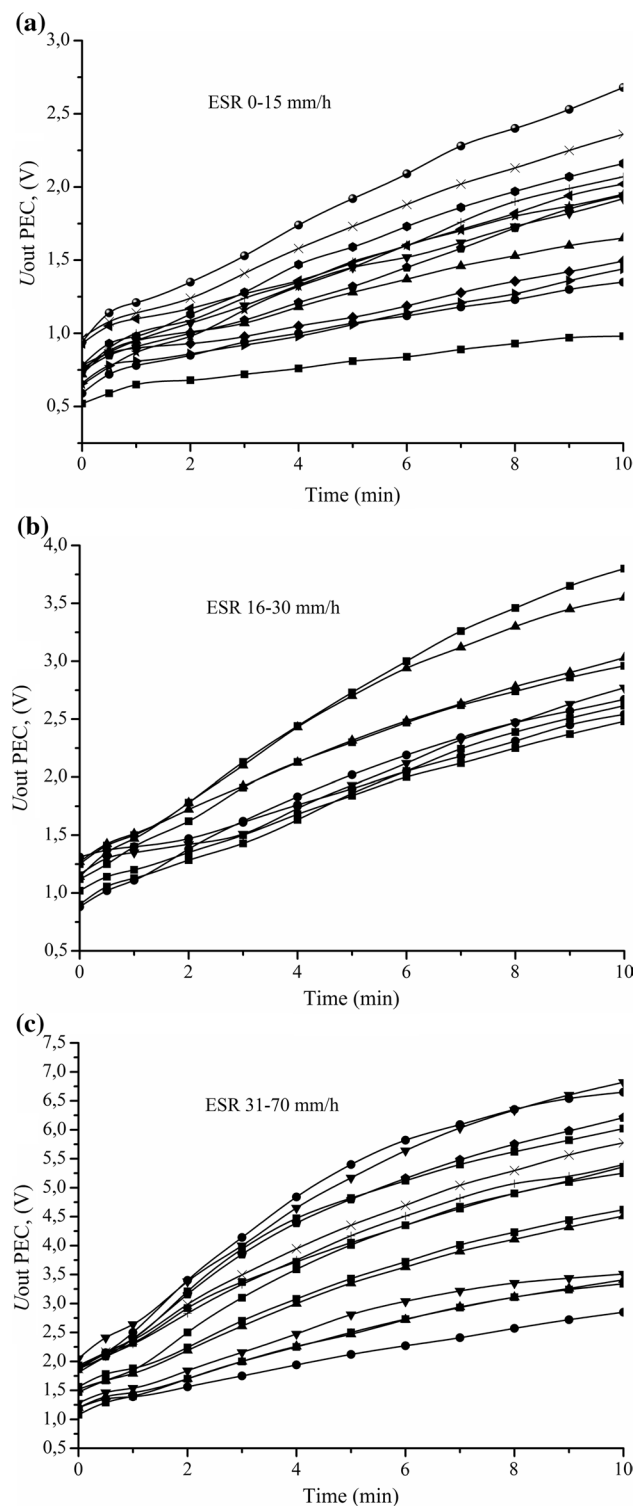


Fig. 3 Dynamics of change of the PEC output voltage for blood samples with different ESR value: **a** blood samples with the ESR value 0–15 mm/h, **b** blood samples with the ESR value 16–30 mm/h and **c** blood samples with the ESR value >31 mm/h

$U_{out}PEC$. For convenience of perception of the curves of light transmission through droplet samples, graphs in Fig. 3 are combined into three groups on the basis of ESR value of samples investigated with the Pachenkov’s micromethod. First group—blood samples with the ESR value 0–15 mm/h (Fig. 3a), second group—ESR value 16–30 mm/h (Fig. 3b) and third group—ESR value >31 mm/h (Fig. 3c). Figure 4 shows cross-plots constructed according to average characteristics for the three groups of samples.

As can be seen from the graphs in Figs. 3 and 4, high-ESR values determined by Pachenkov’s micromethod correspond to a high rate of rise of light transmission graphs for the respective droplet samples of blood. Further analysis of curves to obtain more exact data concerning the correlation between the curve of light transmission and ESR value can be constructed on this fact. It aims to implement this technique in clinical practice.

Although the differences in the dynamics of behavior of light transmission curves for droplet samples depending on ESR value are highly obvious, their deeper analysis for obtaining adequate information about processes happening in sample is required. The accumulation and analysis of large amounts of experimental material are necessary for this purpose. Besides, the creation of mathematical model of droplet sample light transmission that will allow targeted approach to the choice of design of the optical measuring system, parameters of droplet samples and analysis of the obtained information is also necessary.

3.2 Drop photometry in comparison with the classical photometry in flat cuvette

To show the advantages of the photometric analysis of droplet samples to study aggregation and sedimentation processes, we conducted a comparative study of changes in optical properties of the blood samples placed in a flat cuvette and those in the form of drops. Blood samples with the highest and lowest values of ESR only were used in this experiment to estimate the maximum range of signal variation. The photometric analysis of samples placed in the flat cuvette was carried out according to the scheme presented in Fig. 5. The cuvette thickness h corresponds to the height of the droplet sample (2.5 mm) to provide the same value of the tested cell layer.

The experimental light transmission curves for samples in the flat cuvette and droplet samples are presented in Fig. 6. It is seen that for equal sedimentation rates, the rate of the curve growth for droplet samples is significantly higher in comparison with that for the sample in the flat cuvette. For droplet samples, change of $U_{out}PEC$ during the process of erythrocyte sedimentation is about 7 V, and at the same time for sample in flat cuvette is about 1 V (ESR 60 mm/h). For samples with ESR 4 mm/h, change of $U_{out}PEC$ is 1.3 and

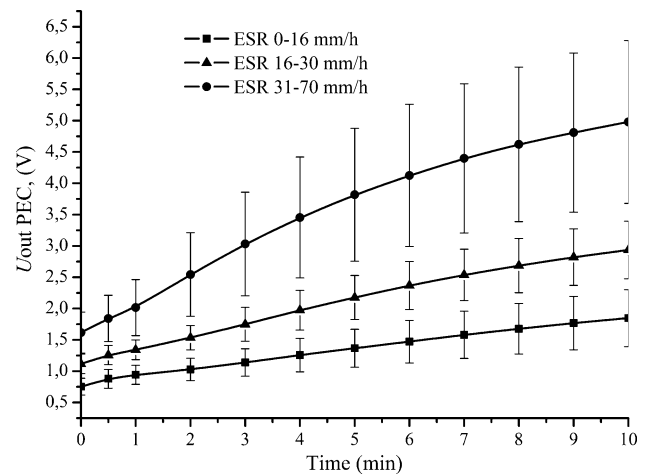


Fig. 4 Graphs of change of the PEC output voltage for samples with different ESR value (normal, increased and high), constructed on average values of selection. The dispersion of values is built by the standard deviation from average value

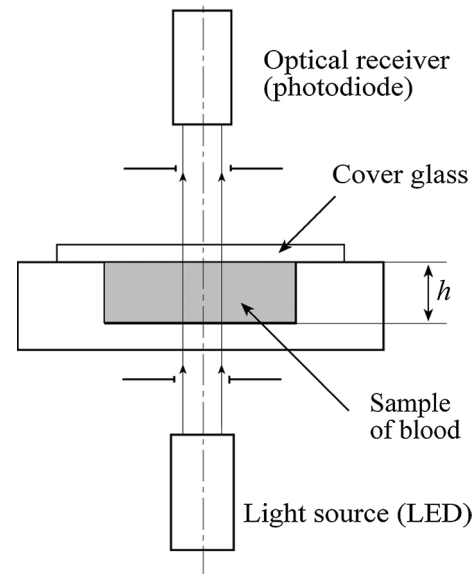


Fig. 5 Scheme of the photometric analysis of the sample in a flat cuvette

0.07 V for droplet sample and sample in flat cuvette, respectively. Also, during drop photometry the difference between the curves for samples with low- and high-ESR values is more distinct as well. Therefore, the accuracy of processing and analysis of curves increase in this case.

3.3 Study of the focusing properties of the droplet blood sample

At assessment of ESR, it is necessary to consider presence of the top transparent plasma layer arising after

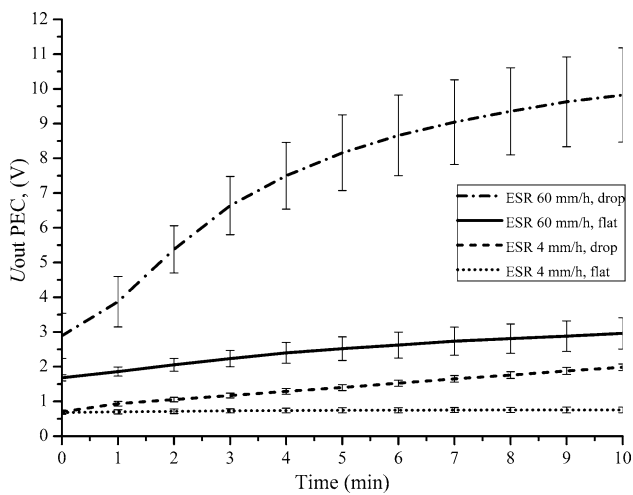


Fig. 6 Experimental curves of the $U_{\text{out}}\text{PEC}$. These curves indicate the dynamics of light transmission during erythrocyte sedimentation in the droplet sample (*drop*) and in the flat cuvette (*flat*) for samples with different ESR values

sedimentation of the particles. As a result, the drop acquires the focusing properties.

At the initial time moment after placing the blood drop on the cuvette surface, red blood cells are evenly distributed throughout its volume. Despite the plano-convex shape of the drop similar to that of the optical lens, it does not have focusing properties due to the sufficiently strong scattering properties of its components. However, in the process of cell sedimentation, a layer of transparent plasma in the form of an aspheric lens is formed above the cells (Figs. 7, 11b, c). This layer can act as a focusing system for the light beams passing through it. We conducted a study aimed to assess the possibility of changing the focusing properties of the droplet sample during cell sedimentation. Research of these properties is necessary for receiving more adequate mathematical model of passing of radiation through the droplet sample.

The experiment was conducted as follows: The blood prepared for the study in the form of drops with a volume of 25 μl and a base diameter of 5.3 mm was placed in cuvette into the chamber of the primary converter. We evaluated the changes in the intensity of the transmitted light radiation through estimation of changes of $U_{\text{out}}\text{PEC}$ during cell sedimentation within 20–25 min (Fig. 7, tags 1–4). During this time period the sedimentation process was almost completed in drops with height of 2–2.5 mm and, consequently, a sufficient layer of plasma is formed above the settled cells. After that, the supernatant layer of plasma in the volume of 3 μl was carefully removed through step-by-step procedure using micropipette. After removing the next portion of plasma, the change in the intensity of the transmitted light was evaluated (Fig. 7, tags 5–7).

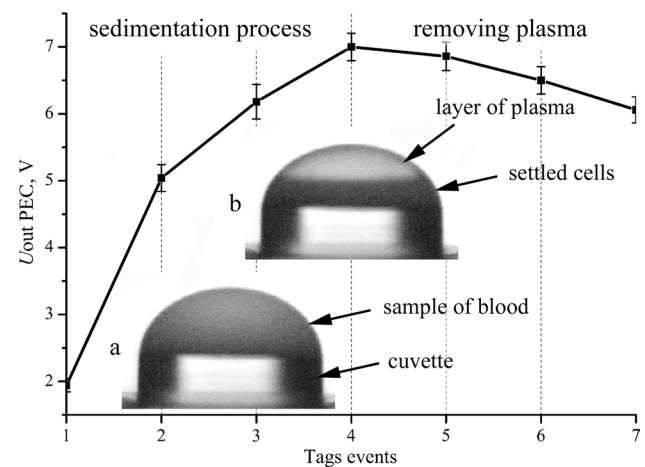


Fig. 7 Verification of change of the focusing properties of droplet blood samples during sedimentation of red blood cells (explanation in *text*). *a* Photograph of droplet sample immediately after placing it to the cuvette (tag 1). *b* Photograph of droplet sample after completion of the erythrocyte sedimentation process (tag 4)

Removing plasma from the drop surface decreases the magnitude of the detected voltage. This means that the density of the light radiation received by the photodetector becomes lower. The experimental studies have shown that after removing the supernatant plasma lens, the change in the intensity of the light radiation passing through the droplet sample can reach 15–20 % of the total change in the radiation intensity.

The droplet sample has a form of an aspheric lens due to the influence of gravity. However, when the diameter of the probing light beam is about 2/3 of the diameter of the drop base (the base diameter being up to 6 mm) the focus laws of lenses used for spherical lenses can be applied. This can be attributed to the shape of the upper part of the drop curvature that is close to the sphere. The experiment has shown that the focusing properties of plasma droplet samples are sufficiently well approximated by the dependence describing the focal length f for thin lenses:

$$\frac{1}{f} = (n - 1) \cdot \left(\frac{1}{R_1} - \frac{1}{R_2} \right), \quad (1)$$

where n is the refractive index of the lens material, R_1 and R_2 are the main radii of the lens surface curvature.

In the experiment, drop of blood plasma of predetermined volume was put on the cuvette and placed into the chamber of the primary converter. The diameter of the probing light beam was 3.5 mm. The diameter of the drop base was 5.3 mm. The angular aperture of the photodetector was approximately 40°. By moving the sensor relative to the drops, the position providing the highest magnitude of the $U_{\text{out}}\text{PEC}$ was found. This distance was adjusted to an experimental focus of the drop (f_{exper}). The video camera recorded

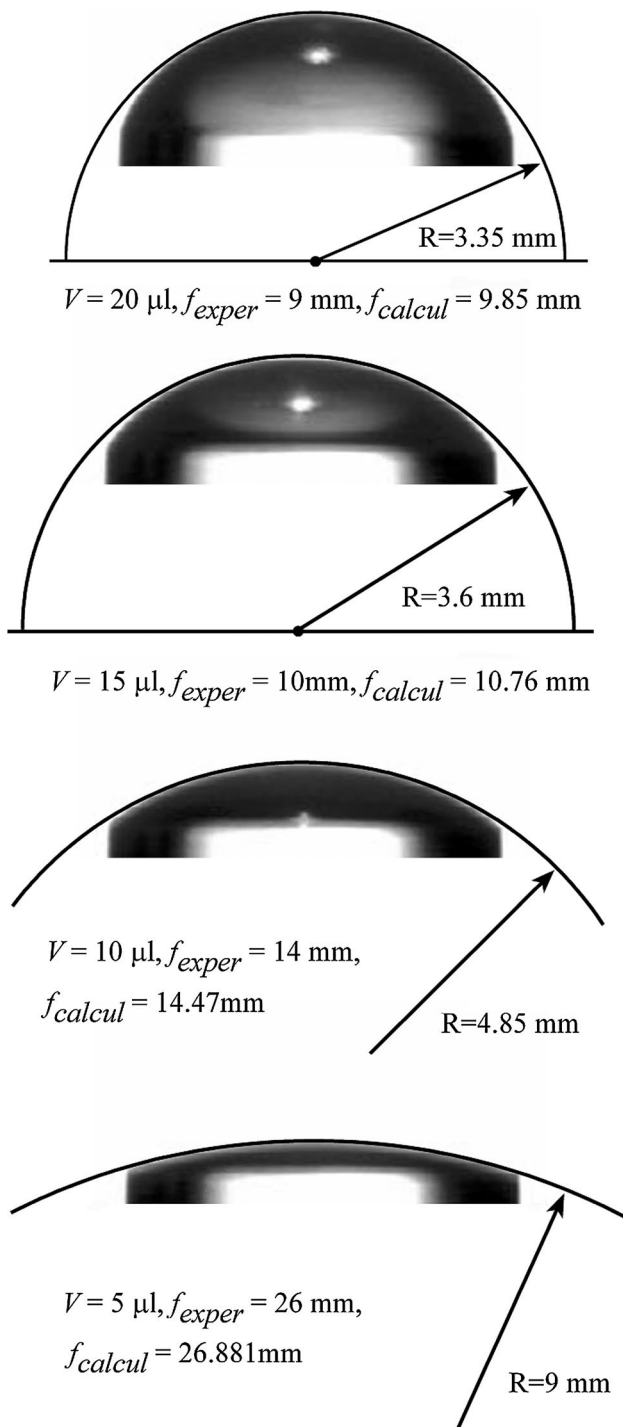


Fig. 8 Radius of the drop curvature (R) and focal length versus volume (V). The diameter of the cuvettes is 5.3 mm

the side view of the drop (Fig. 8) that was used to determine the curvature radius R of the upper part of the drop. Taking into account the refractive index of plasma 1.335 (measured with the refractometer) and using Eq. (1), we calculated the focal length f_{calcul} . The experimental and calculated values of the focal length were sufficiently close (Fig. 8).

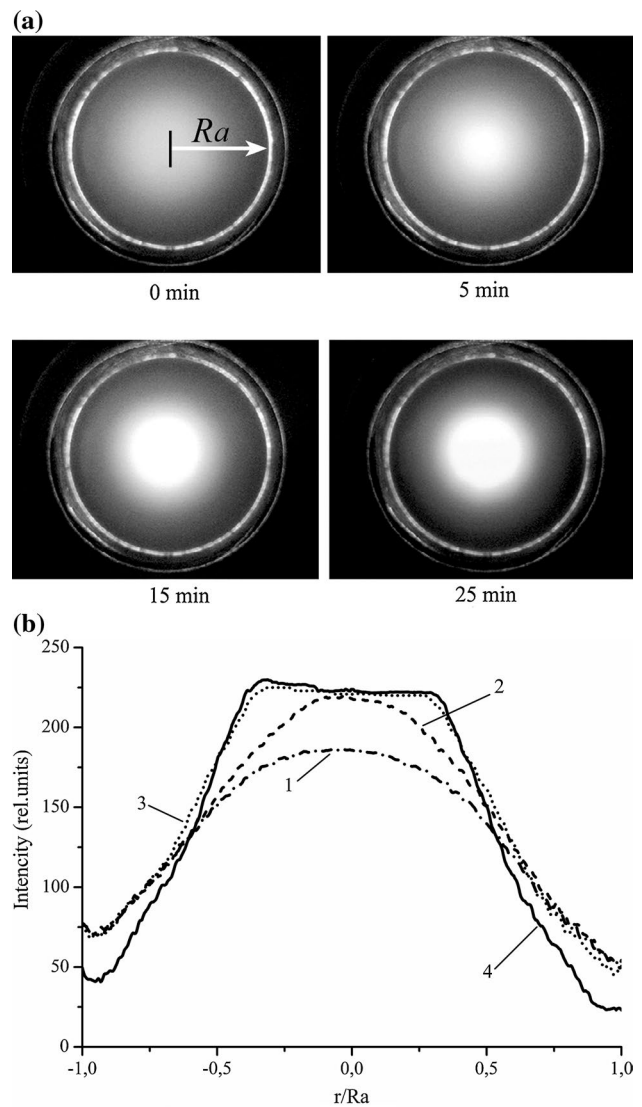


Fig. 9 Change in the pattern of the scattered radiation during erythrocyte sedimentation in droplet sample. **a** Video camera image. **b** Profiles of the scattered radiation intensity distribution over the radius of the sample base. Ra is the radius of the sample base; r is the current value of the distance from the sample center. Curve 1 corresponds to the intensity distribution profile at the initial time moment of the sedimentation process (0 min), curves 2, 3 and 4 indicate the intensity distribution profile at 5, 15, and 25 min after the beginning of the sedimentation process, respectively

Thus, while developing the model of light transmission through the droplet sample during cell aggregation and sedimentation, the spherical plasma layer can be represented as a first approximation of a spherical lens.

The changes in the scattering and focusing properties of droplet blood sample and sample in flat cuvette during cell sedimentation were observed through visual analysis of the images obtained with the video camera located above the sample in the place of photodetector (Figs. 9a, 10a). The graphs of the profiles of the scattered radiation

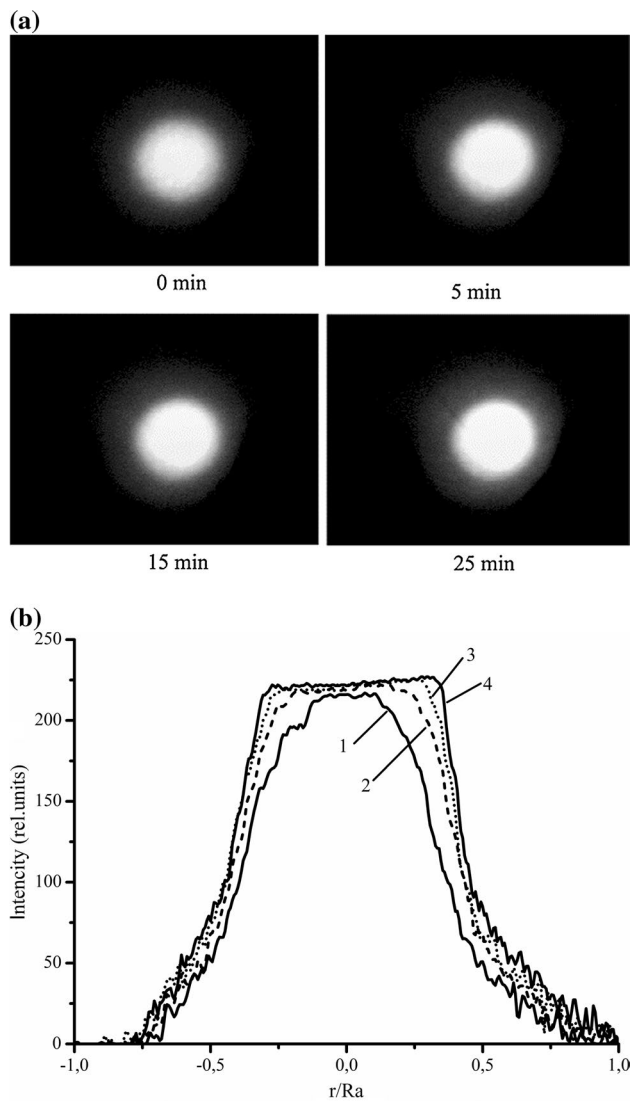


Fig. 10 Change in the pattern of the scattered radiation during erythrocyte sedimentation in the sample in the flat cuvette. **a** Video camera image. **b** Profiles of the scattered radiation intensity distribution over the radius of the sample base. R_a is the radius of the sample base; r is the current value of the distance from the sample center. Curve 1 corresponds to the intensity distribution profile at the initial time moment of the sedimentation process (0 min), curves 2, 3 and 4 indicate the intensity distribution profile at 5, 15, and 25 min after the beginning of the sedimentation process, respectively

intensity distribution along the radius of the sample base for the drop sample and sample in the flat cuvette are shown in Figs. 9b, 10b. These data were obtained by processing the images presented in Figs. 9a, 10a by means of MATLAB (MathWorks, Inc., Natick, Massachusetts).

It should be noted that, light transmission through droplet samples increases due to the decrease in the sample scattering properties (0–10 min), and a decrease in the outer ring of the scattered radiation (15–25 min) (Fig. 9a, b) presumably due to focus. For the flat cuvette (Fig. 10a, b),

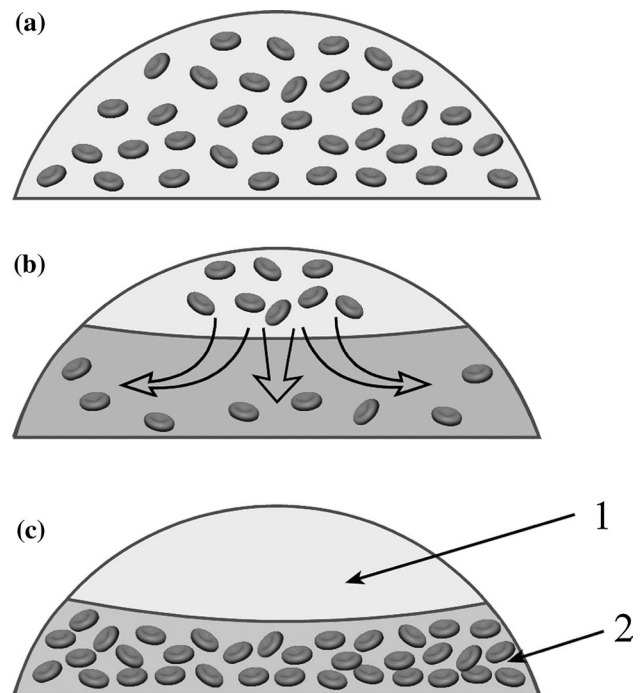


Fig. 11 Model of the processes occurring in the droplet sample during erythrocytes sedimentation. **a** Initial state. **b** Redistribution of deposited cells throughout the volume of the deposited layer. **c** Formation of focusing lens 1 from plasma above deposited cells 2

the effect of increasing of light transmission was observed only.

4 Discussion

The experiments presented in the paper reveal the physics of the processes occurring in droplet samples during sedimentation of blood cells and their effect on light transmission. The proposed method exhibits higher sensitivity for recording sedimentation processes in drops in comparison with classical photometric recording in a flat cuvette. This makes it possible to obtain more informative data on the studied process.

The method proposed for ESR assessment in droplet samples is based on the peculiarities of cell sedimentation in these sample and changes in their optical properties occurring during this process. In case of study of droplet samples of whole blood, these are primarily the processes of cell aggregation and sedimentation under gravity. An increase in the intensity of the transmitted light radiation caused by the reduced dispersion of the medium as a result of diffusing particle aggregation is a known fact, and this effect is used in most aggregometers [5, 7, 18]. The reduced distance between the scatterers in their dense packing that can occur in a sufficiently thick layer of the medium during particle

settling also results in the change of light transmission [10, 15]. In addition to the factors above, a number of specific processes during particle settling in the droplet sample can be identified. They are schematically presented in Fig. 11.

Despite the fact that the surface of the drop at the blood–air interface has a shape close to spherical, the upper limit of the settling cell layer is almost flat or there is a slight meniscus. Consequently, redistribution of cells deposited in the central axial drop region occurs throughout the volume of the deposited layer (Fig. 11b). This leads to a decrease in the number of cells in the axial region and, consequently, to an increase in the transparency of this drop region. Therefore, in order to assess the sedimentation process, as shown in the simulation and experiments, it is necessary to carry out probing of only central region of drops. The diameter of the light beam in this case should be 1.5–1 mm [4]. The formation of the transparent layer of plasma in the form of lens over the deposited layer of cells (Fig. 11c) causes changes in the scattering properties of the drop, i.e., focusing of the light radiation. As a result of these basic processes, the intensity of the light radiation transmitted through the axial region of the drop and received by the photodetector varies in time and, therefore, it is possible to assess the processes of cell aggregation and sedimentation.

The developed optical scheme shows a simple design of the device for conducting these studies. The cuvette for the droplet sample can be easily cleaned. A multi-channel system can be used to increase the number of tests or to implement techniques which require comparative studies of several samples. Additional information on composition of the medium and processes occurring in a drop can be obtained through the analysis of the droplet sample scattering properties. The spectral analysis can be performed. For studies of scattering properties of drops, we designed appropriate device [16].

An undoubted advantage of the proposed method is a small volume of the test material required for the analysis. It is primarily important in medical research, especially in pediatrics. Due to a small volume of test samples, the amount of reagents required for the analysis is reduced. In our studies, we used droplet samples with a volume from 5 μl to 30 μl . More precise optical technological devices make it possible to work with samples of a smaller volume.

5 Conclusion

We believe that this research procedure based on droplet sample photometric analysis can be successfully implemented to assess the results obtained in a number of laboratory diagnostic tests in medical practice and during chemical analysis. In particular, we have also shown the possibility of using this method to estimate the parameters of blood coagulation [3, 14]. The next challenge in terms of

development and implementation of the proposed method of the biological fluid analysis is checking this method in various laboratory tests for possible application areas.

A theoretical study of interaction of optical radiation with droplet samples will help to obtain a mathematical model of radiation transmission through drops taking into account the properties of the medium and the geometry of drops. This will optimize the development of analysis techniques and will help to define the performance requirements (volume, drop base diameter and characteristics of probing radiation, etc.) in order to obtain the maximum sensitivity and information content of the study.

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