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# Optical coherent tomography measurements of the diffusion rate of water and drugs in an isolated and whole cornea

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*Abstract*. **The passive diffusion of drugs through the epithelial surfaces of an eye (the most widespread method for medical treatment of various diseases) is considered. The permeability of water and drugs through rabbit cornea was measured in the isolated cornea (separate from an eye) and in the whole cornea. The permeability coefficients of water and dexamethasone were estimated by the method of optical coherence tomography (OCT). Because multiple photon scattering introduces noise and distortions to the OCT signal, measurements were performed at depths up to 500 μm where most likely single scattering of light occurs in cornea. It is shown that the permeability coefficients in the isolated and whole cornea strongly differ from each other. For example, the water permeability in the isolated and whole cornea is $(7.09 \pm 0.12)\times10^{-5}$ and $(1.71 \pm 0.51)\times10^{-5}$ cm s $^{-1}$, respectively.**

***Keywords***: *optical coherence tomography, diffusion, single and multiple scattering, cornea.*

## 1. Introduction

It is known that eye diseases such as diabetic retinopathy and glaucoma are the main cause of the loss of sight [1 – 3]. The successful medical treatment and prophylaxis of these diseases require a prolonged use of various drugs. The efficient transport of drugs to cornea tissues remains a complicated (and potentially dangerous) procedure due to a low permeability of eye tissues and natural washing out of drugs [4, 5].

At present the passive diffusion of drugs through cornea and sclera is the most widespread method of medical treatment of various eye diseases [6]. This is related to the fact that cornea is penetrable for many solutions containing molecules of different sizes. However, the application of this method is hindered by a low permeability of drugs through a multilayer cornea, washing out of drugs by eye fluids, and absorption in conjunctiva. The development of new methods improving the deliver of drugs through cornea and sclera with the help of gels, ointments, polymer and colloid systems, and cyclodextrins is the main direction of investigations performed in many laboratories and scientific centres [7].

Recently several experimental methods were proposed for studying the diffusion of drugs in epithelial eye tissues such as spectrofluorometry [8 – 12], fluorescence microscopy [13 – 15], microdialysis [16, 17], nuclear magnetic resonance (NMR) [18, 19], and optical spectroscopy [20]. The results obtained by these methods form the basis of our concept about the diffusion of various chemical and biological compounds in eye tissues. The diffusion coefficients of drugs with different molecular masses in sclera, cornea, and other eye tissues are presented in [21].

Biological tissues are prepared differently for experiments performed by different methods. For example, in the case of spectrofluorometry and microdialysis, a part of the eye tissue under study should be isolated, whereas this is not required in NMR studies. As a result, the diffusion coefficient of drugs measured in the same tissue can depend on experimental conditions [21]. The aim of this paper is *in vitro* measurements and comparison of the diffusion rates of water and drugs in isolated and whole cornea by the method of optical coherence tomography (OCT).

Optical coherence tomography is a relatively new noninvasive method for the two-dimensional imaging of the internal microstructure of transparent and strongly scattering objects with a spatial resolution to a few micrometres at a depth achieving several millimetres (depending on the type of scattering objects).

This attracts great interest because it can provide noninvasive information on the internal structure of biological objects with a high spatial resolution in real time. The methods of optical low-coherence interferometry and reflectometry are described in papers [22 – 24]. The first two-dimensional tomogram of eye tissues was obtained by a group of Fujimoto at the Massachusetts Institute of Technology in 1991 [25]. This method and its applications in biology and medicine are described, for example, in [26 – 28]. Optical coherence tomography is based on the detection of radiation reflected by an object within the coherence length of a laser source. In the most popular OCT configuration, radiation from a low-coherence laser source is directed into a two-arm Michelson interferometer and then a part of interferometer radiation is directed by a beamsplitter to an object and another part – to a mirror.

Radiation from the object and reference radiation reflected from a mirror in the reference arm are added in the interferometer. The interference signal is nonzero only in the case when optical paths in the interferometer arms

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coincide within the coherence length of probe radiation. Therefore, scan inside the object is performed by varying the path difference for the signal and reference arms (the A scan) and along the object surface – by using the second mirror located in the signal arm of the interferometer. In this way, the two- and three-dimensional images of objects can be obtained.

The OCT method was recently used for measuring the diffusion of a dye in an agar gel [29]. Changes in the optical properties of a gel sample during the dye penetration were measured by two low-coherence laser sources combined into one system. The method is based on the differential measurement of the distinction between the optical properties of the gel at two wavelengths, at one of which the dye absorbs and does not absorb at the other. The results obtained in [29] show that OCT can be used for the functional description of propagation of absorbing dyes in model objects simulating tissues. However, the OCT method based on measuring the absorption coefficient may be not sensitive enough for determining the diffusion properties of drugs used for the treatment of eye diseases. In this connection a new OCT method was recently proposed for determining the diffusion properties of drugs, which has a higher sensitivity and is based on the measurement of the scattering coefficient [30].

In this paper, we studied the permeability of water and dexamethasone (drug used for the treatment of inflammatory and allergic eye diseases) *in vitro* by the OCT method in the isolated and whole cornea.

We have shown earlier that the propagation of drugs in objects and biological tissues changes the refractive index and scattering coefficient of the medium [31–35]. This occurs due to several biophysical processes [31–33, 36–40], including the matching of the refractive indices of scattering centres and the basic substance due to diffusion of drugs to the tissue, a change in the optical homogeneity of the tissue caused by the osmotic packing of scattering centres (which results in the increase in the refractive index of the basic substance, which become comparable with the refractive index of collagen fibres), a change in pH and reorganisation of collagen fibres due to the biochemical interaction of drugs with biological tissues. For example, in the simplest monodisperse model of scattering dielectric spheres, the scattering coefficient is [41]

$$\mu_s = \frac{3.28\pi r^2 \rho_s}{1-g}\left(\frac{2\pi r}{\lambda}\right)^{0.37}\left(\frac{n_s}{n_m}-1\right)^{2.09}, \quad (1)$$

where $r$ is the sphere radius; $g$ is the scattering anisotropy parameter; $\rho_s$ is the volume density of the sphere; $\lambda$ is the radiation wavelength; $n_s$ and $n_m$ are the refractive indices of scattering centres and the basic substance. Therefore, an increase in the refractive index $n_m$ of the basic substance up to $n_m + \delta n_{ag}$ due to diffusion of drugs reduces scattering coefficient (1).

The attenuation of a laser beam in a weakly scattering biological tissue can be estimated from the Bouguer–Beer law

$$I(z) = (1-R)I_0 \exp(-\mu_s z), \quad (2)$$

where $R$ is the Fresnel reflection coefficient and $I_0$ is the incident light intensity. Because the OCT signal is the relative intensity of the laser radiation distribution over depth (in the single scattering regime), the relative slope of the OCT signal distribution over depth (hereafter, the OCT signal slope) plotted at the logarithmic scale (in conditional units) is proportional to the scattering coefficient of the tissue:

$$\ln\left[\frac{I(z)}{(1-R)I_0}\right] = -\mu_s z. \quad (3)$$

Therefore, a change in the scattering coefficient of a medium causes a change in the slope of the OCT signal, which can be easily measured [30–33, 35, 42] (Fig. 1). Note that Eqns (1)–(4) and OCT signals presented in Fig. 1 are related, strictly speaking, to the single scattering regime. Multiple scattering of photons introduces noise and distortions to OCT signals, so that their linear dependence on depth at the logarithmic scale will be violated, thereby considerably reducing their information content. The influence of single and multiple scattering on the formation of OCT signals is described in detail theoretically and experimentally in [43–47]. In this paper, we studied OCT signals at a depth of 500 μm in cornea, where single scattering occurs most likely.

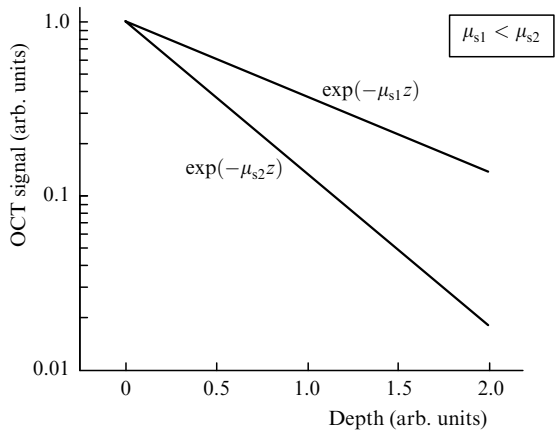


**Figure 1.** Theoretical OCT signals obtained for two monodisperse scattering media with different scattering coefficients.

## 2. Experimental

### 2.1 Experimental setup

Figure 2 shows the experimental setup (Imalux, Cleveland) for measuring the permeability of drugs in cornea. An optical source was a low-coherence 1310 ± 15-nm, 375-μW superluminescent diode with a coherence length of 25 μm. Superluminescent diodes are most convenient for such measurements due to their high reliability, low cost, and a high degree of the transverse spatial coherence and a high spectral radiance. A miniature endoscope probe placed in the object arm of an interferometer was used to scan the object surface along one axis (the $X$ axis). Scan over the object depth (along the $Z$ axis) was performed by performing the piezoelectric modulation of the object length (and, hence, the optical path) in the reference arm of the interferometer.

The parameters of this OCT system allowed us to obtain two-dimensional object images (tomograms) of size $2.2 \times 2.4$ mm and $450 \times 450$ pixels (Fig. 3a). One image

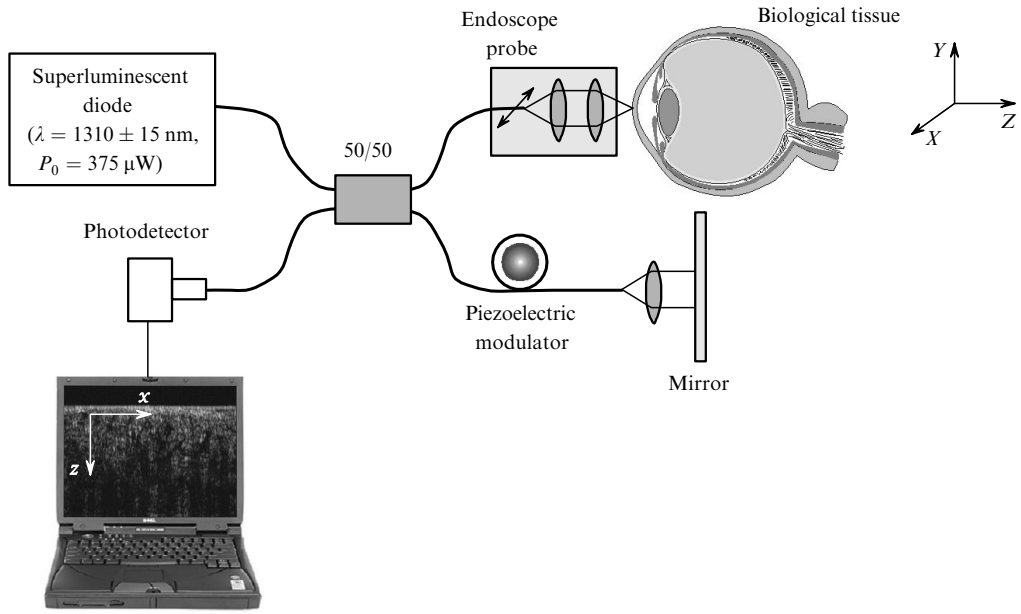


**Figure 2.** Scheme of the experimental OCT setup.

was obtained for $\sim 3$ s. Speckle noise was suppressed by averaging tomograms over length $\sim 1$ mm along the $X$ axis. Figure 3b shows one-dimensional images (OCT signals). The relative slope of an OCT signal was calculated by the method of least squares at a depth of 100 – 400 μm from the cornea surface. All the sizes presented in the paper were obtained by dividing the optical path detected by the OCT method on the refractive index of a biological tissue (approximately 1.4 for cornea).

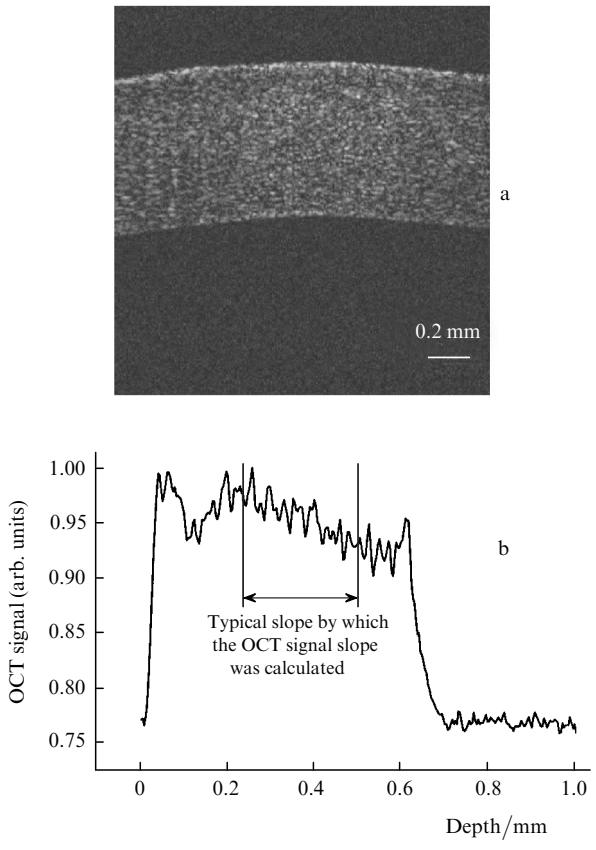


**Figure 3.** Typical OCT tomogram (a) and the corresponding one-dimensional OCT signal (b) obtained from cornea.

### 2.2 Biological tissue and drugs used in experiments

A biological tissue used in experiments was isolated rabbit eyes (Vision Tech. Inc., Dallas), which were kept in a cooled physiological solution (0.9 % sodium chloride) during transportation and storage. Experiments were performed during the first three days after euthanasia, which provided minimal variations in the physiological state of tissues. One hour before experiments, the eyes were removed from the cooling medium and placed into a physiological solution at room temperature (22 °C), which was maintained constant during all experiments. The typical duration of one experiment was 30 – 90 min. Optical coherence tomograms were recorded continuously during each experiment (each for 3 s). Before the addition of water and drugs, tomograms of cornea were recorded for 4 – 10 min.

In this paper, we studied the propagation of pure distilled water and dexamethasone in cornea. Dexamethasone was used as an antiphlogistic, antiallergenic, and antiexudative drug for the medical treatment of conjunctivitis, keratitis, neurite of the optic nerve, and many other eye diseases. The concentration of dexamethasone was 0.2 % (in the aqueous solution of 50 % propylene glycol).

### 2.3 Experimental conditions

Diffusion of water and dexamethasone in cornea was measured in isolated tissues and the whole eye (Fig. 4).

In experiments with isolated tissues, cornea samples of size $\sim 20 \times 15$ mm were accurately cut off from rabbit eyes. During this procedure, the eyes were in a physiological solution at room temperature. Isolated cornea samples were place into a special cell for OCT experiments. The laser beam was directed perpendicular to the epithelial surface of tissues. During experiments the endothelial side of tissues was placed into the physiological solution to maintain hydration (Fig. 4a). On the epithelial surface of tissues in

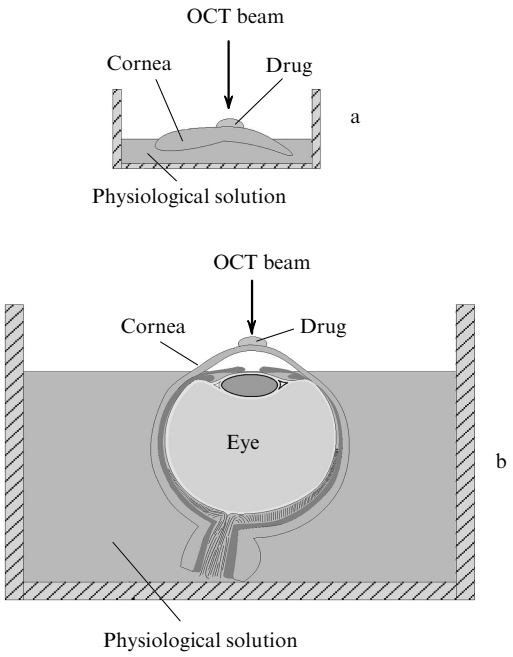


**Figure 4.** Experimental schemes for studying the isolated (a) and whole (b) cornea.

the region of the laser beam scan, $\sim 1$ mm$^3$ of a drug was added within 4 – 10 min after the beginning of the experiment. Cornea samples were not used secondly.

In experiments of the second type, the permeability of drugs was studied in the cornea not separated from the eyeball. Rabbit eyes were placed into a special cell, the lower hemisphere of the eyeball being immersed into the physiological solution (Fig. 4b). Similarly to the previous case, within 4 – 10 min after the beginning of the experiment a preparation drop was added on the epithelial surface of tissues in the laser scan region. The whole rabbit eyes were used no more than in two experiments for three days and were stored in a cooled physiological solution during the time between experiments.

### 2.4 Measurement of permeability

The permeability coefficients (in cm s$^{-1}$) of water and dexamethasone in cornea were calculated by the following method. Two-dimensional optical coherence tomograms were averaged over the $X$ axis to one-dimension curves (at the logarithmic scale) (Fig. 3). The slope of OCT signals was calculated in a certain region of the tissue by the method of least squares. The extent of the selected region in depth and its distance from the tissue surface were determined from the OCT signals for which the single scattering regime was realised. Because the propagation of a drug in tissues is accompanied by a change in the local scattering coefficient [31 – 33, 36], the permeability time for the drug in the selected region was determined from the change time of the OCT signal slope. The permeability coefficient was calculated by dividing the region length on the diffusion time of the drug in this region.

## 3. Results

Figures 5a and 5b present typical normalised slopes of OCT signals obtained in experiments on the diffusion of water in the isolated and whole cornea, respectively. The slopes of the OCT signals were calculated at a depth of $\sim 100$ μm from the epithelial surface of tissues. The length of the region under study, where the OCT signal slopes were calculated, was 314 and 280 μm for the isolated and whole cornea, respectively. The propagation of water in cornea caused a change in the local scattering coefficient, resulting in a change in the OCT signal slope. The increase in the local concentration of water reduced the local scattering coefficient, thereby reducing the OCT signal slope. One can see from Fig. 5 that a drop of water placed on the isolated cornea diffused through it for $\sim 5$ min, while in experiments with the whole eye the diffusion time was 24 min. The permeability coefficients of water measured in experiments with the isolated and whole cornea were $9.5 \times 10^{-5}$ cm s$^{-1}$ and $1.86 \times 10^{-5}$ cm s$^{-1}$, respectively. After the penetration of water into the cornea tissue, the approximate equilibrium was established till the end of experiments.

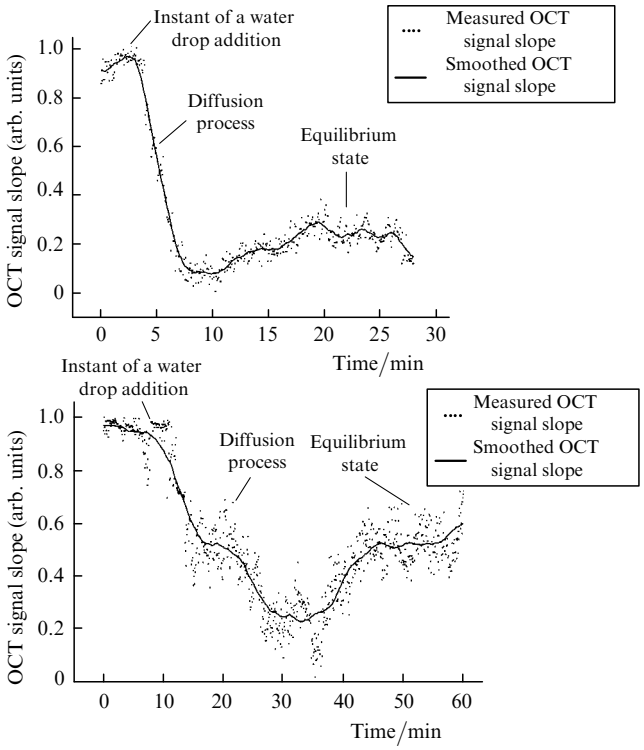


**Figure 5.** Typical OCT signal slopes obtained in experiments on the diffusion of water in the isolated (a) and whole (b) cornea.

Figure 6 presents the normalised OCT signal slopes measured in the isolated and whole cornea in experiments with dexamethasone. The OCT slopes were measured at a depth of $\sim 60$ μm from the epithelial surface of tissues. The length of the region under study was 600 and 280 μm for the isolated and whole cornea. The choice of the region length was determined by the homogeneity of the tissue structure over depth in the measurement site. As in the case of water, the diffusion of dexamethasone caused a change in the local scattering coefficient, which resulted in the change of the OCT signal slope. In the case of the isolated cornea, a dexamethasone drop, added at the tenth minute of the experiment, has diffused through the region under study for 19 min, which gives the permeability coefficient $5.2 \times 10^{-5}$ cm s$^{-1}$. In the case of experiments with the

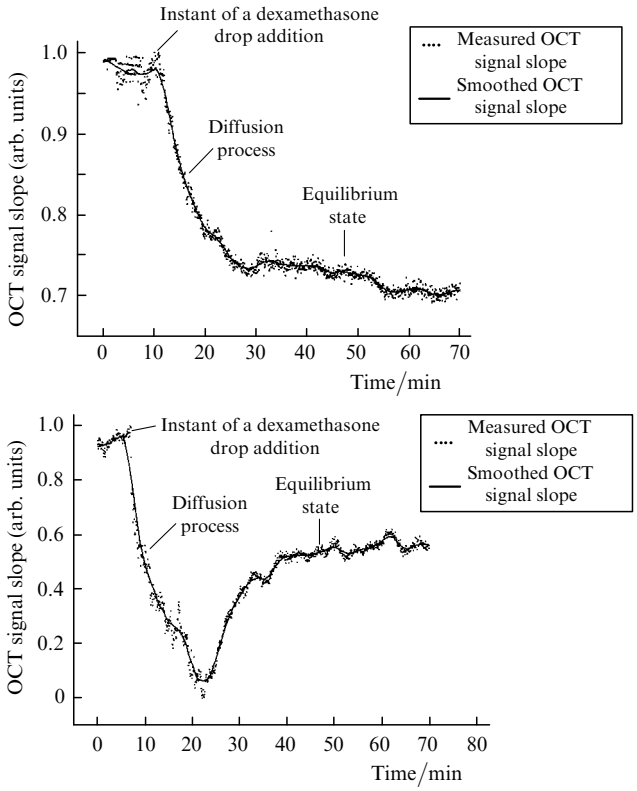


**Figure 6.** Typical OCT signal slopes obtained in experiments on the diffusion of dexamethasone in the isolated (a) and whole (b) cornea.

whole cornea, the permeability coefficient of dexamethasone was $\sim 2.95 \times 10^{-5}$ cm s$^{-1}$.

## 4. Discussion of results

The permeability coefficients of water and dexamethasone were calculated by processing the OCT signals obtained from the rabbit cornea. We performed altogether twenty-two experiments within the framework of this study. The permeability coefficients for water and dexamethasone are presented in Table 1. One can see that the permeability coefficients measured in the whole eye are considerably lower than those measured in the isolated cornea [for example, this coefficient for water is $(1.71 \pm 0.51) \times 10^{-5}$ and $(7.09 \pm 0.12) \times 10^{-5}$ cm s$^{-1}$, respectively). Because experiments with the whole eye are closer to natural conditions than experiments with isolated tissues, we expect that *in vivo* measurements of the permeability coefficients in the eye will correlate with data obtained for the whole cornea.

The slope of OCT signals measured in cornea almost did not change after the addition of a drug and the establishment of equilibrium. As shown above, the diffusion of drugs in biological objects causes a decrease in the scattering coefficient, thereby reducing the OCT signal slope. Note that a decrease in the OCT signal slope was followed by its increase, which was observed almost in all experiments. This can be explained by the dehydration of tissues. As was pointed out previously [39, 40, 48, 49], the scattering coefficient of cornea depends on the degree of its hydration. As the concentration of water in cornea is increased, the cornea tissue swells and its optical homogeneity changes, which in turn causes a decrease in the local scattering coefficient and, hence, in the OCT signal slope. Because the epithelial side of cornea was always in contact with air during experiments, evaporation from the tissue surface caused its dehydration, thereby increasing the scattering coefficient and the OCT signal slope until the establishment of a balance between dehydration through the cornea epithelium and hydration through its endothelium.

**Table 1.** Permeability coefficients of water and dexamethasone in the rabbit cornea obtained for different preparation conditions of samples ($n$ is the number of independent experiments).

| Liquid studied | Permeability coefficient/cm s$^{-1}$ | |
|---|---|---|
| | Isolated cornea | Whole cornea |
| Water | $(7.09 \pm 0.12) \times 10^{-5}$ ($n = 9$) | $(1.71 \pm 0.51) \times 10^{-5}$ ($n = 6$) |
| Dexamethasone | $6.22 \pm 0.12) \times 10^{-5}$ ($n = 3$) | $(3.12 \pm 0.15) \times 10^{-5}$ ($n = 4$) |

In this paper we measured permeability coefficients at room temperature. It is well known that the diffusion coefficient increases with temperature. The temperature dependence of the diffusion coefficient in liquid can be represented in the form [50]

$$D(T_2) = D(T_1)\frac{T_2}{T_1}\frac{\eta(T_1)}{\eta(T_2)}, \tag{4}$$

where $D(T)$ is the diffusion coefficient at temperature $T$ and $\eta(T)$ is the liquid viscosity. Therefore, it is expected that permeability coefficients will be higher at the normal body temperature than at room temperature.

The OCT signal slopes were measured in our experiments in real time. Therefore, the OCT method can be used for the real-time monitoring of the diffusion of drugs in tissues.

## 5. Conclusions

We have estimated and compared the permeability coefficients of water and dexamethasone in a weakly scattering rabbit cornea depending on the experimental conditions of preparation and storage of drugs. However, the monitoring of drug diffusion in strongly scattering tissues such as cornea and skin should take into account the role of multiple scattering in measured signals.

Our studies have shown that: (i) the diffusion of drugs in cornea reduces the OCT signal slope; (ii) the decrease in the OCT signal slope is followed by its increase due to the tissue dehydration; (iii) the permeability coefficients of water and dexamethasone measured in the isolated cornea considerably differ from those measured in the whole eye. Our investigations have shown that the conditions of preparation of a biological tissue for the experimental study of diffusion processes, as well as physical and physiological conditions under which a biological tissue is studied can strongly affect the results obtained and can lead to incorrect or very approximate estimates of the permeability coefficients of drugs in biological tissues.

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