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ABSTRACT

Application of terahertz (THz) spectroscopy for biological tissues is strongly limited by the extremely low penetration depth due to THz absorption by tissue water. One of the possible solution of such problem is the usage of THz wave penetration-enhancing agents (PEA) for optical clearing of tissues. In the present paper, the transmission-mode THz spectroscopy of a set of PEAs (polyethylene glycol with different molecular weight, propylene glycol, ethylene glycol, and dimethyl sulfoxide) was performed in order to reconstruct their dielectric properties and compare them with that of water. The obtained results emphasize the feasibility of using PEG to enhance the depth of THz wave penetration into tissues.

Keywords: terahertz radiation, terahertz spectroscopy, penetration-enhancing agents, optical clearing

1. INTRODUCTION

During the past decades, terahertz (THz) spectroscopy was intensively studied as a novel method of non-invasive, least-invasive and intraoperative label-free diagnosis of malignancies in different localizations, including the skin,[1–4] the oral,[5] the liver,[6] the gastric,[7,8] the colon[9–11] and the breast.[12–17] Having a keen sensitivity to water content, THz spectroscopy employs it for detection of malignant tissues.[18–22] At the same time, strong THz wave absorption by water forms an essential drawback of THz diagnosis – small penetration depth into tissues featuring high water content; thus, THz waves could be used for probing of only the superficial properties of tissues.[23]

Several approaches are used for reducing the THz water absorption in tissues. Among them are tissue freezing,[24–26] dehydration by heating,[27] formalin fixing,[28] paraffin-embedding,[26,29–31] and lyophilization.[32] However, these techniques are time-consuming, need difficult preparations, and predominantly could not be applied *in vivo*. Furthermore, some of them also result in significant structural changes in biotissues under the long-term exposure. Another technique, which demonstrates rather prominent results, is the immersion optical clearing.[26,33–44]

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It is based on the application of specific chemical penetration-enhancing agents (PEA), such as polyethylene glycol. These agents interact with tissues and change their optical properties. In optical range, this leads to changes of dielectric contrast and extinction coefficient; in THz range – changes of water content and, accordingly, of refractive index. These agents should be characterised by hyperosmotic status, high diffusion coefficient, and low THz wave absorption. Nevertheless, the lack of data about the dielectric properties of various PEAs does not allow for selection the optimal one for THz applications and retards the use of immersion optical clearing techniques in THz range.

In the present paper, THz time-domain spectroscopy was applied to investigate a set of PEA, i.e. polyethylene glycol (PEG) with the molecular weight 200, 300, 400, biochemical grade (BC) PEG with the molecular weight 400, propylene glycol (PG), ethylene glycol (EG), and dimethyl sulfoxide (DMSO).[19,45] The obtained results emphasize the potential of using immersion optical clearing for improvement of the penetration depth of THz radiation.

2. MATERIALS AND METHODS

2.1 Penetration enhancing agents

In the experimental studies we used initial solutions of the following agents without further purification and dissolution:

- PEG with the molecular weight 200, 300, 400 (PEG 200, Nizhnekamskneftekhim, Russia; PEG 300, Sigma-Aldrich, Germany; PEG 400, Nizhnekamskneftekhim, Russia);
- biochemical grade PEG solution with the molecular weight 400 (PEG 400 (BC) AppliChem, Germany);
- DMSO (SpektrChem, Russia);
- EG (SpektrChem, Russia);
- PG (Chemical Line Co. Ltd, Russia).

2.2 Experimental setup

The applied THz time-domain spectrometer (TDS) operates in the transmission mode within the range from 0.1 to 2.0 THz with maximal spectral resolution ~ 0.015 THz. LT-GaAs photoconductive antennas were employed for THz emission and detection. The femtosecond laser Toptica FErb780 was used for both antenna-emitter pumping and antenna-detector probing.

The TDS was equipped with the developed cuvette for measuring THz transmission properties of the listed liquid agents (see Fig. 1). It consisted of two metal parts, i.e. housing and lid, which were joined together by 6 tightening screws. Two high-resistivity float-zone silicon (HRFZ-Si) windows of thickness 2 mm were placed inside the cuvette; PEA layer was fixed between them via the thin polyethylene (PE) gasket. The bottom window was glued to the bottom of cuvette housing. Rubber gasket was placed between the upper window and the cuvette lid for exclude agent displacement. After each measurement, the cuvette was disassembled, cleaned by water and dried; and in the case of overly viscous agents, it was cleaned in the ultrasonic bath Elmasonic S30H (Elma Schmidbauer GmbH, Germany). Finally, HRFZ-Si windows were rinsed by deionized water.

2.3 Material parameters reconstruction

The reconstruction of the THz dielectric properties of PEA was performed based on the two time-domain signals of the TDS – the sample and the reference waveforms.[19,45] For the first one, PEA was placed between HRFZ-Si windows (see Fiq. 1 (a)); for the second one, agent layer was removed and THz radiation transmitted only through two closed windows (see Fiq. 1 (b)). The thickness and refractive index of HRFZ-Si windows were known *a priori*, being incomparably higher than those of the considered agents. We ignored the interference in HRFZ-Si windows for the reconstruction procedure, while the Tukey apodization (time-domain window filtration) was applied in order to filter out a contribution of satellite pulses, caused by multiple THz wave interference in a HRFZ-Si windows.

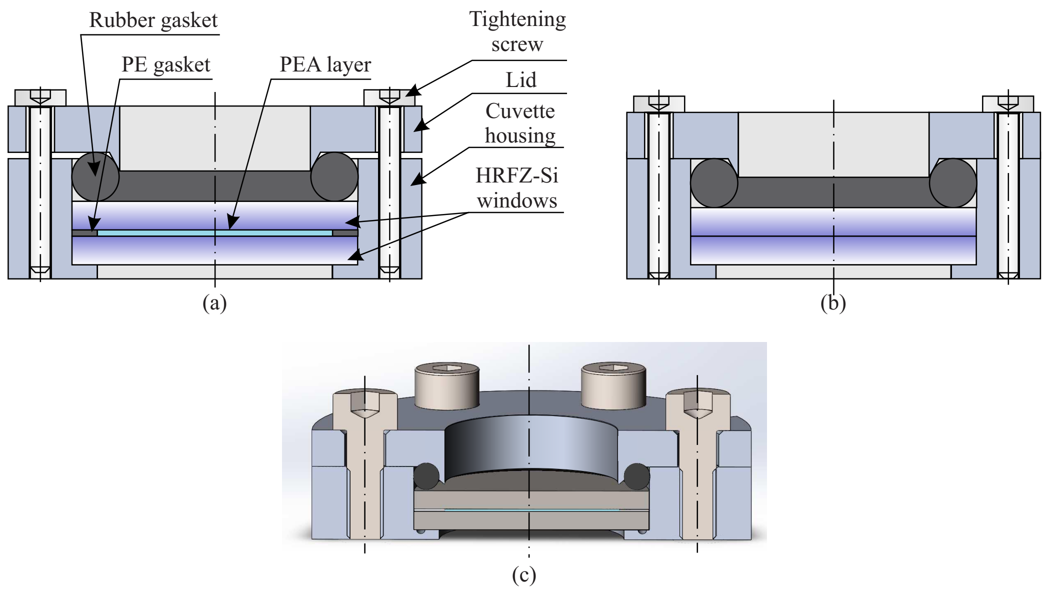

Figure 1. The developed cuvette for measuring PEA agents in two positions; (a) detection of sample waveform; (b) detection of reference waveform; (c) 3D view of the cuvette.

The received waveforms were used further in the material reconstruction algorithm, which is based on the minimization of the vector error functional

$$\Phi(n) = \begin{pmatrix} \| H_{\mathrm{exp}}| - |H_{\mathrm{th}}(n)\| \\ |\angle[H_{\mathrm{exp}}] - \angle[H_{\mathrm{th}}(n)]| \end{pmatrix} \tag{1}$$

where $H_{\mathrm{th}}(n)$ and H_{exp} are the theoretical and experimental frequency-dependent transfer functions, $n = n' - in''$ is the complex frequency-dependent refractive index corresponding to dielectric permittivity $\varepsilon = \varepsilon' - i\varepsilon''$ as $\varepsilon = n^2$, $n'' = \alpha c/4\pi\nu$, where α is the frequency-dependent intensity absorption coefficient and c is the speed of light in vacuum; operators $|...|$ and $\angle[...]$ denote the modulus and the phase of the argument, respectively. The experimental transfer function relies on the measured waveforms

$$H_{\mathrm{exp}} = \mathfrak{F}[E_{\mathrm{s}}]/\mathfrak{F}[E_{\mathrm{r}}] \tag{2}$$

where $\mathfrak{F}[E_{\mathrm{r}}]$ and $\mathfrak{F}[E_{\mathrm{s}}]$ stand for the Fourier spectra of the reference and sample waveforms, respectively. The theoretical transfer function of THz pulse assumes ignorance of interference in the reference windows, and is presented as

$$H_{\mathrm{th}} = [T_{1,2}T_{2,1}/P_0(l_2)] \sum_{j=0}^{N} (P_2(l_2)R_{2,1})^{2j+1} \tag{3}$$

where indices 0, 1 and 2 stand for air, HRFZ-Si and PEA, respectively; T, R, P are the frequency-dependent complex amplitude transmittance, reflectance and propagation operators, respectively; l is the thickness of material. Supposing the normal incidence of the plane THz electromagnetic wave on the window, THz pulse amplitude reflection and transmission at the interface between m^{th} and k^{th} media, as well as its phase delay and attenuation during propagation through q^{th} bulk medium can be described by means of the Fresnel formulas and the Bouguer-Lambert-Beer law

$$R_{\mathrm{m,k}} = \frac{n_{\mathrm{m}} - n_{\mathrm{k}}}{n_{\mathrm{m}} + n_{\mathrm{k}}} \tag{4}$$

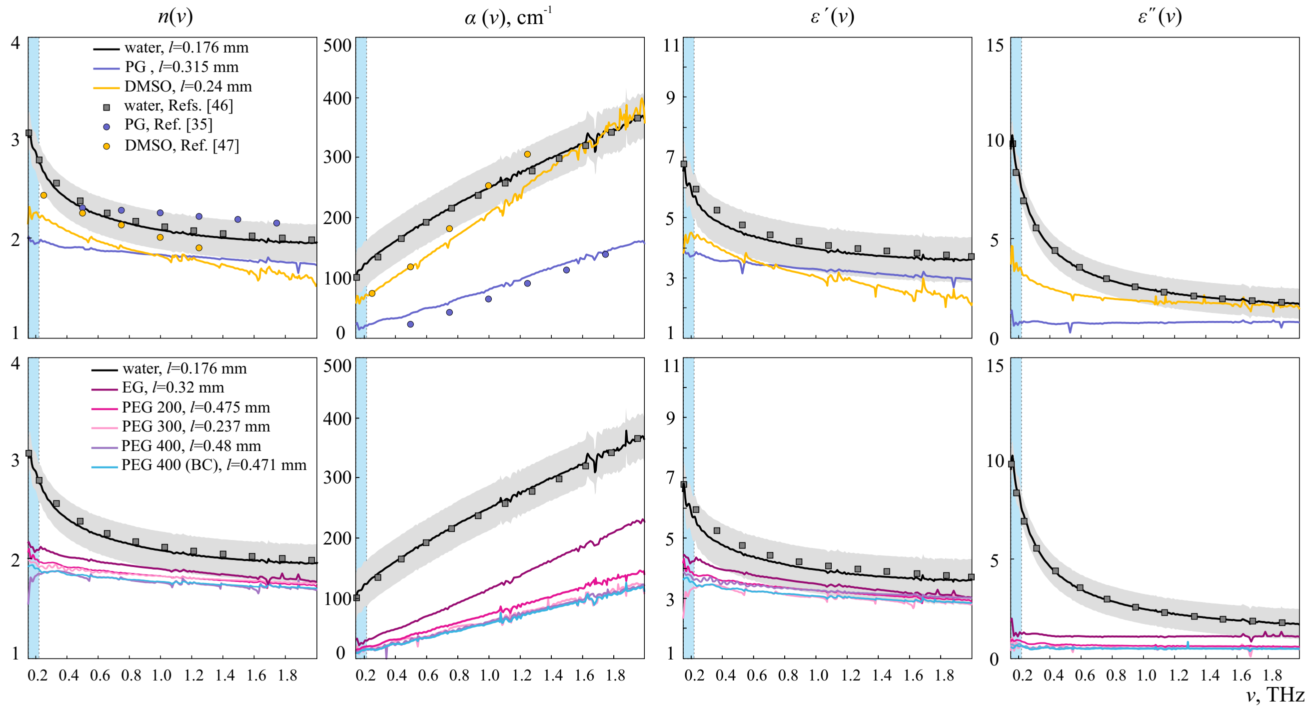

Figure 2. Results of the THz spectroscopy of the considered PEAs with thickness l comparing to water (lines); referent data of the previously measured materials (markers); error range (indicated with gray color) represent 3σ, here σ stands for a standard deviation of measurements. Measurement conditions include room temperature and humidity, hence, typical spectral attributes connected with humidity oscillations are clearly visible. Blue region indicates the spectral range, where the reconstructed dielectric properties could be affected by the distortions due to the THz beam diffraction on the cuvette aperture.

$$T_{\mathrm{m,k}} = \frac{2n_{\mathrm{m}}}{n_{\mathrm{m}} + n_{\mathrm{k}}} \tag{5}$$

$$P(n_{\mathrm{q}}, l_{\mathrm{q}}) = exp\left(-i\frac{2\pi\nu}{c}n_{\mathrm{q}}l_{\mathrm{q}}\right) \tag{6}$$

where indices $m, k, q = 0, 1, 2$ correspond to the air, HRFZ-Si and PEA, respectively. The complex refractive indices of the air n_0, HRFZ-Si n_1, PEA n_2, and the thickness of the reference windows l_1 are known *a priori*.

3. RESULTS

Figure 2 shows the experimental results for the considered agents and water, obtained according to the aforementioned procedure. The dielectric properties were reconstructed in the frequency range from 0.1 to 2 THz. Blue region indicates the spectral range, where the reconstructed dielectric properties could be affected by the distortions due to the THz beam diffraction on the cuvette aperture. The reproducibility of the experimental data and the fluctuations of the THz response were examined by considering different thickness of the sample solutions. As shown in Fig. 2, the observed results agree well with the previously-reported data.[35,46,47]

The results of spectroscopic measurements of various PEAs demonstrate that the lowest absorption in the wide THz spectral range belongs to the polymer group, i.e. PEG agents; thus, they seem to be potential candidates for optical clearing of tissues in THz applications. Nevertheless, the more detailed analysis should account a particular biotissue and THz frequencies, as well as the diffusion velocity and PEAs noninvasiveness, in order to select the optimal optical clearing protocol.

4. CONCLUSIONS

In this paper, we have demonstrated the results of the THz spectroscopy of the clearing agents PEG 200, 300, 400, PG, ethylene glycol, and DMSO. We used THz time-domain spectrometer for the experimental measurements and compared the estimated dielectric properties with the ones of water. The obtained results show the decreased refractive index and absorption coefficient of the polymer clearing agents compared to the PG, EG, and DMSO agents in a wideband THz range. These results highlight the advantage of usage the polymer PEAs to improve penetration depth of THz radiation.

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REFERENCES

[1] Joseph, C., Patel, R., Neel, V., Giles, R., and Yaroslavsky, A., "Imaging of *ex vivo* nonmelanoma skin cancers in the optical and terahertz spectral regions. optical and terahertz skin cancers imaging," *Journal of Biophotonics* **7**(5), 21552–21562 (2011).

[2] Wallace, V., Fitzgerald, A., Hankar, S., Lanagan, N., Pye, R., Cluff, J., and Arnone, D., "Terahertz pulsed imaging of basal cell carcinoma *ex vivo* and *in vivo*," *British Journal of Dermatology* **151**(2), 424–432 (2004).

[3] Woodward, R., Wallace, V., Pye, R., Cole, B., Arnone, D., Linfield, E., and Peppern, M., "Terahertz pulse imaging of *ex vivo* basal cell carcinoma," *Journal of Investigative Dermatology* **120**(1), 72–78 (2003).

[4] Zaitsev, K., Chernomyrdin, N., Kudrin, K., Reshetov, I., and Yurchenko, S., "Terahertz spectroscopy of pigmentary skin nevi *in vivo*," *Optics and Spectroscopy* **119**(3), 404–410 (2015).

[5] Sim, Y., Park, J., Ahn, K.-M., Park, C., and Son, J.-H., "Terahertz imaging of excised oral cancer at frozen temperature," *Biomedical Optics Express* **4**(8), 1413–1421 (2013).

[6] Hua, C., Shi-Hua, M., Wen-Xing, Y., Xiu-Mei, W., and Xiao-Zhou, W., "The diagnosis of human liver cancer by using thz fiber-scanning near-field imaging," *Chinese Physics Letters* **30**(3), 030702 (2013).

[7] Hou, D., Li, X., Cai, J., Ma, Y., Kang, X., Huang, P., and Zhang, G., "Terahertz spectroscopic investigation of human gastric normal and tumor tissues," *Physics in Medicine and Biology* **59**(18), 5423–5440 (2014).

[8] Ji, Y., Park, C., Kim, H., Kim, S.-H., Lee, G., Noh, S., Jeon, T.-I., Son, J.-H., Huh, Y.-M., Haam, S., Oh, S., Lee, S., and Suh, J.-S., "Feasibility of terahertz reflectometry for discrimination of human early gastric cancers," *Biomedical Optics Express* **6**(4), 1398–1406 (2015).

[9] Reid, C., Fitzgerald, A., Reese, G., Goldin, R., Tekkis, P., OKelly, P., Pickwell-MacPherson, E., Gibson, A., and Wallace, V., "Terahertz pulsed imaging of freshly excised human colonic tissues," *Physics in Medicine and Biology* **56**(14), 4333–4353 (2011).

[10] Eadie, L. H., Reid, C. B., Fitzgerald, A. J., and Wallace, V. P., "Optimizing multi-dimensional terahertz imaging analysis for colon cancer diagnosis," *Expert Systems with Applications* **40**(6), 0957–4174 (2013).

[11] Wahaia, F., Kasalynas, I., Venckevicius, R., Seliuta, R., Valusis, G., Urbanowicz, A., Molis, G., Carneiro, F., Silva, C. C., and Granja, P., "Terahertz absorption and reflection imaging of carcinoma-affected colon tissues embedded in paraffin," *Journal of Molecular Structure* **1107**, 214–219 (2016).

[12] Chen, H., Chen, T.-H., Tseng, T.-F., Lu, J.-T., Kuo, C.-C., Fu, S.-C., Lee, W.-J., Tsai, Y.-F., Huan, Y.-Y., Chuang, E., Hwang, Y.-J., and Sun, C.-K., "High-sensitivity *in vivo* thz transmission imaging of early human breast cancer in a subcutaneous xenograft mouse model," *Optics Express* **19**(22), 21552–21562 (2011).

[13] Fitzgerald, A., Wallace, V., Jimenez-Linan, M., Bobrow, L., Pye, R., Purushotham, A., and Arnone, D., "Terahertz pulsed imaging of human breast tumors," *Radiology* **239**(2), 533–540 (2006).

[14] Fitzgerald, A., Wallace, V., Pinder, S., Purushotham, A., OKelly, P., and Ashworth, P., "Classification of terahertz-pulsed imaging data from excised breast tissue," *Journal of Biomedical Optics* **17**(1), 016005 (2012).

[15] Ashworth, P., Pickwell-MacPherson, E., Provenzano, E., Pinder, S., Purushotham, A., Pepper, M., and Wallace, V., "Terahertz pulsed spectroscopy of freshly excised human breast cancer," *Optics Express* **17**(15), 12444–12454 (2009).

[16] Fitzgerald, A., Pickwell-MacPherson, E., and Wallace, V., "Use of finite difference time domain simulations and debye theory for modelling the terahertz reflection response of normal and tumour breast tissue," *PLOS ONE* **9**, 1–9 (2014).

[17] Truong, B., Tuan, H., Fitzgerald, A., Wallace, V., and Nguyen, H., "A dielectric model of human breast tissue in terahertz regime," *IEEE Transactions on Biomedical Engineering* **62**(2), 699–707 (2015).

[18] Meng, K., Chen, T.-N., Chen, T., Zhu, L.-G., Liu, Q., Li, Z., Li, F., Zhong, S.-C., Li, Z.-R., Feng, H., and Zhao, J.-H., "Terahertz pulsed spectroscopy of paraffin-embedded brain glioma," *Journal of Biomedical Optics* **19**(7), 077001 (2014).

[19] Chernomyrdin, N. V., Gavdush, A. A., Beshplav, S.-I. T., Malakhov, K. M., Kucheryavenko, A. S., Katyba, G. M., Dolganova, I. N., Goryaynov, S. A., Karasik, V. E., Spektor, I. E., Kurlov, V. N., Yurchenko, S. O., Komandin, G. A., Potapov, A. A., Tuchin, V. V., and Zaytsev, K. I., "*In vitro* terahertz spectroscopy of gelatin-embedded human brain tumors: a pilot study," *Proceedings of SPIE* **10716**, 107160S (2018).

[20] Yamaguchi, S., Fukushi, Y., Kubota, O., Itsuji, T., Ouchi, T., and Yamamoto, S., "Brain tumor imaging of rat fresh tissue using terahertz spectroscopy," *Scientific Reports* **6**, 6 (2016).

[21] Oh, S., Kim, S.-H., Ji, Y., Jeong, K., Park, Y., Yang, J., Park, D., Noh, S., Kang, S.-G., Huh, Y.-M., Son, J.-H., and Suh, J.-S., "Study of freshly excised brain tissues using terahertz imaging," *Biomedical Optics Express* **5**(8), 2837–2842 (2014).

[22] Ji, Y., Oh, S., Kang, S.-G., Heo, J., Kim, S.-H., Choi, Y., Song, S., Son, H., Kim, S., Lee, J., Haam, S., Huh, Y., Chang, J., Joo, C., and Suh, J.-S., "Terahertz reflectometry imaging for low and high grade gliomas," *Scientific Reports* **6**, 36040 (2016).

[23] Lee, Y.-S., [*Principles of Terahertz Science and Technology*], Springer, New York, NY, USA (2009).

[24] Sim, Y. C., Ahn, K.-M., Park, J. Y., Park, C.-S., and Son, J.-H., "Temperature-dependent terahertz imaging of excised oral malignant melanoma," *IEEE Transactions on Terahertz Science and Technology* **3**(4), 368–373 (2013).

[25] Hoshina, H., Hayashi, A., Miyoshi, N., Miyamaru, F., and Otani, C., "Terahertz pulsed imaging of frozen biological tissues," *Applied Physics Letters* **94**(12), 123901 (2009).

[26] Oh, S. J., Kim, S.-H., Jeong, K., Park, Y., Huh, Y.-M., Son, J.-H., and Suh, J.-S., "Measurement depth enhancement in terahertz imaging of biological tissues," *Journal of Biomedical Optics* **21**(18), 21299–21305 (2013).

[27] Yu, T., Wen, X., Tuchin, V. V., Luo, Q., and Zhu, D., "Quantitative analysis of dehydration in porcine skin for assessing mechanism of optical clearing," *Journal of Biomedical Optics* **16**, 095002 (2011).

[28] Sun, Y., Fischer, B. M., and Pickwell-MacPherson, E., "Effects of formalin fixing on the terahertz properties of biological tissues," *Journal of Biomedical Optics* **14**(6), 064017 (2009).

[29] Meng, K., nan Chen, T., guo Zhu, L., Liu, Q., Li, Z., Li, F., cheng Zhong, S., ren Li, Z., Feng, H., and heng Zhao, J., "Terahertz pulsed spectroscopy of paraffin-embedded brain glioma," *Journal of Biomedical Optics* **19**(7), 077001 (2014).

[30] Wahaia, F., Kasalynas, I., Venckevicius, R., Seliuta, D., Valusis, G., Urbanowicz, A., Molis, G., Carneiro, F., Silva, C. D. C., and Granja, P. L., "Terahertz absorption and reflection imaging of carcinoma-affected colon tissues embedded in paraffin," *Journal of Molecular Structure* **1107**, 214–219 (2016).

[31] Miura, Y., Kamataki, A., Uzuki, M., Sasaki, T., ichi Nishizawa, J., and Sawai, T., "Terahertz-wave spectroscopy for precise histopathological imaging of tumor and non-tumor lesions in paraffin sections," *Tohoku Journal of Experimental Medicine* **223**(4), 291–296 (2011).

[32] Png, G. M., Choi, J. W., Ng, B. W.-H., Mickan, S. P., Abbott, D., and Zhang, X.-C., "The impact of hydration changes in fresh bio-tissue on thz spectroscopic measurements," *Physics in Medicine and Biology* **53**, 3501–3517 (2008).

[33] Genina, E. A., Bashkatov, A. N., Sinichkin, Y. P., Yanina, I. Y., and Tuchin, V. V., "Optical clearing of biological tissues: prospects of application in medical diagnostics and phototherapy," *Journal of Biomedical Photonics & Engineering* **1**(1), 22–58 (2015).

[34] Tuchin, V. V., "Tissue optical clearing: new prospects in optical imaging and therapy," *IEEE Proceedings of 2015 International Conference on BioPhotonics (BioPhotonics)* (7304023), 1–10 (2015).

[35] Kolesnikov, A. S., Kolesnikova, E. A., Popov, A. P., Nazarov, M. M., Shkurinov, A. P., and Tuchin, V. V., "In vitro terahertz monitoring of muscle tissue dehydration under the action of hyperosmotic agents," *Quantum Electronics* **44**(7), 633–640 (2014).

[36] Kolesnikov, A. S., Kolesnikova, E. A., Kolesnikova, K. N., Tuchina, D. K., Popov, A. P., Skaptsov, A. A., Nazarov, M. M., Shkurinov, A. P., Terentyuk, A. G., and Tuchin, V. V., "Thz monitoring of the dehydration of biological tissues affected by hyperosmotic agents," *Physics of Wave Phenomena* **22**(3), 169–176 (2014).

[37] Kolesnikov, A. S., Kolesnikova, E. A., Tuchina, D. K., Terentyuk, A. G., Nazarov, M. M., Skaptsov, A. A., Shkurinov, A. P., and Tuchin, V. V., "In vitro terahertz spectroscopy of rat skin under the action of dehydrating agents," *Proceedings of SPIE* **9031**, 90310D (2014).

[38] Smolyanskaya, O. A., Schelkanova, I. J., Kulya, M. S., Odlyanitskiy, E. L., Goryachev, I. S., Tcypkin, A. N., Grachev, Y. V., Toropova, Y. G., and Tuchin, V. V., "Glycerol dehydration of native and diabetic animal tissues studied by thz-tds and nmr methods," *Biomedical Optics Express* **9**(3), 1198–1215 (2018).

[39] Zhi, Z., Han, Z., Luo, Q., and Zhu, D., "Improve optical clearing of skin *in vitro* with propylene glycol as a penetration enhancer," *Lasers in Surgery and Medicine* **2**(3), 269–278 (2009).

[40] Choi, B., Tsu, L., Chen, E., Ishak, T. S., Iskandar, S. M., Chess, S., and Nelson, J. S., "Determination of chemical agent optical clearing potential using *in vitro* human skin," *Lasers in Surgery and Medicine* **36**(2), 72–75 (2005).

[41] Tuchin, V. V., [*Tissue optics : light scattering methods and instruments for medical diagnosis*], SPIE, Bellingham, Washington 98227-0010 USA (2015).

[42] Vargas, G., Barton, J. K., and Welch, A. J., "Use of hyperosmotic chemical agent to improve the laser treatment of cutaneous vascular lesions," *Journal of Biomedical Optics* **13**(2), 021114 (2008).

[43] Liu, H., Beauvoit, B., Kimura, M., and Chance, B., "Dependence of tissue optical properties on solute-induced changes in refractive index and osmolarity," *Journal of Biomedical Optics* **1**(2), 200–211 (1996).

[44] Tuchina, D. K., Shi, R., Bashkatov, A. N., Genina, E. A., Zhu, D., Luo, Q., and Tuchin, V. V., "*Ex vivo* optical measurements of glucose diffusion kinetics in native and diabetic mouse skin," *J. Biophotonics* **8**(4), 332–346 (2015).

[45] Zaytsev, K., Gavdush, A., Chernomyrdin, N., and Yurchenko, S., "Highly accurate in vivo terahertz spectroscopy of healthy skin: Variation of refractive index and absorption coefficient along the human body," *IEEE Transactions on Terahertz Science and Technology* **5**(5), 817–827 (2015).

[46] Møller, U., Cooke, D. G., Tanaka, K., and Jepsen, P. U., "Terahertz reflection spectroscopy of debye relaxation in polar liquids [Invited]," *J. Opt. Soc. Am. B* **26**(9), A113–A125 (2009).

[47] Kim, K. W., Kim, H., Park, J., Han, J. K., and Son, J., "Terahertz tomographic imaging of transdermal drug delivery," *IEEE Transactions on Terahertz Science and Technology* **2**(1), 99–106 (2012).