Exploring the Absorbable Hemostats' Reaction using ATR THz Time-Domain Spectroscopy

Marie Nedvedova, Vojtech Kresalek, Zdenek Adamik and Norbert Pałka

***Abstract*—This article describes the measurement, analysis and modelling of the absorbable hemostats' kinetic reaction using the THz ATR spectroscopy. As the hemostats are of various origin, their mechanism of action and consequently, their appropriate applications may differ. Two liquid media, physiological saline solution (PSS) and the human blood, were used to initiate the observed dynamic reaction. The time-dependent changes in the measured THz response reflect the reaction kinetics of the materials. Based on the results, the reaction rate is compared among different materials.**

***Index Terms*—Absorbable hemostat, kinetics, terahertz time-domain spectroscopy, ATR.**

I. INTRODUCTION

HEMOSTATS are materials used primarily in surgical medicine to support hemostasis, the body's physiological response to bleeding. Hemostasis is a complex process including vasoconstriction, adhesion and activation of blood platelets, and fibrin blood clot formation [1]. In general, hemostats are based on various natural or synthetic materials, and their origin relates to the dominant mechanism by which they participate in the hemostasis reaction.

Absorbable hemostats work on a principle of hydrogel, a polymer formed by a 3D hydrophilic network capable to absorb a huge amount of water. Because of their structure, hydrogels are insoluble in water, biocompatible, and able to simulate the biological tissue [2]. They can indirectly participate in the hemocoagulation cascade by imitating the physical matrices for clot formation (gelatin and oxycellulose materials) or by supporting blood platelets' adherence and activation (collagen). Biologically active hemostats also participate directly in the hemocoagulation, as they usually contain fibrin and thrombin agents.

The hemostats of different origin are widely used in surgery. Their specific applications are mainly based on clinical experiences, but there is an obvious lack of information about their dynamic parameters such as the rate of hemostasis. The reaction rate is expected to be influenced by both their liquid absorption ability and their ability to form a solid barrier to stop bleeding. The aim of this study is to explore these properties using THz time-domain spectroscopy and provide an objective comparison of the samples based on the measured changes in their physical parameters during the reaction. Understanding the hemostats' kinetics should be helpful in comparing their reaction rates and facilitating their proper selection in specific clinical situations. This experiment follows the previous preliminary measurement published in [3] with the goal of extending the experiment and increasing the accuracy of the results.

II. MATERIALS AND METHODS

A. Instrumentation

As the THz spectroscopy is sensitive to the water content in the measured sample, it appears to be a useful method for monitoring the absorption and hemostatic activity of hemostat materials. However, the condition of no total attenuation of the THz signal by the liquid sample must be met. This condition was verified by previous testing measurements.

TPS Spectra 3000 THz time-domain spectroscopy system (TeraView, Ltd., UK) was used as an analyzing device in this experiment. It is a pulse system based on the general pump-probe principle for generation and detection of THz waves using a photoconductive antenna (GaAs). The attenuated total reflection (ATR) module was used as the most appropriate method for measuring liquid samples. ATR THz spectroscopy is based on measuring the attenuation of the totally internally reflected THz wave by a sample placed in close contact with a high refractive index crystal (silicon with a refractive index of 3.42 and an entering angle of 35°). When THz radiation encounters crystal-sample interface, most of it undergoes total internal reflection and bounces back into the crystal. However, a small portion of electromagnetic field (evanescent wave) penetrates a very shallow distance called penetration depth (typically micrometers to hundreds of micrometers) into the surface of the sample. If the sample absorbs energy from this evanescent wave, the totally reflected radiation inside the crystal will be attenuated at those specific frequencies.

The penetration depth is polarization dependent. As the parallel p-polarized beam exhibits a penetration depth approximately double that of an s-polarized beam, p-polarization was used for ATR calculations. Importantly, since

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Marie Nedvedova is with the Department of Electronics and Measurements, Tomas Bata University, Zlin, Czech Republic (corresponding author, e-mail: nedvedova@utb.cz).

Vojtech Kresalek is with the Department of Electronics and Measurements, Tomas Bata University, Zlin, Czech Republic (e-mail: kresalek@utb.cz).

Zdenek Adamik is with the Department of Health Care Sciences, Tomas Bata University, Zlin, Czech Republic (e-mail: adamik@utb.cz).

Norbert Pałka is with the Institute of Optoelectronics, Military University of Technology, Warsaw, Poland (e-mail: norbert.palka@wat.edu.pl).

the penetration depth is directly proportional to wavelength, longer wavelengths will penetrate deeper, and shorter wavelengths will penetrate less deeply. Therefore, accurate measurement requires good contact between the two optical media. The spectrometer allows measurements in the wavenumber range from 2 cm^{-1} up to 120 cm^{-1} (0.06 – 4 THz). The ATR configuration of the measurement is shown in Fig. 1.

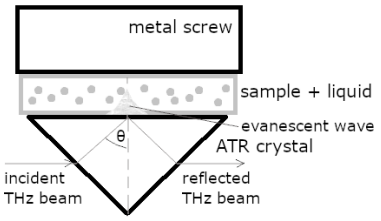

Fig. 1. Schematic diagram of ATR measurement principle.

B. Samples

Five types of absorbable hemostats were used in this experiment: two oxidized cellulose absorbable hemostats, gelatin, collagen, and biologically active hemostats. One reference sample of pure cellulose, without any known hemostatic effect, was also added for comparison, especially with the oxidized cellulose samples.

Surgicel NuKnit and Surgicel Fibrillar (Ethicon, Johnson and Johnson, USA) are forms of oxidized regenerated cellulose and they differ in the structure, fiber density and basis mass. When applicated to a wound, oxycellulose slightly swells and traps blood proteins and platelets, forming a gel-like barrier matrix that blocks further blood leakage [4].

Gelita-Spon (Gelita Medical, Germany) is a gelatin-based sponge hemostat made from purified porcine gelatin. Gelatin is generally characterized by its significant swelling capacity; it can absorb more than 40 times its own weight. Gelatin's porous structure further provides a matrix for the aggregation of thrombocytes.

Hypro-Sorb R (Hypro s. r. o., Komarov, CZE) is a bioabsorbable atelocollagen hemostatic felt made of bovine atelocollagen. It specifically interacts with thrombocytes and releases clotting factors that participate in the fibrin clot formation.

TachoSil (Takeda Pharmaceuticals International GmbH, CHE) is a type of biologically active hemostat, where a layer of human fibrinogen and thrombin is coated onto an equine collagen sponge. Due to its structure, TachoSil combines the properties of an absorbable hemostat and a fibrin sealant.

C. Experimental Design

The samples of dry hemostats were prepared for THz-ATR measurement. The size of each sample was adjusted to maintain approximately the same volume and to ensure saturation with the applied liquid (20 µl). In fact, the hemostat reacts directly with blood. Blood is a complex medium both chemically and physically. These factors increase the variability and uncertainty level of our measurements. Therefore, the basic absorption ability of the hemostats was initially tested using physiological saline solution (Fresenius Kabi, Italia S.r.l.). In contrast to blood, PSS is a uniform and well-defined medium. As the next step, blood was included in the experiment to simulate the natural conditions of hemostat usage. Blood voluntarily donated by human donors was used. The measurement required very small amount (units of µl) of fresh blood (without any anticoagulation factor); therefore, the blood draw had to be repeated for each measurement. Blood was taken from a fingertip of a volunteer using a lancing device. The procedure of the whole experiment was approved by the ethics committee of the Department of Biomedical Engineering, Brno University of Technology (Registration Number: EK03b/2017 from November 20, 2017). This study was conducted in full conformity with the appropriate local laws, and with tenets of the Declaration of Helsinki. All twenty volunteers confirmed their voluntary participation in the experiment by signing the informed consent form. They were fully apprised of the experimental procedure, potential risks, and data processing for research purposes.

First, a liquid medium (PSS or blood) was placed on the crystal using a pipette, and the hemostatic sample was immediately applied and fixed onto it without delay to minimize any potential ex vivo blood activation. The setup of real experiment is shown in Fig. 2. The spectrometer measurement started before the liquid was applied to record all changes associated with the application of each substance. The spectrometer settings were optimized for sufficiently fast scanning and good signal-to-noise ratio (30 averaged scans, spectral resolution 1.5 cm^{-1}, scan rate 30 s^{-1}). Each measurement lasts 1.44 seconds. The recorded raw data consisted of THz waveforms in the time domain, without any ATR parameter calculation.

Fig. 2. Measurement setup. (a) ATR silicon crystal with PSS applied. (b) Hemostat sample applied and fixed.

The measurement was performed in an air-conditioned laboratory maintained at a temperature of 25 °C and 25% relative humidity. A vacuum was maintained in the internal optical chamber of the spectrometer to minimize the effect of water vapor. The clean ATR crystal was measured as a reference before each sample measurement. The measuring procedure was repeated to obtain at least ten time-dependent measurements of each hemostat for further data analysis.

III. Data Analysis and Results

Using the THz-ATR module, the electric field of the THz pulse reflected by the investigated sample was measured in time without use of any apodisation function. In each time scan, the ATR spectrum of the received THz wave was identified using the original Teraview software.

For demonstration of the methodology, Fig. 3 shows an overview of the measured ATR spectra during the reaction between HyproSorb hemostat and blood. The wavenumber 33

cm^{-1} (1 THz) providing a good signal-to-noise ratio (SNR) was chosen for a detailed analysis of changing absorption in time. As the oxycelluloses' responses are significantly weaker compared to the other hemostats, the data were transformed by scaling to a range between 0 and 1. The scaled value ($norm\ y(t)$) of the data y at time t was calculated using (1)

$$norm\ y(t) = \frac{y(t) - y_{min}}{y_{max} - y_{min}} \quad (1)$$

where y_{max} and y_{min} are the maximum and minimum of the variable y, respectively. The normalized signals are shown in Fig. 4 for the reaction with PSS and Fig. 5 for the reaction with blood.

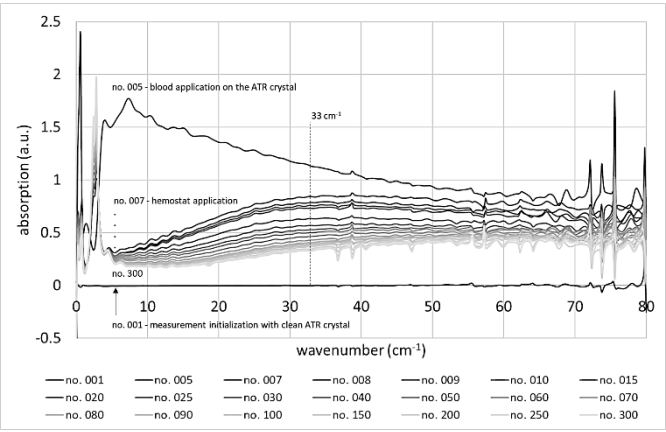

Fig. 3. Evolution of THz ATR spectra presented sequentially: measurement of the clean ATR crystal (no. 001), application of blood (no.005), and subsequent application of hemostat to the blood (no. 007) through to the end of the reaction (no. 300).

Since the measured signal attenuation is related to the water content on the ATR crystal, the lower SNR observed for oxycelluloses (S. Fibrillar, S. NuKnit) suggests their weaker ability to absorb the PSS. Nevertheless, the SNR of oxycelluloses is higher than that of the reference cellulose sample. The gelatin (Gelita) and collagen (HyproSorb, TachoSil) based hemostats exhibit minimal noise in their measured responses, likely due to a more effective and dynamic reaction with PSS. An initial decrease of $norm\ y(t)$ is common for all hemostats. This corresponds to the absorption of PSS by the hemostats from the crystal surface. The exponential decay is obvious for all samples except for TachoSil.

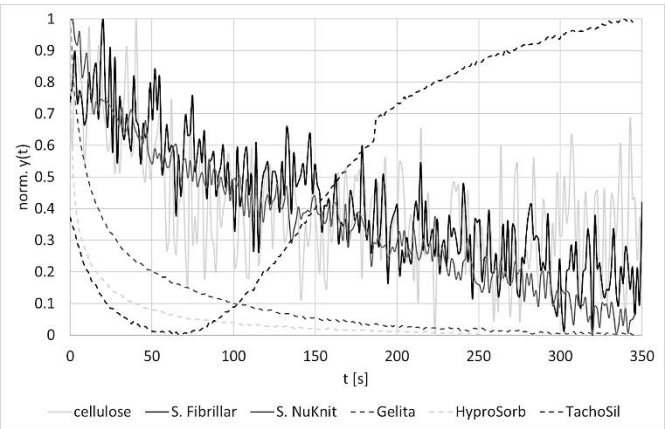

Fig. 4. Normalized time dependence of the THz ATR spectra values at 33 cm^{-1} measured during the reaction of various hemostats with PSS.

When reacting with blood, the measured time-dependent responses of some hemostats demonstrate variations compared to the reaction with PSS, as shown in Fig. 5. A measurement of blood alone was also included to compare its inherent behavior without any added hemostat sample.

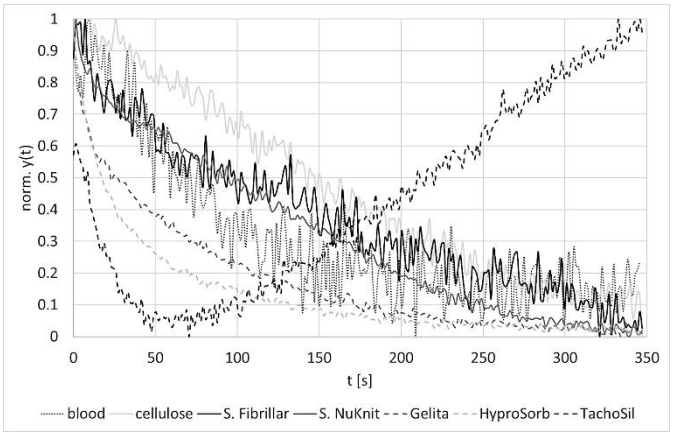

Fig. 5. Normalized time dependence of the THz ATR spectra values measured during the reaction of various hemostats with blood.

The character of the measured data matches the theory of polymer swelling. When a hydrophilic polymer comes into contact with water, the liquid is absorbed into the polymer matrix structure. Consequently, solvent diffusion causes the polymer to swell and increase its volume [5]. Swelling includes three steps: diffusion of water molecules into the polymer matrix, relaxation (hydration of polymer chains), and expansion of the polymer network into the solution. The process can vary from one sample to another with respect to the dominant step. Swelling is evident to varying degrees in all analyzed samples, corresponding to the increase in the measured THz response. Considering the diffusion speed and polymer expansion, the time dependence of sorption is measured and can be described as a fractional approach to equilibrium (2)

$$\frac{M(t) - M_0}{M_\infty - M_0}, \quad (2)$$

where $M(t) - M_0$ is the actual rate of the swelled polymer in time t and $M_\infty - M_0$ is the state of the fully swelled polymer corresponding to the new established equilibrium state, M_0 is the initial mass of the swelled polymer (t = 0), and M_∞ is the final mass of the fully swelled polymer ($t \to \infty$) [6]. When we assume the absolute absence of water in the polymer sample at the reaction initiation ($M_0 = 0$), we get a simplified fraction $\frac{M(t)}{M_\infty}$.

Both theoretical and empirical mathematical models can be used for the precise analysis of sorption processes. Theoretical models are usually based on Fickian diffusion laws; however, their complexity makes them more difficult to apply. Empirical models usually lack a clear physical basis, but they are widely used due to their simplicity (fewer parameters, ease of computation) and very good approximation results. Empirical exponential models were proposed to describe the kinetics of the hemostats' absorption reaction. The absorption model can be derived from sorption processes, since absorption is a component of sorption. The pseudo-first-order model,

described by the following differential equation (3), is the most similar to our data [7]

$$\frac{dM}{dt} = k \cdot (M_\infty - M) \quad (3)$$

Integrating (3) for the boundary conditions $t_1 = 0$ to $t_2 = t$ and $M_1 = 0$ to $M_2 = M$ gives (4).

$$\frac{M(t)}{M_\infty} = (1 - e^{-k \cdot t}) \quad (4)$$

The pseudo-first-order model is represented by a simple exponential growth function that describes the degree of swelling of hydrogel in water. If M_∞ is known, the number of parameters is reduced; $M_\infty \approx 1$ after the data normalization in the interval 0 to 1.

While pseudo-first-order models offer simplicity, they often oversimplify the complex, multi-modal kinetic processes occurring during hemostat hydration and interaction with blood. Because the pseudo-first-order model does not provide a sufficiently accurate description of complex reactions, a model based on the stretched exponential function can be employed. Given that our interest lies in the time required for a certain percentage of a reaction to complete, the Weibull distribution model is a suitable choice. This is because the Weibull survival function is mathematically equivalent to the stretched exponential function [8]. This function is common and effective model for describing the kinetics of various processes within hydrogels, including hydration and drug release [9],[10],[11]. Its applicability extends to the rehydration process of some dried foods [12], which can be analogous to hydrogel hydration due to similar underlying mechanisms of water transport and material rearrangement. The Weibull model, despite its empirical nature, provides a more robust and mechanistically informed description by accommodating the inherent heterogeneity, non-Fickian transport, and dynamic material rearrangements characteristic of these materials. For the hydration process, a two-parameter exponential equation (5) derived from the Weibull model can be used

$$\frac{M(t)}{M_\infty} = \left(1 - e^{-\left(\frac{t}{\tau}\right)^\beta}\right), \quad (5)$$

where τ is the time constant of the process and β is a shape parameter that determines the appearance or shape of the distribution: exponential ($\beta = 1$), sigmoid ($\beta > 1$), or parabolic ($\beta < 1$). The time constant τ indicates the speed of the sorption reaction kinetics and represents the time interval required to complete 63.2% of the process [10].

Three mathematical formulations were derived to approximate the observed processes; a simple exponential model (6) for blood, and an ascending stretched exponential model (7) and a descending stretched exponential model (8) for the absorption kinetics of hemostats and a reference sample of cellulose

$$M(t) = c \cdot e^{-\frac{t}{\tau}}, \quad (6)$$

$$M(t) = 1 - e^{-\left(\frac{t}{\tau}\right)^\beta} \quad (7)$$

$$M(t) = e^{-\left(\frac{t}{\tau}\right)^\beta} \quad (8)$$

The basic exponential function, which is a solution of the pseudo-first-order model kinetics, well approximates the hemocoagulation reaction of blood alone but it was inaccurate for modeling hemostat kinetics. The stretched exponential (Weibull) model is able to approximate the complex absorption time curves of the hemostats due to its shape flexibility. The resulting average values of the model parameters are summarized in Table I; τ (time constant) and c parameter for the exponential model, τ (time constant) and β (shape parameter) for the stretched exponential model. The error of the parameter results is calculated as $t_{n,P} \cdot \frac{s}{\sqrt{n}}$, where $\frac{s}{\sqrt{n}}$ is the sample standard deviation of the arithmetic mean for n measured values, and $t_{n,P}$ is the Student's t-distribution coefficient (for a probability P = 95 %). The approximation curves generated using these model parameters are shown in Fig. 6 for the reaction of hemostats with PSS and in Fig. 7 for the reaction of hemostats with blood.

TABLE I

AVERAGE MODEL PARAMETERS FROM APPROXIMATED DATA OF HEMOSTAT REACTION WITH PHYSIOLOGICAL SALINE SOLUTION (PSS) AND BLOOD

		Hemostat + PSS		**Hemostat + blood**		
Hemostat	**Model**	***τ* [s]**	***β* [-]**	***τ* [s]**	***β* [-]**	***c* [-]**
cellulose	desc. str. exp.	148 ± 36	0.55 ± 0.17	188 ± 17	1.03 ± 0.17	
S. Fibrillar	desc. str. exp.	158 ± 36	0.64 ± 0.11	151 ± 27	1.34 ± 0.46	-
S. NuKnit	desc. str. exp.	149 ± 30	0.88 ± 0.17	126 ± 17	1.11 ± 0.17	-
Gelita	desc. str. exp.	28 ± 8	0.66 ± 0.10	58 ± 13	0.73 ± 0.06	-
HyproSorb	desc. str. exp.	23 ± 7	0.74 ± 0.13	33 ± 4	0.72 ± 0.03	-
TachoSil	desc. str. exp. (phase 1)	23 ± 7	1.21 ± 0.20	43 ± 12	1.06 ± 0.16	-
TachoSil	asc. str. exp. (phase 2)	191 ± 7	3.19 ± 0.90	138 ± 47	1.48 ± 0.38	-
blood	exp. (pseudo-first-order)	-		145 ± 13		0.88 ± 0.04

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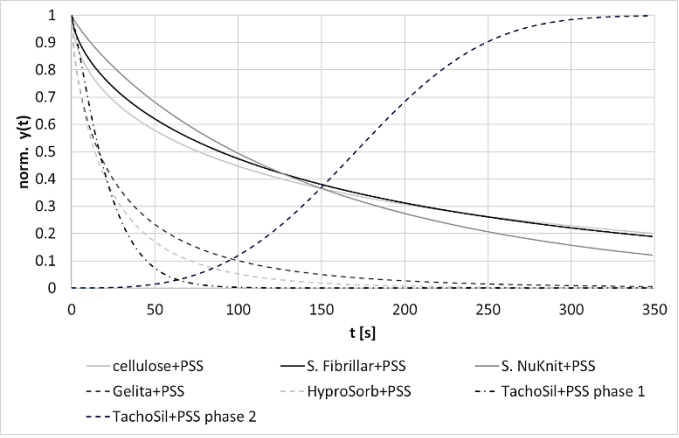

Fig. 6 Approximation curves for hemostat reaction with PSS, based on calculated parameters (Table I).

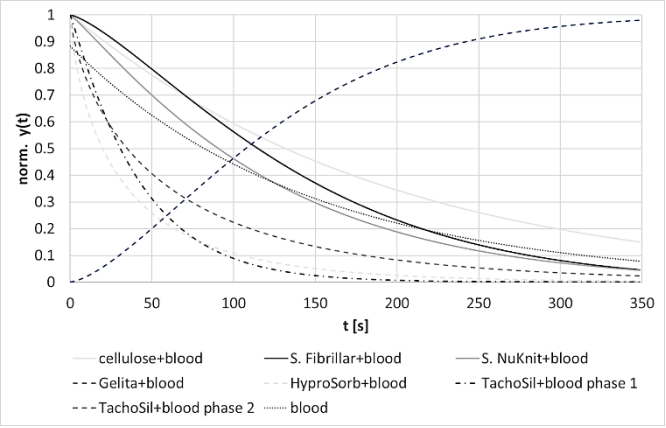

Fig. 7 Approximation curves for hemostat reaction with blood, based on calculated parameters (Table I).

IV. Discussion

The presented study focuses on exploring the reaction mechanism of hemostats using experimental THz spectroscopy method. The reaction efficiency is tested with two liquid media – physiological saline solution and blood. When the hemostat reacts only with PSS, the absorption is the dominant phenomenon. When reacting with blood, other sorption mechanisms (such as adsorption and chemisorption) or structural changes due to the adherence of blood elements can be expected.

As the THz wave passes through the sample reacting with PSS/blood, changes are detected in the ATR spectra, caused by the attenuation of the THz wave and a phase change. The absorption kinetics are analyzed using the ATR absorption spectral value at the wavenumber 33 cm^{-1} over time (Fig. 3). The weakest absorption is evident for the oxycelluloses (S. Fibrillar, S. NuKnit); even though the cellulose fibers bind to water, the crystal surface remains covered with the liquid. Conversely, the response of collagen hemostats (HyproSorb, TachoSil) and gelatin hemostat (Gelita) is stronger and more dynamic. After normalization of the measured signals *norm. y(t)* (Fig. 4), a clear decreasing trend in the signals is observed as the hemostat absorbs the liquid from the crystal surface. The reference cellulose sample shows the lowest SNR, which suggests a poorer absorption ability compared to oxycelluloses. While the oxidized celluloses maintain their structure unmodified, the collagen and gelatin sponges typically gel and swell. A special phenomenon is observed with the TachoSil sample: an initial decrease in *norm. y(t)* is followed by an exponential increase. This could be a consequence of two different participating mechanisms that correspond to the heterogeneous composition of this hemostat (a combination of collagen and a fibrinogen-thrombin layer). The initial decrease in the signal (phase 1) is related to the initial absorption of PSS, similar to other hemostats. The coagulation factors released from the wet fibrinogen-thrombin layer are activated to form the final fibrin layer, which attenuates the THz response because of increasing absorbance of the sample (phase 2).

The reaction of hemostats with blood brings some changes. For the oxycelluloses, the signals are similar to those observed during reaction with PSS, but with a considerably higher SNR. The measured signal of blood coagulation over time shows a similar decreasing exponential trend to the reaction of oxycelluloses with blood. The dynamic character of the hemostatic reactions of HyproSorb, Gelita and TachoSil with blood remains preserved, similar to their reactions with PSS.

Given the exponential character of the measured data, empirical models leading to solutions in the form of exponential functions were derived. The Weibull stretched exponential model was used to approximate the measured reactions of hemostats with both types of liquid. The calculated model parameters are summarized in Table 1. The time constant τ is the fundamental parameter for the comparison of the hemostat reaction rates. When reacting with PSS, both oxycelluloses and reference cellulose sample exhibit similar τ values. However, when reacting with blood, oxycelluloses demonstrate significantly faster kinetics (shorter τ values) than the cellulose sample. Within the oxycellulose group, S. NuKnit exhibits a faster reaction with blood than S. Fibrillar, suggesting that specific properties such as textile structure, density, or material thickness can significantly influence the reaction rate for individual hemostats. In contrast, the reference cellulose samples show considerable differences in τ between the reaction with PSS (148 seconds, comparable to oxycelluloses) and blood (188 seconds). Given that the τ of the oxycelluloses' reaction is shorter than the τ of the reference cellulose reaction with blood, this shorter τ of the oxycelluloses suggests their hemostatic activity. For Gelita and HyproSorb samples, the τ value for reaction with PSS is always shorter than that for reaction with blood. This difference is almost double for Gelita (28 seconds for PSS, 58 seconds for blood). This suggests the reaction is more complex than pure diffusion. Specifically, for HyproSorb, strong adhesion of blood elements occurs, especially platelets, which have a naturally higher affinity for collagen.

TachoSil exhibits a unique reaction profile that can be divided into two phases: a descending phase 1 and an ascending phase 2. The time constant τ of the first phase is shorter for its reaction with PSS (23 seconds) than with blood (43 seconds). Given that the τ of phase 1 is practically very close to the τ of the HyproSorb reaction (also based on collagen), we suggest this phase represents the time during which the liquid is absorbed and the coagulation factors dissolve. The time constant τ of the

second phase is shorter (138 seconds) for the reaction with blood compared to that with PSS (191 seconds). This observation probably reflects the faster activation of the hemocoagulation cascade. This suggestion is further supported by the comparable value of the time constant τ of blood reacting alone (without an added sample, 145 seconds) to the τ of the phase 2 of TachoSil reacting with blood (138 seconds).

When analyzing the β of the descending stretched exponential, its value is always lower for reactions with PSS than for reactions with blood for the oxycelluloses, Gelita, and reference cellulose samples. Conversely, the collagen-based hemostats (HyproSorb, TachoSil) demonstrate a higher β for reactions with PSS. The β value can also be used to determine the type of transport process [10]. Cellulose, S. Fibrillar, Gelita, and HyproSorb in reactions with PSS have a β value smaller than or very close to the border value of 0.75, which indicates dominant Fickian diffusion. When reacting with blood, the β value for Gelita and HyproSorb remains quite unchanged. However, for cellulose and oxycelluloses, β exceeds 1, indicating transport controlled by a complex mechanism (relaxation phenomenon). Similarly, the observation of β values greater than 1 for both phases of TachoSil's reaction with PSS and blood also indicates transport controlled by a complex mechanism. For S. NuKnit, a β value of 0.88 indicates a combined mechanism of Fickian diffusion and swelling.

V. Conclusion

This study demonstrates the capability of THz time-domain spectroscopy to observe the kinetics of absorbable hemostat reactions. Several key findings from the measurements can be summarized as follows:

a) Oxycelluloses (S. Fibrillar, S. NuKnit) show the weakest absorption ability compared to the collagen (HyproSorb) and gelatin (Gelita) hemostats.
b) The measured hemostatic activity of blood corresponds to the simple descending exponential function and is approximated by the pseudo-first-order model.
c) During the interaction of the hemostats with liquid media, swelling and relaxation processes are observed. Because these differ significantly from Fickian diffusion principles, models based on the analogy with reabsorption processes, rather than diffusion, were derived for approximation.
d) The descending exponential trend of the measured reaction between hemostats and PSS/blood corresponds to the absorption of the liquid into the inner structure of the sample. A descending stretched exponential model with two parameters (τ, β) was used for approximation.
e) According to the calculated time constant value, there is a significant difference in the reaction rates of the two types of oxycellulose. S. NuKnit exhibits a faster reaction with blood than S. Fibrillar, suggesting that specific properties of the material can significantly influence the reaction rate.
f) Gelita and HyproSorb react with PSS faster than with blood. This is likely due to the complexity of the reaction with blood (swelling, specific adhesion of blood elements to HyproSorb).
g) TachoSil kinetics typically exhibits two phases: an initial descending exponential trend followed by an ascending exponential trend. This biphasic reaction suggests two distinct processes, reflecting the complex structure of TachoSil. The initial descending phase likely represents the absorption of the liquid medium, while the subsequent ascending phase corresponds to the dissolution and activation of coagulation factors leading to fibrin barrier formation. This observation is also supported by the correspondence between the time constant of Tachosil's second phase and that of the hemostatic reaction of blood alone.

We acknowledge that laboratory measurements under static conditions simplify the complex in vivo environment, where dynamic blood flow (shear stress) and intricate tissue interactions are present. Nevertheless, our current study provides fundamental insights into the kinetics and hydration properties of hemostats under simplified conditions.

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Marie Nedvedova received the M.Sc. (2012) and Ph.D. (2022) degrees in biomedical engineering from Brno University of Technology, Czech Republic. Her studies involved research into the electric properties of biological cells and tissues, and electrotherapeutic methods. Since 2013, she has been a member of the Department of Electronics and Measurements at Tomas Bata University in Zlin, Czech Republic. Her current research focuses on spectroscopic methods and their biological applications, along with the analysis and mathematical statistics of biological signals.

Vojtech Kresalek received the RNDr and Ph.D. degree in physical optics in 1979 and 1984, respectively. For a brief time, he was with Chalmers University in Göteborg, Sweden. Since his habilitation in 1993 at the Faculty of Technology in Zlin, his research has focused on the electric properties of polymer and composite materials and their impedance spectroscopy. His more recent research interests include the properties of nanocomposite materials and metamaterials, electromagnetic compatibility, and terahertz spectroscopy.

Zdenek Adamik received the M.D. and Ph.D. degrees from Palacký University in Olomouc, Czech Republic, in 1984 and 2007, respectively, first and second degree attestations in gynecology and obstetrics in 1987 and 1991, and attestations in urogynecology and fetal medicine in 2007 and 2009, respectively. He has been the head physician of the Maternity and Gynecological Detachment of Tomas Bata Regional Hospital in Zlin. He is also the lecturer at the Department of Health Care Sciences at Tomas Bata University in Zlin, Czech Republic. His research focuses on overactive bladder (OAB) syndrome, the treatment of incontinence, and the development of surgical techniques for pelvic floor reconstruction.

Norbert Pałka received the M.S. degree in physics (with a focus on fiber optics technology) and the Ph.D. degree in optoelectronics from the Military University of Technology, Warsaw, Poland, in 1999 and 2003, respectively. In 1999, he joined the Military University of Technology as a Researcher with the Institute of Optoelectronics. His interests include various security sensors and systems: fiber optics, CCTV, and thermal cameras. Since 2008, he has been focusing on terahertz technology for detection of explosives, body scanners, and nondestructive evaluation of composite materials.