Dagmar FAKTOROVÁ, Mária PÁPEŽOVÁ

University of Žilina

Optimization of mild microwave hyperthermia interconnection with targeted delivery of nanoparticles

***Abstract**. The paper deals with interconnection of microwave hyperthermia with controlled biodistribution of nanoparticles in order to maximize the exposure tumorous tissue and minimize heating the neighbouring healthy tissue. We investigated in our research the delivering nanoparticles to the tumorous tissue as a function of time in order to optimize the beginning time of microwave hyperthermia treatment. We also follow the other parameters which could affect the effect process of microwave hyperthermia – the value of dielectric parameters of treated tissues.*

***Streszczenie.** W artykule rozważany jest problem połączenia mikrofalowej hipertermii ze sterowaną biodystrybucją nanocząstek. Celem tego współdziałania jest maksymalizacja ekspozycji tkanki guza przy jednoczesnej minimalizacji nagrzewania się zdrowych tkanek sąsiednich. Zbadana została zależność wprowadzania nanocząstek od czasu w celu optymalizacji rozpoczęcia procesu hipertermii. Zbadano również inny parametr, mogący wpływać na efekty hipertermii, mianowicie wartość parametrów dielektrycznych leczonej tkanki. (**Optymalizacja łagodnej hipertermii mikrofalowej w powiązaniu z dystrybucją nanocząstek**).*

Keywords: microwave hyperthermia, nanoparticles biodistribution, dielectric parameters.
Słowa kluczowe: hipertermia mikrofalowa, biodystrybucja nanocząstek, parametry dielektryczne.

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Introduction

Mild microwave hyperthermia comes under emerging therapeutic methods in oncology which effect is not in destruction of cancer cells but in improving the effectiveness of chemotherapy or radiotherapy. One of the major problems connected with microwave hyperthermia in general is the achievement very precise beam focusing to the volume of treated tissue in the case of local microwave hyperthermia. Nanotechnology become as one of the next promising and important methods in the process of diagnostics and treatment of cancer diseases. The therapeutic effect of nanoparticle using is connected with very precise selective heat deposition directly in tumorous cells. In this way there is possible to affect the process of pharmacodynamics in the in terms of increasing of drug concentration in cancer cells. In our research we connect the mild microwave hyperthermia with temperature sensitive liposome application. Liposomes acts in two roles: to delivery drug in tumorous cells and in the role of highlossy dielectric carrier (HDC). HDC delivered to the tumour volume increase the focusing effect of microwave energy.

It is very important to specify the optimal time for mild microwave hyperthermia application regarding to time dependent administration of liposomes delivery to the tumour volume. We have used the pharmacokinetics mathematical model, where the variation of parameters (time, surface charge, concentration of agent - nanoparticles, frequency of agent – nanoparticles rendering, type of agent - nanoparticle) [1] allowed us to appoint the optimal time of mild microwave hyperthermia setting-in and its duration after addressing the drugs and nanoparticle covered by liposomes into the patient body.

Numerical results

We have used in our research the two kind of liposomes – in the role of higlossy dielectrics and in the role of chemotherapy drug carrier and followed up their uptake in tumorous tissue and their biodistribution. We have chosen liposomes, which are able to be accumulated in tumorous tissue. Very important factor connected with uptake of nanoparticle agent in tumorous tissue volume is surface charge of nanoparticles and also the frequentness of nanoparticles drugs administration. We follow up in mathematical analysis the intersection of curves biodistribution of both liposomes into tumorous tissue. This time we marked as a setting-in time for application of microwave hyperthermia. In Fig. 1 are results of analysis the nanoparticle uptake in tumorous tissue. The optimal time for microwave hyperthermia starting – 8min – was calculated and was set in the point of intersection of two curves. The course of curves in Fig. 1 was calculated by using mathematical pharmacokinetics model with compartments which represent tumorous tissue and blood stream: slim curve represents the metabolism of liposomes in the role of carrier of highlossy drugs and second one represents the metabolism of liposomes in the role of carrier chemotherapy drugs.

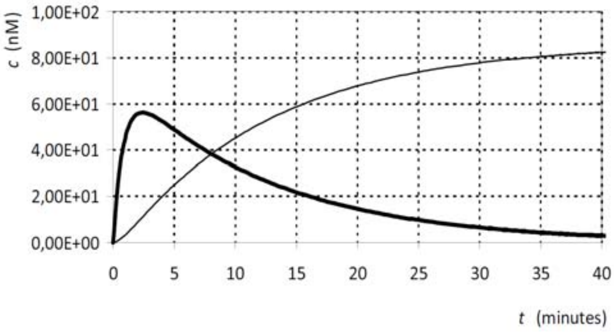


Fig.1. The assessment of optimal time MW hyperthermia setting

Our goal was to find the intersection of both curves which represents the optimal time of microwave hyperthermia starting which means the time in which the concentration of both liposomes in volume of cancer tissue achieved the relative maximum.

Experimental results and discussion

Very important parameters which affect the process of microwave hyperthermia are dielectric properties of biological tissues. Our experimental work was directed to develop appropriate methods for dielectric properties of living tissues measurement. The permittivity of biological tissues is determined by several dispersion phenomena. Our effort was to delimit the influence of this mechanism in the separate microwave X band. From this point of view we were interested in the tissue behavior with different “free” water content. Also the temperature dependences for particular states were examined and anomalous dispersion was noticed.

Waveguide technique was used for measurement. The investigated samples were placed in rectangular waveguide with dimensions a = 22.9 mm, b = 10.2 mm, Fig. 1 (K – klystron, KPS – klystron power supply, FM – frequency meter, SA – selective amplifier, IM – impedance match, FI – ferrite isolator, VA – variable attenuator, MT – magic T, SWD – slotted section, W – waveguide, SC – short circuit, A – adapter, CD – crystal detector). Different tissues were measured and results were compared with the values obtained by numerical computation [2].

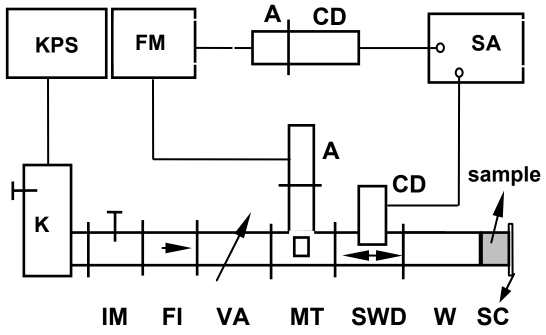


Fig.2. Experimental set-up for complex dielectric properties of living tissues measurement

The measuring methods were used in the standard laboratory arrangement at frequency 10GHz, Fig. 2 but we modified Hippel´s method by the short circuit as mentioned above and at the Poley´s method the waveguide with the piston was placed in a vertical position without the mica window to avoid the influence of mica on measurement. For other materials was used the “minimum shift method.”

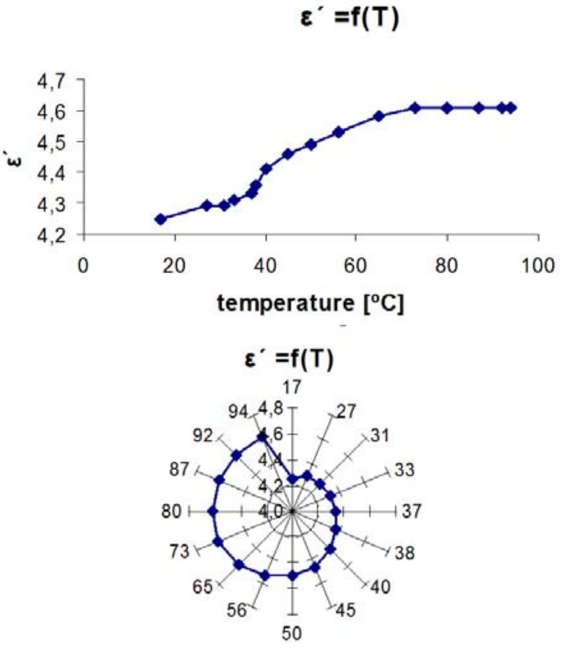


Fig.3. Temperature dependence of relative permittivity of pig bone

First we made use of determining the complex permittivity the shorted – line technique, where a slotted section is used to measure the shift of minimum position of a standing wave and the change in the standing – wave ratio. The minima of the standing – wave pattern occurs at intervals of one-half wavelength from the short circuit when the sample is absent. When the sample is inserted in front of the short circuit, the minima shift toward the short circuit as shown in Fig.2. The shift of minimum is a measure of the dielectric constant. The signal that is lost in the form of heat in the dielectric causes a decrease in the standing – wave ratio. The decrease in standing – wave ratio is a measure of the loss tangent – $\mathrm{tg}\delta = \varepsilon'' / \varepsilon'$.

In Fig. 3 and 4 are displayed the temperature dependence of relative permittivity and loss tangent of pig bone. The pig bone is the example of low loss biological tissue. The knowing of dielectric properties of bone is very important because their influenced the electromagnetic energy distribution during microwave hyperthermia.

Very important for investigation of new method in microwave hyperthermia is to know not only dielectric properties of biological tissue, but also dielectric properties of their phantoms. The phantoms are very often used to replace the using real biological materials.

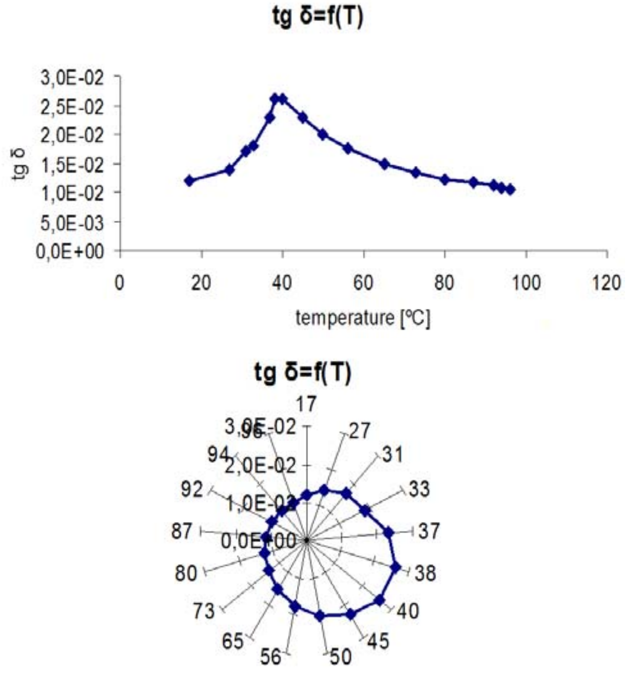
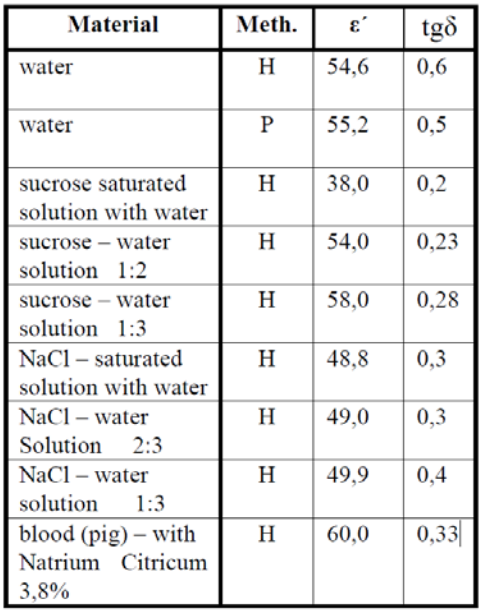


Fig.4. Temperature dependence of pig bone loss tangent

The choice of phantoms materials was orientated to ones having their behaviour close to the biomedical orientation. Polyurethane was chosen with regards to the similarity to dielectric properties of bones, and sucrose solution to its similarity to dielectric properties of muscles and blood. It should be mentioned that into the blood sample was added Natrium Citricum to keep its fluidity. The measuring results are in the table and in the figures. As it can be seen from the Tab. 1 (H – Hippel method, P – Poley method) the increasing sucrose concentration decreases the dielectric constant. (In general the concentration of sucrose is considered as the determining factor in establishing phantom of tissue characteristics). On the other hand the salt content did not show a distinct influence. The both methods used for the measuring of water showed approximately the same results, but we would prefer the Poley´s method.

Our next work will be directed to the research of two topics: a) finding the optimal time of both drug uptake which will represent the maximum of both drug concentration in tumorous tissue and b) finding of optimal focusing of microwave energy to the volume of tumour and finding of optimal duration of microwave hyperthermia application to the treatment area following the changing of dielectric parameters of heated area during the treatment with microwave hyperthermia.

Table 1. The phantom materials dielectric properties



Material	Meth.	ε´	tgδ
water	H	54,6	0,6
water	P	55,2	0,5
sucrose saturated solution with water	H	38,0	0,2
sucrose – water solution 1:2	H	54,0	0,23
sucrose – water solution 1:3	H	58,0	0,28
NaCl – saturated solution with water	H	48,8	0,3
NaCl – water Solution 2:3	H	49,0	0,3
NaCl – water solution 1:3	H	49,9	0,4
blood (pig) – with Natrium Citricum 3,8%	H	60,0	0,33

Conclusion

Our results showed that microwave hyperthermia can become very effective tool for increasing effectiveness of chemotherapy which used temperature sensitive liposomes in the role of drug carrier. In our paper we have shown, that optimisation process in the microwave hyperthermia connected with targeted delivery of nanoparticles and the knowing the dielectric properties of living tissues and their change with temperature can became the effective tool for cancer therapy.

In view of the fact that microwave investigation it is mostly a case of interaction with surface layers containing a great percentage of water it will be necessary to pay attention also in future to investigation of mineral solution in water especially in the sphere of anomalous dispersion as we have measured with fat. Because at microwave therapy [3], [4] there always a necessary heating occurs, thermal dependences will create an unavoidable part of information for practical applications.

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***Authors**: assoc. prof. Dagmar Faktorová, University of Žilina, Faculty of Electrical Engineering, Univerzitná 1, 010 26 Žilina, E-mail: dagmar.faktorova@fel.uniza.sk; Mária Pápežová, University of Žilina, Faculty of Electrical Engineering, Univerzitná 1, 010 26 Žilina, E-mail: maria.papezova@fel.uniza.sk*