Study on In-vivo Measuring Method of Solubility for Cerebral Thrombus Dissolution.

Zhongwei JIANG*, Minoru MORITA*, Tetsuyou WATANABE*,
Shoichi KATO**, Michiyasu SUZUKI**

* Dept of Mechanical Engineering, Yamaguchi University, 755-8611, Japan
Tel : +81-00-111-2345 Fax : +81-00-111-6789
E-mail: {jiang, a089fb, t-wata}@yamaguchi-u.ac.jp

**Dept of Neurosurgery, School of Medicine, Yamaguchi University, 755-, Japan
Tel : +81-75-999-8765 Fax : +81-75-999-4321
E-mail: kato-ygc@umin.ac.jp; michi@yamaguchi-u.ac.jp

Abstract: A cerebral thrombus or blood clot might cause cerebral stroke and even decease if the clot could not be dissolved within several hours after it was formed. This paper presents a fundamental study on development of a new type of mechanical micro stirrer for assisting the dissolution of the thrombus with a few amount of thrombolytic agent. The micro stirrer is made of a slight beam embedded with a piezocell. An efficient excitation method for stirring up the thrombus to get a quick dissolution is investigated. Furthermore, to evaluate the dissolution state in vivo, the method using the piezo-stirrer as both the stimulator to beat the clot and the probe to evaluate its solubility is proposed. The potential of the piezo-stirrer has been validated experimentally.

Keywords: Micro-stirrer, Beam, Piezocell, Thrombus, Clot, Stroke, Dissolution, Solubility, Measurment

1. INTRODUCTION

The cerebral stroke is one of the sicknesses from which many elderly people are being to suffer. The cerebral stroke is happened due to a thrombus formed in the vessel blocks the blood flow in the brain and induces the brain cell necrosis. Due to enhancement of people's living standards, many people recently suffer from the hypertension, the hyperlipemia and the hypercholesterolemia, which means there exists high possibility of the cerebral stroke. Furthermore, the mortality or the complication rate due to the cerebral thrombus would be very high if the cerebral blood vessel is not recanalized in time. The complication rate could become lower, if the clot is taken away in the early stage or within the therapeutic time window at which the ischemic organ is still reversible. In the present clinical treatment, the thrombus within the vessel is dissolved by infusion of the thrombolytic agent directly into the artery. The direct infusion needs a large amount of the agent to dissolve the clot, so it has a high risk of intracerebral hemorrhage, or some kind of adverse reactions. There are some attempts on this problem, such as using transcranial Doppler stimulator to assist the dissolution effect, and using a ultrasonic catheter device to deliver the drugs to the affected area and to stimulate the clot for a quick recanalization.[1-3] This method is considered efficient to use a few drugs but how to deal with the ultrasonic energy for fast dissolution needs advanced investigation.

In consideration as mentioned above, this paper is concerned with the study on development of a mechanical micro stirrer that can be used in the catheter to assist the clot dissolution speed with a few agents. The proposed stirrer is made of a slight beam embedded with the piezocell. An excitation method for the stirrer, how to beat the clot to get an efficient dissolution of the clot with a few thrombolytic agents, is investigated.

Furthermore, evaluation of the solubility of the blood clot in vivo is a still unsolved problem. It is well known that the piezoelectric material has both actuator function and sensor function. It come an ideal to use the same stirrer for beating the blood clot and at same time evaluating its dissolution state. In common sense, as the clot is dissolving the contraction to the motion of the stirrer goes weakly, which leads a change in the stirrer mechanical impedance. So the problem to be solved comes to that how to measure the mechanical impedance change easily and precisely. The piezoelectric impedance based technique is therefore introduced for this study and its potential is validated experimentally.

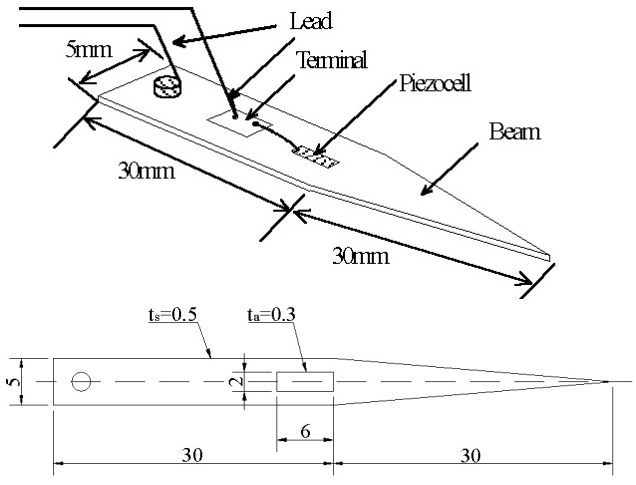


Fig.1. Schematic of piezo-stirrer.

2. MICRO STIRRER & EXCITATION

Figure 1 shows the schematic of a hand-made stirrer in a size suitable for fundamental test in the laboratory. The base beam is aluminum cut in size of 60x5x0.5mm and the piezocell of 6x2x0.3mm is bonded on it as an actuator and also sensor. The experimental system for driving the stirrer is shown in Fig.2. The beam is driven in the following way. The input signals, such as sine and pulse waveforms, are formed by a waveform generator (HIOKI 7050) and amplified to 50V through a power amplifier (FN 4010), then added to the piezocell. Figure 3 shows a picture in which a micro-stirrer is fixed on a hand–made fixator and the vessel filled with the testing liquid is set on a three-dimension manipulator (M-152) so that the inserting depth of the stirrer could be easily adjusted.

In the experiment, the depth of the stirrer tip is set at 7mm from the liquid surface. Instead of blood, water is used in the experiment say about 1.8ml. In order to investigate the stirring effect, four resonant frequencies at 0.155, 0.228, 0.55 and 2.56kHz, is selected and two kind waveforms, sine and pulse waveforms, were tested, and the stirrer is driven for 10 minutes. Further, as for pulse waveform, its duty ratio is changed by 10, 30 and 50%.

The obtained results are summarized and described in Table 1. Since the motions of the stirrer is difficult to measure in the experiment, the whirlpool or ripple on the water surface is observed for evaluation of the stirring effect. Further, the sound from the stirrer is also used as an important factor. The mark '○' in the table means the case that the ripple has been observed and mark '×' means the ripple was not observed by eyes. Furthermore, mark '●' means the case that the whirlpool has been observed on the water surface. In the column of Sound mark '○' means one can hear the sound form the stirrer by ears and mark '×' means not. Furthermore, mark '●' represents a strong sound has been observed. It is found that the excitation using pulse waveform with 50 % duty ratio at 2.56 kHz seems most effective for stirring the liquid.

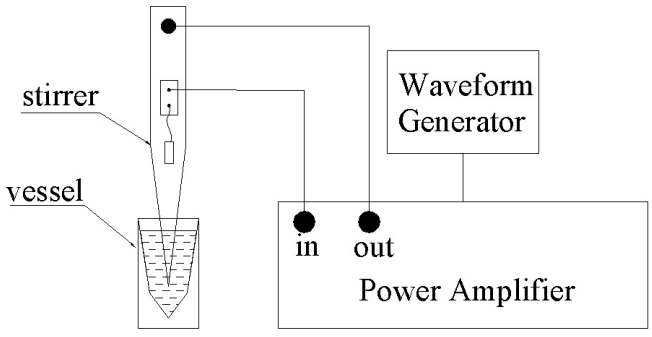


Fig.2. Experimental setup for the stirrer driving test.

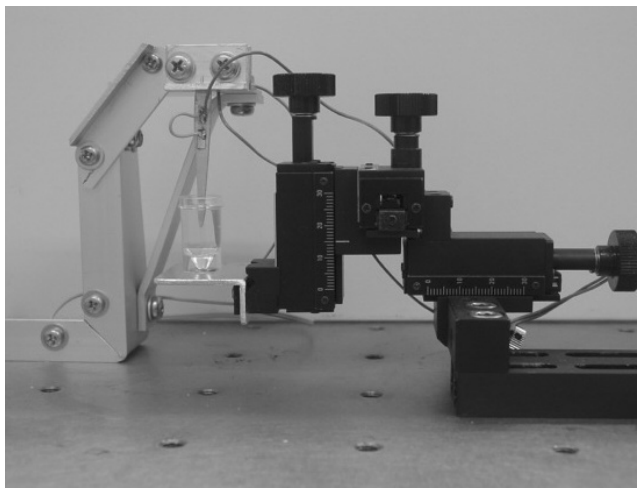


Fig.3. Experimental setup photo.

Table 1. Stirrer or excitation effect.

Input waveform & frequency		Duty ratio (%)	Ripple in liquid	Sound from stirrer
0.155 kHz	Sine wave		×	×
	Pulse wave	10	×	○
		30	×	○
		50	×	○
0.228 kHz	Sine wave		×	×
	Pulse wave	10	×	○
		30	×	○
		50	×	○
0.55 kHz	Sine wave		×	×
	Pulse wave	10	○	○
		30	○	○
		50	●	●
2.56 kHz	Sine wave		●	●
	Pulse wave	10	○	○
		30	○	○
		50	●	●

Note : × not observed, ○observed, ●well observed

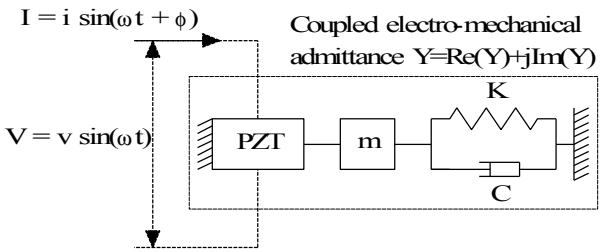


Fig.4. Concept of piezoelectric impedance based measuring technique.

3. THROMBUS SOLUBILITY MEASURMENT

As mentioned above, the thrombus solubility might be estimated according to the ripple on the water surface observed by eyes or to the sound by ears in the present condition. It is firmly difficult to evaluate the dissolution effect in vivo when a catheter type stirrer is used. Also no efficient method has been established in present literature to measure or evaluate the thrombus solubility in vivo. In this section, an ideal using the same stirrer to beat the clot and also to measure its solubility is thereat proposed. This ideal is based on a change in the piezoelectric effect due to the thrombus dissolution, when a change of the concentration in the blood existed.

In common sense, as the clot is dissolving the contraction to the motion of the stirrer goes weakly, which leads a change in the stirrer mechanical impedance. This stirrer mechanical impedance change can be measured by a piezocell bonded on it, because the mechanical impedance induces a change in the piezoelectric impedance. The thrombus solubility is therefore inferred by the piezoelectric impedance. The piezoelectric impedance based technique is expressed as follows.

The model of the stirrer with the piezocell can be simplified as shown in Fig.4. Therefore the admittance of the piezocell is then represented as:[4]

$$Y = iw\frac{w_a l_a}{h_a}\left[e_{33}^{T}(1-id) - \frac{Z_S(w)}{Z_S(w)+Z_a(w)}d_{3x}^{2}Y_{xx}^{E}\right] \qquad (1)$$

where Z_a and Z_S are mechanical impedance of the piezocell and the stirrer, Y_{xx}^{E} is the complex modulus of the piezocell at zero electric field, d_{3x} is piezoelectric constant, e_{33}^{T} is complex dielectric constant, d is the dielectric loss factor and w_a, l_a and h_a are the width, length and thickness. The admittance is reciprocal of piezoelectric impedance. The mechanical impedance of the piezocell is assumed constant. In the equation (1), the piezoelectric impedance is therefore controlled by the mechanical impedance of the stirrer. The mechanical impedance of the stirrer is influenced by the testing liquid. Therefore, the condition of the liquid could be estimated by measuring the stirrer piezoelectric impedance, which means the solubility of blood clot could be assessed by measuring the piezoelectric impedance of the stirrer.

The experimental impedance measuring system is shown in Fig.5. The piezocell is connected to the impedance analyzer (HP 4192), so that a sweep sine voltage generated by the analyzer is added to the piezocell. The piezoelectric impedance change due to different kind of the testing liquid is measured and transmitted to a computer for data processing. Some obtained results are plotted in Figs.6 and 7. Therefore, the impedance and the frequency shift of the responses are used for assessment. In the experiment, the volume of the testing liquid, the position of stirrer and the vessel type are fixed for obtaining the measurement repeatability. Figure 6 shows the real part of piezoelectric impedance obtained along a selected frequency region 2-100kHz.

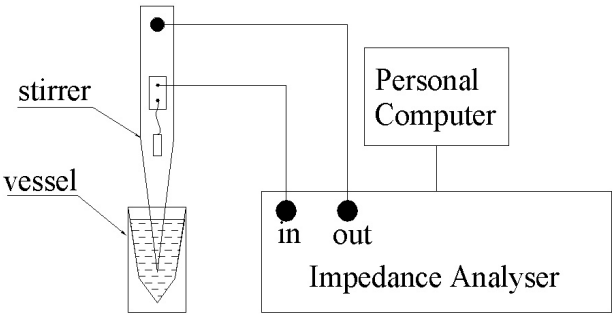


Fig.5. Experimental setup for impedance measurement.

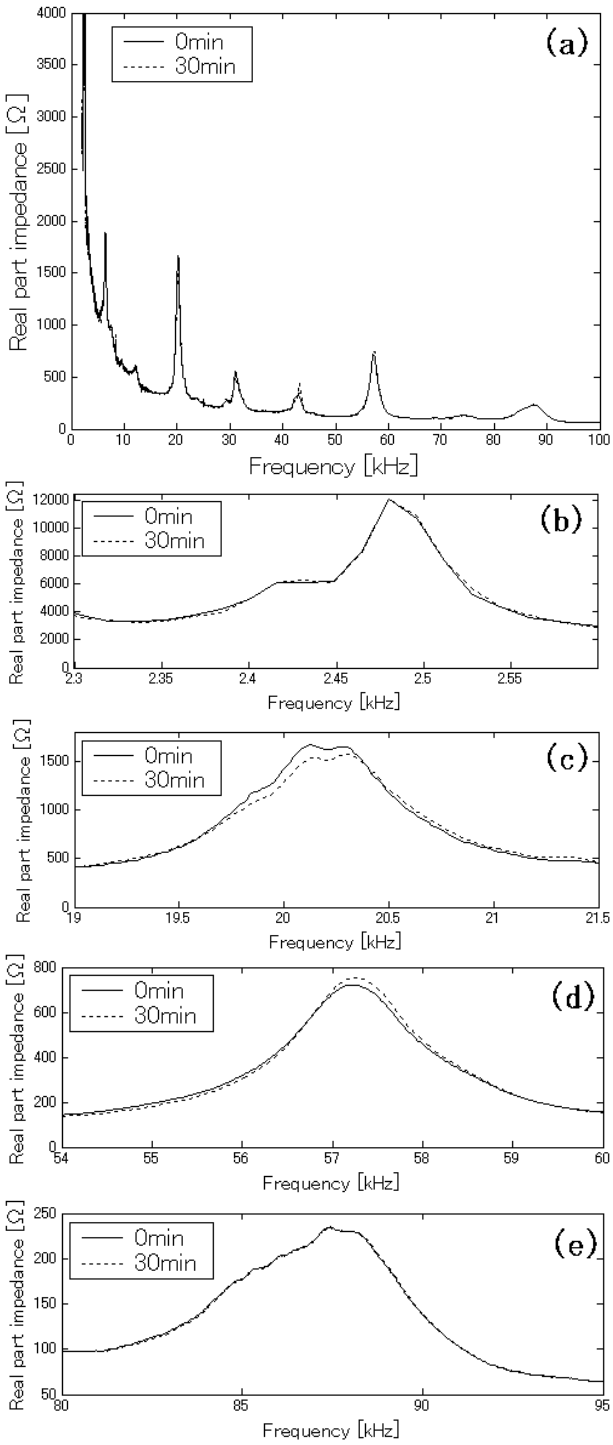


Fig.6. Real part impedance response and its repeatability. (a) 2-100kHz, (b) 2.3-2.6kHz, (c) 19-21.5, (d) 54-60, (e) 80-95

The measurement repeatability is verified by comparing the data obtained twice before and after 30 minuets in the same experiment condition. Figure 7 shows the impedance response variations along the frequency region [2.5-2.6]kHz obtained when the concentration of the sugar solution is confected with water and sugar syrup at 10, 20, 30, 40, 50 and 60% respectively. It is clear that the impedance waveform shifts to left and its amplitude goes lower monotonously with an increase of the concentration. Therefore, it comes to a conclusion that the solubility could be estimated by evaluation of the impedance waveform variation. In following, three parameters are introduced for evaluation of the solubility by analyzing the waveforms.

Now, suppose the peak frequency of the waveform for water is given by F_W and its amplitude by A_W and the ones for sugar solution at x% are F_x and A_x as defined in Fig.8. Then the parameters named as peak frequency shift ratio d_F and peak amplitude ratio d_A are defined by

$$d_F = 20\log\left|\frac{F_w - F_x}{F_w}\right| \tag{2}$$

$$d_A = 20\log\left|\frac{A_w - A_x}{A_w}\right| \tag{3}$$

Further, the concentration of sugar solubility might affect the damping effect as the stirrer is under drive. According the waveforms in Fig.7, their damping coefficient z can be easily calculated by

$$z = \frac{F_x^2 - F_x^1}{2F_x^0} \tag{4}$$

where, F^0 is the peak frequency, and F^2 and F^1 are obtained from the peak amplitude $A_{\max}$ as described in Fig.9. Imitating the above definitions Eqs.2 and 3, the third parameter is then given by

$$d_z = 20\log\left|\frac{z_w - z_x}{z_w}\right| \tag{5}$$

Figure 10-12 show the plot of the parameters d_F, d_A and d_z calculated from the data in Fig.7. It is found the parameters d_F, d_A and d_z are almost linear to the sugar solution concentration and their approximate lines is thereat calculated by the least mean square method and plotted in superposition to the figures. Therefore, the solubility, if defined as x (%), could be estimated by

$$x = 2.5d_F + 145 \tag{6}$$

$$x = 2.5d_A + 82.5 \tag{7}$$

$$x = 2.5d_z + 72.5 \tag{8}$$

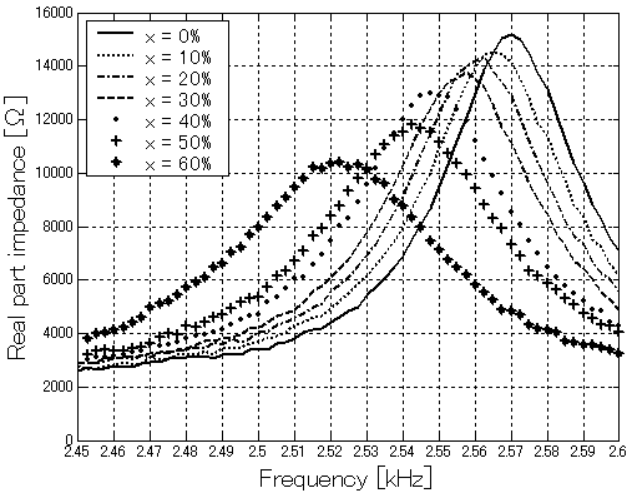
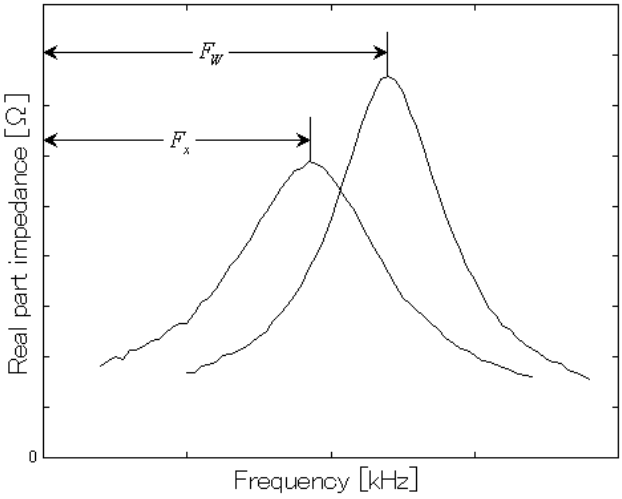
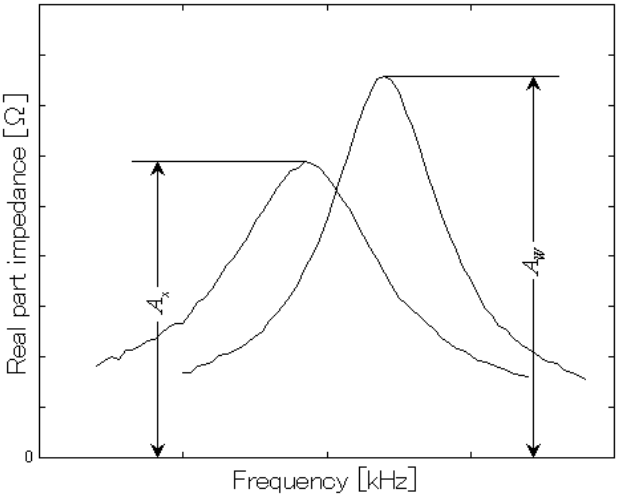


Fig.7. Impedance variation corresponding to concentration of sugar solution.



(a) Value of peak



(b) Frequency shift

Fig.8. Parameter definition of frequency shift and peak ratio.

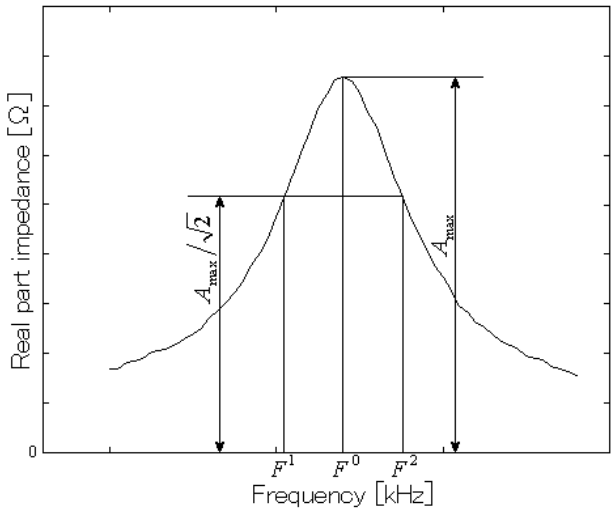


Fig.9. Definition for damping ratio.

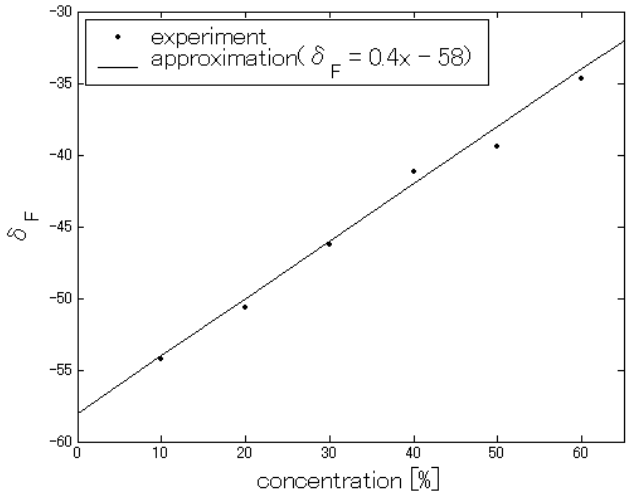


Fig.10. Frequency shift as a function of sugar solution concentration.

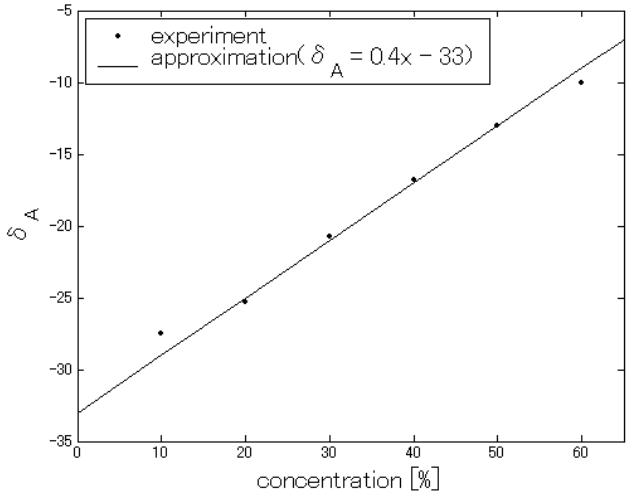


Fig.11. Peak ratio vs. sugar solution concentration.

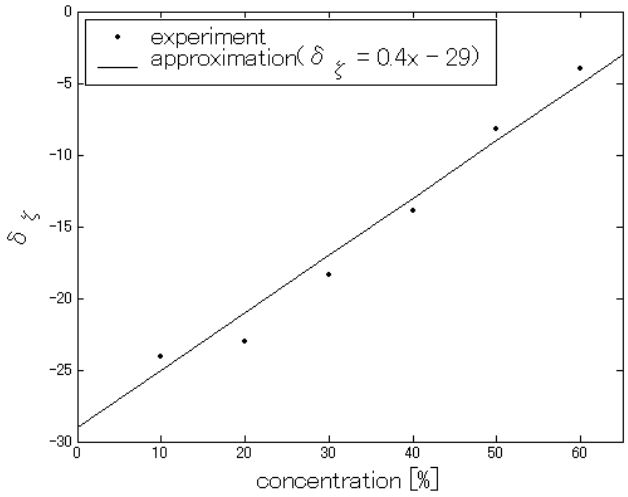


Fig.12. Damping ratio vs. sugar solution concentration.

Finally, an experiment is carried out to validate the dissolution effect with the aid of the proposed measuring method. For excitation of the stirrer, the pulse waveform at 2.56kHz and with 50% duty ratio is selected. The input amplitude is 50V, and the stirrer is driven for 10 minutes. The testing liquid is confected by 1.3ml water with 0.5ml sugar syrup and the stirrer is inserted about 7mm from its surface. At the beginning, the sugar syrup is precipitated down the vessel. Figure 13 shows the obtained impedance waveforms for three cases, (1) before the excitation, (2) after excited the stirrer for 10 minutes and (3) completely dissolved by hand. It is evident that the stirrer driven by the piezocell is powerful for the dissolution of sugar syrup and the solubility measurement using the same stirrer shows its potential to in vivo measurement.

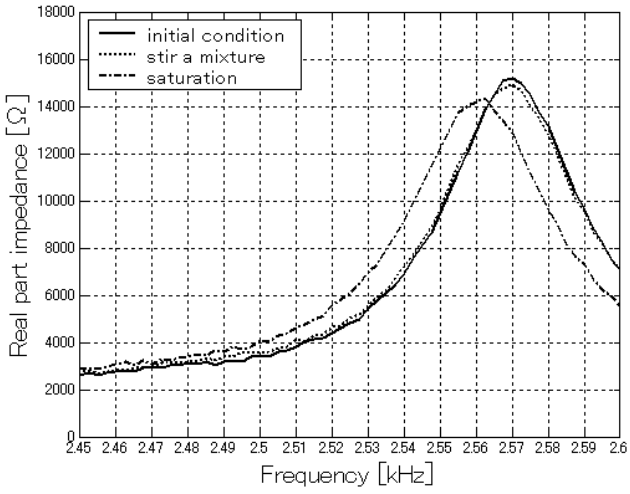


Fig.13. Stirring effect validation.

4. CONCLUSION

A novel method using a mechanical excitation for dissolving the cerebral thrombus and a impedance based measurement for evaluating the solubility are proposed and the fundamental experiments show that the piezo-stirrer has high potential to be used both for dissolving the blood clot and for evaluating the thrombus solubility in vivo.

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