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Dielectric properties of glycosuria at 0.2-50 GHz using microwave spectroscopy

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In this study, we analyzed the dielectric behavior of urine among subjects with diabetes mellitus. The measurements were conducted using an open-ended coaxial probe at microwave frequencies between 0.2 and 50 GHz at room temperature (25 °C), 30 °C and human body temperature (37 °C), respectively. The strongest statistically significant difference in dielectric properties across different glycosuria groups (F (2, 41) = 8.681; $p < 0.01$) was reported at room temperature (25 °C). Dielectric constant increased with glycosuria level more than 500 mg/dl (>0.5%) at low frequencies. Dielectric constant correlated positively with glycosuria level at frequency above 40 GHz while loss factor correlated negatively with glycosuria level at frequency above 15 GHz. The experimental data closely matched the Debye model.

Keywords: dielectric properties; glucose; urine; temperature; frequency; Debye model

1. Introduction

Dielectric properties have been proposed as a form of non-invasive measurement of biological solutions such as blood [1,2] and urine.[3–6] Initially, dielectric properties of biological tissues were widely determined to provide informative data to the literature. Gabriel et al. [7] reviewed the studies that involved dielectric property differences in biological tissues. Further comparative measurements showed that dielectric properties changed with tissue type, biological fluid, temperature, and frequency, respectively.[8] These dielectric properties of tissues have been compared under both *in vivo* and ex-vivo conditions [9] or *in vivo* and *in vitro* conditions.[10] Studies related to biological fluids reported biomaterial dependency of dielectric changes. The variation of hematocrit, ionic salt, and glucose levels in blood resulted in changes to dielectric properties.[11–13] Different composition of bile between porcine and ovine also showed the difference in dielectric properties.[14]

Generally, the presence of glucose drastically affects the chemical and physical characteristics of the viable fluid. The dielectric properties of glucose solution have been investigated.[15] It was reported that the dielectric constant decreased while loss factor increased with respect to the glucose concentration in solution at the particular frequency of 2.45 GHz. The temperature effect of glucose solutions on the dielectric

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properties was determined by Liao et al. [16]. Meriakri et al. [2] obtained the dielectric dispersion at a wider microwave frequency range up to 20 GHz. Smulders et al. [17] discovered that the dielectric properties changed differently in glucose solution compared to that of glucose solution containing 0.9% NaCl salt. They concluded that the presence of salt in the biological solution could affect the sensitivity of dielectric properties in the glucose concentration. The presence of 0.9% NaCl salt in the glucose solution as representative of biological solution caused the dielectric constant to decrease at frequencies below 20 GHz while loss factor increased at frequencies below 40 GHz and vice versa at the frequencies above, and up to 67 GHz.[17]

In terms of biological solutions, although glucose is considerably lighter in mass compared with other components in blood, its effects are found in the changes of electrical and dielectric properties. Park et al. [1] reported that the correlation of dielectric constant changed with hamster blood glucose at a low frequency range. Park et al. [1] found that the dielectric measurement of analyzer produced higher accuracy than the blood glucose meter. The influence of human blood glucose in dielectric constant was studied at frequencies up to 3 GHz.[18] The results yielded dielectric properties that were varied in different blood glucose concentrations and frequencies, respectively.[13,18–20] Meriakri et al. [2] found no visible changes in dielectric properties during the inverse process of glucose loading in blood, especially between 41 and 42 GHz. This happened because the temperature increased with the mobility of ions transported in excised blood.[13]

Glycosuria is a condition characterized by the presence of glucose in urine. Diabetes patients who fail to break down glucose in blood for energy will eventually present with glycosuria.[21,22] In the context of diabetes control, urine glucose monitoring is essential for a noninvasive approach. Diabetes test strips that use the color chart to determine glycosuria variability are less accurate compared with numerical readouts.[23] The application of dielectric property measurement is generating interest for clinical utility. The physiological range of glucose levels (100–400 mg/dl) was reported to have a direct impact on the impedance modulus of the physiological solution (0.9% NaCl) and consequently changed the dielectric properties.[24,25] The dielectric properties of blood glucose concentration are well-established.[26–28] Some studies had looked into the glucose-induced dielectric properties of urine.[4,5] However, those studies were limited to dielectric properties for glycosuria up to 3 GHz and they had no temperature control for the investigations. In addition, broadband dielectric properties of biological solutions have never been validated statistically. Liao et al. [16], Meriakri et al. [2], and Smulders et al. [17] reported that the differences in respective temperatures and frequencies resulted in a change of the dielectric properties in glucose solution. Hence, the characterization of dielectric properties at frequency and temperature exposure levels could have an important impact on the reliable and accurate determination of dielectric properties of biological solutions.

In this study, we aim to investigate and analyze dielectric properties and dispersive behavior of urine among groups with diabetes glycosuria at room temperature (25 °C), at 30 °C, and at body temperature (37 °C), respectively, at microwave frequencies up to 50 GHz. This study determines the significant differences in dielectric properties among subjects with different glycosuria levels. The correlations between dielectric properties and different glycosuria levels are investigated. The experimental data were fitted to Debye model.

2. Materials and method

2.1. Subjects

Forty-four subjects with Type II diabetes mellitus were recruited from University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. These subjects were currently prescribed diabetes medication, in the form of Metformin. The medication was excreted unchanged in urine through tubular metabolism yielded no metabolites and has been identified to increase renal clearance of the subjects.[29] No statistically significant difference ($p > 0.05$) was found between the intake dosages of Metformin across the subject groups. The subjects were grouped into three groups based on their urinary glycosuria levels: Group 1 (0 mg/dl), Group 2 (100–500 mg/dl), and Group 3 (500–1000 mg/dl). The characteristics of the subject groups are shown in Table 1. None of these recruited subjects had diabetes nephropathy. Medical ethics approval was obtained from the Institutional Ethics Review Committee, UMMC, Kuala Lumpur, Malaysia. All subjects gave their informed consent before the urine collection.

2.2. Urine collection and storage

Random spot urine samples of 60 ml were collected from each subject. For each collected urine sample, 10 ml was used to measure urine clinical chemical variables and microscopy by routine methods at the Division of Laboratory Medicine, UMMC.

The urine samples were collected in sterile urine containers. Fresh urine samples were stored at a temperature of 4 °C before measurement for no more than 4 h. No preservatives were added upon the urine collection.

2.3. Measurement setup and calibration

The dielectric properties measurement system consisted of: (1) Agilent E8364C personal network analyzer (PNA; 10 MHz–50 GHz) operated with Agilent 85,070 software through Agilent 82357A GPIB interface (Agilent Technologies, Santa Clara, CA); and (2) 50 GHz flexible cable connected to open-ended coaxial slim probe (nickel) with a diameter of 2.2 mm and length of 200 mm designed by Agilent Technologies for liquids and semi-solid materials.

Table 1. Characteristics of the subject groups.

Group	1	2	3
Total (*N*)	15	13	16
Age (years)	60 ± 9.7	59 ± 6.4	60 ± 10
Diabetes duration (years)	12 ± 6.7	13 ± 7.0	13 ± 9.0
pH	5.5 ± 0.7	5.8 ± 0.4	6.0 ± 0.5
Glycosuria (mg/dl)	0	100–500	500–1000
Average glycosuria (mg/dl)	0	307.2 ± 105.9	860.5 ± 110.5
Proteinuria (mg/dl)	0	0	0
Ketonuria (mg/dl)	0	0	0
Hematuria (mg/dl)	0	0	0
Epithelial cell	Nil	Nil	Nil
Casts	Nil	Nil	Nil
Crystal	Nil	Nil	Nil
Bacteria	Nil	Nil	Nil
HbA_{1c} (%)	6.9 ± 1.0	7.6 ± 0.7	8.2 ± 1.3
Fasting blood glucose (mmol/L)	6.5 ± 1.4	7.6 ± 2.6	8.9 ± 2.4

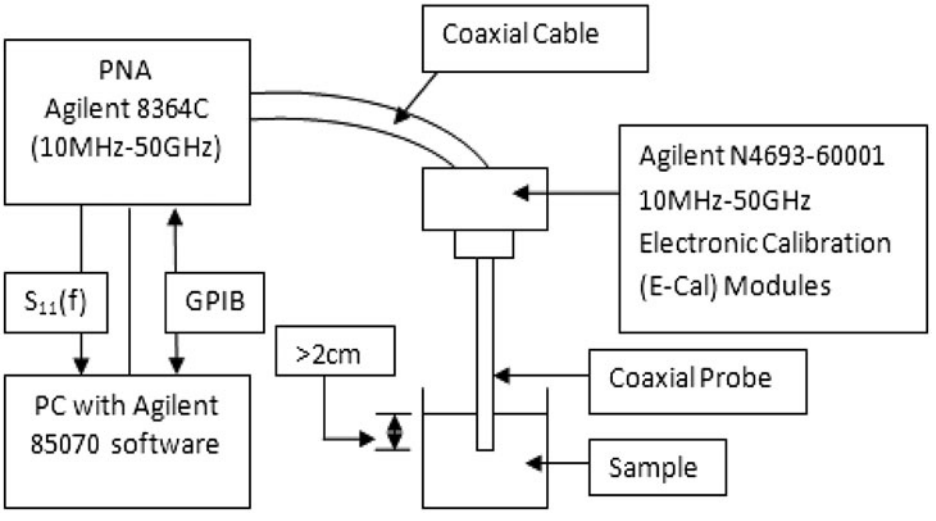

Figure 1. Schematics representation of the measurement setup.

The PNA was calibrated with references for air, short circuit, and deionized water before measurements took place. Electronic-calibration (E-Cal) was used as the standard for refresh calibration. The calibration was repeated using E-Cal after no more than five measurements. The integrity of the system was checked with repeated measurements on standard liquids (e.g. distilled water and methanol) and conducted at different calibration sessions using E-Cal. Uncertainties were reduced by determining the difference between the measured and reference values of standard liquids.[30,31]

Before measurements were conducted, urine samples were heated to room temperature (25 °C) using WNB 7 water bath (Memmert, Duesseldorf, Germany) with a precision of ±0.1 °C and the samples were gently stirred. Movement of the test table and probe was avoided by adjusting the sample to the probe to remove random error of the measurements.[30] The measurements were taken when the probe was immersed >2 cm with perfect contact and no presence of air bubbles under the probe tip as shown in Figure 1. Experiments were repeated by heating the urine samples to 30 and 37 °C, respectively. For each experiment, three measurement readings were recorded for each urine sample throughout the frequency range of 0.2–50 GHz.

2.4. *Data analysis*

Dielectric properties in terms of dielectric constant (ε') and loss factor (ε'') were obtained from the measurements at the microwave frequency range of 0.2–50 GHz. A total of 250 frequency points were measured with an interval of 200 MHz. Statistically significant differences across subject groups were determined using the one-way ANOVA test of SPSS Statistic 21.0 (SPSS, Chicago, IL). Tukey's *post hoc* tests were conducted to multicompare the group mean among the subject groups. Apart from that the Pearson correlation test was also conducted to determine the correlation between glycosuria levels and the dielectric properties. The level selected for statistical significance was set at a probability value of <0.05.

2.5. Curve fitting

Theoretically, the dielectric spectrum of body fluid follows the Debye model.[14] The Debye model describes the wideband frequency dependent of dielectric relaxation response.[32,33] Dielectric spectrum of urine presented in this study was measured from 0.2 to 50 GHz. Single-pole Debye equation, as below, was applied to fit the experimental data over the measured frequency range using the Matlab fitting function:

$$\varepsilon(\omega) = \varepsilon_\infty + \frac{\Delta\varepsilon}{1 + j\omega\tau} - j\frac{\sigma_s}{\varepsilon_0\omega} \tag{1}$$

where ε (ω) is the complex relative permittivity (dielectric properties) and ω is the angular frequency. Infinite frequency permittivity (ε_∞), magnitude of dispersion ($\Delta\varepsilon$), relaxation time (τ), and static conductivity (σ_s) are the parameters of the variables to fit the experimental data. Limits such as $\varepsilon_\infty \geq 1$, $\Delta\varepsilon \geq 0$, $\sigma_s \geq 0$, and $\tau \geq 0$ were set on the fitting parameters so that they would remain within physical ranges.

The fitting analysis was conducted using a genetic algorithm (GA) to compute the function score of complex curve-fitting programs with iterations. GA performs direct search optimized parameters with best fitness from a population. The level of population size was selected at 1500, with crossover fraction set at 0.5. The program calculates the root-mean-square percentage error (RMSPE) between the differences of experimental value and the value obtained from the model for fitting. The data were fitted independently for each subject group at the respective temperature.

3. Results

3.1. Reproducibility and accuracy

Reproducibility of the experiment was obtained by measuring the dielectric properties of distilled water five times at 25, 30, and 37 °C, respectively, with independent calibration session as suggested by Gabriel and Peyman [30], and Zhadobov et al. [31]. According to Agilent Technologies [34], the accuracy of the measurement coaxial slim probe is within ±0.05 or ±5% at temperature of 23 ± 3 °C. To assess the accuracy of the technique, measurements for methanol were conducted. However, it is inappropriate to determine the experimental accuracy at high temperature for methanol that has different dielectric properties spectra with water, especially at the millimeter wave range.[31] Thus, the measurement of methanol was conducted at 25 °C. No statistically significant differences ($p > 0.05$) were obtained between measured data with different calibration sessions at the frequency range of 0.2–50 GHz. The reproducibility of measurements for urine was the same with those obtained from reference liquid.

Table 2 shows the comparison of Debye parameters for measured distilled water with data extracted from Ellison [35]. The measured data were close to the reference data with deviation less than 1.5%.

Table 2. Comparison of Debye parameters of measured distilled water with reference data at 25, 30, and 37 °C.

	Measurement (this study)		Ellison [34]	
Temperature (°C)	$\Delta\varepsilon$	τ (ps)	$\Delta\varepsilon$	τ (ps)
25	73.38	8.20	72.38	8.28
30	71.61	7.30	70.83	7.35
37	69.19	6.22	68.71	6.29

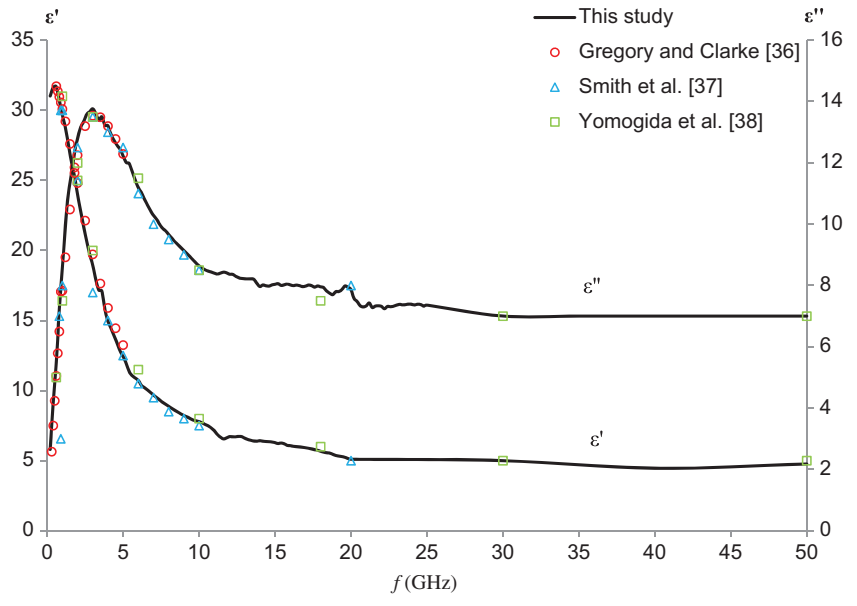

Figure 2. The comparison of measured dielectric properties of methanol with reference data at 25 °C.

Figure 2 shows the comparison of measured dielectric properties of methanol with references data presented in Gregory and Clarke [36], Smith et al. [37], and Yomogida et al. [38]. Overall, the deviations were within 1–5%.

3.2. *Overview*

The results of the dielectric properties were obtained from subjects with non-glycosuria (Group 1), 100–500 mg/dl (Group 2), and 500–1000 mg/dl (Group 3) glycosuria levels at the respective temperatures of 25, 30, and 37 °C. A closer look at the measured dielectric properties of the subject groups is presented in Figures 3 and 4 for wideband analysis of 0.2–50 GHz at 25 °C (same observation trend for 30 and 37 °C).

At low frequency range, less observable change of dielectric properties is reported with urinary glucose concentration. Group 3 showed the increment of dielectric constant at frequency range between 0.2 and 3 GHz, as well as between 25 and 40 GHz (Figure 3). The changes of dielectric properties with glycosuria level were prominent at higher frequencies. Dielectric constant was increased, while loss factor was decreased with glycosuria level at frequencies above 40 and 15 GHz, respectively. Relaxation frequency was shifted toward lower values with glycosuria concentration.

3.3. *Statistical analysis*

Overall, the temperature of 25 °C produced the strongest statistically significant differences ($p < 0.05$) across subject groups compared to 30 and 37 °C. The highest observed F number, $F\ (2,\ 41) = 8.681$; $p < 0.01$ was obtained at frequency 35.2 GHz between measured frequency range of 0.2–50 GHz. The statistically significant difference was defined at critical F value, $F_{crit} \geq 3.226$. Table 3 shows the observed

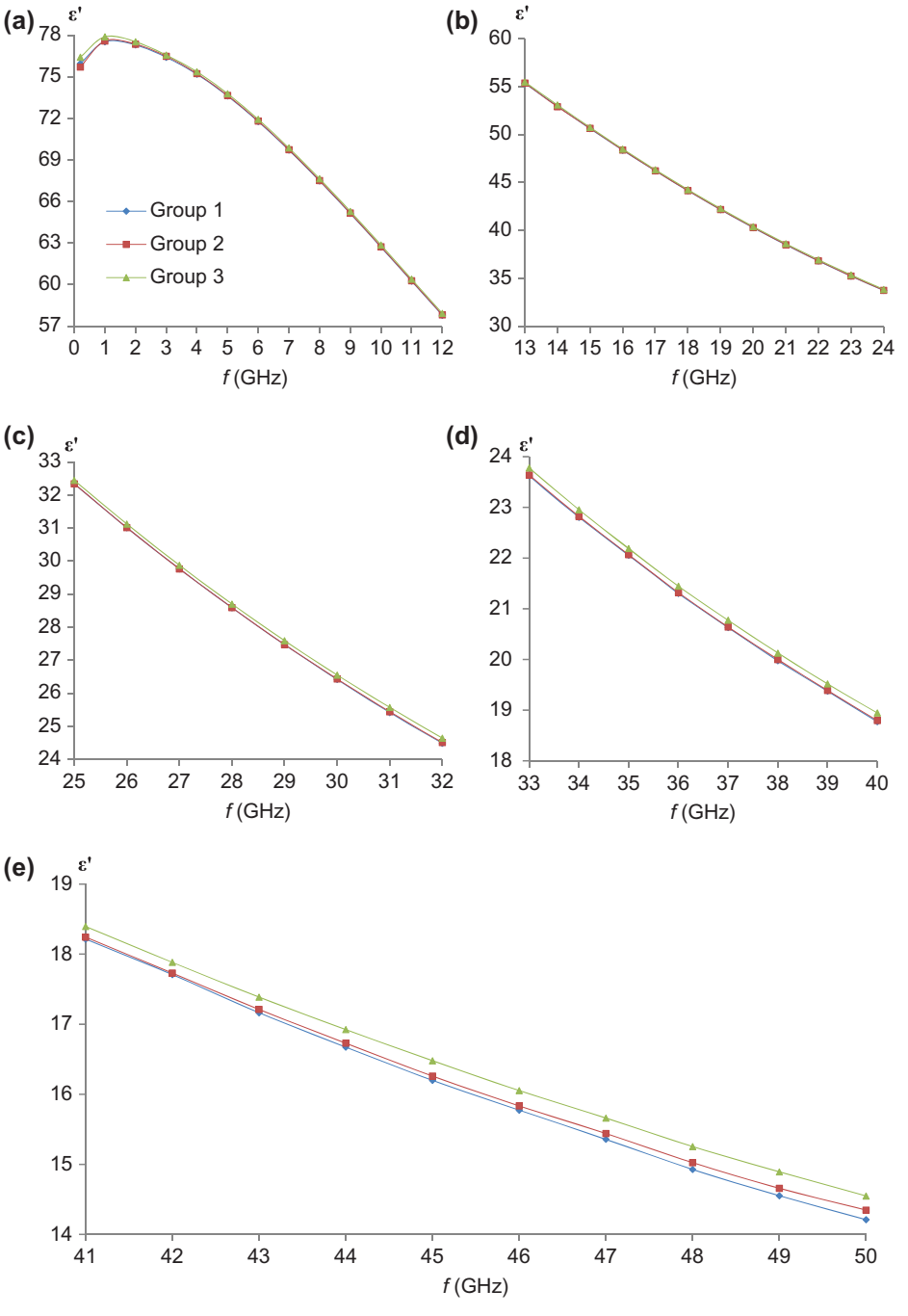

Figure 3. Measured dielectric constant of urine among subject groups at 25 °C for frequency range between (a) 0.2 and 12 GHz, (b) 13 and 24 GHz, (c) 25 and 32 GHz, (d) 33 and 40 GHz, and (e) 41 and 50 GHz. The blue diamond, red square, and green triangle represent subjects of Group 1, 2, and 3, respectively.

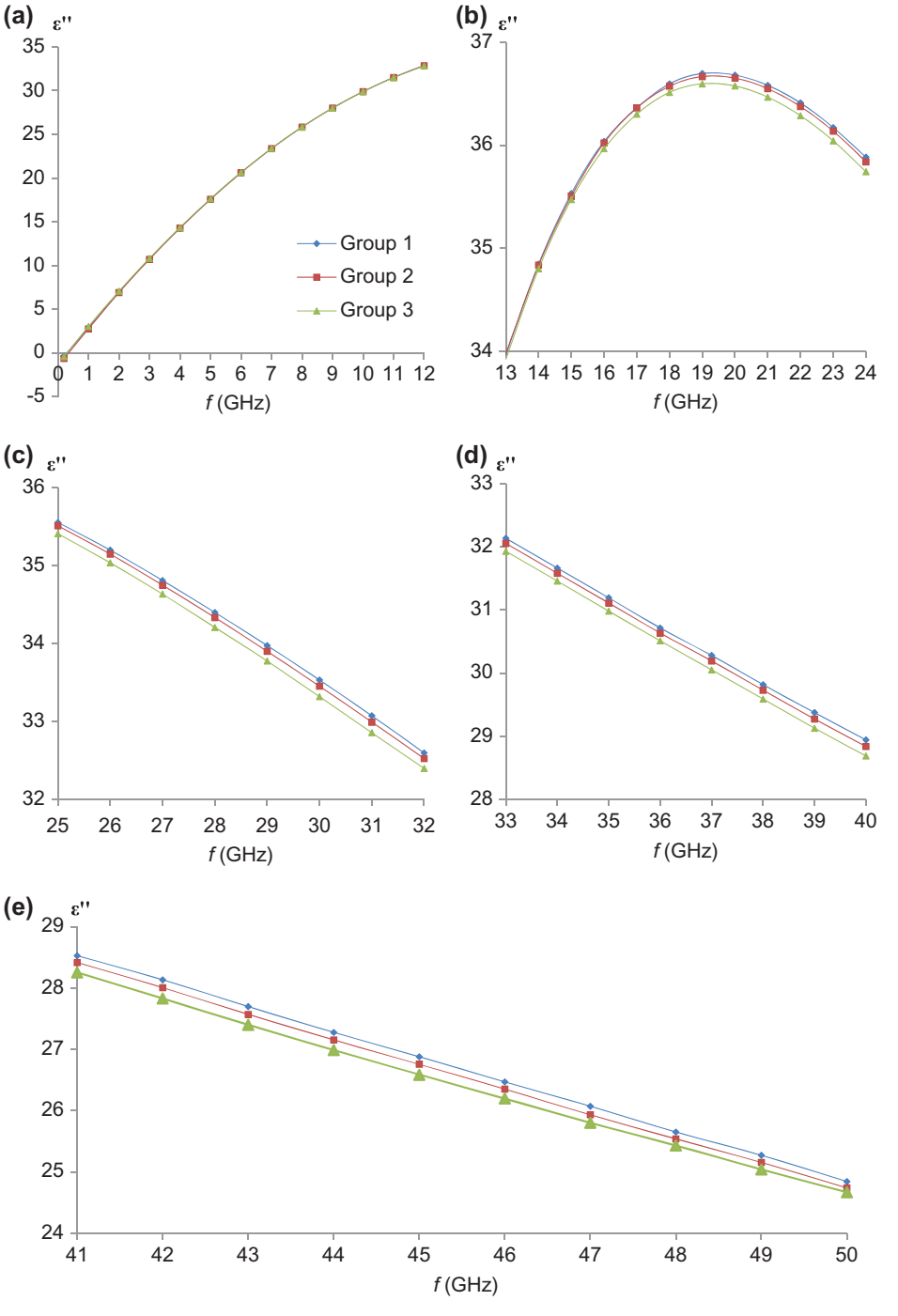

Figure 4. Measured loss factor of urine among subject groups at 25 °C for frequency range between (a) 0.2 and 12 GHz, (b) 13 and 24 GHz, (c) 25 and 32 GHz, (d) 33 and 40 GHz, and (e) 41 and 50 GHz. The blue diamond, red square, and green triangle represent subjects of Group 1, 2, and 3, respectively.

Table 3. F number and P value of dielectric properties across the subject groups at different microwave frequencies.

Frequency (GHz)	25 °C				30 °C				37 °C			
	ε'		ε''		ε'		ε''		ε'		ε''	
	F number	P value	F number	P value	F number	P value	F number	P value	F number	P value	F number	P value
5	3.898	0.026	0.422	0.658	0.539	0.586	1.145	0.326	1.555	0.221	1.397	0.256
10	4.886	0.011	0.056	0.945	2.388	0.102	0.468	0.629	1.045	0.359	1.303	0.280
15	4.762	0.013	1.149	0.325	4.181	0.021	0.359	0.7	1.801	0.175	0.573	0.567
20	6.425	<0.01	3.313	0.044	4.524	0.015	0.021	0.98	2.265	0.114	0.025	0.975
25	7.286	<0.01	2.889	0.064	5.100	0.009	0.273	0.762	2.484	0.093	0.529	0.592
30	7.648	<0.01	2.453	0.096	4.024	0.024	1.530	0.226	2.786	0.071	0.844	0.436
35	7.873	<0.01	1.777	0.179	3.645	0.033	2.233	0.117	3.542	0.036	1.319	0.276
40	8.229	<0.01	1.581	0.215	2.135	0.128	3.350	0.043	3.299	0.045	1.534	0.225
45	5.193	<0.01	1.457	0.242	0.031	0.97	4.609	0.014	0.891	0.416	2.559	0.087
50	2.964	0.06	0.669	0.517	1.282	0.287	4.483	0.016	1.082	0.346	1.696	0.193

Table 4. Statistically significant difference in dielectric properties of group pairwise comparison.

	25 °C		30 °C		37 °C	
Frequency (GHz)	ε'	ε''	ε'	ε''	ε'	ε''
5	1–3					
10	1–3, 2–3					
15	1–3, 2–3		1–3			
20	1–3, 2–3		1–3			
25	1–3, 2–3		1–3			
30	1–3, 2–3		1–3			
35	1–3, 2–3		1–3		1–3	
40	1–3, 2–3			2–3	1–3	
45	1–3, 2–3			2–3		
50				1–3		

F number and *P* value of dielectric properties across subject groups at different microwave frequencies. Dielectric constant had stronger significant differences across subject groups than loss factor.

Table 4 shows the group-pairs that have significant differences in dielectric properties. Group 1 and Group 3 showed the best pair group significant differences of dielectric constant at 25 °C, followed by Group 2 and Group 3. Meanwhile, Group 1 and Group 2 showed no significant pair differences in the measured microwave frequency range.

The Pearson correlation test indicated that dielectric constant showed positive correlation ($r = 0.559$; $p < 0.01$) with glycosuria level. Loss factor had negative correlation ($r = -0.491$; $p = 0.015$) at frequencies >15 GHz.

3.4. Comparison with Debye model

Figure 5 shows dielectric properties of experimental and Debye fit data of non-glycosuria at 25 °C. The experimental data were fitted to the Debye model with deviations of about 1–2%.

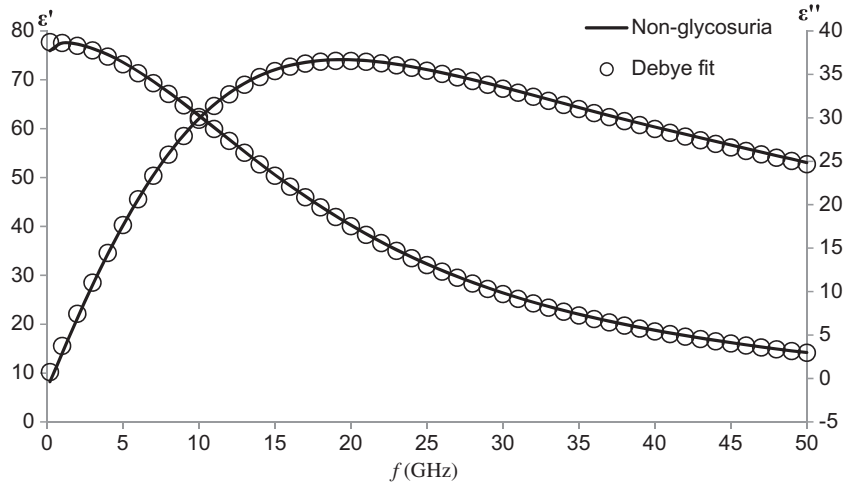

Figure 5. Dielectric properties of experimental and Debye fit data of non-glycosuria at 25 °C.

Table 5. Debye dielectric parameters of different subject groups at 25, 30, and 37 °C.

Group	25 °C					30 °C					37 °C				
	ε_∞	$\Delta\varepsilon$	τ (ps)	σ_s (S/m)	RMSPE (%)	ε_∞	$\Delta\varepsilon$	τ (ps)	σ_s (S/m)	RMSPE (%)	ε_∞	$\Delta\varepsilon$	τ (ps)	σ_s (S/m)	RMSPE (%)
1	4.60	73.13	8.16	0.03	0.25	4.92	71.56	7.23	0.01	0.11	4.68	69.35	6.14	0.01	0.12
2	4.77	74.30	8.69	0.02	0.13	4.85	71.73	7.55	0.01	0.11	4.57	69.46	6.22	0.02	0.18
3	4.87	76.50	9.25	0.09	0.11	4.84	72.21	8.09	0.06	0.17	4.74	69.77	6.65	0	0.22

Table 5 shows Debye dielectric parameters of different subject groups at 25, 30, and 37 °C, which were calculated using Equation (1), and $\Delta\varepsilon$ and τ were increased and decreased with glycosuria level and temperature, respectively.

4. Discussion

Dielectric material allows the absorption and transmission of microwave frequencies that excite molecular rotation. This study documented wider frequency dependency of urinary glucose dielectric measurement up to a range of 50 GHz, which was not performed by the previous studies.[4,5]

To report the dielectric properties of glycosuria, additional reproducible and accurate procedures were conducted at 30 and 37 °C in order to determine strong temperature dependency of dielectric properties in high water content urine. Arai et al. [39] and Chen et al. [40] reported that dielectric properties measured at temperatures higher than room temperature produced lower accuracies due to technical problems in thermal expansion and temperature gradient of coaxial probe. To overcome this issue, the coaxial slim probe was heated to 30 and 37 °C in a water bath before measurements were taken at the respective temperatures. This increased the reproducibility of measurements >90%.

Temperature is an important factor that affects the dielectric properties. In fact, the temperature of biological solutions would decrease from body temperature (37 °C) to room temperature (25 °C) in the process of collection. Dielectric properties of the spectra of urine (Figures 3 and 4) were observed to be close to water since >90% of urine is water content. Dielectric properties of subject groups were observed to have changed across temperatures from 25 to 37 °C. The explanation of this could be due to the increased temperature affecting the stretching of intramolecular hydrogen bonds and Brownian movement in solution that accounts for the changes of dielectric properties.[33,35,41] However, randomizing agitation of molecules at high temperature reduced the significant effect of glucose. This is the reason that the strongest statistically significant differences ($p < 0.05$) were found across subject groups at 25 °C. Our study validated the reliability of dielectric measurement at room temperature.

Zhadobov et al. [31] reported that glucose solution below concentration of 1% had similar dielectric properties with distilled water. In this study, statistical analysis showed that dielectric properties had significant differences ($p < 0.05$) across subject groups with different glycosuria levels. Correlation tests validated the relationship of dielectric properties to change with different glycosuria levels.

According to Figure 3, dielectric constant showed an increasing trend at frequency of 0.2–1 GHz, a finding which is in agreement with the study by Smulders et al. [17]. The presence of salt content in urine (physiological solution) causes a decrease of the dielectric constant compared to pure water at low frequencies.[17] Different trends of dielectric properties of glycosuria were observed when compared to glucose solution.[16,17] Lonappan et al. [4,5] reported that dielectric constant increased with glycosuria level more than 1.5% at frequency of 2.4–3 GHz. Our results are in agreement with Lonappan et al. [4,5]. We found that dielectric constant increased at physiological glycosuria level more than 500 mg/dl (>0.5%) at frequency range of 0.2–3 GHz and 20–40 GHz, respectively. Significant correlation between dielectric properties and glycosuria levels was prominent at high frequencies (as shown in Figures 3 and 4). Maritim et al. [42] found the presence of oxidative stress in biological solution due to free radicals formed by glucose oxidation under normal physiological condition that

increases free charges. Studies reported higher free radicals (8-iso prostaglandin $F_{2\alpha}$) in the urine of diabetes patients with glucose variability compared to normal subjects.[43,44] Increments in dielectric constant and relaxation time are due to the free radicals of glucose bio-oxidation process that increases the density of dipoles.[13]

There is limited data available to compare the dielectric properties of urine. Peyman and Gabriel [14] compared the dielectric properties of porcine urine with Debye model for frequency between 50 and 20 GHz. Thus, we propose to compare our data with Debye model. It is sufficient to model the experimental dielectric data with single-pole Debye model using Equation (1) as a main dispersion was observed at the measured frequency between 0.2 and 50 GHz. Overall, the experimental data were well fitted to the Debye model. The model appears to be sufficient to estimate the dielectric evolution of urine. We found the deviations between measured data and Debye fit data were mostly observed at low frequencies with about 2% (Figure 5). This may be due to the instability of the high frequency dielectric system to measure low frequencies below 1 GHz. However, the variations were within the acceptable range of standard error of ±5%.

According to Table 5, ε_∞ was close to 5 across all the subject groups and temperatures as the major component of urine is water molecules. This indicates that the water content of urine was not affected by glycosuria. Peyman and Gabriel [14,45] reported that the variation of up to 25% for the value of ε_∞ has very little impact on the other fitted parameters. We found that $\Delta\varepsilon$ and τ increased with glycosuria level, but decreased with temperature. The strength of changes across subject groups was observed to decrease with the increase in temperature from 25 to 37 °C. Dielectric properties of glycosuria were more prominent at room temperature (25 °C) rather than at body temperature (37 °C). Static conductivity, σ_s, was negligible across subject groups and temperatures. Conductivity of urine was relatively small in a constant field as human physiological solution is quoted with only about 0.9% of salt content.[17,46] The temperature and concentration of urinary glucose affect the overall dielectric dispersion and relaxation.

At the current stage, the differences in dielectric properties between non-glycosuria and glycosuria are insufficient to apply dielectric spectroscopy as a diabetes diagnostic and monitoring tool. We suggest that a cross-comparison of dielectric techniques may be required for determining the differences. In this study, we provide data on dielectric properties and identify the dielectric behavior of glycosuria that is relatively important for dielectric studies of biological solution since the measurement of dielectric properties is of interest. This study is not relevant for new cases or early detection of diabetes patients who may have higher glycosuria levels. Hence, future studies will require larger patient groups, cross-comparison among different dielectric techniques of interest, and measurements taken with a wider range of microwave frequency measurement.

5. Conclusions

This study investigated glycosuria dielectric behavior at microwave frequency between 0.2 and 50 GHz. The strongest statistically significant difference in dielectric properties across different glycosuria groups was reported at room temperature (25 °C). Dielectric constant increased with glycosuria level more than 500 mg/dl (0.5%) at low frequencies. Dielectric constant correlated positively with glycosuria level at frequency above 40 GHz while loss factor correlated negatively with glycosuria level at frequency above 15 GHz. The experimental data closely matched the Debye model.

Funding

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