

Salivary Dielectric Properties in Oral Cancer (OSCC) Through Time Domain Reflectometry at Microwave Region: The Future Alternative for Diagnosis and Treatment

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Abstract

Oral cancer is one of the 11 most frequently occurring cancers worldwide and has a higher proportion of deaths per number of cases than breast cancer or cervical cancer because of late detection. In the present study we found out the difference in the dielectric properties of saliva between controls, controls with tobacco habit but having no lesion and patients with squamous cell carcinoma. The dielectric parameters have correlated with histopathological grades and clinical stages of oral squamous cell carcinoma. Methods: Dielectric relaxation studies have been carried out for saliva of 88 (48 oral cancer and 40 healthy) patients having tobacco habit but no squamous cell carcinoma (SCC) and those having tobacco habit with SCC using picoseconds time domain reflectometry over the frequency range of 10 MHz to 20 GHz at room temperature.

Index terms— conductivity, dielectric properties, oral squamous cell carcinoma, permittivity, saliva, relaxation time, time domain reflectometry.

1 I. Introduction

Oral cancer is one of the 11 most frequently occurring cancers worldwide and has a higher proportion of deaths per number of cases than breast cancer or cervical cancer because of late detection. In India, oral cancer is highly prevalent, comprising 35-40% of all malignancies, due to habit of tobacco chewing. Oral cancer refers to all malignancies arising from the lips, the oral cavity, and pharynx (1), and it affects more than 481,000 new patients worldwide. The 90% of oral cancers are oral squamous cell carcinoma. This cancer, when found early, has an 80 to 90% survival rate. Despite this fact and the great treatment advances, the World Health Organization has reported oral cancer as having one of the highest mortality ratios amongst other malignancies with a death rate at five years from diagnosis at 45% (2,3). This high morbidity rate can definitely be attributed to the late diagnosis of the disease (4). At the moment, a lack in national screening programs together with a lack of definitive and satisfactory biological markers (5)(6)(7) for early oral cancer detection has resulted in late stage diagnosis of oral cancer (8). The routine clinical practice to detect oral cancer is initially made by visual inspection, followed by biopsy of any suspicious lesions found. However, oral cancer can go unnoticed and therefore visual inspection is incapable of effectively screening or detecting cancerous changes in the oral cavity. Such delay in diagnosis may adversely affect patient prognosis. That is why most oral cancer patients present with advanced disease, have secondary tumours and suffer from other co-morbidities. On the other hand, biopsy is an invasive method and this approach increases the emotional trauma to the patient waiting for a diagnosis. New methods for reliable, lowcost, noninvasive, and real-time screening or detection of oral cancer are thus warranted. In recent times, 'light biopsy' with various optical methods, such as Fluorescence, (9,10) Raman (11) and Elastic Scattering (12) spectroscopy, have been investigated to establish techniques for the screening or detection of oral cancer. However, none of these techniques has been proved to be totally reliable in screening or detecting oral cancer

and limitations still exist. For example, Fluorescence spectroscopy can be significantly hindered by the presence of tissue scattering and absorption and fail to account for confounding factors such as inflammatory changes that may produce fluorescence emission spectra, resulting in false-positive results. Raman spectroscopy shares the major limitation of other point-detection methods in that only a very small tissue volume is interrogated and it can be very sensitive to mucosal movement. Also, Raman spectroscopy technique is expensive, complex and difficult to adapt for in vivo use due to superimposed optical fiber and auto-fluorescence complicating the spectra. Elastic Scattering spectroscopy is insensitive and imaging is very difficult. Source and detector fibers need to be sufficiently separated for the diffusion approximation to be valid, i.e., >0.5 cm, but at this distance would be insensitive to the size and shape of scattering centers. The intention of this study was therefore to investigate a new approach, namely bioimpedance, for reliable, lowcost, noninvasive, and real-time screening or detection of oral cancer. Bioimpedance is the measurement of the bioimpedance signal, which is obtained by injecting lowlevel sinusoidal current in the tissue and measuring the voltage drop generated by the tissue impedance. Bioimpedance signal gives information about electrochemical processes in the tissue and can hence be used for characterizing the tissue or for monitoring physiological changes. The electrical properties of tissue vary with the frequency of the applied electric field as seen from ϵ' , ϵ'' and $\tan \delta$ -dispersion (13). The ϵ' dispersion occurs at low frequencies (10 Hz to 10 kHz) and is mainly affected by the ionic environment that surrounds the cells. The ϵ'' dispersion (10 kHz to 10MHz) is a structure relaxation. At higher frequencies, the $\tan \delta$ -dispersion is found related to water molecules. The ϵ'' and $\tan \delta$ -dispersion regions are more interesting in medical applications, since most changes between pathological and normal tissue occur in this range (14).

The present study was carried out in the microwave frequency range from 10 MHz-20 GHz. The electrical properties of saliva were measured at ϵ'' and $\tan \delta$ -dispersion regions.

An increasing number of systemic diseases and conditions, amongst them oral cancer, have been shown to be reflected diagnostically in saliva. Moreover, using saliva as a diagnostic fluid meets the demands for inexpensive, noninvasive, and accessible diagnostic methodology. Whole saliva is the product of the secretions of the 3 major salivary glands (parotid, submandibular, sublingual) and the numerous minor salivary glands mixed with crevicular fluid, bronchial and nasal secretions, blood constituents from wounds or bleeding gum, bacteria, viruses, fungi, exfoliated epithelial cells and food debris (15,16). Saliva has been long proposed and used as a diagnostic medium (17)(18)(19) because it is easily accessible and its collection is non-invasive, not time-consuming, inexpensive, requires minimal training and can be used for the mass screening of large population samples (19,20). Whole saliva can be collected with or without stimulation. Stimulation can be performed with masticatory movements or by gustatory stimulation (citric acid) (21).

Stimulated saliva however, it can be collected in larger quantities, is a little bit altered in content (22). Unstimulated saliva can be collected by merely spitting in a test tube or by leaving saliva drool from the lower lip (23) and it is more often used for the diagnosis or follow up of systemic diseases. Saliva has long been used for the monitoring of drug abuse (drugs and addictive substances) such as cocaine, heroin, amphetamine, barbiturates etc. (24). Moreover salivary testing has largely performed for the diagnosis of HIV infection (25,26). Analysis of salivary parameters such as salivary flow rate, pH, buffer capacity, lactobacillus, and yeast content, presence of IgG, IgM and anti-La auto antibodies and raised protein levels such as that of lactoferrin and cystatin C as has been proposed for the diagnosis of Sjogren's syndrome (27,28). Concerning cancer diagnostics and follow up altered levels of certain mRNA molecules (29) have been detected in saliva in oral cancer patients and of certain proteins in several cancers (30,31).

In the mouth, the surface layer of cells is replaced about every 2-4 hours; and the turnover time of the oral epithelium is about 4.5 days. If a person is developing an oral cancer, cancer cells can be shed into saliva at very early stage of the cancer; and the number of cancer cells in saliva can be a measure of the cancer stage. Mauk et al., reported that more than 1000 cells/ml and 9000 cells/ml of OSCC cells were separated from tumor stage 1 and 4 patient saliva, respectively (32). This makes saliva an ideal sample for early screening and detection of oral cancers. The impedance-based method has the potential to be a sensitive non-invasive screening method for detecting early stage cancer by detecting cancer cells in saliva, and an approach to obtain quantitative information about cancer stage or to monitor the progress of cancer treatment.

According to the polar and non-polar types of dielectric materials, salivary molecular system can be said to be a polar dielectric system. Saliva acts as a suspension of protein molecules are frequency dependent. Thus, protein relaxation is interpreted in terms of molecular dipole moment and/or in terms of surface conductance. In order to discuss the dielectric properties of biological cell suspensions and thus in turn those of tissue at ultra-high frequencies, we need to have knowledge of dielectric properties of water (which is present upto 99% in saliva). Dispersion of water is of polar origin. Thus, the objective of the present study is undertaken to find out the difference in the dielectric properties (parameters) of saliva between controls, controls with tobacco habit but having no lesion and patients with squamous cell carcinoma. It is also undertaken to throw light on the correlation between these dielectric parameters and histopathological grades and clinical stages of oral squamous cell carcinoma and to prepare a database of the bioimpedance measurements in terms of microwave absorption for the use in local hyperthermia treatment and imaging of cancers of soft tissues (33,34).

2 II. Materials and Method

Of the patients visiting the outpatient department of Government Dental College and Hospital, Aurangabad, subjects with oral lesions suspicious of malignancy were selected as a study group. Relevant history of each patient was recorded thoroughly. Only those patients who were subsequently diagnosed histopathologically, to have oral squamous cell carcinoma (and verrucous carcinoma) and who had not received any therapy prior to study were included in the oral squamous cell carcinoma (OSCC) group, and the remaining was excluded. The control group mucosal specimens were harvested after informed consent from individuals, who were admitted for incidental elective surgery. These biopsies were all harvested from clinically normal mucosal sites. The mucosal specimens from the control group were taken from an age and sex matched group with unremarkable oral health and no obvious systemic disease.

Accordingly, the subjects for the study were grouped as follows:

Group I (Control): This control group was divided into two subgroups i.e. I (a) and I(b). First group considered of controls (C) i.e. 20 healthy age and sex matched subjects free from any other systemic disease and tobacco related habits. I(b) subgroup consisted of controls (CT) i.e. 20 age, sex and tobacco habit matched subjects (with SCC group) but having no lesion.

Group II (OSCC): 48 (age, sex and habit matched) patients having oral squamous cell carcinoma and verrucous carcinoma. These 48 patients were diagnosed after taking biopsy and were clinically staged as well as histopathological graded. Clinical staging of the patients with OSCC was done using the TNM classification as given by the American Joint Committee for cancer staging and End result reporting (AJCCS) (35). The histopathological grading of OSCC was done according to malignancy grading system proposed by Anneroth et al (36).

A total number of 48 cases of OSCC and verrucous carcinoma cases were screened and all consented to biopsy. Punch biopsies were taken from the representative sites after achieving anesthesia by 2% lignocaine with 1: 80,000 adrenaline.

3 a) Procedure for collection of resting (unstimulated) whole (mixed) saliva

Patient was asked to remain empty stomach or NBM in the morning and also asked to thoroughly brush his teeth without paste and clean his/her mouth. Saliva was allowed to accumulate in the patient's mouth for 5 min and then they were to spit in 30 ml borosil glass air sealed bottles. Then the saliva was poured in centrifuging tubes and immediately centrifuged by using Remi-DGL-721 centrifuging machine at 1000 rpm for 10 minutes.

4 b) Experimental Procedure for Analysis of Dielectric

Parameters Dielectric property measurements were performed immediately after the collecting the saliva. The elapsed time from excision to measurement was between 15-20 minutes. The Time domain reflectometry technique in reflection mode as developed at Dr. Babasaheb Ambedkar Marathwada University has been used for the measurement of dielectric parameters. All details are already described elsewhere (37,38). The sample cell of digitizing oscilloscope was cleaned with acetone and dried with tissue paper rolls. Then empty cell reading of air i.e. $R_a(t)$ was taken for 30 seconds by keeping the temperature bath on the cell and maintaining the temperature at 35°C to 37°C in order to simulate oral temperature conditions. Then, the filled cell reading i.e. $R_x(t)$ was taken for 30 seconds. For each Saliva sample two readings were taken. Frequency range used during the measurements was 10 MHz to 20 GHz. Procedure was repeated for all saliva samples of control and OSCC groups and the waveform data stored in the oscilloscope memory was transferred to 1.44 MB floppy. The data was analyzed by Fourier transformation method and values of dielectric parameters i.e. dielectric permittivity (ϵ'), relaxation time (τ) and conductivity (σ) were obtained and compared with the histopathological grades and clinical stages of the malignancy.

5 III. Results and Discussions

Oral squamous cell carcinoma (OSCC) comprises 90-95% of all oral malignancies. The five-year survival rate is 80% when diagnosed in early stages, 40% when involvement of regional lymphnodes is present, and less than 20% in case of metastasis. Thus early detection of OSCC not only increases the survival rate but also improves the quality of life by reducing the need for aggressive and disfiguring treatments. Unfortunately, early detection of oral cancerous lesions has proved difficult, because as many as 50% of patients have regional or distant metastasis at the time of diagnosis. The rather high proportion of late diagnosis of OSCC is a clear cause of concern, especially when OSCCs arise over the epithelial surface giving rise to clearly visible changes on the surface.

Histological and biochemical changes always precede visible signs. The cellular changes in malignancy are also reflected in their electrical properties like permittivity, conductivity and relaxation time. The dielectric properties of biological samples are determined by several important dispersion phenomena whose contributions are normally confined to specific bands in the electromagnetic (EM) spectrum (13,14,34,(39)(40)(41). The behavior of biological tissues, cell suspensions and saliva at radio frequencies and microwave frequencies is largely determined by the electro-chemical behavior of cells and its cellular structure as well as the intra-cellular fluid

in which the cells are suspended and the internal cellular elements, including the nucleus. The cell membrane exhibits capacitance and supports a potential difference across it such that at low frequencies current flows around the cells but at higher frequencies current flow may penetrate the cells.

Moderate variations in the permittivity and conductivity values are reflected by various types of normal tissue, saliva etc. In contrast to these rather homogenous observations, malignant tissues demonstrate substantially increased permittivity and conductivity. These differences are probably attributable to:

1) The physico-chemical bulk properties i.e. properties of body fluids like saliva and tissues which include temperature, electrolyte, protein concentration and pH. 2) Microstructural properties i.e. the geometry of microscopic components.

3) The amount of extracellular fluid. 4) Membrane properties and packing density. 5) Orientation of malignant cells. 6) Changes in the water content-tumour tissues have significantly higher water content than homologous normal tissues. Associated with these differences, one expects that at UHF (ultra high frequency) and microwave frequencies, neo plastic tissues will exhibit somewhat higher permittivity and conductivity values than homologous normal tissues.

7) The rate of necrosis. At audio and radio frequencies substantial differences are expected between normal and neoplastic tissues, in particular those associated with necrosis in tumour nodules. Schwan et al has described basically three frequency bands within which the permittivity of many biological tissues showed a characteristic decrease with the increase in frequency respectively (34). The ϵ'' dispersion was observed at high frequencies and was mainly due to rotation of permanent dipoles of water molecules. The conductivity also exhibited frequency dependence. The ϵ'' -dispersion was observed at medium frequencies. The present study was carried out in the microwave frequency range from 10MHz-20GHz. In case of solutions or suspensions the ϵ'' -dispersion was due to rotational relaxation of permanent dipoles. But in case of biological tissues, cell suspensions and saliva etc. the ϵ'' -dispersion was mainly caused by the Maxwell-Wagner type of relaxation which occurred in any microscopically inhomogeneous medium due to interfacial polarization and dipole relaxation (42). The ϵ'' -dispersion reflects the relaxation of nonpermanent dipoles which are induced by the displacement of small ions along the charged surface of large molecules or cell membranes. In this study the electrical properties of saliva were measured at ϵ'' and ϵ'' -dispersion regions.

Permittivity depends on polarization which in turn depends on effective dipole moments per unit volume. If polarization increases, then the effective dipole moments per unit volume also increases. Water molecules have high dipole moments. Increased permittivity values thus indicate that the status of water molecules in a given system is changed. Since 99% of saliva is water and the other 1% is composed of organic and inorganic molecules, so the permittivity of the group C, CT and OSCC did not differ much.

Conductivity indicates the presence of mobile ions in the biological system. Thus, if ions increase, then electrical conductivity also increases. If conductivity increases, then microwave absorption is more. Schepps JL, et al showed that conductivity was a more reliable parameter to predict microwave absorption as compared to permittivity (43).

In biological systems electrical currents are carried by both ionic conduction and electron semiconduction. Therefore, the electrical properties of biological systems are dependent on all the physical mechanisms which control the mobility and availability of the relevant ions such as sodium, chloride, potassium, magnesium and calcium (44)(45)(46)(47).

Relaxation time depends on the surrounding environment of water molecules. If the relaxation time increases then it means that the surrounding macromolecules are influencing water molecules in such a way that water molecules rotate slower. From the nature of strong forces between the bound water and its neighboring macromolecules it is expected that the relaxation time should be longer than that of free water (48,49).

In the present study the values of salivary permittivity, relaxation time and conductivity compared among the control group (C), control subjects having tobacco habit but no lesion (CT) group and patients of squamous cell carcinoma (SCC) group. The evaluated values of permittivity, relaxation time and conductivity are represented in Figure 1(a), 1(b) and 1(c), respectively.

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Comparison of the values of permittivity, conductivity and relaxation time according to the group showed in Table 1. It is observed that the mean values of conductivity and relaxation time were higher in the OSCC group compared to the control group, while the mean permittivity was more in the control group compared to the OSCC group. The statistical evaluation of the comparisons was done using 't' test. This test was applied to two groups at a time. From the statistical analysis it is observed that the difference between the values of C and SCC groups for conductivity is statistically highly significant ($p < 0.01$) and that for relaxation time is statistically significant ($p < 0.05$). In case of conductivity parameters the difference of values between CT and SCC group is also found to be statistically highly significant ($p < 0.01$), but the difference of values between C and CT groups is not significant ($p > 0.05$). In case of relaxation time the difference of values between C and CT groups is found to be statistically highly significant ($p < 0.01$), but the difference of values between CT and SCC groups is not significant ($p > 0.05$). In case of permittivity parameter the difference of values between C and CT, C and SCC and CT and SCC groups are not found to be statistically significant ($p > 0.05$).

The values of conductivity, relaxation time and permittivity within the SCC group were correlated with the histopathological grading and clinical staging. These values were also compared within different grades and stages. In the sample of 48 patients having squamous cell carcinoma only two grades were found (grade I and grade II). In which 9 cases belonged to grade I and 30 cases belonged to grade II.

The differences between the mean values of conductivity, relaxation time and permittivity of different histopathological grades were calculated and statistical evaluation was done using t'testare recorded in Table 2. It is observed that the mean permittivity and conductivity values of OSCC increased from grade I to grade II, but the mean relaxation time decreased from grade I to grade II. The difference between the mean conductivity values of grade I and grade II diseases is found to be statistically highly significant ($p < 0.01$) and that between the mean permittivity is found to be statistically significant ($p < 0.05$). The difference between the mean relaxation time values of grade I and grade II diseases is found to be statistically highly significant ($p < 0.001$).

In the sample size of 48 squamous cell carcinoma patients, 5 cases belonged to stage I, 6 cases belonged to stage II, 29 cases belonged to stage III and 8 cases belonged to stage IV. Comparison of the values of permittivity, conductivity and relaxation time according to the clinical stages in OSCC group showed in Table 3. The statistical evaluation was done using unpaired 't'test. From this table it is found that the mean value of permittivity of stage I is lowest than stage II, III and IV. The value of stage II is higher than stage IV but lower than stage III. The mean values of conductivity of stage II, III and IV are greater than those of stage I. The value of stage III is lower than that of stage II and greater than stage IV. The mean value of relaxation time of stage IV was higher than stage II, but lower than stage III. While the mean value of relaxation time of stage I is greatest than Stage II, III and IV.

In case of mean conductivity values the difference between stage I and stage II disease is also highly significant ($p < 0.01$). The differences between stage I and stage II is also significant ($p < 0.01$), but that between stage I and stage IV is not significant ($p > 0.05$). In case of mean relaxation time difference between the values of stage I and stage II, stage I and stage III and stage I and stage IV diseases are all statistically highly significant ($p < 0.001$). In case of mean permittivity, the differences between values of stage I and stage II, stage I and stage III and stage I and stage IV diseases are all statistically highly significant ($p < 0.001$). Thus, the mean conductivity and permittivity values show an increasing trend with increase in clinical stages whereas the mean relaxation time values show a decreasing trend for the same. The results were analyzed as follows: [Figure 1(a), 1(b) and 1(c)].

In the present study the mean values of conductivity(S/m) were significantly increased in oral squamous cell carcinoma (0.2527 ± 0.0850) as compared to the C (0.1939 ± 0.0436) and CT (0.1684 ± 0.0581). The difference between the mean conductivity values of C and CT groups was not found to be statistically significant. The mean values permittivity showed to statistically significant differences between C (74.54 ± 3.1133) and CT (77.099 ± 5.9407), CT and OSCC (74.81 ± 16.1001) and C and OSCC groups. These findings were similar to those of the earlier workers, who reported that the values of permittivity and conductivity were more in cancerous tissues as compared to normal tissues (43,(50) ??51) ??52).

The mean relaxation time values were significantly increased in OSCC group (12.9079 ± 4.6749) as compared to the control (C) group (11.2980 ± 1.0090). The mean relaxation time values were significantly increased in the control (CT) group as compared to control (C) group i.e. 12.3870 ± 0.6706 in CT group vs 11.2980 ± 1.0090 in C group. The difference between the mean relaxation time values of CT and OSCC groups was not found to be statistically significant.

The values of the dielectric parameters, in the present study were correlated with the different clinical stages and histopathological grades of OSCC. The mean values conductivity and permittivity increased and relaxation time values decreased from grade I to grade II malignancy respectively and the differences between the two were statistically significant. Thus the values of dielectric parameters correlated well with the histopathological grades of OSCC and the difference was found to be statistically significant. The available literature did not reveal any study in which correlation between dielectric parameters and histopathological grades was done. Hence comparison with reported literature was not possible. The correlation of histopathological grades of OSCC with the dielectric parameters, however, cannot be ignored, because histopathology depicts the actual cellular picture of the disease process.

The mean conductivity and permittivity values increased and relaxation time values decreased from stage I to stage II, stage I to stage III and stage I to stage IV. The differences between the mean values of the above stages were statistically significant except that of stage I and stage IV conductivity values. The differences between the mean values of all three dielectric parameters for stage II and III, stage III and IV and stages II and IV however, were not statistically significant. Diagnostic accuracy of clinical staging depends on the use of advanced diagnostic aids.

In the present study higher values of permittivity and conductivity were observed in the OSCC group as compared to those of the control group. As stated previously, increase in conductivity causes an increase in microwave absorption (43, ??2). The microwave absorption of cancer cells is greater than that of normal cells. Thus, from the present study it could be inferred that the differences in microwave absorption of normal and cancer saliva can help us to develop techniques for diagnosis oral cancer.

7 IV. Conclusions

Salivary Dielectric Properties in Oral Cancer (OSCC) Through Time Domain Reflectometry at Microwave Region have been reported. The present study shows that the salivary conductivity of squamous cell carcinoma patients is more than that of the normal subjects. Hence, the microwave absorption of squamous cell carcinoma patients is more. So microwaves can be used for diagnosis (imaging and detection) as well as for therapy (hyperthermia treatment) of oral squamous cell carcinoma. Also salivary dielectric parameters can act as useful noninvasive diagnostic tools for cancer detection and determination of histopathological grades of malignancy. Further, salivary relaxation time can be useful as an indicator of the possible occurrence of oral squamous cell carcinoma in subjects having tobacco habit. The present study also shows that the clinical stages and dielectric values have to be carried out to determine the dose of microwave radiation according to clinical stages of malignancy.



Figure 1: F

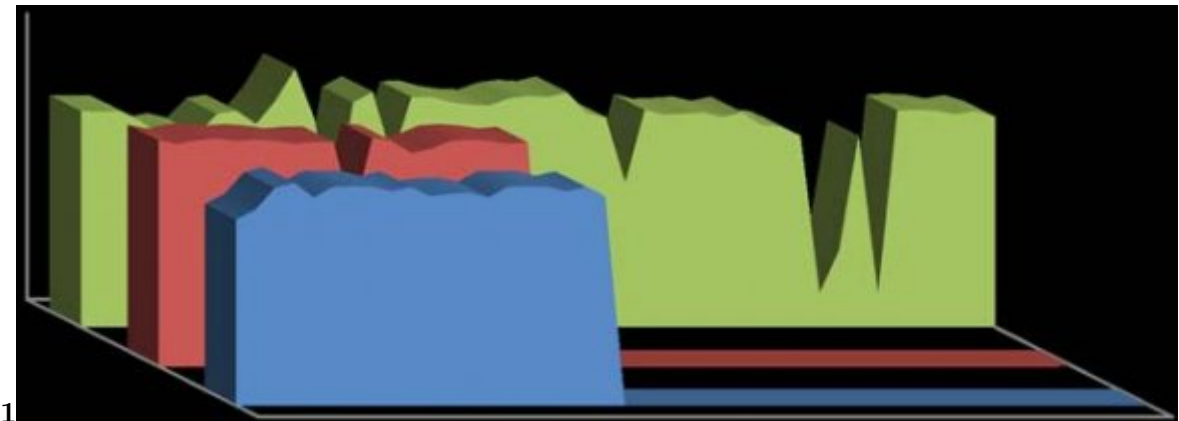


Figure 2: Figure 1

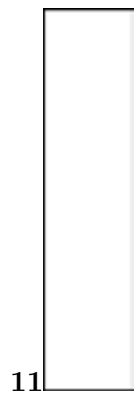


Figure 3: Figure 1 Figure 1

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Figure 4: Table 1 :

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	Permittivity		Conductivity (S/m)		Relaxation time (ps)	
	Grade I	Grade II	Grade I	Grade II	Grade I	Grade II
Min.	11.70	11.87	0.1175	0.1172	10.22	6.86
Max.	82.22	82.12	0.5064	0.4881	38.74	21.32
N	9	39	9	39	9	39
Mean	67.62	70.71	0.2345	0.2569	16.50	12.07
S.D.	± 25.2678	± 13.5778	± 0.1152	± 0.0777	± 8.000	± 2.5806

Figure 5: Table 2 :

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Min.

Permittivity Stage I Stage II Stage III 11.87 69.89 50.40

Stage IV
Conductivity (S/
26.93

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Max. N Mean 47.76 75.70 5 S.D. ± 32.90 ± 2.345 75.57 6 73.14 90.36 82.22 0.2909 0.3654
29 8 6 0.2333 0.26
73.35 70.18 ± 0.055 7 ± 0.08 0
 ± 9.69 18.27
3

[Note: © 2016 Global Journals Inc. (US)]

Figure 6: Table 3 :

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