An Energy-Resolved Optical Non-invasive Device Detects Essential Electrolyte Balance in Humans at Point-of-Care

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Abstract
Regular monitoring of electrolyte balance is essential for patients suffering from chronic kidney disease (CKD), particularly those undergoing dialysis. In the context of the recent COVID-19 pandemic, more severe forms of infection are observed in elderly individuals and patients having co-morbidities like CKD. The repeated blood tests for the monitoring of electrolyte balance predispose them not only to COVID-19 but also to hospital-acquired infections (HAI). Therefore, a non-invasive method for easy detection of essential electrolyte (K+ and Na+) levels is urgently needed. In this study, we developed an optical emission spectroscopy-based non-invasive device for simultaneous monitoring of salivary Na+ and K+ levels in a fast and reliable way. The device consisted of a closed spark chamber, micro-spectrometer, high voltage spark generator, electronic circuits, optical fiber, and an indigenously developed software based on the LabVIEW platform. The optical emission originating from the biological sample (i.e., saliva) due to recombination of ions energized by impingement of electrons returning from high voltage spark provides necessary information about the concentration of electrolytes. A small-scale clinical trial on 30 healthy human subjects shows the potential of the indigenously developed device in determining salivary Na+ and K+ concentration. The low-cost, portable, point-of-care device requires only 2 mL of sample, and can simultaneously measure 1.0–190.0 mM Na+, and 1.0–270.9 mM K+. To our understanding, the present work will find its relevance in combating COVID-19 morbidities, along with regular CKD patient-care.

Keywords Non-invasive essential electrolyte measurement · Spectroscopic instrument · CKD management

Introduction
The SARS-CoV-2 virus which causes the COVID-19 infection has immensely impacted the world and caused a global pandemic with over 91 million infections and over 1.9 million fatalities till January 2021 (JHU 2021). Patients, especially those with kidney transplants, cardiovascular diseases, and diabetes are at high risk of COVID-19 infection. Moreover, patients undergoing hemodialysis have to visit medical centers frequently, thereby loses their ability to self-isolate and become prone to nosocomial infections (Ajaimy and Melamed 2020). While looking at the pathophysiology of COVID-19, many researchers are focusing attention on a specific protein, namely, Angiotensin-Converting Enzyme 2 (ACE 2) that aids the virus to infect the human cells. The spike protein on the surface of the SARS CoV-2 virus attaches to ACE 2 for their entry to human cells and replicates to spread infection. This becomes lethal for patients having chronic kidney diseases (CKD). ACE 2-inhibition
by the virus also leads to vasoconstriction increasing blood pressure and causes hypernatremia leading to water retention in the body resulting in electrolyte imbalance in humans (Behl et al. (2020); Mizuiri and Ohashi 2015; Soler 2013). The relative expression of ACE and ACE 2 synergistically controls the electrolyte balance (Wakahara 2007; Pinheiro 2019; Rieder 1999). In CKD patients, disruption in the balance between intra-renal ACE and ACE 2 expression gives rise to high levels of angiotensin 2, contributing to the progression of renal damage (Hamming 2007). Thus, necessary diagnostic information for the treatment of several diseases like CKD, acute cardiac arrhythmias hypertension, etc. is determined based on the analysis of the vital electrolyte levels, especially sodium (Na+) and potassium (K+) in the human body (Garcia 1992). In this context, Hyponatremia, another very common electrolyte disorder, especially in the elderly, is associated with significant morbidity, mortality, and disability in the context of the COVID-19 pandemic. Thus, easy access to the essential electrolyte monitoring (preferably at home) in a non-painful way is essential to control the comorbidity of CKD and elderly subjects in the context of the COVID-19 pandemic (Fraser and Blakeman 2016).

Despite being the most familiar analytes, very few techniques are available for the measurement of Na+ and K+ in clinical chemistry laboratories. Ion-selective electrodes (ISEs), flame photometry, and atomic absorption spectrometry (AAS) are the conventional technologies for quantifying the essential ion levels in plasma or other biological fluids (Giavarina 2019; Rose 2014; Lee 2019; Delanghe 2019). Although ISEs, AAS, and flame photometry are used extensively, some limitations exist. High cost, immobility, utilization of various chemical reagents, use of dedicated electrodes for each electrolyte, the requirement of an expert operator, are a few to mention (Durst 1978; Delves 1987; Diwakar and Kulkarni 2012). These drawbacks make it difficult to use the aforementioned methodologies in point-of-care diagnostics, which is vital for the current healthcare situation. Depending on the type of instrument, the sample is selected from urine, saliva, and whole blood. Extraction of blood by pricking needles is not only painful but also has the risk of excessive bleeding, infection, pain, loss of consciousness, and multiple hospital visits which may cause Hospital Acquired Infections (HAI) (Zungu et al. 2008). Thus, low-cost non-invasive techniques for the detection of electrolyte levels from other biological fluids, are preferred. A recent study from our group used a spark emission spectroscopy-based method for the detection of electrolyte levels from the human blood serum (Halder 2019). However, no detailed study using other body fluids was performed. Moreover, the method required a great volume of sample for detection which makes it a bit difficult for clinical diagnosis at point-of-care. In this study, we have successfully lowered the minimum detectable Na+ level to 1 mM from 100 mM. Installation cost and cost per sample test have been decreased to a substantial amount. Thus, the primary objective of the present work is to develop a non-invasive, portable device that would be able to detect the concentration of electrolyte contents in humans at point-of-care using the wash of oral cavity without a rigorous sample preparation procedure.

Materials and Methods

Instrumental Setup

Figure 1a schematically describes the detailed arrangement of the device, which includes a closed spark chamber (CSC), vaporizer, micro-spectrometer, high voltage control electronics, optical fibers, and an indigenously developed software. Figure 1b, c show the digital photographs of the prototype device. The CSC, a metal tube of 1.9 cm diameter, comprises two opposing copper electrodes (standard spark plug, Model- CPR8EA-9, NGK Spark Plug India Pvt. Ltd., India) having a 0.1 cm distance in between (Fig. 1a) for spark discharge (Staack 2008; Singh 2014; Hnatiuc et al. 2011; Sher et al. 1992; Shrivastava and Gupta 2011). Intending to reduce the manufacturing cost, we used commercially available copper electrodes having a very low corrosion rate instead of noble metal electrodes. The low corrosion rate ensures no possible interference with optical observations to occur. The CSC also hosts a multimode optical fiber (numerical aperture: 0.10; core: 10.5 cm; Thor Labs, USA) placed at a right angle to the spark plug at a distance of 0.85 cm from the center to carry the optical information to the microspectrometer. The micro-spectrometer was developed using a MEMS-based chip from Hamamatsu Photonics, Japan (Model: C12880MA). The high voltage electronics include a transformer that supplies the required voltage to generate a spark. The vaporizer breaks the liquid sample into small aerosol droplets and pushes them to the CSC.

Working Principle

The working principle remained the same as our previous study (Halder 2019). The major modification in the setup i.e., closing the spark chamber resulted not only in the requirement of less amount of sample but also reduction of fluctuations. In brief, spark plugs in the CSC generate plasma utilizing high voltage sources and excite the vaporized samples (i.e., aqueous solutions of electrolytes, or biological fluids). The optical emission originating from each sample (i.e., optical plume, Fig. 2a) due to recombination of ions energized by impingement of electrons resulting from high voltage plasma discharge is collected by using the...
optical fiber setup and detected by the micro-spectrometer. The control of the system including interfacing and IoT strategy is executed by an indigenously developed software in the LabVIEW platform (National Instruments, USA).

**Calibration of the Device**

For calibration of the instrument, different concentrations of sodium chloride (NaCl; Sigma, USA) and potassium chloride (KCl; Sigma, USA) solutions were prepared using Millipore water. The concentrations of NaCl used were 25, 50, 75, 100, 150, and 200 mgL⁻¹. While for KCl, the concentrations were 50, 75, 100, 150, and 200 mgL⁻¹. The chemicals were of the highest commercially available grade and used without further purification.

For measurement, a 2 mL solution was placed in the sterilized sample holder and subsequently measured using the principle stated in the previous section. Instrument index value (i.e., the emission intensity corresponding to the emission peaks of Na⁺, and K⁺ ions) was obtained for each calibrating sample and finally correlated with the known concentrations to obtain the calibration equations which were included in the software (vide infra). In between two consecutive sets of measurements, the spark plugs were turned on for 25 min to clean the electrodes and avoid possible contamination among samples.

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**Fig. 1** a The schematic of the experimental arrangement for non-invasive detection of essential electrolytes in humans. b, e The digital photographs of the prototype device.
Validation of the Device using Biological Fluids

Study Population and Ethical Considerations

The study was conducted following the guidelines approved by the Institutional Ethics Committee (Ref: CREC-STM/2018-AS27, dated 29.12.2018). All studies involving human subjects were performed according to the guidelines of the Declaration of Helsinki (Declaration 2014) and Indian Council for Medical Research (ICMR), Govt. of India.

As a proof-of-concept study, the sample size was estimated to be 30. Written informed consent was obtained from the volunteers who agreed to participate in the study after understanding the particulars and consequences of the study. All data and information about the subjects are kept confidential and utilized only for this study.

Sample Collection

After preliminary mouthwash with regular water, 4 mL of deionized water was poured into the oral cavity of the subject. After one minute, the water mixed saliva i.e., the sample (~4.5 mL) was collected. 1.5 mL of the collected sample was diluted with 0.5 mL of deionized water, placed into the sterilized sample holder, and subsequently measured using the method described in the earlier section. From the instrument index values, respective concentrations of the ions were obtained according to the calibration equations. Multiplying the obtained values with proper dilution factor provided actual levels of Na\(^+\) and K\(^+\) in the saliva.
**Statistical Analysis**

Data are expressed as Mean ± Standard Deviation (SD) unless otherwise stated. All statistical analyses including linear, and non-linear regression were performed using Origin Pro 8.5 (Origin Lab, USA). For reference interval calculations we used the parametric method considering the Gaussian distribution of the values. The difference between study results and reference standards was estimated using an unpaired t test (GraphPad Prism 9.0, GraphPad Software, USA). P < 0.05 were considered significant.

**Results and Discussion**

In the present study, we used the energy-resolved optical emission signatures associated with Na⁺ and K⁺ for the determination of their respective concentrations in the samples of interest. Figure 2b shows the emission spectral pattern of the electrolytes. The observed peaks at 589 and 824 nm corresponds to Na⁺ and K⁺, respectively (Slanger and Osterbrock 2000). As stated in the methods section, calibration curves were obtained using different concentrations of Na⁺ and K⁺ solutions. As evident from Fig. 2c, d, emission intensities were linearly dependent upon the electrolyte concentrations for both Na⁺ and K⁺. Linear regression analysis leads to the following calibration equations with adj. $R^2$ of 0.999 (Na⁺), and 0.988 (K⁺).

$$\text{Intensity}_{\text{Na}^+} (\text{counts}) = 23.31 + 20.82 \times \text{Concentration}_{\text{Na}^+} (\text{mEq/L})$$

(1)

$$\text{Intensity}_{\text{K}^+} (\text{counts}) = -2.29 + 19.5 \times \text{Concentration}_{\text{K}^+} (\text{mEq/L})$$

(2)

where, Intensity i.e., instrument index value refers to the optical emission intensities (counts) of the electrolytes at their respective peaks, and concentration refers to the concentration of the samples in the holder. The calibration equations served as standard curves and were incorporated into the software to calculate electrolyte concentrations of unknown samples from their emission intensities.

Next, we aimed to quantify Na⁺ and K⁺ concentrations from salivary samples. Salivary glands are non-excitable effector organs in which appreciable translocation of fluid and electrolytes occurs from the interior of the organism to the outside, usually in response to the neural stimulation (Schneyer et al. 1972). The salivary secretion does not regulate the body’s electrolyte balance, rather functions as an indicator to it. It is even considered a better physiological marker of electrolyte imbalance than the serum or blood. Despite having huge potential as a disease marker, the salivary electrolyte levels received less attention in medical diagnosis due to the unavailability of standardized measurement techniques in clinical chemistry laboratories. The first hurdle in measuring electrolyte concentration from saliva was to standardize the sample collection protocol. Here, we used a non-stimulated method by washing the oral cavity with 4 mL of deionized water for 60 s. The comprehensive wash of the oral cavity for 60 s is expected to overcome the physiological factors on which salivation depends. As showed in Fig. 3a, the volume of salivary secretion by this method reached a stable condition between 60 and 120 s. The salivary Na⁺ or K⁺ concentration also remained nearly constant during this period (Fig. 3b, c). Furthermore, < 60 s...
is too little to monitor for the patients suffering from acute illness. Therefore, the washing time was set at 60 s.

Figure 4a shows the salivary Na⁺ values of each patient obtained using our device. As all the volunteers were healthy in terms of electrolyte balance, we plotted a frequency distribution curve for salivary Na⁺ concentration (Fig. 4b) to estimate the reference range for the study population. The observed frequency distribution curve for salivary Na⁺ levels showed a bell-shaped pattern (i.e., Gaussian distribution) indicating normal distribution, one of the major criteria for reference range determination. The central tendency (i.e., mean) was found to be 17.5 mEqL⁻¹, with a 2SD of 2.7 mEqL⁻¹ (i.e., full-width-half-maxima of the frequency distribution plot). As per definition, the reference range for a given population for a given parameter (i.e., analyte or measurand) ranges from Mean + 2SD to Mean - 2SD. It is expected that 95% of the individuals if tested, will have their analyte values within this range. Thus, in our case, the reference range for salivary Na⁺ was found to be 14.8 mEqL⁻¹ (lower limit of variation) to 20.2 mEqL⁻¹ (upper limit of variation).

The calculated limits of variation were in good agreement with the published limits of salivary Na⁺ concentration (26.4 ± 11.8 mEqL⁻¹). It is worth mentioning here that, if the population is healthy and the instrument provides accurate measurements, a frequency distribution curve, would tend to have the same general shape if the number of population is increased, or if the groupings were varied to some small degree (White 1955; Chiles et al. 1996). Therefore, the observed statistically insignificant difference between the frequency distribution curve obtained from the developed device and previously published values, in turn, indicates the efficacy of the device in clinical settings.

Figure 5a shows the salivary K⁺ levels of the 30 healthy volunteers who participated in the study. Figure 5b shows the frequency distribution curve. Similar to Na⁺, the frequency distribution curve for salivary K⁺ levels were found to be bell-shaped. The central tendency was 27.2 mEqL⁻¹, with a 2SD of 2.7 mEqL⁻¹. The reference range for salivary K⁺ was calculated to be 25.5 mEqL⁻¹ (lower limit of variation).
for the detection of analytes from blood samples. Here, the
also proposed a device with the same working principle
invasive electrolyte detection techniques. Previously, we
from the mouth wash as an alternative to the conventional
observed similar results. The salivary Na\(^+\) level found in
our study is ~ 8 times lower than that found in serum. Similarly,
the salivary K\(^+\) concentration in this study is ~ 7 times
higher compared to serum. The higher concentration of Na\(^+\)
observed in the blood could be due to the higher volume
and surface area of blood (Wankasi 2019). Moreover, blood
is an extracellular fluid from where a lot of nutrients and
electrolytes are cleared out from the body or transported to
other cells, tissues, and body fluids for systemic sustenance
(Wankasi 2019). On the other hand the high concentration of K\(^+\)
in saliva is due to the filtration of potassium into the
saliva and the active release to the saliva by nerves stimula-
tion as reported by Carlos et al. (Labat 2018). Also, Na\(^+\) ions
are actively reabsorbed from all the salivary ducts and K\(^+\)
ions are actively secreted in exchange for the Na\(^+\) (Wankasi
2019). Therefore, the Na\(^+\) ion concentration of the saliva
becomes greatly reduced, while the K\(^+\) ion concentration
becomes increased. Figure 5b-inset shows a sample cor-
relation between serum and salivary concentration of K\(^+\)
(Horiba 2017). However, we found no authentic report that
established a similar correlation between serum and sali-
vary Na\(^+\) concentration. Therefore, a detailed large-scale
systemic clinical study is required to find the exact correla-
tion between serum and salivary electrolytes, which we are
planning to do in the future.

It is worth mentioning here, the salivary electrolyte con-
centration is very much dependent on circadian rhythm. It
also varies greatly depending upon the time of daily meal
intake. We have measured the salivary electrolyte concentra-
tions at different times of the day and observed the variation
as depicted in Fig. 6. However, for maintaining uniformity,
we collected all the samples used for the determination of
the reference range at fasting conditions. This kind of strat-
egy is often used while measuring certain blood parameters
to avoid diurnal variations.

This is a very preliminary proof of concept study, the
sole aim of which was to test whether the newly developed
device can measure salivary Na\(^+\) and K\(^+\) concentration
from the mouth wash as an alternative to the conventional
invasive electrolyte detection techniques. Previously, we
also proposed a device with the same working principle
for the detection of analytes from blood samples. Here, the
installation and maintenance cost, and amount of sample
required for testing have been reduced to a remarkable
extent compared to our previously proposed device. Due
to covered CSC, and more integrated systems the proposed
device causes no known medical hazard since no chemi-
cal or biomedical waste is exhausted (unlike our previous
design) to the surroundings. Moreover, it helped to lower
the minimum detection limit for Na\(^+\) to 1 mM, which adds
to its clinical significance. Table 1 depicts a detailed com-
parative analysis of our proposed device with other stand-
ard devices and our previous design.

There are some limitations of the study, which lay the
foundation stone for future investigations. First of all, we
restricted our study to only normal volunteers since we
did not have ethical permission to work on the patients,
particularly the COVID-19 infected ones. It is of particular
concern whether cough and cold could affect our measure-
ments or salivary electrolyte levels. But, previous stud-
ies have demonstrated that although cough and cold alter
several other salivary contents like expelled nucleic acid,
glucose, protein, and digestive enzyme (e.g., amylase) lev-
ecls, it has little implications on the secreted electrolytes
(Farzan 1990). Therefore, we can assume that our method
will also be suitable for those patients. Another drawback
of this study is that due to ethical issues we could not
measure electrolyte levels in other biological fluids like
sweat, or urine. Theoretically, there is no apprehension
in measuring electrolyte levels of other biological fluids, but
experimentally it needs to be checked. A reference
range of Na\(^+\) and K\(^+\) has to be determined for each of the
biological fluids for the inclusion of this technique in regu-
lar clinical practices. A more comprehensive large scale
clinical study will follow this work to answer the clinical
issues in details.
Table 1  Comparative analysis of our proposed device with few other standard devices and our previous design

| Type                  | ISE                                      | ABG                                      | ICP-OES                                 | OES                                      | OES                                      |
|-----------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| Device                | AU480 chemistry analyzer, Beckman Coulter Inc., USA | OPTI® CCA-TS2, OPTI Medical Systems Inc., USA | Optima 7300 V PerkinElmer, Inc. Shelton, CT, USA | NaLiK | Proposed technique |
| Measurement principle | Spectrophotometry and potentiometry      | Optical fluorescence and reflectance     | Inductively coupled plasma-optical Emission spectroscopy (ICP-OES) | Optical emission spectroscopy | Optical emission spectroscopy |
| Sample type           | Demonstrated in serum or plasma, urine and other fluids (AU480 Chemistry Analyzer) | Demonstrated in whole blood, serum or plasma (OPTI® CCA-TS2) | Demonstrated in human milk (Geddes and Perrella 2019) | Serum or plasma | Wash from mouth cavity |
| Sample volume         | 1.0–25 mL                                | 125 mL                                  | 50 mL                                   | 10–500 mL                                | 2 mL                                    |
| Calibration time      | < 60 s                                   | < 90 s                                   | < 90 s                                  | < 60 s                                   | < 40 s                                  |
| Measurement time      | < 120 s                                  | < 120 s                                  | < 90 s                                  | < 90 s                                   | ~ 37 s                                  |
| Operating temperature | 18–32 °C                                 | 10–30 °C                                 | 15–35 °C                                | 15–37 °C                                 | 15–47 °C                                |
| Measurement range     | Na⁺ 90–200 (mM)                          | 100–180 (mM)                            | 2.59–21.50 (mM)                        | 100–320 (mM)                            | 1.0–190.0 (mM)                          |
|                       | K⁺ 1.9–9.93 (mM)                         | 0.8–9.99 (mM)                           | 7.91–15.20 (mM)                        | 1.0–9.95 (mM)                           | 1.0–270.9 (mM)                          |
| Display resolution    | Na⁺ 1/0.1                                | 1/0.1                                   | 0.1/0.01                               | 0.1/0.01                                | 0.1/0.01                                |
|                       | K⁺ 0.1/0.01                              | 0.1/0.01                                | 0.1/0.01                               | 0.1/0.01                                | 0.1/0.01                                |
| Installation cost     | 39,513.15 USD                           | 4324.05 USD                             | 38,012.65 USD                          | 1153.08 USD                             | 1000.00 USD                             |
| Test cost (per sample)| Between 4.90 and 11.82 USD              | Between 4.90 and 11.82 USD              | Between 4.90 and 11.82 USD              | 1.44 USD                                | 0.65 USD                                |
| Maintenance cost      | High                                    | High                                    | High                                   | 150 USD/5 year                          | 50 USD/5 year                           |
| Flexibility of use in different ambience | Laboratory settings                   | Laboratory settings                     | Laboratory settings                     | Portable                                | Portable                               |
| Manpower to operate   | One trained technician                   | One trained doctor                      | One trained technician                  | One trained paramedical staff           | No expertise                           |
| Medical safety        | Chances of biomedical waste             | Chances of biomedical waste             | Chances of biomedical waste exposure to air | No medical hazard; No chemical exhaust | No medical hazard; No chemical exhaust |
In the present work, we have developed a non-invasive technique for the detection of essential electrolyte levels in human subjects using optical emission spectroscopy from samples collected from the wash of the mouth cavity. We have also developed a user interfacing software in the LabView platform to acquire the optical signals and to calculate the electrolyte concentration instantaneously. The technique has been validated through a small-scale clinical trial on 30 healthy volunteers. The obtained values of Na\(^+\) and K\(^+\) concentrations are found to be consistent with that of the reported values. The advantages of the developed system over the conventional blood sample-based technique include real-time analysis of the data, painless, needle-free sample collection and IoT-enabled e-healthcare strategy as remarkable as shown in Fig. 7. To our understanding, the co-morbidity of CKD and elderly patients due to frequent hospital visits and immune-compromised conditions can be managed in the COVID-19 pandemic situation through the developed device. A large-scale clinical study will be followed to address the clinical issues in further detail. Since our study was restricted with limited ethical permission, we are aiming to do further studies using other biological fluids, such as urine and sweat samples.

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**Author contributions** NB developed the instrument, and was involved in the planning of the study; coordinated data collection carried out the primary analyses, and drafted an initial manuscript. SS developed the software and revised the manuscript. AH was involved in the design and development of the instrument and reviewed the manuscript. AA analyzed the data, interpreted it, and revised the manuscript. RG made a substantial contribution to data acquisition and interpretation. DS helped in the design and development of the device. SKT, AKM, and PM planned the study interpreted the data, and reviewed the manuscript. SKP conceptualized and planned the study, interpreted the data, and revised the manuscript.

**Data availability** The datasets generated for this study are available on legitimate request to the corresponding author.

**Compliance with ethical standards**

**Conflicts of interest** There are no conflicts to declare.

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