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A handheld-type total integrated capillary electrophoresis system for SARS-CoV-2 diagnostics: Power, fluorescence detection, and data analysis by smartphone

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ABSTRACT

A micro-capillary electrophoresis (μCE) system is one of the widely adopted techniques in the molecular diagnostics and DNA sequencing due to the benefits of high resolution, rapid analysis, and low reagent consumption, but due to the requirements of bulky high-power suppliers and an expensive laser-induced fluorescence detector module, the conventional set-up of μCE system is not adequate for point-of-care (POC) molecular diagnostics. In this study, we constructed a miniaturized and integrated μCE system which can be manipulated by a smartphone. The smartphone not only powers two boost converters and an excited laser, but also controls the relay for the power switch. Moreover, the complementary metal-oxide-semiconductor (CMOS) camera of the smartphone was used for detecting the fluorescence signal of amplicons amplified with reverse transcription-polymerase chain reaction (RT-PCR). We also developed a web-based application so that the raw data of the recorded fluorescence intensity versus the running time can display typical capillary electropherograms on the smartphone. The total size of the hand-held μCE system was 9.6 cm [Width] × 22 cm [Length] × 15.5 cm [Height], and the weight was ~1 kg, which is suitable for POC DNA testing. In the integrated smartphone-associated μCE system, we could accurately analyze two genes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), namely N gene and S gene along with two bracket ladders in 6 min to identify SARS-CoV-2. Such an advanced μCE platform can be applied for a variety of on-site molecular diagnostics fields with user-friendliness.

1. Introduction

SARS-CoV-2, one of the most hazardous infectious viruses, became global pandemics causing unusual viral pneumonia (Acter et al., 2020). Until now, more than 160 million people have been infected from SARS-CoV-2 and approximately 3.5 million patients died (World Health Organization, 2021). Recently, the Delta variant shows a high rate of infection and human death as well as viral toxin, making it difficult to hold SARS-CoV-2 under control worldwide. In order to prevent the pandemic spreading and take action for timely treatment, the development of advanced diagnostic tools as well as vaccines has been intensively focused. Regarding the diagnosis fields, molecular diagnostic techniques such as PCR are essential for the definitive assessment of the virus, and the production of the POC testing systems has progressed and commercialized. The most adopted detection methods for the PCR amplicons are the real-time fluorescence module or the gel electrophoresis assay (Cunha et al., 2020; Nőlvák et al., 2012; Stellwagen, 2009). Although the fluorescence detector can be easily incorporated into the POC diagnostic instruments, the gel electrophoresis assay is not adequate to be integrated into a portable genetic analysis platform due to bulky buffer reservoirs and complicated electrical connection. On the other hand, μCE has demonstrated its high performance of molecular...
analysis with high speed, high resolution, and low sample consumption (Hajba and Guttmann, 2017; Khatri et al., 2017; Kim et al., 2012; Lacná et al., 2017; Lin et al., 2017; Pan et al., 2018; Voeten et al., 2018), and has been extensively applied for the separation and detection of chemicals and biomolecules, such as nucleic acid, protein or amino acid enantiomers (Curts Saunders et al., 2013; Heiger et al., 1990; Kong et al., 2019; Li et al., 2018; Liang et al., 2019; Sveidsvoll and Ueland, 1996; Sudor and Novotny, 1994; Sunada and Blanch, 1997). μCE on a chip was also developed for a simple and miniaturized format using diverse substrates including glass (Chen et al., 2010; Kim et al., 2010; Manz et al., 1992; Woolley and Mathies, 1995), quartz (Zhang et al., 2018), polymer (Hong et al., 2001; Nguyen et al., 2019; Roy et al., 2013; Yingjie et al., 2001), wax-like materials (Adamski et al., 2016), and mineral paper (Lee et al., 2017). Similar to other electro-kinetic separation techniques, on-chip μCE employs an electric field as a driving force to migrate biomolecules in a sub-millimeter diameter tube, and the elution time of biomolecules is different depending on the size and charge (Harrison et al., 1992; Lee et al., 2017). If the high separation resolution is required such as DNA sequencing with a single base resolution, the μCE channel should be narrower and longer and high power supplies (500–1800 V) are needed to apply an electric field in the μCE channel (Chen et al., 2010; Choi et al., 2012; Kim et al., 2010; Lee et al., 2017). The equipment of the high-power supplies and the sensitive fluorescence detector such as a photomultiplier tube renders the whole system bulky, making the μCE system unsuitable for the POC molecular diagnostics.

To deal with this issue, some studies using a mobile power bank or a lithium battery to operate a μCE chip have been reported (Khan et al., 2019; Kong et al., 2019; Wang et al., 2019). Our group also presented a smartphone-powered μCE chip (Nguyen et al., 2019). However, most works have limitations in manual operations for the power switch, and the fluorescence detection was conducted by a separate detector system. Regarding the detection module, the smartphone camera could be used for colorimetric chiral recognition (Ping et al., 2018), colorimetric pathogenic detection (H. Van Nguyen et al., 2020), HUE value based isothermal amplification detection (H. Q. Nguyen et al., 2020), and fluorescence detection (Gou et al., 2018; Priye et al., 2018), but the digital images were simply stored, lacking of quantitative data analysis on the smartphone.

In this study, we fully utilized the function of the smartphone to construct an automatic μCE system to be applied for the detection of SARS-CoV-2. The whole system consists of a μCE chip, two booster converter circuits, a relay, a micro-controller, a laser, and a smartphone.
The power of the smartphone is supplied for the CE operation as well as the laser turn-on process. In addition, the CMOS camera of the smartphone equipped with a 520 nm band pass filter is used for recording the fluorescence signal of the RT-PCR amplicons. The recorded data of the fluorescence intensity versus the time can be plotted on the smartphone to display the µCE electropherogram using an in-house Javascript software. Owing to the superior functionality of the smartphone, an advanced smartphone-associated µCE system can be established with high portability, full automation, and total integration, which would make an ideal platform for the hand-held type POC molecular diagnostics.

2. Materials and methods

2.1. Design and fabrication of a sample-stacking µCE chip

The sample-stacking µCE chip was designed by a software of Cut2D (version 9.010) and fabricated by a computer numerical control (CNC) milling machine (Tinyrobo, TinyCNC-6060C, Korea). The µCE chip is comprised of three layers: from top to bottom, a 2 mm-thick polymethyl methacrylate (PMMA) for making four reservoirs, a 1 mm-thick PMMA with micro-channel patterns for CE, and a 0.175 mm-thick PMMA as a base plate. The sample-stacking µCE chip has a double-T-structure with a 0.5 mm sample-stacking region in the injection channel for accumulating the loaded RT-PCR amplicons prior to the separation step (Fig. 1B), resulting in the increment of the detection sensitivity. The information of the RT-PCR amplicons is described in the Supplementary Information. The micro-channels have a dimension of 200 μm in width and 200 μm in depth, and the separation channel is 25 mm in length. There are four reservoirs (the sample (S) reservoir, the waste (W) reservoir, the anode (A) reservoir and the cathode (C) reservoir) with 2.5 mm in diameter for the electric connection. When the three layers were prepared by CNC milling processes, they were cleaned by sonication, and were treated with O2 plasma for 3 min. After treated with 70% ethanol, they were thermal-bonded by a heat press at 65 °C for 30 min. Prior to the µCE operation, the chip was treated with O2 plasma for 1 min, and incubated with a dynamic coating solution (DEH-100, The Gel, San Francisco, CA, USA) for 15 min. Linear polyacrylamide gel (5 wt %) was prepared (Section 3 of the Supplementary Information) and loaded from the anode reservoir to fill in the microchannel. Three μL of 1 × TBE buffer were added to the C, A and W reservoirs. After injecting 3 μL of RT-PCR products in the S reservoir, the µCE operation was initiated.

2.2. Design of the circuit for the power switch

The power of the smartphone was used for supplying power to a 488 nm blue dot laser (12 mm in diameter, 50 mW), and two separate boost converters. For the automatic power supply and power switch, it is necessary to design an electrical circuit. The overall connection of the electrical components is presented in Fig. 1C. The whole system consists of a smartphone, an Arduino micro-controller which connected a laser and a relay, a 488 nm blue dot laser, a 2-channel relay for switching the electrical flow, two boost converters, each of which supplies voltage used for the injection and separation of the amplicons on a chip. The power for the laser was supplied directly from the 3 V pin of the Arduino micro-controller. The detailed circuit connection lines are described in Fig. 1D. The voltage common collector (V_CCC) port and the ground (GND) port of the relay was linked to the 5 V and the GND pins of the micro-controller, respectively. The digital input (IN) pins of the relay, known as the signal triggering terminal, were linked to the digital pins of the micro-controller for controlling the on-off state of two boost converters. At the output of the relay, the normal close (NC) port was connected to the V_R pin of the booster circuit, while the common (COM) port was linked with the V_R pin of the micro-controller. Finally, the GND ports of two booster circuits were connected to the GND pin of the micro-controller. The python code for controlling the switch of the two boost converters for the µCE operation was prepared in the Arduino software (Fig. S1) and loaded into the Arduino micro-controller. Then, the python code was initiated by the Arduinodroid app of the smartphone, so that the µCE process such as injection, separation, and detection was automatically operated.

2.3. Construction of the hand-held type µCE system

To form a portable and integrated µCE platform, we designed a 3D box by Autodesk Fusion 360 software and prepared it by a 3D printer (HM-300S, Hotmine 3D, Korea) (Fig. 2). The CMOS camera of the smartphone was covered with a 520 nm band pass filter and was placed in a 70° angled plane. Circuit parts including a micro-controller and a relay were equipped on a base plate (90 mm [Width] × 90 mm [Length]). In the inside of the rectangle pivot, a 488 nm blue dot laser was installed with a 20 × objective for the convergence of the excited light, two boost converters were attached on the side, and the chip base was placed on the top. In order to acquire good focus on the detection point in the separation microchannel as well as high contrast of the fluorescent signal with the black background, the distance between the CMOS camera of the smartphone and the detection point on the chip was optimized and set as 115 mm. Moreover, the angle of the chip base was selected at 45°, so that highest energy of the convergent light was irradiated on the chip, while the diffraction of the excited light on the PMMA chip was minimized. To balance the height between the detection point on the microchannel and the CMOS camera, the height of the rectangle pivot was determined as 84 mm, and the chip was placed on it.

The overall size of the integrated µCE system was 9.6 cm [Width] × 22 cm [Length] × 15.5 cm [Height] and the weight was ~1 kg, which could be carriable by a hand (Fig. 2A). Fig. 2B shows the digital image of the integrated µCE system. Since we employed the laser-induced fluorescence detection on a µCE chip, we covered the whole system to prevent the light disturbance from the outside sources. The top view in Fig. 2C shows the main components for a smartphone, a micro-controller, a relay, two boost converters, a laser, a 20 × objective, and a µCE chip with a chip basement.

2.4. On-chip µCE operation

When the RT-PCR products were loaded in the sample reservoir, the µCE chip was inserted in the chip basement, and four electrodes were connected to the four reservoirs in the chip. The operation process for µCE involves in two main steps, the injection-stacking (IS) step and the separation-detection (SD) step. To initiate the µCE operation, we opened the Arduinodroid app on the smartphone screen. We clicked the toggle menu icon at the right top corner of the smartphone display and chose the “Action” and then the “Monitor” option in the drop-down list (Fig. 3A–C). In the Monitor screen, we typed the control command “a” (see the code in Fig. S1), which started the IS step (Fig. 3D). Once received, the micro-controller activated the gate-opening process of the first relay module through the digital gates. Consequently, the first booster circuit, which generated the output voltage of 380 V, was activated and the resultant 380 V was used for transferring the RT-PCR product from the sample reservoir to the waste reservoir as shown in the fluorescence signal in the microchannel (Fig. 3E). The IS step took 100 s to be completed. When the IS step was finished, the control command “b” in the Arduinodroid app of the smartphone was executed by the second module of the relay, resulting in the turn-off of the first booster circuit and the turn-on of the second one (Fig. 3F). The second booster circuit supplies 295 V between the cathode and anode reservoirs, performing the SD step. During this step, the accumulated RT-PCR amplicons (Fig. 3E) in the stacking zone were loaded and separated in the separation channel (25 mm in length) depending on the size (Fig. 3F). As shown in the real fluorescence image, the smaller size of the
amplicon moved faster than the larger one, and the fluorescent signal was detected at the end of the channel. This SD step took approximately 220 s. Then, the control command “c” was input in the Arduinodroid app of the smartphone to stop the operation of the boost converter circuits (Fig. 3D). The control command “d” included all the command from “a” to “c” for the automatic operation of the integrated µCE, so the IS and SD step was performed in a consecutive order with the control command “d”.

3. Results and discussions

3.1. The structure of the integrated µCE system

The typical µCE on a chip has a design of a cross-microchannel with a sample-stacking zone to increase the detection sensitivity (Fig. 1B). In general, the operation of the µCE has two steps for injection and sampling.
separation. During the injection step, the electrical field is applied between S reservoir and W reservoir, so that the RT-PCR amplicons are moved from S to W to fill in the sample stacking zone (Fig. 3E). Then, the power supply should be switched to C reservoir and A reservoir, so the stacked amplicons are transferred toward A and separated according to separation. During the injection step, the electrical field is applied by V.D. Nguyen et al. while that for the SD produced 295 V by the preset potentiometer. We phone, while controlling the output voltage separately for the IS and SD voltage of the smartphone is only 5 V. Thus, we employed the two booster converters, each of which has a pair of electrodes for working for the injection and separation. The relay module can control the on-and-off power switch between the two booster converters, so that the injection step and the separation step can be automatically and sequentially operated. Such a management is manipulated by the commands ‘a’, ‘b’, ‘c’, or ‘d’ in the python code (Fig. S1), which is uploaded in the Arduino microcontroller. In order to automatically operate the μCE on a chip, we simply open the Arduino app on the smartphone and execute the ‘d’ command that serially executed the injection and separation step.

3.2. The power supply to operate the μCE chip

The μCE operation consists of two steps, the IS and SD step. For the CE performance, we needed to increase the power, since the output voltage of the smartphone is only 5 V. Thus, we employed the two booster converters to augment the voltage from the 5 V of the smartphone, while controlling the output voltage separately for the IS and SD step. The booster circuit for the IS generated the output voltage of 380 V, while that for the SD produced 295 V by the preset potentiometer. We optimized the output voltage of the IS and SD by considering the μCE channel, the size of the amplicons, and the power source. We selected two RT-PCR amplicons of SARS-CoV-2 (S gene (159 bp) and N gene (241 bp)) together with two bracket ladders (80 bp and 320 bp) for μCE analysis. Because the length of the separation channel is relatively short (25 mm), we designed the amplicon size with an interval of 80 bp to minimize the overlap of the CE peak. The size of the short bracket ladder, the S gene, the N gene, and the long bracket ladder was 80 bp, 159 bp, 241 bp and 320 bp, respectively. Due to the large interval of length (80 bp), it is necessary to optimize the power supply and injection time to load all the four amplicons into the stacking section equally. Otherwise, the amount of each amplicon in the stacking zone could be different, leading to the unbalanced fluorescent peaks or even the drop-out of the smallest or largest peak. We fixed the injection time with 100 s and screened the output voltage in the range of 295 V–380 V by a potentiometer. It turned out that 380 V for 100 s in the IS step resulted in equal distribution of the four amplicons in the stacking section, showing the balanced peaks in the electropherogram. In case of the SD step, 295 V was optimal for the explicit separation of four amplicons to display four isolated peaks in the electropherogram. All four peaks could be well-separated with low background signals and detected within 220 s. Detailed optimization processes are described in section 4 of the Supplementary Information.

3.3. The optical set-up for the fluorescence detection in the integrated μCE system

The power of the smartphone is also utilized for turning on the blue dot laser. When the command ‘b’ is actuated, the power of the laser is switched on upon the completion of the injection step, and the video recording is initiated. To detect the fluorescence signal of the separated amplicons during μCE, we needed to match the focus of the CMOS camera on the bottom of the separation channel. In addition, the fluorescence contrast with black background should be maximized in order to increase the signal resolution. Therefore, we optimized the standing angle of the smartphone and the μCE chip as well as the distance between the camera and the detection point of the μCE chip. First, we tilted the baseline of the μCE chip with various angles and irradiated it with the blue dot laser. When the angle was 45°, the detection point could receive the converged light of the excited laser with highest energy. If the tilted angle was smaller or larger than 45°, the light was divergent on the detection point with lower energy, causing high background noise. With fixation of the baseline of the μCE chip at 45°, the standing angle of the smartphone was also determined. The detection point of the chip was displayed at the center of the smartphone screen at the angle of 70°, so it was chosen as a standing angle of the smartphone. Besides the standing angle of the smartphone and the μCE chip, the length between the camera and the μCE chip was also optimized. Short distance rendered the camera out of focus, while long distance made the detection point appear too small in the smartphone screen, revealing blur fluorescent images during the data process. We found out that the best camera focus was 115 mm, at which the contrast between the fluorescence signal and the background was high. So, the background noises were reduced and the detection sensitivity of fluorescence was improved. Detailed optimization processes are described in section 5 of the Supplementary Information. As soon as the second booster circuit was turned on, the web-based app was immediately opened and recorded the fluorescent signals of the separated DNA bands.

3.4. Software for recording the fluorescence signal and data analysis on a smartphone

The fluorescence signal is recorded using the smartphone camera and is analyzed by an in-house web-based app written by Javascript, which is available in our lab website (https://nanobiomers.khu.ac.kr/CE/). After opening the web apps, the user can press the button “Choose file” (Fig. 4A) that includes two options for data analysis: “Camcorder” or “Files” as shown in the bottom of the smartphone screen (Fig. 4B). The “Files” option lets the saved video to be analyzed, while the “Camcorder” leads to the recording display. When the “Camcorder” is chosen, the camera focus is adjusted prior to the real-time record of the fluorescence signals during the SD step on μCE chip (Fig. 4C). As soon as the signal recording is finished, the data analysis is immediately conducted to show the CE electropherogram on the screen (Fig. 4D). Owing to the fine focus of the “Camcorder” option, the fluorescence signal of the amplicon could be monitored. When the RT-PCR amplicon approached the detection point, the fluorescence intensity gradually increased, maximized and then faded away (Fig. 4E and Supplementary Video 1). Fig. 4E(i)-4E(iv) show the snapshots of the amplicon positioned before the detection point (Fig. 4E(i)), close to the detection point (Fig. 4E(ii)), at the detection point (Fig. 4E(iii)), and after the detection point (Fig. 4E(iv)). For the fluorescence calculation, the frame size of the video image was cropped down surrounding the detection point to minimize the effect of the background noise on the fluorescence signal. In order to obtain the cropped image, we could define the X and Y value as well as area to locate the region of interest (Top panel of Fig. 4D). The green pixel intensities within the defined area were averaged every second, and were plotted according to the time, producing a typical CE electropherogram (Bottom panel of Fig. 4D). Supplementary Video 2 shows the overall procedure for the CE data processing on the
3.5. SARS-CoV-2 analysis on the integrated μCE system

The proposed handheld-type μCE system was applied for analyzing SARS-CoV-2 by targeting two RT-PCR amplicons of S gene (159 bp) and N gene (241 bp). Since the absolute migration time of the peaks in the electropherogram may be affected by various factors such as CE operation conditions, gel matrix conditions and temperature, a short bracket ladder (SL) (80 bp) and a long bracket ladder (LL) (320 bp) were included during the CE analysis to calculate the relative migration time ratio. The use of the bracket ladders as a reference improves the peak assignment of target peaks with high accuracy regardless of the absolute elution time. First, we separated the two bracket ladders, in which the elution time of the short and long ladders was 53 s and 148 s, respectively (Fig. 5A). Then, the amplicon (159 bp) targeting S gene was analyzed together with the two bracket ladders. Fig. 5B shows three explicit peaks, in which the SL peak, the S gene peak, and the LL peak appeared at 94 s, 131 s, and 204 s, respectively. Thus, the relative migration time ratio of the peak of the S gene collected from triplicate experiments was calculated as 0.3334 ± 0.003 by the following equation:

\[
\text{The relative migration time ratio} = \frac{\text{The migration time between the target peak and the short bracket ladder}}{\text{The migration time between the two bracket ladders}}
\]

Similarly, the amplicon of the N gene was analyzed with the two ladders (Fig. 5C), and the elution time of the SL, the N gene and the LL was measured at 73 s, 134 s and 168 s. So, the relative migration time ratio of the peak of the N gene was determined as 0.6380 ± 0.004.

Fig. 4. Fluorescent signal recording and peak assignment on the smartphone with the support of the self-designed web app. (A) Open the play screen of the CE analysis web app and press the ‘Choose File’ button. (B) There are two options of the file selection for the peak assignment, the Camcorder and the Files. (C) If the Camcorder option is selected, the smartphone opens the camera app and adjusts the camera focus as well as the brightness of the video frame. (D) After recording, the video is automatically uploaded into the web app for the CE analysis. In this screen, the target coordinates in x and y axis, and the detection area can be tuned for better signal analysis. (E) The amplicon is positioned (i) before the detection point, (ii) starts to appear, (iii) positioned at the detection point, and (iv) passed through. (v) By cropping down the frame size of the video, the detection point was enlarged, and the fluorescence intensity of the defined area was calculated every second to produce the CE electropherogram.
Finally, both genes of the SARS-CoV-2 with the bracket ladders were separated for the multiplex μCE analysis on the proposed system. All four peaks were clearly separated with the baseline background and two target peaks were positioned in the middle of the two bracket ladders (Fig. 5D). Although the absolute elution time for each peak was changed compared with that of Fig. 5A–C, the relative migration time ratio for the S gene and N gene was determined as 0.3304 and 0.6339, which are quite consistent with those of the monoplex analysis data (Table S2). In addition, we performed the LOD and the resolution test on the integrated μCE system. For the LOD test, the serially diluted particle samples ranging from $10^4$ copy number/μL to 1 copy number/μL were prepared and even the diluted sample of 1 copy number/μL generated similar peak patterns to that of $10^4$ copy number/μL (Figs. S4A–S4E). In the peak resolution test, the two PCR amplicons with 20 bp interval were clearly distinguishable (Fig. S4F). Thus, we could accurately confirm the presence of the SARS-CoV-2 with high fidelity.

4. Conclusion

In summary, we proposed the handheld-type μCE analyzer which is fully integrated, automatic, and operated by the smartphone to identify SARS-CoV-2. The power of the smartphone was not only used for two boost converters for CE operation, but also for the blue dot laser as a light source. The CMOS sensor of the smartphone camera with a band pass filter was employed for the fluorescence detection, and the in-house web app of the smartphone was utilized for data analysis to produce a CE electropherogram. With an aid of python codes, the whole process was automatically proceeded simply by inserting the command in the smartphone. Since the information and communication technology is vital to develop an advanced healthcare monitoring system in the fourth industrial revolution era, we believe that our proposed platform can enhance the development of the future POC DNA testing technology in the fields of molecular diagnostics.

CRediT authorship contribution statement

Van Dan Nguyen: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Visualization. Huynh Quoc Nguyen: Conceptualization, Methodology, Writing – original draft. Khang Hoang Bui: Conceptualization, Investigation, Methodology. Young Soo Ko: Investigation, Methodology. Bum Jun Park: Conceptualization, Methodology, Writing – review & editing, Supervision. Tae Seok Seo: Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bios.2021.113632.

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