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Wettability alteration in a functional capillary tube for visual quantitative point of care testing†

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Capillarity is an extremely common physical–chemical phenomenon related to wettability in nature, which has wide theoretical and practical interest. Herein, we reported a facile sensing device based on capillary force change in a vertical capillary tube. In this height-based capillary sensor (HCS), the inner surface of the capillary tube was modified with a layer of molecules with wetting responsibility based on the well-known simple surface chemistry. With targets in different concentrations, the wettability of the surface modified with responsive molecules would produce different changes. The responsive surfaces would change the capillary force of the vertical capillary tube, and result in different column heights. Like a thermometer, H^+ and phenol have been quantified visually based on the height of the liquid inside the capillary tube.

Capillarity is the ability of a liquid to flow in narrow spaces without the assistance of external forces, which is essential for wicking fabrics, thin layer chromatography, the body's exocrine system (lacrimal gland and sweat glands) and so on.[1,2] Surface wetting is one of the main factors affecting capillarity.[3,4] Smart surfaces with reversibly regulatable wettability have been widely studied. External stimuli, such as DNA, counterions, temperature, solvents, electrical potential, pH, and others, can change the surface conformation and/or morphology of stimuli-sensitive materials, which results in the change of the surface wetting behavior.[5] The capillary force could be altered with the change of wettability in a capillary tube, as it can generate a visual signal without measuring the contact angle (CA).[6] In particular, the use of this phenomenon shows great promise in the fields of visual quantitative sensors.

With the rapid progress of analytical technology, point-of-care testing (POCT) has shown great advantages in home healthcare, accident points and emergency situations, and is especially necessary in a variety of situations where laboratory equipment is lacking.[7–10] A variety of POCT diagnostic systems, including blood glucose monitors, pregnancy tests, lateral flow immunoassays and paper-based microfluidics, have been reported and commercialized.[11–13] Even though qualitative POCTs have been available as test paper or lateral flow assays,[14–18] quantitative POCTs remain a significant challenge that cannot be easily achieved in an inexpensive and convenient manner. However, quantitative assays which provide real-time accurate readout to users are important, especially in low-resource developing countries. Among various quantitative approaches, distance-based visual quantitative detection methods are developed that rely on reading the visual signal length for the corresponding target concentrations. In recent years, another novel length-based readout method was developed using visualized ink bars using volumetric expansion in gas-generation reactions. In the sealed devices, the generated gas could push up the ink bars to move along channels, where the moving distance is closely related to the target concentrations.[19–22] The distance-based methods are user-friendly and can be integrated into portable analytical devices. An excellent distance-based POCT should be real-time, affordable, sensitive, specific, equipment-free, and deliverable to the end user without any training, acting like a thermometer.[22–24] While the use of the current instruments is promising, they may still be too expensive and complicated for developing areas, where various challenges need to be addressed.

Herein, we have developed an accessible, reusable and quantitative POCT device based on capillary force change in a vertical capillary tube without auxiliary equipment. Like a thermometer, the alteration can be read with the naked eye through the height of the liquid column in the capillary tube (Scheme 1). In this height-based capillary sensor (HCS), the inner surface of the capillary tube was simply modified with a layer of molecules with wetting responsibility. With targets in different concentrations, the wettability of the surface modified with responsive molecules would produce different changes.[25–27] The responsive surfaces would change the capillary effect of the vertical capillary tube, and result in different

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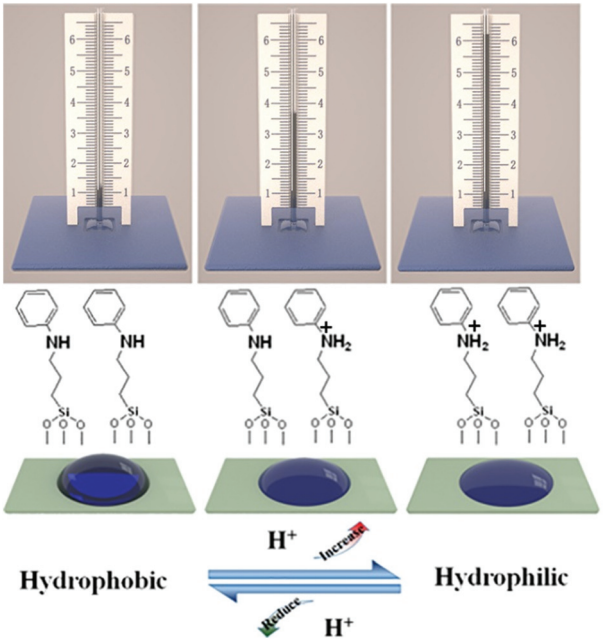

Scheme 1 The working principle of the height-based capillary sensor.

column heights. Based on this principle, we have verified the feasibility of the proposed method by testing the H^+ solution from 10^{-7} M to 1 M. Compared with the traditional analytical methods using glass electrodes or colorimetric cards, this method could break through the limitations of trace or colored samples, and achieve an accurate, quantitative result more conveniently. More importantly, different from the previously reported application of the capillary tube, which utilizes capillary forces to only carry the solution, this method could realize convenient, sensitive detection through the difference of the transport capacity and capillary forces induced by the detection target with different concentrations. Moreover, given the design flexibility of wettability-responsive molecules,[28,29] the described methodology could be expected to extend to a wider analyte analysis, and the detection of phenol has also been proven in this work.

In practice, according to Poiseuille's law expressing the balance between viscous forces and capillary and hydrostatic forces (ignoring inertial effects),[6,30,31] the pressure difference ΔP is given by:

$$\Delta P = \frac{2\gamma \cos\theta}{R_S} - \rho g h \quad (1)$$

where γ and ρ are the surface tension and density of the liquid, respectively, θ is the advancing contact angle of the liquid on the solid, R_S is the mean static radius of pores, g is the acceleration due to gravity, and h is the height reached by the liquid. At equilibrium (ΔP = 0), the maximum height h_{eq} reached by the liquid front is given by:

$$h_{eq} = \frac{2\gamma \cos\theta}{\rho g R_S}. \quad (2)$$

It is clear that the impact factors of the capillary liquid column are surface tension, density, and contact angle in a certain temperature range. Stimuli-responsive molecules can be applied to tune the surface wettability because the free energy or morphology of the surface is sensitive to the change of external environments. The configuration or charge state of functional molecules on the surface could be changed by the external stimuli of molecules, and surface wettability would change correspondingly. Capillary effects can be just used to detect the changes of surface wettability sensitivity.

As reported in the literature, *N*-[3-(trimethoxysilyl) propyl]-benzenamine can be protonated when the H^+ concentration is high; meanwhile, the molecular layer becomes hydrophilic. When the concentration of H^+ is lower than a certain value, the protonated molecules can be deprotonated, so that the molecular layer becomes hydrophobic (Scheme 1). In our previous work, an H^+-responsive free-blockage release system was achieved based on the conversion between the hydrophobic and hydrophilic internal surfaces of nanopores.[32,33] Such studies inspired us to further make a thorough exploration whether the change between hydrophilicity and hydrophobicity can be observed directly by the height of the liquid column in the capillary tube shown in Scheme 1. More importantly, the switchable wettability materials in the capillary tube is flexibly replaced based on the object to be detected, so the HCS will hold great potential for portable detection. As schematically shown in Fig. S1,† the HCS device consists of only one capillary tube with scale. The HCS device is brought into contact with a drop of solution, and the height of the liquid column can be observed with the naked eye. In practice, the capillary tube is fixed on a graduated cardboard with an adhesive, and the capillary tube is exposed 0.5 cm at the bottom of the cardboard to conveniently contact the target solution. Besides, we drew a black line under the capillary tube shown in Fig. S1(c)† in order to make the colorless liquid level in the capillary tube easier to read.

In order to prove the feasibility of the HCS, some influencing factors need to be ruled out. Firstly, the surface tension and density of H^+ solution (10^{-7} M to 1 M) was measured. The test results are shown in Fig. S2,† and the relative standard deviation (RSD) was 0.4% (surface tension) and 0.5% (density), suggesting that the surface tension and density are essentially constant. Furthermore, solutions with different H^+ concentrations were tested using unmodified capillaries. As shown in Fig. 1a, the height of the liquid column is basically the same, and this indicated that the capillary height is less affected by the surface tension and density according to formula (2) in 10^{-7} M to 1 M H^+ solution. In principle, the change in the contact angle between the inner surface of the capillary tube will directly determine the rising height of the solution with a specific concentration range (10^{-7} M to 1 M).

For optimizing the device design, the capillary tube with the inner surface functionalized by different amounts of PhAPTMS (0.05%, 0.5%, and 5%) was used to detect 1 M and 10^{-7} M H^+ solution. As shown in Fig. 1b, the difference in capillary height between the minimum (10^{-7} M H^+ solution) and maximum (1 M H^+ solution) values is 1.3 cm (0.05% PhAPTMS-modified capillary), 2.75 cm (0.5% PhAPTMS-modi-

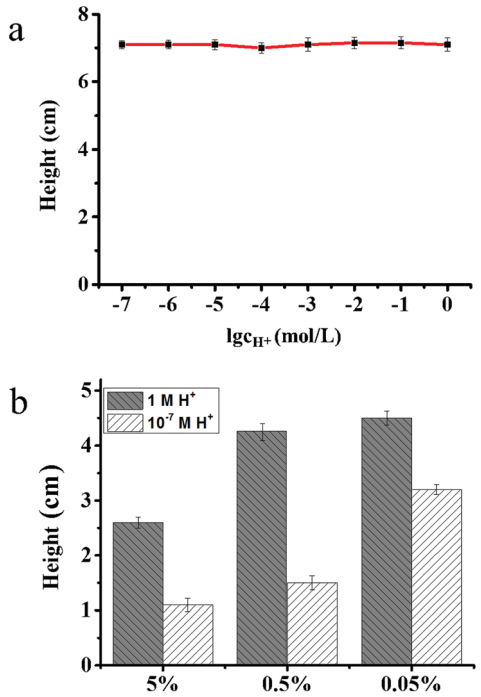

Fig. 1 (a) The feasibility investigation of the HCS device. Different H^+ (left to right: 10^{-7} M, 10^{-6} M, 10^{-5} M, 10^{-4} M, 10^{-3} M, 10^{-2} M, 10^{-1} M, 1 M) concentration solutions were demonstrated by unmodified capillaries. The size of the capillaries is 0.2 mmΦ × 100 mm. (b) HCS with different modification proportions (5%, 0.5% and 0.05%) were used to detect H^+ solution of 10^{-7} M and 1 M (20 μL). Each point was the average of five repeated tests.

fied capillary) and 1.5 cm (5% PhAPTMS-modified capillary). Therefore, the HCS has an optimal modification proportion of the responsive molecules in a certain detection range. Herein, 0.5% is preferred when the H^+ solution within the concentration range of 10^{-7} M to 1 M was detected.

In the preparatory work, the change of wettability on the PhAPTMS-modified surfaces was determined by contact-angle (CA) measurements. Fig. 2 shows the profiles of a water droplet on a smooth glass substrate modified with PhAPTMS (0.5% PhAPTMS-modified capillary). The CA for the liquid drop with different H^+ concentrations is 53° (1 M), 55° (10^{-1} M), 61° (10^{-2} M), 65° (10^{-3} M), 68° (10^{-4} M), 72° (10^{-5} M), 74° (10^{-6} M), and 77° (10^{-7} M). Such results indicate that the protonation of PhAPTMS molecules could indeed lead to a macroscopic change in CA, and the higher the protonation degree, the larger the CA change. As illustrated in Fig. 2, in the case of lower H^+ concentration, the hydrophobic backbone of PhAPTMS is exposed on the surface. Therefore, the surface is hydrophobic and the CA value is high. Nevertheless, in the case of higher H^+ concentration, some or all of the secondary amino groups of the PhAPTMS molecules are protonated, which shows better hydrophilic property, leading to the decrease of the CA.

After the optimization of the experimental conditions, the detection of different concentrations of H^+ (10^{-7} M, 10^{-6} M, 10^{-5} M, 10^{-4} M, 10^{-3} M, 10^{-2} M, 10^{-1} M, and 1 M) using the HCS (0.5% PhAPTMS-modified capillary) was carried out. The device was in contact with the H^+ solution in the vertical state until the solution in the HCS no longer rose, and the capillary height was recorded (Fig. 3a). The capillary height was linearly correlated to the concentration of H^+ within the range from 10^{-7} M to1 M, as shown in Fig. 3b. We can compute the sample H^+ concentration using the formula in the figure through the HCS. These results established the feasibility of the HCS for sensitive and quantitative detection. By changing the molecules with responsibility, the HCS can be applied to detect a great variety of targets.

To investigate the selectivity of the HCS for H^+ detection, Na^+ (1 M), K^+ (1 M), pepsin (2%), and a mixture of 0.01 M H^+ and 1 M Na^+ were chosen (as a selectable case, Na^+, K^+ and pepsin were usually found in gastric fluid), as shown in Fig. 4a. In addition to that, to explore whether the device can be used in more complex environments, we used the devices

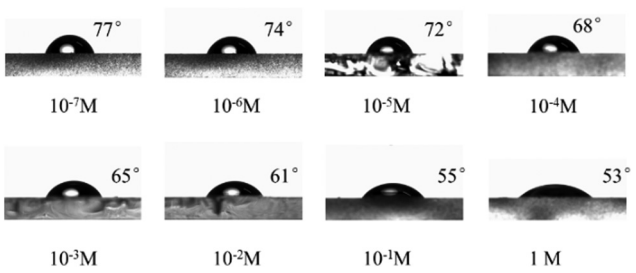

Fig. 2 Static contact angles (CAs) of 2.0 μL H^+ (10^{-7} M, 10^{-6} M, 10^{-5} M, 10^{-4} M, 10^{-3} M, 10^{-2} M, 10^{-1} M, 1 M) solution on the surface of glass slides modified with a PhAPTMS molecular layer (0.5%).

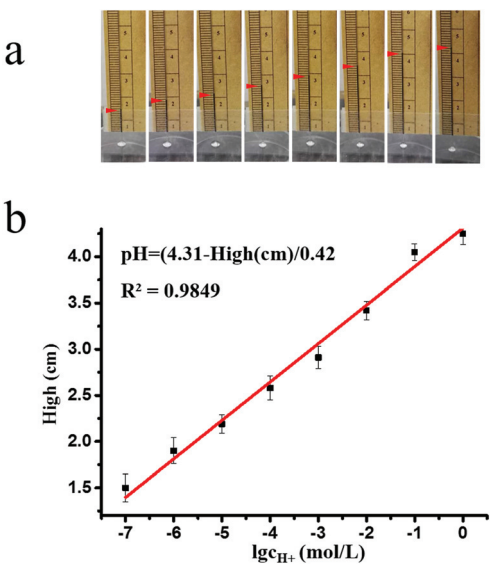

Fig. 3 (a) Photos of H^+ concentration detection from 10^{-7} to 1 M using the HCS. (b) Relationship of capillary height with H^+ concentration with the standard deviation obtained from three measurements.

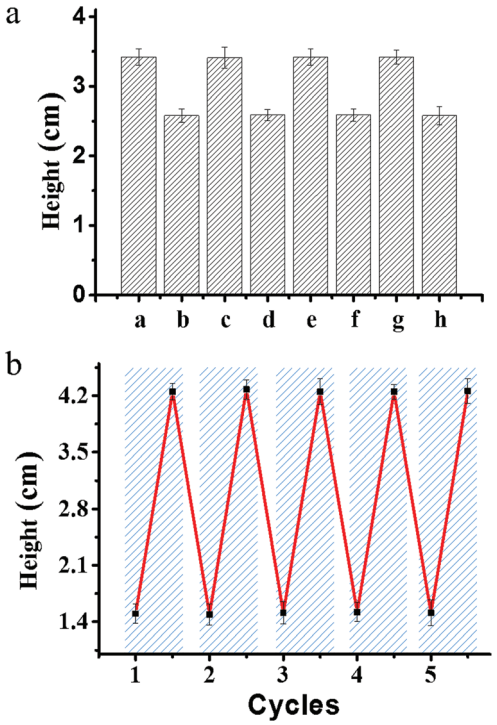

Fig. 4 (a) The selectivity of the HCS for H^+ detection (a, 1 M H^+; b, 0.01 M H^+; c, 1 M H^+ and 1 M Na^+; d, 0.01 M H^+ and 1 M Na^+; e, 1 M H^+ and 1 M K^+; f, 0.01 M H^+ and 1 M K^+; g, 1 M H^+ and 2% pepsin; h, 0.01 M H^+ and 2% pepsin). (b) The repeatability of the HCS was tested through detecting 10^{-7} M and 1 M H^+ solution five times.

to detect common cations in organisms and several buffer solutions which are used to simulate different biological substrates (Fig. S3 and S4†). These results showed that the capillary height of the above solution was clearly measured, while only negligible difference were detected. The PhAPTMS molecules cannot be protonated by other molecules and ions to cause wettability changes. Therefore, we demonstrated a quantitative detection method for H^+ with a visual and highly sensitive readout using the HCS for human gastric fluid. Even more, PhAPTMS is protonated when the H^+ solution is detected by the HCS, and the molecular layer will be deprotonated when the H^+ is kept at a low concentration. The reversibility between the protonation and deprotonation process also makes this device valuable for reuse. The used HCS (0.5%) devices were filled 10^{-8} H^+ solution in a horizontal position for 20 min, and then washed by 50% and 100% ethanol twice, and blown dry with N_2. The above steps are repeated five times to confirm that the device can be used repeatedly as shown in Fig. 4b; thus it was concluded that the sensor is stable and reusable for repeated analysis.

To investigate whether the HCS device is convenient to use, ten volunteers without the experience of using the sensor were randomly recruited to test the device. With the same concentration of H^+ solution (10^{-3} M), similar results were obtained with RSD less than 7.5% as shown in Fig. S5,† suggesting the fabrication reproducibility and working stability of the HCS. Beyond that, the quantitative detection device is independent of the pipette. A pipette is a laboratory tool commonly used in analytical chemistry to transport a measured volume of liquid, often as a media dispenser. However, the pipette is not common equipment in ordinary families. Different volumes (10 μL, 200 μL, 1 mL, 10 mL and 100 mL) of 10^{-3} M H^+ solution were analyzed. The RSD in the travel distance in response to 10^{-3} M H^+ solution of different sample volumes was 9.6%, demonstrating that the detection result of this device is not related to the sample volume and the excellent convenience of this proposed analytical system as shown in Fig. S6.†

The relative response of the same sample (10^{-3} M H^+ solution) extract was monitored in 10 analytical devices to check the robustness and accuracy of the biosensor methods. The ten parallel test results are shown in Fig. S7,† and the relative standard deviation (RSD) was 4.3% (n = 10), suggesting excellent reproducibility and robustness of the method. These results demonstrated the fabrication reproducibility and working stability of the HCS.

To further assess the applicability and reliability of the method proposed, herein, the recovery tests of 10 diluted normal human gastric juice samples were conducted. These samples were assayed according to the general procedures, and the "found" concentrations were estimated from the corresponding signals of the flow-through height changes and the regression equations. The assay of each sample was carried out 10 times and the results are summarized in Table S1 (ESI†). One can find from Table S1† that the obtained recovery results range from 95.5 to 107.9% and the RSDs are in the range of 2.7 to 9.5%, thus validating the acceptable recovery and practicability of this new H^+ assay technique.

To verify the universal applicability of the device, phenol, a metabolic product with a toxic effect on the central nervous system, was used as a target for portable detection. We speculate that phenol and the benzene ring fixed in the capillary wall formed a conjugate bond, so that the inner wall of the glass tube could have a hydrophilic hydrogen bond. Different concentrations of phenol resulted in different wettability of the capillary wall. As shown in Fig. S8,† the capillary height was linearly correlated with the concentration of phenol within the range of 10 mg mL^{-1} to 50 mg mL^{-1}. This example indicates that the HCS is highly applicable for the sensitive detection of a wide variety of targets.

In conclusion, we have developed a new concept POCT device based on the principle of capillary action. Like a thermometer, in the proposed device, the concentration of the analyte can be read with the naked eye through the height of the liquid column in the capillary tube. In this device, the H^+ in the solution can cause some changes of wettability of the inner surface of the capillary tube. This change would affect the capillary action, and result in different heights of the liquid column in the capillary tube under different H^+ conditions. Using this device, we have achieved the quantitative detection of the H^+ concentration from 10^{-7} M to 1 M. This POCT device has the advantages of simplicity, portability, high sensitivity, good reproducibility, no requirement of equipment,

no need for complex sample preparation or processing, and user-friendly operation. More importantly, the functional molecules with wettability responsibility can be flexibly designed according to the object to be detected.[25,28,29,34,35] In this way, this capillary-based method could be expected to find wide, potential application in clinical diagnostics, forensic analysis, environmental monitoring, *etc*.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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