

METHODS AND DEVICES FOR MEASURING URINE OSMOLALITY

Technical Field

5 The present disclosure generally relates to urine osmolality measurement. More particularly, the present disclosure relates to methods and devices for measuring urine osmolality.

Background

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Urine osmolality is vital for assessing health, reflecting renal function and hydration, typically expressed as mOsm/kg. Elevated levels may indicate medical conditions, like dehydration or kidney issues, while lower levels can be linked to issues such as diabetes insipidus. Monitoring osmolality after a 12-14 hour water deprivation helps
15 diagnose diabetes insipidus.

Urine osmolality aids in diagnosing nocturia, where the need to urinate during the night impacts well-being. Various conditions, including nocturnal polyuria, can lead to nocturia. Management can be challenging due to uncertain underlying causes, leading
20 to potentially ineffective treatments.

Accurate diagnosis is crucial, and osmolality complements clinical evaluation and bladder diaries, helping to guide treatment decisions. However, current osmolality testing is often costly and inconvenient, requiring specialized clinics and bulky
25 laboratory devices. For example, the freezing point method measuring osmolality through freezing point depression in specialized clinics, requires patients to visit clinics for monitoring urine osmolality.

Recently, portable osmometers have been developed to provide a quick estimation of
30 the urine osmolality based on urine specific gravity. However, research showed that urine specific gravity has poor correlation to urine osmolality, especially for pathological urines.

Summary

According to an aspect of the present disclosure, a method for measuring urine osmolality is provided. The method comprises: receiving a urine sample; mixing an adsorbent with the urine sample to obtain a urine-adsorbent mixture; determining an electrical impedance of the urine sample; measuring a refractive index of the urine-adsorbent mixture; determining an osmolality of the urine sample using the electrical impedance of the urine sample and the refractive index of the urine-adsorbent mixture. The adsorbent may comprise activated carbon powder.

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The adsorbent allows the refractive index of the urine-adsorbent mixture to correctly reflect the urea concentration in the urine sample. The method may thus accurately determine the osmolality of the urine sample through the combination of electrical impedance and refractive index.

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The electrical impedance of the urine sample may be determined either by measuring the impedance of the urine sample before mixing the adsorbent with the urine sample, or by measuring the electrical impedance of the urine-adsorbent mixture.

20 The procedure of determining the osmolality of the urine sample may comprise determining a molar concentration of conductive solutes in the urine sample based on the electrical impedance of the urine-adsorbent mixture using an electrical impedance model which models a relationship between the molar concentration of conductive solutes and the electrical impedance; determining a molar concentration of urea in the urine sample based on the refractive index of the urine-adsorbent mixture and the molar concentration of conductive solutes in the urine sample, using a refractive index model which models a relationship between the refractive index and the molar concentrations of both conductive solutes and urea; and determining the osmolality of the urine sample using the molar concentration of conductive solutes and the molar concentration of urea.

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The determination of osmolality of the urine sample may further comprise combining the molar concentration of conductive solutes and the molar concentration of urea,

thereby obtaining an initial result; and adjusting the initial result with an empirical factor, thereby obtaining the osmolality of the urine sample.

5 The method may further comprise selecting the electrical impedance model from a plurality of pre-calibrated electrical impedance models, and selecting the refractive index model from a plurality of pre-calibrated refractive index models.

10 The method may comprise measuring a current ambient temperature and select the electrical impedance model and the refractive index model based on the current ambient temperature, wherein each electrical impedance model of the plurality of pre-calibrated electrical impedance models models a relationship between the molar concentration of conductive solutes and the electrical impedance at a respective ambient temperature, and each refractive index model of the plurality of pre-calibrated refractive index models models a relationship between the refractive index and the
15 molar concentrations of both conductive solutes and urea at a respective ambient temperature.

According to another aspect of the present disclosure, a device for measuring urine osmolality is provided. The device comprises: a receptacle containing a urine-adsorbent mixture comprising a urine sample and an adsorbent; a measuring unit
20 configured to determine an electrical impedance of the urine sample and measure a refractive index of the urine-adsorbent mixture; a processing unit configured to determine an osmolality of the urine sample using the electrical impedance of the urine sample and the refractive index of the urine-adsorbent mixture. The adsorbent may
25 comprise activated carbon powder.

The device is simple to use, as the only action required by the device from an end user of may be collecting urine with the receptacle.

30 The processing unit may comprise a memory storing an electrical impedance model which models a relationship between the molar concentration of conductive solutes and the electrical impedance and a refractive index model which models a relationship between the refractive index and the molar concentrations of both conductive solutes

- and urea; and a processor. The processor is configured to determine a molar concentration of conductive solutes in the urine sample based on the electrical impedance of the urine-adsorbent mixture using the electrical impedance model; determine a molar concentration of urea in the urine sample based on the refractive index of the urine-adsorbent mixture and the molar concentration of conductive solutes, using the refractive index model; and determine the osmolality of the urine sample using the molar concentration of conductive solutes and the molar concentration of urea.
- 10 The processor may be configured to determine the osmolality of the urine sample by combining the molar concentration of conductive solutes and the molar concentration of urea, thereby obtaining an initial result; and adjusting the initial result with an empirical factor, thereby obtaining the osmolality of the urine sample.
- 15 The memory may store a plurality of pre-calibrated electrical impedance models and a plurality of pre-calibrated refractive index models and the processor may be configured to select the electrical impedance model from the plurality of pre-calibrated electrical impedance models, and to select the refractive index model from the plurality of pre-calibrated refractive index models.
- 20 The measuring unit may further comprise a thermometer configured to measure a current ambient temperature, and the processor is configured to select the electrical impedance model and the refractive index model based on a current ambient temperature measured by the measuring unit, wherein each electrical impedance
- 25 model of the plurality of pre-calibrated electrical impedance models models a relationship between the molar concentration of conductive solutes and the electrical impedance at a respective ambient temperature, and each refractive index model of the plurality of pre-calibrated refractive index models models a relationship between the refractive index and the molar concentrations of both conductive solutes and urea
- 30 at a respective ambient temperature.

The receptacle and the measuring unit may be configured to be attachable such that the measuring unit seals the receptacle and mixes the adsorbent with the urine sample when the receptacle and the measuring unit are attached.

- 5 The measuring unit may be configured to determine the electrical impedance of the urine sample by measuring an electrical impedance of the urine sample.

The measuring unit may be configured to determine the electrical impedance of the urine sample by measuring an electrical impedance of the urine-adsorbent mixture.

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The adsorbent may be arranged in the receptacle, wherein the receptacle may be further configured to receive the urine sample.

- 15 The receptacle may enclose a sealed space containing the adsorbent, the receptacle and the measuring unit may be configured such that the sealed space opens when the measuring unit is inserted, allowing the adsorbent to come into contact with the urine sample and be mixed with the urine sample by the measuring unit.

- 20 The device may further comprise a display, for displaying a value of the osmolality of the urine sample.

- 25 In embodiments, the device may have a smaller size than a laboratory device and thus have a low manufacturing cost, offering the patient an affordable way to measure urine osmolality. In some embodiments, the device is portable, allowing the patient to use at home conveniently without paying a visit to a clinic.

- 30 Methods and devices for measuring urine osmolality according to the present disclosure are thus disclosed herein. Various features, aspects, and advantages of the present disclosure will become more apparent from the following detailed description of the embodiments of the present disclosure, by way of non-limiting examples only, along with the accompanying drawings.

Brief Description of the Drawings

In the following, embodiments of the present invention will be described as non-limiting examples with reference to the accompanying drawings in which:

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FIG. 1 illustrates a flowchart of a method for measuring urine osmolality.

FIG. 2 illustrates a procedure of the method for measuring urine osmolality.

10 FIG. 3 illustrates a prototype of a device for measuring urine osmolality.

FIG. 4 illustrates a calibration process for an electrical impedance model.

FIG. 5 illustrates a graph representing the electrical impedance model.

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FIG. 6 illustrates a calibration process for a refractive index model.

FIG. 7 illustrates graphs representing the refractive index model.

20 FIG. 8 illustrates the relationship between urine osmolality estimated by the method and urine osmolality determined by clinical test.

FIG. 9A and 9B illustrate results from a validation test of the method for measuring urine osmolality.

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FIG. 10 illustrates a first device and corresponding procedures for measuring urine osmolality.

FIG. 11 illustrates a second device for measuring urine osmolality.

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FIG.12 illustrates a third device for measuring urine osmolality.

FIG. 13 illustrates procedures corresponding to the third device for measuring urine osmolality.

FIG. 14A, and 14B illustrate results from another validation test of the method for
5 measuring urine osmolality.

Detailed Description

For purposes of brevity and clarity, descriptions of embodiments of the present
10 disclosure are directed to methods and devices for measuring urine osmolality, in
accordance with the drawings. While aspects of the present disclosure will be
described in conjunction with the embodiments provided herein, it will be understood
that they are not intended to limit the present disclosure to these embodiments. On
the contrary, the present disclosure is intended to cover alternatives, modifications and
15 equivalents to the embodiments described herein, which are included within the scope
of the present disclosure as defined by the appended claims. Furthermore, in the
following detailed description, specific details are set forth in order to provide a
thorough understanding of the present disclosure. However, it will be recognized by
an individual having ordinary skill in the art, i.e. a skilled person, that the present
20 disclosure may be practiced without specific details, and/or with multiple details arising
from combinations of aspects of particular embodiments. In a number of instances,
well-known systems, methods, procedures, and components have not been described
in detail so as to not unnecessarily obscure aspects of the embodiments of the present
disclosure.

25 In embodiments of the present disclosure, depiction of a given element or
consideration or use of a particular element number in a particular figure or a reference
thereto in corresponding descriptive material can encompass the same, an equivalent,
or an analogous element or element number identified in another figure or descriptive
30 material associated therewith.

References to “an embodiment / example”, “another embodiment / example”, “some
embodiments / examples”, “some other embodiments / examples”, and so on, indicate

that the embodiment(s) / example(s) so described may include a particular feature, structure, characteristic, property, element, or limitation, but that not every embodiment / example necessarily includes that particular feature, structure, characteristic, property, element or limitation. Furthermore, repeated use of the phrase
5 "in an embodiment / example" or "in another embodiment / example" does not necessarily refer to the same embodiment / example.

The terms "comprising", "including", "having", and the like do not exclude the presence of other features / elements / steps than those listed in an embodiment. Recitation of
10 certain features / elements / steps in mutually different embodiments does not indicate that a combination of these features / elements / steps cannot be used in an embodiment.

As used herein, the terms "a" and "an" are defined as one or more than one. The use
15 of "/" in a figure or associated text is understood to mean "and/or" unless otherwise indicated. The term "set" is defined as a non-empty finite organization of elements that mathematically exhibits a cardinality of at least one (e.g. a set as defined herein can correspond to a unit, singlet, or single-element set, or a multiple-element set), in accordance with known mathematical definitions. The recitation of a particular
20 numerical value or value range herein is understood to include or be a recitation of an approximate numerical value or value range.

FIG. 1 is a flowchart showing a method of measuring urine osmolality according to an embodiment of the present invention. As shown in FIG. 1, the method 100 comprises
25 a step 110 of receiving a urine sample and a step 120 of mixing an adsorbent with the urine sample, resulting in a urine-adsorbent mixture. The method 100 comprises a step 130 of determining an electrical impedance of the urine sample and a step 140 of measuring a refractive index of the urine-adsorbent mixture. The step 130 may be accomplished by measuring the electrical impedance of the urine sample or the urine-adsorbent mixture. Finally, the method 100 comprises a step 150 of determining an
30 osmolality of the urine sample using both the electrical impedance of the urine sample and the refractive index of the urine-adsorbent mixture.

The adsorbent comprises a material that can absorb components of large molecular weight, such as activated carbon, activated charcoal and/or wood charcoal.

5 In a normal urine sample, the urine composition may be divided into conductive ions and non-conductive solutes. The conductive ions (~44%) consist of sodium ions (~18%), potassium ions (~7%), chloride ions (~19%), and trace amounts of other dissolved ions. The non-conductive solutes (~56%) consist of predominantly urea (~55%) and remaining solutes (~1%) such as creatinine, inorganic sulphur, and other inorganic and organic compounds. The urine osmolality can be determined by the
10 summation. The urine osmolality can achieve an accuracy of up to approximately 99% by quantifying the conductive ions (~44%) and non-conductive urea (~55%) present in the urine sample.

15 An electrical impedance measurement can effectively characterize the molar concentration of conductive solutes in a urine sample. However, it does not work for determining the concentration of urea, which is the largest non-conductive component in urine.

20 A refractive index measurement of liquids finds widespread use to measure the concentration of solutes in a solution. However, determining the concentration of urea in a urine sample solely based on the overall refractive index is not feasible. This limitation arises because the urine sample further contains large molecular weight components and conductive solutes. Large molecular weight components like creatinine, uric acid, glucose, and protein have a greater impact on the refractive index
25 of the urine sample than the dominant components (conductive solutes and urea). Additionally, the existence of conductive solutes also affects the overall refractive index reading. For example, solutions with 1 mol/kg sodium chloride (dominant conductive solute in urine) and solutions with 1 mol/kg urea have almost identical refractive index readings while the osmolality of the former is double that of the latter.

30 To address the limitation, the method 100 illustrated in FIG. 1 integrates a refractive index measurement with an electrical impedance measurement to determine the osmolality of a urine sample, with the help of activated carbon absorption. The

activated carbon absorbs urine components of large molecular weight, such as creatinine, uric acid, glucose and protein, thereby reducing their impact on the refractive index reading. The electrical impedance measurement is employed initially to assess the contribution of conductive solutes to osmolality, followed by the refractive index measurement to determine the contribution of urea.

FIG. 2 shows a procedure 200 for measuring urine osmolality. In the procedure 200, a urine sample 210 is received and mixed with an activated carbon 220 to obtain a urine-activated carbon mixture 230. Subsequently, a step 130 of measuring an electrical impedance of the urine-activated carbon mixture 230 and a step 140 of measuring a refractive index of the urine-activated carbon mixture 230 is included.

The electrical impedance reading 242 measured by step 130 is input to an electrical impedance model 240, to determine a molar concentration of NaCl 244 in the urine sample 210. Simultaneously, the refractive index reading 252 measured by step 140 is input to a refractive index model 250, to determine a molar concentration of Urea 254 of the urine sample 210. The molar concentration of NaCl 244 and the molar concentration of urea 254 are combined in step 150 with an empirical factor 270 to determine the osmolality 260 of the urine sample 210.

The electrical impedance model 240 models a relationship between the molar concentration of conductive solutes and the electrical impedance, and the refractive index model 250 models a relationship between the refractive index and the molar concentrations of both conductive solutes and urea.

FIG. 3 shows a device 300 for measuring urine osmolality. The device 300 includes a receptacle 310 to contain the urine sample 210 and the activated carbon 220 before step 120. After step 120, the receptacle 310 contains the urine-activated carbon mixture 230.

A first droplet (300 μ l) of the urine-activated carbon mixture 230 is measured by an impedance analyzer 320. Alternatively, which is not shown in the figure, it may be a droplet of the urine sample 210 that is measured by the impedance analyzer 320. The

impedance analyzer 320 consists of a Printed Circuit Board (PCB) 322 with electrodes 324 and an impedance analyzer module 326. The electrodes 324 connects to the impedance analyzer module 326. The first droplet of the urine-activated carbon mixture 230 is dripped onto the PCB 322 to cover the area of electrodes 324, allowing
5 the impedance analyzer module 326 to determine the electrical impedance reading 242 of the urine-activated carbon mixture 230. A second droplet (300 μ l) of the urine-activated carbon mixture 230 is measured by a refractometer 330. The refractometer 330 consists of a light source 332, a measurement chamber 334 and a photodiode 336. The second droplet of the urine-activated carbon mixture 230 is dripped onto the
10 measurement chamber 334, allowing the refractometer 330 to determine the refractive index reading 252 of the urine-activated carbon mixture 230 using the light source 332 and the photodiode 336. The impedance analyzer 320 and the refractometer 330 collectively form a measuring unit 340.

15 The osmolality 260 of the urine sample 210 is determined by a processing unit 350 using both the electrical impedance reading 242 and the refractive index reading 252.

FIG. 4 illustrates an exemplary calibration process 400 for the electrical impedance model 240. The calibration process 400 starts with a step 410 of preparing six sodium chloride (NaCl) solutions with molarity varying from 0.05 mol/kg to 0.5 mol/kg. In a step
20 420, each of the six NaCl solutions is loaded to cover the area of electrodes 324 of the Printed Circuit Board (PCB) 322. A step 430 follows, where the impedance analyzer module 326 is turned on to determine the electrical impedance of the NaCl solutions. The calibration process 400 ends with a step 440, where the electrical
25 impedance model 240 is generated.

A graph 500 representing the electrical impedance model 240 generated by the step 440 is shown in FIG. 5. The graph 500 illustrates a relationship between the molar concentration of conductive solutes and the electrical impedance by plotting the
30 reciprocal of R_{NaCl} (the electrical impedance of the NaCl solution determined by the step 430) as a function of the NaCl molar concentration. Solid dots show the experimental readings of the reciprocal of R_{NaCl} at NaCl molar concentration of 0.05

M, 0.10 M, 0.20 M, 0.30 M, 0.40 M and 0.50 M, respectively. The solid line is the optimal fitting curve obtained by constraining the curve to pass through the origin.

The constraint fit which ensures the fitting curve passes origin shows a high goodness of fit with $R^2=0.9936$. This indicates that $1/R_{NaCl}$ is linearly proportional to the NaCl molar concentration, M_{NaCl} , in the unit of mol/kg. Alternatively, the electrical impedance model 240 may be expressed by an equation as below:

$$1/R_{NaCl} = C_0 M_{NaCl}, \quad (1)$$

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where the coefficient $C_0 = 0.0266 \text{ kg}/(\text{mol} \cdot \Omega)$.

FIG. 6 shows an exemplary calibration process 600 for the refractive index model 250. The calibration process 600 includes a step 610 for preparing sample mixtures containing: NaCl in concentrations of 0.05 mol/kg, 0.10 mol/kg, 0.20 mol/kg, 0.30 mol/kg, 0.40 mol/kg and 0.50 mol/kg; and urea in concentrations of 0 mol/kg, 0.10 mol/kg, 0.20 mol/kg, 0.30 mol/kg, 0.40 mol/kg and 0.50 mol/kg. A step 620 follows, where 36 calibration samples are obtained. With reference to the device 300, the calibration process 600 also includes a step 630 of loading 300 μl of each calibration sample to the refractometer 330, and a step 640 of obtaining the refractive index of the calibration sample at a room temperature (25 °C). The calibration process 600 concludes with a step 650, where the refractive index model 250 is generated.

FIG. 7 shows graphs 700 representing the refractive index model 250 generated by the step 650. The graphs 700 include a graph 710 plotting the refractive index of the NaCl-urea mixture obtained in the step 620 as a function of the urea molar concentration, and a graph 720 plotting the refractive index of the NaCl-urea mixture obtained in the step 620 as a function of the NaCl molar concentration.

In the graph 710, the circular marks ($\circ$) are the experimentally measured refractive indexes at 0.05 mol/kg NaCl, rectangle marks ($\square$) are the experimentally measured refractive indexes at 0.1 mol/kg NaCl, cross marks ($\times$) are the experimentally

measured refractive indexes at 0.2 mol/kg NaCl, diamond marks ($\diamond$) are the experimentally measured refractive indexes at 0.3 mol/kg NaCl, asterisk marks (*) are the experimentally measured refractive indexes at 0.4 mol/kg NaCl, and triangle marks (∇) are the experimentally measured refractive indexes at 0.5 mol/kg NaCl. In the

5 graph 720, the circular marks ($\circ$) are the experimentally measured refractive indexes without urea, rectangle marks ($\square$) are the experimentally measured refractive indexes at 0.1 mol/kg urea, cross marks ($\times$) are the experimentally measured refractive indexes at 0.2 mol/kg urea, diamond marks ($\diamond$) are the experimentally measured refractive indexes at 0.3 mol/kg urea, asterisk marks (*) are the experimentally

10 measured refractive indexes at 0.4 mol/kg urea, and triangle marks (∇) are the experimentally measured refractive indexes at 0.5 mol/kg urea. The solid lines in both graph 710 and graph 720 are the best fitting curves. A strong linear relationship between the refractive index and the molar concentrations of both urea and NaCl is found, as the goodness of fitting R^2 for all fitted lines in graphs 700 are at least 0.995.

15 A linear model may relate the refractive index of the calibration sample, denoted by n_s , with the molar concentrations of both urea and NaCl, in the units of mol/kg, respectively denoted by M_{NaCl} and M_{urea} :

$$n_s = c_{NaCl}M_{NaCl} + c_{urea}M_{urea} + C_0, \quad (2)$$

20 where C_{NaCl} and C_{urea} , in the units of kg/mol, are the coefficients defining the contributions of per unit molar contributions of NaCl and urea to refractive index, respectively, and $C_0 = 1.333$ is a constant due to pure deionized (DI) water. Based on data presented in the graphs 700, it is found that the $C_{NaCl} = 0.01041$ kg/mol and $C_{urea} = 0.00966$ kg/mol lead to the best fitting results with $R^2 = 0.997$.

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The impedance reading may vary among devices, and the refractive index reading is affected by the surrounding temperature. Therefore, the three coefficients C_0 , C_{NaCl} and C_{urea} may need recalibration following the process 400 and the process 600 when

30 setting up a device for measuring urine osmolality at a different ambient temperature.

For simplicity, an end user of the device for measuring urine osmolality may only measure two samples with known chemical concentrations to calibrate the three coefficients (C_0 , C_{NaCl} and C_{urea}). For example, the end user could measure the electrical impedance and refractive index of a 300 μ l 0.5 mol/kg NaCl solution. The two coefficients C_0 and C_{NaCl} can therefore be determined based on Equations (1) and (2). The end user may then measure the refractive index of 300 μ l mixture with 0.5 mol/kg NaCl and 0.5 mol/kg urea, the last one coefficient C_{urea} can be determined by equation (2). According to experimental estimation, the calibration process takes approximately 6 minutes.

After the effects of conductive solutes and urea on the electrical impedance and refractive index are calibrated, in other words, the electrical impedance model 240 and the refractive index model 250 are generated, an osmolality of the urine sample can be determined.

With reference to the procedure 200, 600 μ l of the urine sample 210 is first mixed with 50 mg of activated carbon 220, obtaining a urine-activated carbon mixture 230. With reference to the device 300, the urine-activated carbon mixture 230 is then split into two of equal volumes. One portion is loaded onto the impedance analyzer 320 for an electrical impedance (R_{NaCl}) measurement, and the other is dripped onto the refractometer 330 to take a refractive index reading (n).

With reference to the step 150, the urine osmolality is determined by combining the molar concentration of NaCl and the molar concentration of urea using Equations (1) and (2), which gives,

$$(M_{osm})_{estimate} = 2M_{NaCl} + M_{urea} = \frac{2}{C_0} \left(1 - \frac{C_{NaCl}}{C_{urea}} \right) \frac{1}{R_{NaCl}} + \frac{n_s - n_{DI}}{C_{urea}}, \quad (3)$$

where $(M_{osm})_{estimate}$ is the urine osmolality estimated by the method 100 in FIG. 1 before combining with the empirical factor 270. While activated carbon shows excellent absorption degrees to some chemical compounds in the urine such as creatinine and uric acid, the absorption degrees do not reach 100% and many chemical compounds other than conductive solutes and urea cannot be absorbed by activated carbon.

These chemicals tend to increase the refractive index reading of the urine sample, leading to an overestimation of the urine osmolality. Therefore, an empirical factor, e , may be used to correct the urine osmolality value. With reference to the step 150, the exact urine osmolality, $(M_{osm})_{exact}$, may be determined by multiplying estimated urine osmolality with the empirical factor,

$$(M_{osm})_{exact} = e \cdot (M_{osm})_{estimate} \quad (4)$$

The factor e , may be empirically determined.

Ten calibration experiments are conducted to determine the empirical factor 270. The urine osmolality is first measured by inputting the electrical impedance and refractive index readings to Equation (3), and the urine osmolality is compared with that from a commercial freezing point osmometer (6002 Touch Micro OSMETTE™, Precision System, USA). The relationship between the urine osmolality estimated by Equation (3) ($(M_{osm})_{estimate}$) and the urine osmolality determined by the freezing point osmometer ($(M_{osm})_{exact}$) is illustrated in graph 800, as shown in FIG. 8. In the graph 800, circle marks represent the experimental data, and the line is the optimal fitting curve which is forced to pass through the origin. The constrained fitting, forcing the fitting line to pass through the origin, demonstrates a strong goodness of fit with $R^2 = 0.994$, showing a strong linear relationship between the two osmolality readings. In this example, the empirical factor e , may be calculated as 0.9082.

A clinical validation test is conducted to investigate how the method 100 can measure urine osmolality accurately in a blind test manner. Urine samples were obtained from 10 subjects respectively taken at four time-points: 1) before dinner, 2) before sleep, 3) middle of the night and 4) first wake-up in the morning. Table 1 summarized the results of the clinical trial for first 40 urine samples.

Sample (ID)	Our results (mOsm/kg H ₂ O)	Clinical results (mOsm/kg H ₂ O)	Accuracy (%)
N001-01	880	814	91.9
N001-02	883	843	95.2
N001-03	630	558	87.1
N001-04	367	391	94.0
N003-01	499	495	99.2
N003-02	211	209	98.9
N003-03	234	232	99.4
N003-04	264	252	95.2

N002-01	104	100	95.6
N002-02	271	261	96.3
N002-03	211	231	91.2
N002-04	160	182	87.8
N004-01	379	400	94.8
N004-02	458	449	97.9
N004-03	277	295	93.9
N004-04	479	443	91.9
N005-01	664	657	99.0
N005-02	645	662	97.4
N005-03	688	683	99.2
N005-04	617	632	97.6
N013-01	548	529	96.4
N013-02	276	274	99.4
N013-03	139	128	91.4
N013-04	310	312	99.3
N007-01	729	721	98.9
N007-02	392	394	99.4
N007-03	213	205	96.3
N007-04	402	421	95.5
N014-01	603	552	90.7
N014-02	557	545	97.8
N014-03	359	319	87.6
N014-04	387	396	97.7
HV12-01	807	810	99.6
HV12-02	1004	1036	96.9
HV12-03	573	632	90.6
HV12-04	421	460	91.6
HV13-01	594	629	94.4
HV13-02	397	406	97.7
HV13-03	205	226	90.8
HV13-04	781	813	96.1

Table 1

As shown in Table 1, the method 100 predicts the urine osmolarity with up to 95.3 ±
5 3.6 % accuracy compared to the results obtained from the validation test using a
clinical freezing point osmometer. The urine osmolality determined by the method 100
is plotted against and the urine osmolality determined by the freezing point osmometer
(based on 224 urine samples) in a graph 900 of FIG. 9A. In the graph 900, the
constrained fitting forcing the fitting line to pass through the origin, reveals a high
10 goodness of fitting with $R^2 = 0.9959$. The linear correlation coefficient between these
two osmolalities is 0.9975 and an average accuracy of 94.4 ± 5.0 %.

Alternatively, instead of the linear empirical factor shown in Equation (4), other curve
fitting functions, such as power function and polynomial, are also applicable. For

example, the power function relationship between $(M_{osm})_{estimate}$ and $(M_{osm})_{exact}$ can be expressed as:

$$(M_{osm})_{exact} = A \cdot [(M_{osm})_{estimate}]^B, \quad (5)$$

5 where the coefficient A and B were determined from the experiment data. Using the data from Table 1 and additional 103 urine samples, the empirical values are determined: $A = 1.176$ and $B = 0.9625$. Among these 103 additional urine samples. There are pathological urine samples with presence of high glucose concentration exceeding 1000 mg/dL from diabetic patients. The presence of these glucose
10 molecules would cause a significant over estimation of the urea concentration from the refractometer. Therefore, an addition protocol is administered. If the concentration of the measured conductive solutes, [Conductive] is less than 0.1 M and the [non-conductive] solutes is more than 0.5 M, the upper bound of the [non-conductive] solutes is set to 0.5 M. This is to be consistent with the calibration range shown in FIG.
15 7.

A relationship between the urine osmolality obtained with Equation (5) and the urine osmolality determined by the freezing point osmometer (based on 143 urine samples) is shown in FIG.9B. As plotted in graph 910, the linear correlation coefficient between
20 these two osmolalities is 0.9962 with an average accuracy of 94.5 ± 4.7 %.

An exemplary point-of-care device 1010 derived from the device 300 is depicted in schematics 1000 of FIG. 10. The device 1010 consists of a measurement unit 1020 and a disposable urine container 1030. The disposable urine container 1030, designed
25 for one time use, is prefilled with a portion of activated carbon (e.g., 40 mg activated carbon powder) and may be sealed with a plastic film 1032. Note that other ratios of activated carbon amount to urine volume can also be used, and the respective empirical factors would need to be determined. With reference to the FIG. 1, the disposable urine container 1030 may receive a urine sample in the step 110, allowing
30 the urine sample to be mixed with the activated carbon in the step 120, resulting in a urine-activated carbon mixture. In the measurement unit 1020, a temperature probe 1022, a pair of impedance probes 1024 and a refractometer 1026 are comprised. When the disposable urine container 1030 and the measurement unit 1020 are

attached, the temperature probe 1022, the pair of impedance probes 1024 and one of the prism's surfaces of the refractometer 1026 are in contact with the urine-activated carbon mixture.

- 5 Exemplary electronic components in the measurement unit are shown in a schematic 1040. A power supply module 1042 with direct current power supply, for example two AA batteries, drives a main board 1044 which takes and processes the temperature, electrical impedance and refractive index readings from the probes (the temperature probe 1022, impedance probes 1024 and the refractometer 1026), determines a urine
10 osmolality value and displays the urine osmolality value to a display module 1046 (e.g., LCD screen). The main board 1044 may select an electrical impedance model and a refractive index model to determine the urine osmolality value based on the temperature reading taken from the temperature probe 1022.
- 15 With reference to the device 300, the disposable urine container 1030 serves as the receptacle 310, the measurement unit 1020 serves as the measuring unit 340 and the main board 1044 serves as the processing unit 350.

- As illustrated by steps 1040 in FIG. 10, the usage of the device may comprise six
20 operation steps. For example, an end user may first peel off the plastic film 1032 from the disposable urine container 1030. After that, the end user may fill a urine sample to the position indicated by a thick marker line 1034. Thirdly, the end user may hold the disposable urine container 1030 and turn the measurement unit 1020 to seal the liquid. Thereby, the three probes are in contact with the urine sample and mixing it with the
25 prefilled activated carbon. Threads 1036 are designed on the neck of the disposable urine container 1030 to serve the purpose that, when the disposable urine container 1030 is sealed by the measurement unit 1020, the temperature probe 1022 and the pair of impedance probes 1024 mix the activated carbon with the urine sample. After a 3-minute waiting time, the urine osmolality reading may be displayed on the display
30 module 1046. In the last step, the end user may open the point-of-care device 1010 and dispose the used disposable urine container 1030 into a trash bin.

Compared to existing devices in the market, the design shown in FIG. 10 ensures that the point-of-care device 1010 has a much smaller footprint than a laboratory based freezing point osmometer. With an excellent measurement accuracy provided by the method, as shown in Table 1, the device is simple to use and envisioned to have a much cheaper manufacturing cost. It is suitable as a point-of-care device for elderly people to use at home, and it offers diagnostic utility in large-scale screening events with a short turnaround time. The consumable per test is a plastic container pre-filled with activated carbon, which is expected to be affordable to the general public while ensuring sustainable revenue growth for the manufacturer.

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An exemplary tethered portable urine osmometer 1100 derived from the device 300 is depicted in FIG. 11. The tethered portable urine osmometer 1100 consists of a reader unit 1110, a detachable measurement probe 1120 and a urine cup 1130 preloaded with a portion of activated carbon powder. The reader unit 1110 may comprise a mother board, a battery and a display. The detachable measurement probe 1120 serves to measure electrical impedance, refractive index and temperature. The reader unit 1110 may select an electrical impedance model and a refractive index model to determine the urine osmolality value based on the temperature reading taken from the detachable measurement probe 1120.

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With reference to the device 300, the urine cup 1130 serves as the receptacle 310, the detachable measurement probe 1120 serves as the measuring unit 340 and the reader unit 1110 serves as the processing unit 350.

25 An exemplary integrated portable urine osmometer 1200 derived from the device 300 is shown in FIG. 12. The integrated portable urine osmometer 1200 consists of a reader unit 1210 and a urine cup 1220 preloaded with a portion of activated carbon powder. The reader unit 1210 comprises a refractive index module 1212, which may consist of a Light Emitting Diode (LED) light, a prism and a linear Charge Coupled Device (CCD) sensor. The reader unit 1210 further comprises an electrode 1214 for measuring electrical impedance and a temperature sensor 1216. The refractive index module 1212 can be mounted on the vertical side wall of the reader unit 1210 to avoid trapping bubbles. Besides, other necessary components such as a motherboard, a

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battery, a display, a probe and a memory are also comprised in the reader unit 1210. The reader unit 1210 may select an electrical impedance model and a refractive index model to determine the urine osmolality value based on the temperature reading taken from the temperature sensor 1216.

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The urine cup 1220 serves to receive a urine sample. It may enclose a measurement chamber 1222, which comes preloaded with activated carbon powder. The urine cup 1220 is designed with a mechanism that allows the measurement chamber 1222 to open (e.g., in a spring-loaded manner) when the probe comprised in the reader unit 1210 is inserted, enabling the mixing of the activated carbon powder with the urine sample. Additionally, the urine cup 1220 may further comprise a component, such as a vibrator, to mix the activated carbon powder and the urine sample through vibrating. Alternatively, the activated carbon powder and the urine sample may be mixed using other feasible methods such as magnetic stirring or manually shaking. The measurement chamber 1222 may be a sealed space before being inserted by the probe.

It is possible in implementation, although not shown in FIG. 12, that the device is configured to measure the electrical impedance of the urine sample, before mixing the urine sample with the activated carbon powder. It may be achieved by configuring the electrode 1214 outside of the measurement chamber 1222, so that the electrode 1214 may measure the electrical impedance of the urine sample before the mixing mechanism is activated.

The integrated portable urine osmometer 1200 may be further configured to automatically detect the presence of a urine sample, initiate a timer for a specified incubation period (e.g., 3 minutes), and transmit data to a digital device (e.g., a mobile phone) for viewing a urine osmolality profile. The probe comprised in the reader unit 1210 may have additional features, such as being replaceable and waterproof, allowing for submersion in urine and easy cleaning.

With reference to the device 300, the urine cup 1220 serves as the receptacle 310, while the reader unit 1210 serves as both the measuring unit 340 and the processing

unit 350. In the reader unit 1210, the refractive index module 1212, the electrode 1214 and the temperature sensor 1216 serve as the measuring unit 340.

An exemplary process 1300 of urine osmolality measurement by the integrated portable urine osmometer 1200 is presented in flowcharts in FIG. 13. With reference to FIG. 12, the process 1300 starts with a step 1310, where an end user collects a urine sample (e.g., by urinating) in a sample bottle (the urine cup 1220). In a next step 1320, the end user attaches the sample bottle (the urine cup 1220) to a device for measuring urine osmolality (the integrated portable urine osmometer 1200). The process 1300 proceeds to a step 1330, in which the measurement chamber 1222 opens (spring-loaded) when the probe is inserted to mix the urine sample with the activated carbon powder for measurement. After that, in a step 1340, the device (the integrated portable urine osmometer 1200) detects if the urine sample volume is sufficient, for example, through change in electrical impedance. In a subsequent step 1350, the device (the integrated portable urine osmometer 1200) determines temperature, electrical impedance and refractive index.

In the step 1350, multiple sub-steps are included. In a sub-step 1351, a temperature of the urine sample is measured. With reference to the calibration process 400, a sub-step 1352 of measuring electrical impedance of the urine sample is followed by another sub-step 1353, where a NaCl concentration (denoted as [NaCl]) of the urine sample is determined from a calibration curve generated in the step 440. With reference to the calibration process 600, a sub-step 1354 involves measuring light intensity profile from linear CCD sensor, and this is followed by a sub-step 1355, where a refractive index of the urine sample is calculated from a calibration curve generated from the step 650. Additionally, there is another sub-step 1356, where an equivalent urea concentration (denoted as [Urea]) is determined.

The NaCl concentration and the urea concentration determined in the step 1350 are combined in a step 1360 to calculate osmolality of the urine sample based on an equation as below:

$$\text{urine osmolality} = 2[\text{NaCl}] + [\text{Urea}].$$

The process 1300 may end with a step 1370 of displaying the urine osmolality value on the device (the integrated portable urine osmometer 1200) through the display (e.g., a small Liquid-crystal/Organic light-emitting diode screen) comprised in the reader unit
5 1210.

A clinical validation test is conducted to investigate how the method 100 can measure urine osmolality accurately and specifically in a blind test manner. Urine samples were obtained from in total 48 subjects, among which, there are 41 Nocturnal Polyuria (NP)
10 patients and 7 healthy volunteers. Urine samples were obtained from subjects respectively taken at four time-points: 1) before dinner, 2) before sleep, 3) middle of the night and 4) first wake-up in the morning.

A graph 1400 shows sensitivity and specificity of a freezing point osmometer and an
15 activated carbon method (i.e., the method 100) in FIG. 14A. In a chart 1402, the evaluation results for a freezing point osmometer is recorded. As shown in the chart 1402, for individuals experiencing nocturia, 28 tested positive, while 13 tested negative. In the healthy group, 2 tested positive, and 5 tested negative. The sensitivity of the method, indicating its ability to correctly identify true positives among those with
20 nocturia, is 0.683. The specificity, representing the method's capacity to accurately identify true negatives among healthy individuals, is 0.714.

Another chart 1404 included in the graph 1400, shows the evaluation results for the
25 activated carbon method as follows: among individuals experiencing nocturia, 29 tested positive, and 12 tested negative. In the healthy group, 2 tested positive, and 5 tested negative. The sensitivity of this method is 0.707. The specificity is 0.714.

Comparing results shown in the chart 1404 with those in the chart 1402, it seems that
30 the activated carbon method shows a slightly higher sensitivity while maintaining a similar level of specificity. In summary, the activated carbon method shows better, or at least similar, performance compared to the freezing point osmometer.

In FIG. 14B, a graph 1410 illustrates urine osmolality measurements obtained from the freezing point osmometer versus the activated carbon method for NP patients (non-shaded) and healthy volunteers (shaded). It can be seen that, the urine osmolality obtained from the activated carbon method gives a similar trend to the

5 freezing point osmometer.

Claims

1. A method for measuring urine osmolality, the method comprising:
receiving a urine sample;
5 mixing an adsorbent with the urine sample to obtain a urine-adsorbent mixture;
determining an electrical impedance of the urine sample;
measuring a refractive index of the urine-adsorbent mixture; and
determining an osmolality of the urine sample using the electrical impedance of
the urine sample and the refractive index of the urine-adsorbent mixture.
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2. The method according to claim 1, wherein determining the osmolality of the
urine sample comprises:
determining a molar concentration of conductive solutes in the urine sample
based on the electrical impedance of the urine sample using an electrical impedance
15 model which models a relationship between the molar concentration of conductive
solute and the electrical impedance;
determining a molar concentration of urea in the urine sample based on the
refractive index of the urine-adsorbent mixture and the molar concentration of
conductive solutes in the urine sample, using a refractive index model which models
20 a relationship between the refractive index and the molar concentrations of both
conductive solutes and urea; and
determining the osmolality of the urine sample using the molar concentration of
conductive solutes and the molar concentration of urea.
- 25 3. The method according to claim 2, wherein determining the osmolality of the
urine sample comprises:
combining the molar concentration of conductive solutes and the molar
concentration of urea, thereby obtaining an initial result; and
adjusting the initial result with an empirical factor, thereby obtaining the
30 osmolality of the urine sample.
4. The method according to claim 2 or 3, further comprising selecting the electrical
impedance model from a plurality of pre-calibrated electrical impedance models, and

selecting the refractive index model from a plurality of pre-calibrated refractive index models.

5 5. The method according to claim 4, further comprising measuring a current ambient temperature and selecting the electrical impedance model and the refractive index model based on the current ambient temperature, wherein

 each electrical impedance model of the plurality of pre-calibrated electrical impedance models models a relationship between the molar concentration of conductive solutes and the electrical impedance at a respective ambient temperature, and each refractive index model of the plurality of pre-calibrated refractive index models models a relationship between the refractive index and the molar concentrations of both conductive solutes and urea at a respective ambient temperature.

15 6. The method according to claim 1, wherein determining the electrical impedance of the urine sample comprises measuring an electrical impedance of the urine sample.

 7. The method according to claim 1, wherein determining the electrical impedance of the urine sample comprises measuring an electrical impedance of the urine-adsorbent mixture.

 8. The method according to any of claims 1 to 7, wherein the adsorbent comprises activated carbon powder.

25 9. A device for measuring urine osmolality, comprising:
 a receptacle configured for containing a urine-adsorbent mixture comprising a urine sample and an adsorbent;
 a measuring unit configured to:
 determine an electrical impedance of the urine sample and measure a refractive index of the urine-adsorbent mixture; and
30 a processing unit configured to:

determine an osmolality of the urine sample using the electrical impedance of the urine sample and the refractive index of the urine-adsorbent mixture.

- 5 10. The device according to claim 9, wherein the processing unit comprises:
a memory storing an electrical impedance model which models a relationship
between the molar concentration of conductive solutes and the electrical impedance
and a refractive index model which models a relationship between the refractive index
and the molar concentrations of both conductive solutes and urea; and
10 a processor configured to:
determine a molar concentration of conductive solutes in the urine
sample based on the electrical impedance of the urine-adsorbent
mixture using the electrical impedance model;
determine a molar concentration of urea in the urine sample based on
15 the refractive index of the urine-adsorbent mixture and the molar
concentration of conductive solutes, using the refractive index model; and
determine the osmolality of the urine sample using the molar
concentration of conductive solutes and the molar concentration of urea.
- 20 11. The device according to claim 10, wherein the processor is configured to
determine the osmolality of the urine sample by:
combining the molar concentration of conductive solutes and the molar
concentration of urea, thereby obtaining an initial result;
adjusting the initial result with an empirical factor, thereby obtaining the
25 osmolality of the urine sample.
12. The device according to claim 10 or 11, wherein the memory stores a plurality
of pre-calibrated electrical impedance models and a plurality of pre-calibrated
refractive index models and the processor is configured to select the electrical
30 impedance model from the plurality of pre-calibrated electrical impedance models, and
to select the refractive index model from the plurality of pre-calibrated refractive index
models.

13. The device according to claim 12, wherein the measuring unit further comprises a thermometer configured to measure a current ambient temperature, and the processor is configured to select the electrical impedance model and the refractive index model based on a current ambient temperature measured by the measuring unit,
5 wherein
each electrical impedance model of the plurality of pre-calibrated electrical impedance models models a relationship between the molar concentration of conductive solutes and the electrical impedance at a respective ambient temperature, and each refractive index model of the plurality of pre-calibrated refractive index
10 models models a relationship between the refractive index and the molar concentrations of both conductive solutes and urea at a respective ambient temperature.
14. The device according to any of claims 9 to 13, wherein the receptacle and the
15 measuring unit are configured to be attachable such that the measuring unit seals the receptacle and mixes the adsorbent with the urine sample when the receptacle and the measuring unit are attached.
15. The device according to any of claims 9 to 14, comprising the adsorbent
20 arranged in the receptacle, wherein the receptacle is further configured to receive the urine sample.
16. The device according to claim 15, wherein the receptacle encloses a sealed space containing the adsorbent, the receptacle and the measuring unit are configured
25 such that the sealed space opens when the measuring unit is inserted, allowing the adsorbent to come into contact with the urine sample and be mixed with the urine sample by the measuring unit.
17. The device according to claim 9, wherein the measuring unit is configured to
30 determine the electrical impedance of the urine sample by measuring an electrical impedance of the urine sample.

18. The device according to claim 9, wherein the measuring unit is configured to determine the electrical impedance of the urine sample by measuring an electrical impedance of the urine-adsorbent mixture.

5 19. The device according to any of claims 9 to 18, wherein the adsorbent comprises activated carbon powder.

20. The device according to any of claims 9 to 19, further comprising:
a display, for displaying a value of the osmolality of the urine sample.

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