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(54) **Title:** INGESTIBLE BIOSENSING CAPSULE WITH INTEGRATED THREAD-BASED SENSORS

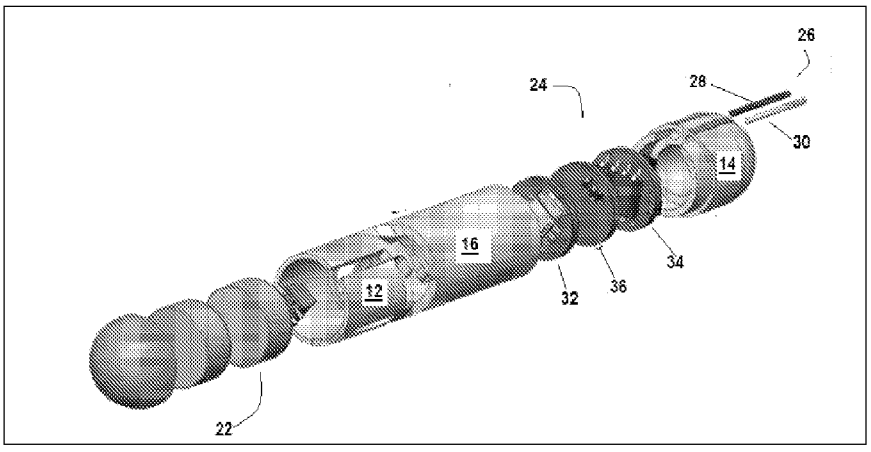


FIG. 2

(57) **Abstract:** A capsule for passage through a gastrointestinal tract includes an electrochemical sensor disposed thereon and circuitry disposed within it. The circuitry uses the electrochemical sensor to obtain a measurement of a parameter within said gastrointestinal tract.

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INGESTIBLE BIOSENSING CAPSULE WITH INTEGRATED THREAD-BASED SENSORS

RELATED APPLICATIONS

This application claims the benefit of the Feb. 8, 2022 priority date of U.S. Provisional Application 63/307,863, the contents of which are incorporated herein by reference.

FIELD OF INVENTION

The invention relates to sampling the content of the gastrointestinal tract and, in particular, to sampling using an ingestible sampler.

BACKGROUND

A human being comprises a gastrointestinal tract having a first orifice that receives food as input. As the food proceeds along the gastrointestinal tract, it undergoes various processes that result in extraction of nutrients. These nutrients are then absorbed into the human being's interior volume and used for various purposes. What remains is then ejected through a second orifice.

The gastrointestinal tract occasionally suffers from various disorders. Among these are gastric ulcers, Crohn's colitis, and inflammatory bowel disease. These diseases are often characterized by localized changes in the environment of the gastrointestinal tract. It is therefore useful, in the study and treatment of such diseases, to be able to ascertain the conditions within a limited portion of the gastrointestinal tract.

There do exist methods for observing conditions within different parts of the gastrointestinal tract. However, these tend to be invasive procedures that involve such activities as surgery, biopsy, and endoscopy. Among these procedures are those that also require considerable pre-operative cooperation from the patient, such as colonoscopy.

SUMMARY

As one proceeds along the gastrointestinal tract, the local environmental properties change. For example, within the stomach, the environment is highly acidic. As one proceeds into the duodenum, the environment, though still acidic, begins to approach neutrality. Eventually, within the colon, the environment becomes essentially neutral.

Meanwhile, the dissolved oxygen concentration also begins to drop as one travels from the stomach towards the colon. Within the stomach, the concentration of dissolved oxygen. Within the duodenum, it will have dropped to less than half its original concentration.

As a result, it is possible to use measurements of these and other environmental variables to locate one's approximate position within the gastrointestinal tract. Knowledge of one's location makes it possible to coordinate the activity of an ingested capsule with that location, thereby making it possible to study a targeted location within the gastrointestinal tract.

In one aspect, the invention features a capsule, an electrochemical sensor disposed on the capsule, and circuitry disposed within the capsule, the circuitry being configured to use the electrochemical sensor to obtain a measurement of a parameter within the gastrointestinal tract as the capsule passes therethrough.

Embodiments include those in which the electrochemical sensor includes a conductive thread and those in which it includes a screen-printed conductor that extends along an outer surface of the capsule.

The electrochemical sensor is one that has been functionalized to make any one of a variety of measurements or combinations thereof. Among these are electrochemical sensors that have been functionalized for measurement of acidity or alkalinity, bile, glucose levels, lactate levels, dopamine levels, serotonin levels, amounts of short-chain fatty acids in the gastrointestinal tract, dissolved oxygen concentration, and concentrations of one or more neurotransmitters, all in the gastrointestinal tract. Accordingly, among the embodiments are those in which the electrochemical sensor is functionalized to sense more than one of the foregoing parameters and to do so concurrently with each other.

In some embodiments, the circuitry includes a controller and a shut-down circuit. The shut-down circuit is configured to prevent the circuitry from storing a signal provided by the electrochemical sensor.

Still other embodiments feature a sampling mechanism for drawing liquid into the capsule. In such embodiments, the controller actuates the sampling mechanism in response to information provided by the electrochemical sensor. Examples of such information include

information about acidity or alkalinity, bile, glucose levels, lactate levels, dopamine levels, serotonin levels, amounts of short-chain fatty acids in the gastrointestinal tract, dissolved oxygen concentration, and concentrations of one or more neurotransmitters.

Still other embodiments include an auger and a motor that turns the auger, both of which are in the capsule. The capsule, in such embodiments, includes an opening through which the auger draws liquid. The controller is configured to start the motor automatically in response to information provided by the electrochemical sensor. Among these are embodiments in which the controller starts the motor in response to a measurement of pH, a measurement of dissolved oxygen concentration, or a combination thereof.

Also among these embodiments are those that include a reed switch. The reed switch changes state in response to an applied magnetic field so as to start the motor. This enables the controller to be overridden.

In another aspect, the invention features a method that includes providing a capsule for ingestion. This capsule has an electrochemical sensor on a surface thereof. The electrochemical sensor connects to circuitry configured to receive a signal indicative of a parameter. After the capsule has been ingested, the controller receives information from the electrochemical sensor concerning an environmental variable within a gastrointestinal tract into which the capsule has been ingested.

Among the practices are those that includes causing the controller to store information provided by the electrochemical sensor within a memory that is in the capsule and then eventually recovering the information from the memory after the capsule has been ejected from the gastrointestinal tract.

Also among the practices are those that include using the information provided by the electrochemical sensor to initiate sampling of liquid that is within the gastrointestinal tract and recovering the sample from the capsule after the capsule has been ejected from the gastrointestinal tract. Among these practices are those in which using the information includes using information indicative of pH of liquid around the capsule, using information indicative of dissolved oxygen concentration in liquid around the capsule, and using both the information

indicative of dissolved oxygen concentration in liquid around the capsule and the information indicative of pH of the liquid around the capsule.

Other practices include initiating sampling of liquid that is within the gastrointestinal tract by applying a magnetic field to actuate a reed switch in the capsule and then recovering the sample from the capsule after the capsule has been ejected from the gastrointestinal tract.

In yet another aspect, the invention features using additive manufacturing to manufacture an ingestible capsule, inserting circuitry into that capsule, placing an electrochemical sensor on its outer surface, and connecting the circuitry to the electrochemical sensor.

Among these practices are those in which placing the electrochemical sensor includes placing an electrochemical sensor that is configured to measure pH, those in which placing the electrochemical sensor includes placing an electrochemical sensor that is configured to measure dissolved oxygen concentration, and those in which placing the electrochemical sensor includes placing an electrochemical sensor that is configured to measure both pH and dissolved oxygen concentration.

Also among the practices of the invention are those that further include incorporating a reed switch into the ingestible capsule to permit collection of a sample to be initiated by application of an external magnetic field.

In still another aspect, the invention features an ingestible sensor for sensing the environment of a gastrointestinal tract. Such a sensor includes a capsule, an electrochemical sensor disposed on the capsule, and circuitry disposed within the capsule. The circuitry is configured to use the electrochemical sensor to obtain a measurement of a parameter within the gastrointestinal tract.

Embodiments include those in which the electrochemical sensor comprises a conductive thread and those in which it comprises a screen-printed conductor that extends along an outer surface of the capsule.

Depending on how the electrochemical sensor has been functionalized, the measurement includes one or more of a measurement of acidity or alkalinity of the gastrointestinal tract, a

measurement of one or more bile acids in the gastrointestinal tract, a measurement of glucose levels in the gastrointestinal tract, a measurement of lactate levels in the gastrointestinal tract, a measurement of dopamine levels in the gastrointestinal tract, a measurement of serotonin levels in the gastrointestinal tract, a measurement of amounts of short-chain fatty acids in the gastrointestinal tract, a measurement of oxygen in the gastrointestinal tract, and a measurement of a neurotransmitter in the gastrointestinal tract.

Further embodiments include those in which the circuitry comprises a controller and a shut-down circuit. In such embodiments, the shut-down circuit is configured to prevent the circuitry from receiving a signal provided by the electrochemical sensor.

In yet another aspect, the invention includes a method comprising providing a capsule for ingestion. The capsule includes an electrochemical sensor on a surface thereof, the electrochemical sensor being connected to circuitry configured to receive and store a signal indicative of a parameter. The method further includes, after the capsule has been ingested, causing a controller in the capsule to prevent storage of the signal.

Among the practices of the method are those that include causing the controller to enable storage of the signal and, after having done so, causing the controller to prevent storage of the signal.

Still other practices include, after having caused ingestion of the capsule, recovering the capsule.

In yet another aspect, the invention features using additive manufacturing to manufacture an ingestible capsule, inserting circuitry into the capsule, placing an electrochemical sensor on an outer surface of the capsule, and inserting circuitry into the capsule, the circuitry being connected to the electrochemical sensor. Such an additive manufacturing uses stereolithography and two-photon polymerization to promote higher resolution and finish.

In preferred practices, additive manufacturing is used for such features as a screw, a reservoir, an inlet, and an outlet. Other components, such as the thread-based flexible sensors, battery and custom flexible printed circuit boards with electronics therein are manually inserted and epoxied in place using a resin that cures when exposed to ultraviolet light.

These and other features of the invention will be apparent from the following detailed description and the accompanying figures, in which:

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows an ingestible capsule having a sensor at an end thereof;

FIG. 2 is an exploded view of the capsule in FIG. 1;

FIG. 3 shows components within the middle compartment of the capsule shown in FIG. 2;

FIG. 4 shows the interconnections of the circuit components shown in FIG. 3;

FIG. 5 shows details of the shut-down circuit in FIG. 4; and

FIG. 6 shows an embodiment in which information obtained by the sensor is used to control sampling of matter from the gastrointestinal tract.

DETAILED DESCRIPTION

FIG. 1 shows an ingestible capsule **10** formed using an additive manufacturing process. The capsule **10** comprises first and second end-compartments **12**, **14** and a middle compartment **16** therebetween. Recesses **18** on the second end-compartment **14** terminate in openings **20** that lead into the middle compartment **16**.

At least a portion of the capsule **10** is fluorescent to promote its recovery after use. The capsule **10** is small enough to easily swallow. In the illustrated embodiment, the capsule **10** is thirty-three millimeters long and between eight and nine millimeters in diameter.

As shown in the exploded view of FIG. 2, the first end-compartment **12** houses a power source **22**. In the illustrated embodiment, the power source **22** comprises a pair of silver oxide coin cell batteries, each of which provides 1.55 volts of potential and a total charge of 45 milliamp-hours.

On its outer surface, the second end-compartment **14** supports an electrochemical sensor **26**. As shown in FIG. 2, the electrochemical sensor **26** interacts with circuitry **24** within the middle compartment **16**. In the illustrated embodiment, the electrochemical sensor **26** comprises

first and second threads **28**, **30** nestled within the recesses **18**. The first and second threads **28**, **30** connect to the circuitry **24** via the openings **20**.

In some embodiments, the electrochemical sensor **26** comprises conductive material that has been printed directly on the outer surface of the second end- compartment **14** during an additive manufacturing process. In such embodiments, recesses **18** are optional. The conductive material that has been printed onto the outer surface connects to the circuitry **24** through corresponding vias. In such embodiments, the second-end compartment **14** is essentially a printed-circuit board that exists on a curved manifold.

In those embodiments that are configured to sense acidity or alkalinity the first thread **28** is a reference electrode that comprises silver and the second thread **30** is a working electrode that comprises a carbon-coated linen thread that has been further coated with a conducting polymer, such as polyaniline.

Within the gut, there are many other parameters other than acidity or alkalinity that may be of interest.

For example, in some embodiments, it is useful to sense the concentration of dissolved oxygen. In addition, it is useful to be able to measure concentrations of such substances that are known to be high at selected locations since doing so provides an indication of where the capsule **10** is located. For example, an electrochemical sensor **26** that is tuned to sense bile would provide a way to recognize that the capsule **10** has reached the neighborhood at which the bile duct empties into the intestine.

The electrochemical sensor **26** is by no means limited to sensing only one parameter. After all, there is plenty of space on the second end-compartment **14** for threads **28**, **30** or conductive strips that have been functionalized in different ways to sense different substances or environmental conditions within the gastrointestinal tract.

In effect, the set of all measurable properties at a location within the gastrointestinal tract defines a multi-dimensional space. Measurement of one or more coordinates of a point in that space provides information from which it is possible to make inferences concerning the location of the capsule at the time of measurement. The more coordinates one samples using the

electrochemical sensor **26**, the more precisely one can distinguish the location of the capsule **10**. For example, if two locations have the same pH, one could not distinguish them by measuring only pH. But if one location differed from the other in dissolved oxygen concentration, then a measurement of those two coordinates in the measurement space would provide a basis for distinguishing the two locations.

The use of pH and pO_2 (i.e., partial pressure of dissolved oxygen) rather than pH alone is particularly helpful because pH varies only within a narrow range in both the small and large intestines, because it fluctuates locally, and because the spatial distribution of pH is likely to vary among individuals. The use of pH and pO_2 in concert provides enough spatial resolution to determine whether the capsule **10** is within the stomach, duodenum, jejunum, ileum, ascending colon or descending colon.

Embodiments of the electrochemical sensor **26** thus include sensors that have been configured to measure any one or more of: acidity, alkalinity, presence of bile, glucose levels, lactate levels, dopamine levels, serotonin levels, oxygen levels, and concentrations of various fatty acids, such as short-chain fatty acids.

FIG. 3 shows a typical layout of the circuitry **24** within the middle compartment **16**. The illustrated circuitry **24** is spread across first, second, and third printed-circuit boards **32**, **34**, **36**. Each circuit printed-circuit boards **32**, **34**, **36** is a circular structure that extends across the capsule's diameter. The circuit boards **32**, **34**, **36** are separated along the capsule's longitudinal axis.

The first circuit board **32**, which is closest to the power source **22**, supports a microcontroller **38**, an oscillator **40**, and a programming connector **42** that permits one to program the microcontroller **38**.

The second circuit board **34**, which is that closest to the second end-compartment **14**, interfaces with the electrochemical sensor **26** using a voltage buffer **44** that provides an analog signal to an analog-to-digital converter **46**. The analog-to-digital converter **46** converts the analog signal from the electrochemical sensor **26** into data that can be stored in a memory **48**, such as an EEPROM, that is on the third printed-circuit board **34**. This third printed-circuit board

36 lies between the first and second printed-circuit boards **32**, **34**. In a preferred embodiment, the analog-to-digital converter **46** is a delta-sigma converter, and in particular, a 16-bit ΔΣ converter.

Operation of the electrochemical sensor **26** draws considerable power. In an effort to conserve the finite supply of power, it is useful to collect data only when the capsule **10** is traversing a region of interest within the tract. It is thus useful to provide a shut-down circuit **50** on the second printed-circuit board **34**. This shut-down circuit **50** enables or disables operation of the analog-to-digital converter **46** and the voltage buffer **44** in response to commands from the microcontroller **38**.

FIG. 4 is a block diagram showing the interconnection of the components discussed in connection with FIG. 3.

In response to a signal from the microcontroller **38**, the shutdown circuit **50** permits the voltage buffer **44** to buffer an analog signal from the electrochemical sensor **26**. It also permits the analog-to-digital converter **46** to convert that analog signal into data that it then provides the microcontroller **38**. The microcontroller **38** receives this data and stores it in the memory **48**. Following the capsule's ejection from the GI tract and its subsequent recovery, the data is read from the memory **48** using a suitable protocol, such as SPI or UART.

FIG. 5 shows a particular implementation of a shutdown circuit **50** featuring first and second conducting paths **52**, **54**, both of which connect the power source **22** to ground. The load, i.e., the voltage buffer **44** and the analog-to-digital converter **46**, lies along the second conducting path **54**.

First and second transistors **56**, **58** that lie along the first and second conducting paths **52**, **54** cause the paths **52**, **54** to transition between conducting and non-conducting states. The microcontroller **38** provides a signal to the first transistor's gate. Meanwhile, the second transistor's gate connects to the first conducting path **52** at a point whose voltage depends on whether the first transistor **56** is allowing the first conducting path **52** to conduct. As a result, the microcontroller **38** also controls flow along the second conducting path **54**, thereby enabling or disabling the voltage buffer **44** and the analog-to-digital converter **46**.

The electrochemical sensor **26** and its associated circuitry **24** provide a basis for controlling activity by the capsule **10**. In the embodiments described thus far, that activity involves gathering of measured data. However, in some embodiments, the activity involves gathering of matter, and in particular, of matter contained within the gastrointestinal tract.

FIG. 6 shows one such embodiment of a capsule **10**. In this embodiment, the electrochemical sensor **26** has been moved to surface of the first end-compartment **12**. This move arises because the second end-compartment **14** is now being used for sampling. In particular, the second end-compartment **14** now has an inlet **62** for admitting liquid and an outlet **64** for allowing exit of air displaced by the incoming liquid. For those embodiments that are intended to sample from the colon, it is useful to provide an enteric coating that dissolves only upon arriving at the neutral pH environment of the colon.

A screw **66** extends along the capsule's axis between the inlet **62** and a motor **68**. Such a screw **66** is typically made using an additive manufacturing process.

The screw **66** is enclosed by a bore **70** and a silicone tube **72**. In operation, the motor **68** turns the screw **66**. The turning screw **66** then draws liquid into the capsule through the tube **72** in a manner similar to an Archimedean screw. This liquid eventually fills a reservoir **74**, displacing air through the outlet **64** as it does so.

The capsule **10** includes a switch **76** that turns the motor **68** on and off. To sample at a particular location, it is necessary to use the switch **76** to turn the motor **68** on only once the capsule **10** has reached that location.

In some embodiments, the switch **76** incorporates a reed switch that operable from outside, for example by using a magnet. This permits a clinician to override the autonomous sampling feature provided by the controller **38**. Thus, a clinician could use a magnet to activate sampling or recordation of data upon confirming, using a non-invasive imaging method, (e.g., ultrasound or CT scanning) that the capsule **10** has arrived at a region-of-interest. Such an alternative activation mechanism will ensure accurate spot sampling to assess inter-individual variability in response to dietary perturbations and in patients with GI tract disturbances, which

affect pH and pO_2. For example, inflammation of the gut increases pO_2. Thus, the ability to override autonomous control is particularly relevant to individuals with these types of disorders.

The motor **38** is typically a miniaturized DC motor that can turn hundreds of times per minute, thus providing rapid sampling. For example, for a typical screw **66** with four turns that traps half a microliter between adjacent blades, a readily achievable rotation rate of 1200 RPM can fill a 300-microliter reservoir in under ten seconds, independently of viscosity of the liquid being transported. This rapid sampling improves spatial resolution of the sampling process.

Preferably, the inlet **62** is sufficiently narrow to suppress movement of fluid into the capsule **10**, thereby preventing contamination of the sample as the capsule continues its journey and reducing loss of the sample. It is also preferable to use a tightly sealed screw **66** inside the tube to prevent movement of fluid in either direction when the screw **66** is not turning.

The controller **38** receives information from the electrochemical sensor **26** concerning the environment surrounding the capsule **10**. Based on this information, the controller **38** determines that the capsule has arrived at a desired location. The controller thus activates the switch **76**, thereby initiating a sampling process. The oscillator **40** provides a basis for knowing how long sampling has taken place. After some predetermined interval, the controller **38** signals the switch **76** to turn off the motor **68**, thereby halting the sampling process.

In preferred implementations, the controller **38** executes algorithms for eliminating fluctuations in the environmental parameters being measured, e.g., pH and pO_2. An example of such an algorithm is a moving average filter algorithm. The controller **38** is pre-programmed before ingestion to activate autonomously after encountering specific values of environmental parameters (e.g., pH and pO_2) over time.

Upon completing its traversal of the gastrointestinal tract, the capsule **10** is disassembled to permit the sampled liquid to be subjected to microbiota analysis. To stabilize the microbial DNA and avoid bacterial proliferation as the capsule **10** makes its way to the end of the gastrointestinal tract, it is useful to provide a small volume of chaotropic salt in the reservoir **74**.

Having described the invention and a preferred embodiment thereof, what is claimed as new and secured by letters patent is:

CLAIMS

1. An apparatus for passage through a gastrointestinal tract, said apparatus comprising a capsule, an electrochemical sensor disposed on said capsule, and circuitry disposed within said capsule, said circuitry being configured to use said electrochemical sensor to obtain a measurement of a parameter within said gastrointestinal tract.

2. The apparatus of claim **1**, wherein said electrochemical sensor comprises a conductive thread.

3. The apparatus of claim **1**, wherein said electrochemical sensor comprises a screen-printed conductor that extends along an outer surface of said capsule.

4. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized for measurement of acidity or alkalinity of said gastrointestinal tract.

5. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized for measurement of bile in said gastrointestinal tract.

6. The apparatus of claim **1**, wherein said measurement is a measurement of glucose levels in said gastrointestinal tract.

7. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized for measurement of lactate levels in said gastrointestinal tract.

8. The apparatus of claim **1**, wherein said measurement is a measurement of dopamine levels in said gastrointestinal tract.

9. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized for measurement of serotonin levels in said gastrointestinal tract.

10. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized for measurement of amounts of short-chain fatty acids in said gastrointestinal tract.

11. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized for measurement of dissolved oxygen concentration in said gastrointestinal tract.

12. The apparatus of claim **1**, wherein said wherein said electrochemical sensor is functionalized for measurement of a neurotransmitter in said gastrointestinal tract.

13. The apparatus of claim **1**, wherein said circuitry comprises a controller and a shut-down circuit, said shut-down circuit being configured to prevent said circuitry from receiving a signal provided by said electrochemical sensor.

14. The apparatus of claim **1**, wherein said electrochemical sensor is functionalized to sense plural parameters.

15. The apparatus of claim **1**, further comprising a sampling mechanism for drawing liquid into said capsule, wherein said controller is configured to actuate said sampling mechanism in response to information provided by said electrochemical sensor.

16. The apparatus of claim **1**, further comprising an auger and a motor that turns said auger, wherein said capsule comprises an opening through which said auger draws liquid, wherein said controller is configured to start said motor automatically in response to information provided by said electrochemical sensor.

17. The apparatus of claim **1**, wherein said controller is configured to start sampling automatically in response to a measurement of pH provided by said electrochemical sensor.

18. The apparatus of claim **1**, wherein said controller is configured to start sampling automatically in response to a measurement of dissolved oxygen concentration provided by said electrochemical sensor.

19. The apparatus of claim **1**, wherein said controller is configured to start sampling automatically in response to measurements of both dissolved oxygen concentration and pH, said measurements having been provided by said electrochemical sensor.

20. The apparatus of claim **1**, further comprising a reed switch that is configured to change state in response to an applied magnetic field so as to start sampling, thereby enabling said controller to be overridden.

21. A method comprising providing a capsule for ingestion, said capsule comprising an electrochemical sensor on a surface thereof, said electrochemical sensor being connected to circuitry configured to receive a signal indicative of a parameter and, after said capsule has been ingested, receiving information from said electrochemical sensor concerning an environmental variable within a gastrointestinal tract into which said capsule has been ingested.

22. The method of claim **21**, further comprising causing said controller to store information provided by said electrochemical sensor within a memory that is in said capsule and recovering said information from said memory after said capsule has been ejected from said gastrointestinal tract.

23. The method of claim **21**, further comprising using said information provided by said electrochemical sensor to initiate sampling of liquid that is within said gastrointestinal tract and recovering said sample from said capsule after said capsule has been ejected from said gastrointestinal tract.

24. The method of claim **21**, wherein said information provided by said electrochemical sensor is indicative of pH of liquid around said capsule and wherein said method further comprises using said information provided by said electrochemical sensor to initiate sampling of liquid that is within said gastrointestinal tract and recovering said sample from said capsule after said capsule has been ejected from said gastrointestinal tract.

25. The method of claim **21**, wherein said information provided by said electrochemical sensor is indicative of dissolved oxygen concentration in liquid around said capsule and wherein said method further comprises using said information provided by said electrochemical sensor to initiate sampling of liquid that is within said gastrointestinal tract and recovering said sample from said capsule after said capsule has been ejected from said gastrointestinal tract.

26. The method of claim **21**, wherein said information provided by said electrochemical sensor is indicative of dissolved oxygen concentration in liquid around said capsule and pH of said liquid around said capsule around said capsule and wherein said method

further comprises using said information provided by said electrochemical sensor to initiate sampling of liquid that is within said gastrointestinal tract and recovering said sample from said capsule after said capsule has been ejected from said gastrointestinal tract.

27. The method of claim **21**, further comprising initiating sampling of liquid that is within said gastrointestinal tract and recovering said sample from said capsule after said capsule has been ejected from said gastrointestinal tract, wherein initiating said sampling comprises applying a magnetic field to actuate a reed switch in said capsule.

28. A method comprising using additive manufacturing to manufacture an ingestible capsule, inserting circuitry into said capsule, placing an electrochemical sensor on an outer surface of said capsule, and connecting said circuitry to said electrochemical sensor.

29. The method of claim **28**, wherein placing said electrochemical sensor comprises placing an electrochemical sensor that is configured to measure dissolved oxygen concentration.

30. The method of claim **28**, wherein placing said electrochemical sensor comprises placing an electrochemical sensor that is configured to measure both pH and dissolved oxygen concentration.

31. The method of claim **28**, further comprising incorporating a reed switch into said ingestible capsule to permit collection of a sample to be initiated by application of an external magnetic field.

32. The method of claim **28**, wherein placing said electrochemical sensor comprises placing an electrochemical sensor that is configured to measure pH.

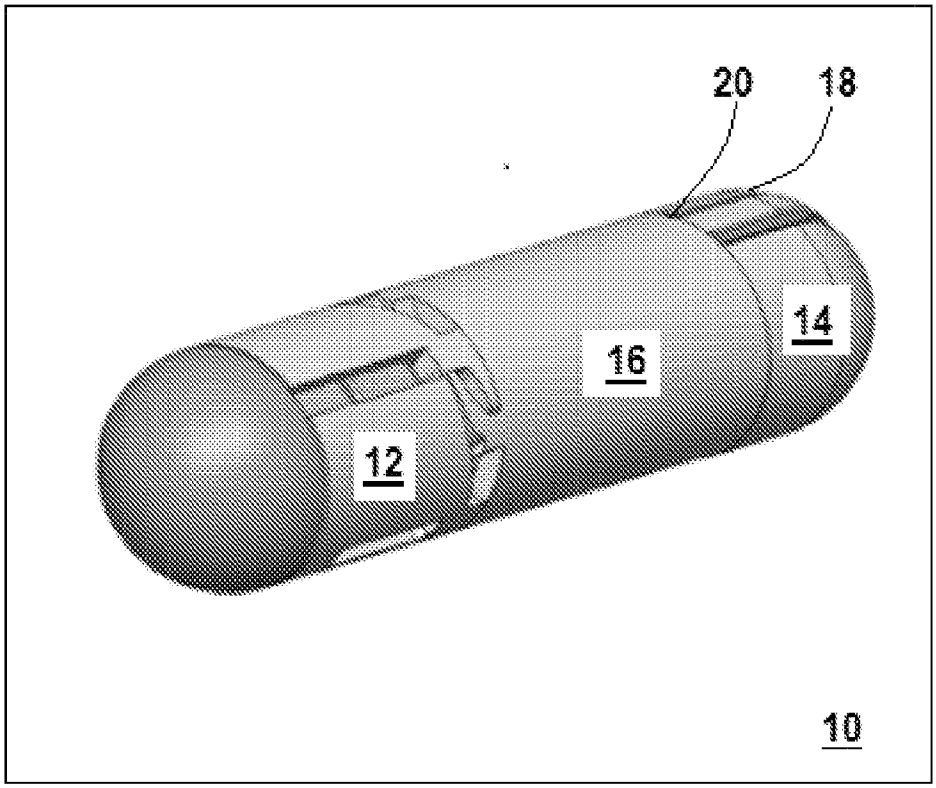


FIG. 1

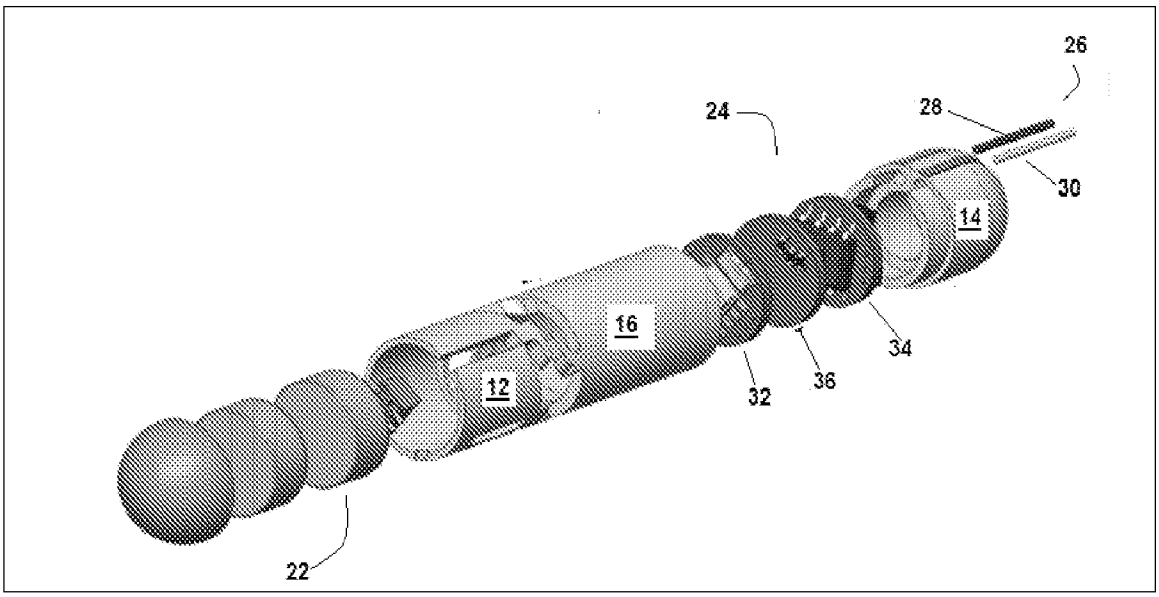


FIG. 2

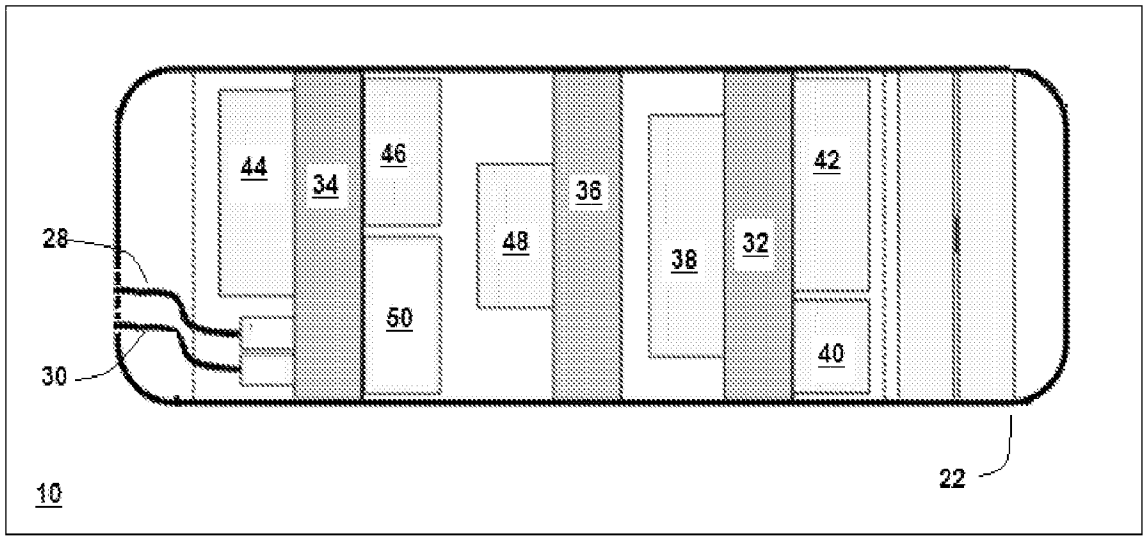

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FIG. 3

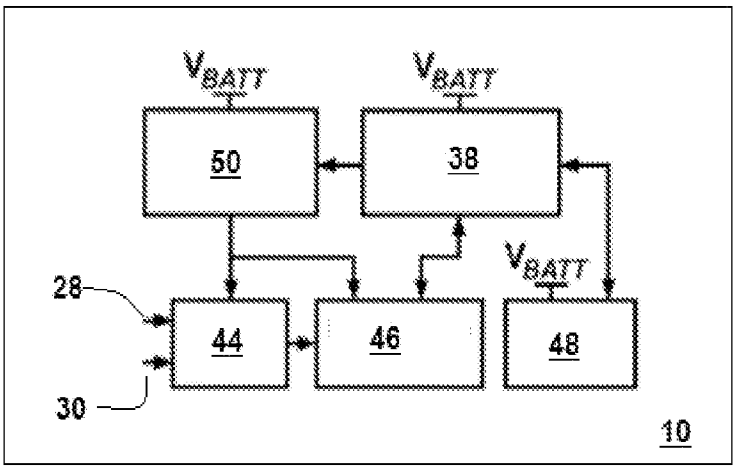

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V_{BATT}
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38
V_{BATT}
28
44
46
48
30
10

FIG. 4

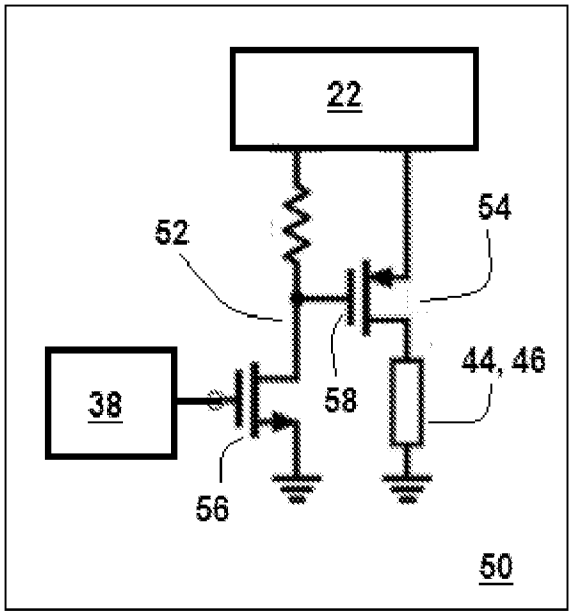


FIG. 5

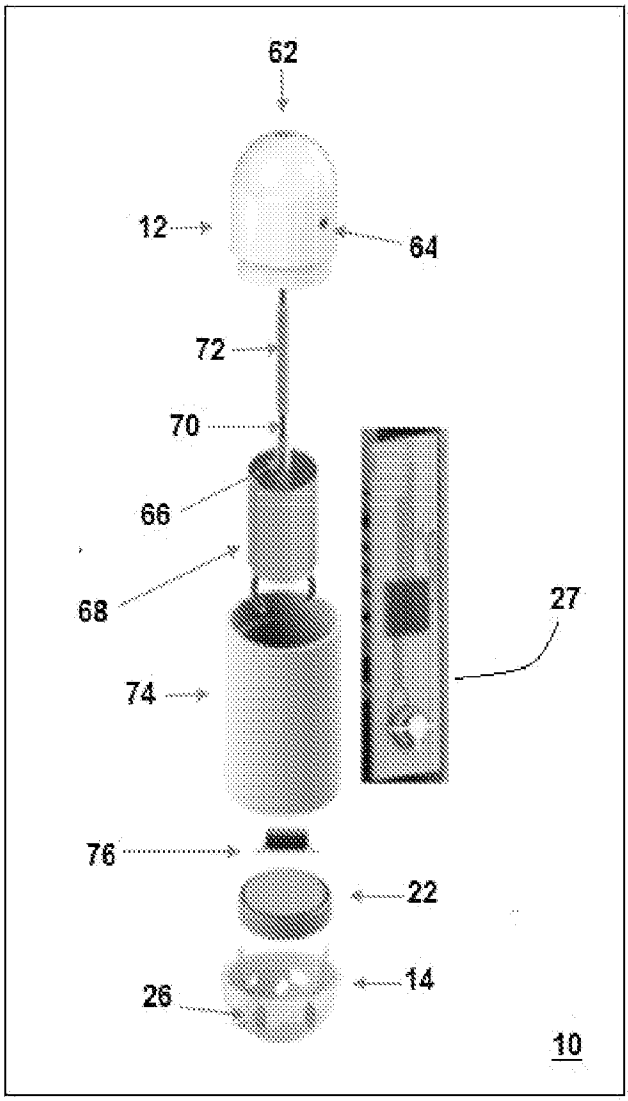


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/12392

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61B 5/07 (2023.01)
ADD.

CPC - INV. A61B 5/073

ADD. A61B 5/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0018280 A1 (LEWKOWICZ et al.) 23 January 2003 (23.01.2003) Entire document.	1-2, 4
X	US 2019/0254608 A1 (JIANG et al.) 22 August 2019 (22.08.2019) Entire document.	1, 3-4
X	US 2002/0132226 A1 (NAIR et al.) 19 September 2002 (19.09.2002) Entire document.	1, 4-12, 14
X	US 2002/0198470 A1 (IMRAN et al.) 26 December 2002 (26.12.2002) Entire document.	1, 4, 14
X	US 2004/0158138 A1 (KILCOYNE et al.) 12 August 2004 (12.08.2004) Entire document.	1, 13, 17-19
X	US 2021/0000453 A1 (SONKUSALE et al.) 07 January 2021 (07.01.2021) Entire document.	1, 15-16, 20
A	WO 2021/038464 A1 (AJM MED-I-LTD) 04 March 2021 (04.03.2021) Entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 April 2023	JUN 27 2023
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/12392

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: claims 1-20, drawn to a capsule apparatus
Group II: claims 21-32, drawn to method of ingesting and using a capsule

The inventions listed as Groups I - II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

-- see extra sheet ---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-20

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.

PCT/US 23/12392

---------- Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet) ----------

Group II includes the special technical features of method steps including particular use steps (claim 21) providing a capsule for ingestion; after said capsule has been ingested, receiving information from said electrochemical sensor concerning an environmental variable within a gastrointestinal tract into which said capsule has been ingested, not required by Group I.

Group I-II are related to an apparatus (Group I) and method(s) of using the apparatus (Group II). These groups therefore share the technical features of the apparatus of claim 1, however, these shared technical features fail to provide a contribution over the prior art of US 2002/0132226 A1 to NAIR et al. (hereinafter: Nair). As per claim 1, Nair describes an apparatus for passage through a gastrointestinal tract (Abstract: "indigestible capsule"), said apparatus comprising a capsule (outer shell 20, FIG. 1), an electrochemical sensor disposed on said capsule (sensor membrane 12, FIG. 1, para[0017]; para[0013]: "disclosed is a method for obtaining diagnostic medical information by ingesting a capsule including a sensor membrane characterized as identifying predetermined detectable information by changing its electrochemical properties"; para[0022]: "In an alternate embodiment of sensor membrane 12, a functionalized electrode, and more particularly, a thin film metal electrode is coated with molecules that are sensitive to the chemical or biological materials that are to be sensed. "), and circuitry disposed within said capsule (FIG. 1, para[0017]), said circuitry being configured to use said electrochemical sensor to obtain a measurement of a parameter within said gastrointestinal tract (para[0017]: "Components 12, 14, 16 and 18 are interrelated to provide for the detection of a predetermined factor or condition, such as the presence of an enzyme, antigen, antibody, specific pH level, or the like").

Thus, Groups I-II lack unity of invention because they do not share a same or corresponding special technical feature providing a contribution over the prior art.