HIGHLY RELIABLE INGESTIBLE EVENT MARKERS AND METHODS FOR USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

Pursuant to 35 U.S.C. § 119 (e), this application claims priority to the filing date of United States Provisional Patent Application Serial No. 61/173,511 filed April 28, 2009 and to the filing date of United States Provisional Patent Application Serial No. 61/173,564 filed April 28, 2009; the disclosure of which applications are herein incorporated by reference.

INTRODUCTION

There are many instances in both medical and non-medical applications where one desires to note a personal event, i.e., an event that is specific to a given individual. Examples of medical applications where one may wish to note an event that is specific to a given individual include, but are not limited to, the onset of one or more physiological parameters of interest, including disease symptoms, the administration of a medication, etc. Examples of non-medical applications where one desires to note an event that is specific to a given individual include, but are not limited to: the ingestion of certain types of foods, e.g., for individuals on controlled diets, the commencement of an exercise regimen, etc.

Because there are many instances where one wishes to note a personal event, a variety of different methods and technologies have been developed to make such notation possible. For example, log books and techniques have been developed in which individuals, e.g., patients and/or their health care provides, can record, e.g., by manually writing or data entry, time and date of an event.

However, there continues to be a need for improvements in personal event monitoring. For example, manually logging when an event takes place can be time consuming and prone to error.

SUMMARY

Event markers, e.g., ingestible event markers, having high reliability are provided. Aspects of the event markers include a support, a control circuit physically associated with the support to control the highly reliable event marker, a first electrochemical material physically associated with the support and electrically coupled to the control circuit, a second electrochemical material electrically coupled to the control circuit and physically associated with the support at a location different from the location of the first material, such that the first and second electrochemical materials are electrically isolated from each other; and a membrane physically associated to the support and positioned relative to the first electrochemical and second electrochemical materials to generate a virtual dipole length larger than an actual dipole length defined by the first and the second electrochemical materials.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A to 1F provide views of various IEM configurations according to different aspects of the invention.

FIGS. 2A and 2B provide illustrations of an IEM that includes a membrane having deployable arms.

FIG. 3 provides a view of an IEM in which the IEM component is positioned off-center relative to the membrane.

FIG. 4 provides a view of an IEM having a weight positioned on one side of the membrane.

FIG. 5 provides a view of an IEM having a water-swellable component positioned on side of the membrane.

FIGS. 6A and 6B provide views of different IEM configurations which incorporate effervescent structures.

FIGS. 7A, 7B and 8 provide different views IEMs having a tablet configuration.

DETAILED DESCRIPTION

Event markers, e.g., ingestible event markers ("IEMs", sometimes referred to herein as "identifiers"), having high reliability are provided. Aspects of the ingestible event markers include a support, a control circuit physically associated with the support to control the highly reliable event marker, a first electrochemical material physically associated with the support and electrically coupled to the control circuit, a second electrochemical material electrically coupled to the control circuit and physically associated with the support at a location different from the location of the first material, such that the first and second electrochemical materials are electrically isolated from each other; and a membrane physically associated to the support and positioned relative to the first electrochemical and second electrochemical materials to generate a virtual dipole length larger than an actual dipole length defined by the first and the second electrochemical materials.

INGESTIBLE EVENT MARKERS

As summarized above, ingestible event markers (IEMs) of the invention are highly reliable. By "highly reliable" is meant that the ingestible event markers of the invention correctly generate and transmit a signal when employed in an application for which they are intended at a frequency of 80 % or greater, such as 90% or greater, including 95% or greater. Highly reliable ingestible event markers of the invention may correctly generate and transmit a signal at a frequency of 99.5% or greater, such as 99.9% or greater, and in some instances correctly generate and transmit a signal at a frequency of 100%. As further developed below, the highly reliable characteristic of the ingestible event markers may arise from one or more components and/or structural features of the IEM, as described in greater detail below. As reviewed in greater detail below, one or more components and/or structural features of the IEM may impart to the IEM one or more of the following characteristics: enhanced signal strength, extended lifetime, enhanced wetting by stomach fluid, reduced propensity for blockage by GI lining, reduced propensity of blockage by bubbles and/or anti-foaming, reduced propensity for floating, as compared to a suitable control. These

desirable characteristics may be imparted to a given IEM by one or more structural features and/or chemical constituents, as reviewed in greater detail below.

An ingestible event marker is a device that is dimensioned to be ingestible and includes an IEM made up of an IEM circuitry component and a membrane. The IEM may also include a vehicle. A pharmaceutically active agent may be present in the membrane and/or vehicle. As the IEMs are dimensioned to be ingestible, in certain instances they are sized so that they can be placed in a human mouth and swallowed. In some instances, IEMs of the invention have a longest dimension that is 30 mm or less, such as 20 mm or less, including 5 mm or less.

Various aspects of event markers, e.g., ingestible event markers, of interest are described in PCT application serial no. PCT/US2006/016370 published as WO/2006/116718; PCT application serial no. PCT/US2007/082563 published as WO/2008/052136; PCT application serial no. PCT/US2007/024225 published as WO/2008/063626; PCT application serial no. PCT/US2007/022257 published as WO/2008/066617; PCT application serial no. PCT/US2008/052845 published as WO/2008/095183; PCT application serial no. PCT/US2008/053999 published as WO/2008/101107; PCT application serial no. PCT/US2008/056296 published as WO/2008/112577; PCT application serial no. PCT/US2008/056299 published as WO/2008/112578; and PCT application serial no. PCT/US2008/077753 published as WO2009/042812; the disclosures of which are herein incorporated by reference. In certain aspects, the ingestible event markers are disrupted upon administration to a subject. As such, in certain aspects, the compositions are physically broken, e.g., dissolved, degraded, eroded, etc., following delivery to a body, e.g., via ingestion, injection, etc. The compositions of these aspects are distinguished from devices that are configured to be ingested and survive transit through the gastrointestinal tract substantially, if not completely, intact.

Highly Reliable Event Marker

In various aspects, the highly reliable event marker includes a support, a control circuit physically associated with the support to control the highly reliable

event marker, a first electrochemical material physically associated with the support and electrically coupled to the control circuit, a second electrochemical material electrically coupled to the control circuit and physically associated with the support at a location different from the location of the first material, such that the first and second electrochemical materials are electrically isolated from each other; and a membrane physically associated to the support and positioned relative to the first electrochemical and second electrochemical materials to generate a virtual dipole length larger than an actual dipole length defined by the first and the second electrochemical materials.

The highly reliable event marker may be configured to be activated upon contact with fluid at the target site, such as a conducting fluid, e.g., a stomach fluid, providing, for example, a voltage potential difference. In various aspects, the control circuit controls the conductance through logic that alters the overall impedance of the system. The control circuit, for example, may be electrically coupled to a clock. The clock may provide a clock cycle to the control circuit. Based upon the programmed characteristics of the control circuit, when a set number of clock cycles have passed, the control circuit alters the conductance characteristics between electrochemical materials. This cycle may be repeated and thereby the control circuit may produce a unique current signature characteristic, sometimes referred to herein as a “current signature”. The control circuit may also be electrically coupled to a memory. Both the clock and the memory may be powered by the voltage potential created between the materials when in contact with a conducting fluid.

With respect to current signatures, the current signatures may distinguish one class of highly reliable event marker from other types or may be universally unique, such as where the current signature is analogous to a human fingerprint which is distinct from any other fingerprint of any other individual and therefore uniquely identifies an individual on a universal level. In various aspects, the control circuit may generate a variety of different types of communications, including but not limited to: RF signals, magnetic signals, conductive (near field) signals, acoustic signals, etc.

Receivers, as heretofore described in various aspects of the present invention, do not require any additional cable or hard wire connection between

the device and a receiver of the communication, sometimes referred to herein as a detector.

In some instances, the highly reliable event marker includes two dissimilar electrochemical materials which serve as a cathode and an anode. When the two dissimilar electrochemical materials come in contact with the body fluid, such as stomach fluid, a potential difference (voltage) is generated between the cathode and the anode as a result of the respective oxidation and reduction reactions occurring at the two dissimilar electrochemical materials. The dissimilar electrochemical materials making up the electrochemical materials can be made of any two materials appropriate to the environment in which the IEM circuitry component will be operating. The active materials are any pair of materials with different electrochemical potentials. The electrochemical material materials may be chosen to provide for a voltage upon contact with the target physiological site that is sufficient to drive a signal generation element of the IEM circuitry component. Where desired, the voltage provided by the two dissimilar electrochemical materials upon contact of the metals of the power source with the target physiological site is 0.001 V or higher, including 0.01 V or higher, such as 0.1 V or higher, e.g., 0.3 V or higher, including 0.5 volts or higher, and including 1.0 volts or higher, where in certain aspects, the voltage ranges from about 0.001 to about 10 volts, such as from about 0.01 to about 10 V.

Anode materials of interest include, but are not limited to: magnesium, zinc, sodium, lithium, iron and alloys thereof, e.g., Al and Zn alloys of Mg, which may or may not be intercalated with a variety of materials such, as graphite with Li, K, Ca, Na, Mg, and the like. Cathode materials of interest include, but are not limited to, copper salts, such as copper salts of iodide, chloride, bromide, sulfate, formate, Fe^{3+} salts, e.g., orthophosphate, pyrophosphate, etc. One or both of the metals may be doped with a non-metal, for example to enhance the voltage output of a partial power source or a battery. Non-metals that may be used as doping agents in certain aspects include, but are not limited to: sulfur, iodine and the like. In certain aspects, the electrochemical material materials are cuprous iodine (CuI) or cuprous chloride (CuCl) as the anode and magnesium (Mg) metal or magnesium alloy as the cathode. Aspects of the present invention use electrochemical material materials that are not harmful to the human body. When the materials are exposed and come into contact with the body fluid, such as

stomach acid or other types of fluid (either alone or in combination with a dried conductive medium precursor), a potential difference, that is, a voltage, is generated between the electrochemical materials as a result of the respective oxidation and reduction reactions incurred to the two electrochemical material materials. A voltaic cell, or battery, can thereby be produced. Accordingly, in embodiments of the invention, such power supplies are configured such that when the two dissimilar materials are exposed to the target site, e.g., the stomach, the digestive tract, etc., a voltage is generated.

Electrochemical material materials of interest include those that generate substantially little, if any, gaseous bubbles upon contact with an aqueous physiological fluid, such as stomach acid. Electrochemical material materials of interest include metal alloys, where alloys of interest include, but are not limited to, alloys of Mg, Zn, Al, and Li. When present, the amount of metal alloy may range from 0.01 to 15, such as 0.1 to 15 including 1 to 15% by weight. One or more different alloy elements may be present in the alloy. Of interest in some aspects are "bubble-free" Mg alloys which are MgAl or MgZn alloys, such as but not limited to: AZ31 magnesium alloy, AZ61 magnesium alloy, and the like.

Highly reliable event markers, e.g., IEMs, may include a solid support. In certain aspects, the solid support is small, e.g., where it is dimensioned to have a width ranging from about 0.01 mm to about 20 mm, e.g., from about 0.1 mm to about 10 mm, including from about 0.5 mm to about 2 mm; a length ranging from about 0.01 mm to about 20 mm, e.g., from about 0.1 mm to about 20 mm, including from about 0.5 mm to about 2 mm, and a height ranging from about 0.01 mm to about 10 mm, e.g., from about 0.05 mm to about 2 mm, including from about 0.1 mm to about 0.5 mm. The solid support element may take a variety of different configurations, such as but not limited to: a chip configuration, a cylinder configuration, a spherical configuration, a disc configuration, etc, where a particular configuration may be selected based on intended application, method of manufacture, etc. While the material from which the solid support is fabricated may vary considerably, in certain aspects the solid support is made up of a semiconductor material, e.g., silicon.

The phrase "single integrated circuit" refers to a single circuit structure that includes all of the different desired functional blocks for the device. In these aspects, the integrated circuit is a monolithic integrated circuit (also known as IC,

microcircuit, microchip, silicon chip, computer chip or chip) that is a miniaturized electronic circuit (which may include semiconductor devices, as well as passive components) that has been manufactured in the surface of a thin substrate of semiconductor material. The integrated circuits of certain aspects of the present invention may be hybrid integrated circuits, which are miniaturized electronic circuits constructed of individual semiconductor devices, as well as passive components, bonded to a substrate or circuit board.

IEMs may be fabricated using any convenient protocol. IEM fabrication protocols of interest include, but are not limited to, those described in PCT application serial no. PCT/US2006/016370 published as WO/2006/116718; PCT application serial no. PCT/US2007/082563 published as WO/2008/052136; PCT application serial no. PCT/US2007/024225 published as WO/2008/063626; PCT application serial no. PCT/US2007/022257 published as WO/2008/066617; PCT application serial no. PCT/US2008/052845 published as WO/2008/095183; PCT application serial no. PCT/US2008/053999 published as WO/2008/101107; PCT application serial no. PCT/US2008/056296 published as WO/2008/112577; PCT application serial no. PCT/US2008/056299 published as WO/2008/112578; and PCT application serial no. PCT/US2008/077753, the disclosures of which are herein incorporated by reference.

A given IEM may include a single IEM, or two or more IEMs, such as three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, or ten or more IEMs.

In some instances, an IEM may include a swellable or water-absorbing coating that serves to control the microenvironment of the IEM in a desired manner. Of interest in certain instances as swellable coatings are hydrogel coatings. Hydrogel coatings are polymeric coatings made up of one or more different types of non-water soluble polymers, where the coatings absorb water upon contact with an aqueous medium to produce a hydrated gel-structure that has a high water content, such as 90% or more w/w, including 95% or more w/w, such as 99% or more w/w. Any physiologically acceptable hydrogel composition may be employed as a coating, where hydrogel compositions of interest may include one or more of the following polymers: polyethylene oxides, acetates, etc. In some instances, the hydrogel coating may include one or more agents which provide for a controlled environment (for example in terms of conductivity or pH)

when the ingestible event marker reaches the target physiological site. Agents of interest include, but are not limited to: salts of physiologically acceptable electrolytes, such as but not limited to: sodium ion, chloride ion, potassium ion and calcium ion, magnesium ion, etc. Specific physiologically compatible salts of interest include, but are not limited to: KCl, NaCl, $MgCl_2$, and the like. Desired pH may range from 1 to 8, such as 2 to 7, and may be imparted by the presence of any suitable buffering agent.

Coatings may take a variety of different configurations, such as layers, snap-fit pre-made capsule components, etc. When present, coatings may cover only a portion of the ingestible event marker envelope the entire device. The coating may be uniform in terms of thickness.

Membrane

IEMs may include at least a pair of signal transmission elements, e.g., in the form of first and second electrochemical materials, which have an actual dipole length. Also present is a membrane which, for example, produces a virtual dipole length between the pair of transmission elements that is larger than the actual dipole length. In addition to controlling the magnitude of the current path between the materials, a membrane (sometimes referred to herein as "amplifier") is used to increase the "length" of the current path and, hence, act to boost the conductance path, as disclosed in the U.S. Patent Application Serial No. 12/238,345 entitled, "In-Body Device with Virtual Dipole Signal Amplification" filed September 25, 2008, and in the U.S. Patent Application Serial No. 12/564,017 entitled, "Communication System with Partial Power Source" filed September 21, 2009 the entire content of which are incorporated herein by reference. Alternatively, throughout the disclosure herein, the terms "membrane", and "amplifier" are interchangeably with the term "current path extender" without impacting the scope or the present aspects and the claims herein. While the length of the virtual dipole provided by the membrane may vary, in certain instances the length of the virtual dipole is two or more times, such as three or more times, e.g., five or more times, twenty or more times, etc., longer than the length of the actual dipole that exists between the pair of transmission elements. As the length of an actual dipole in a given IEM may vary, ranging in certain

instances from 100 μm to 2 cm, such as 300 μm to 1 mm, the length of the virtual dipole may range, in certain instances, from 200 μm to 20 cm, such as 600 μm to 20 mm. In addition to the IEMs of the invention further include a membrane, where the membrane includes a pharmaceutically active agent.

The membrane may have a variety of different configurations, so long as it serves to provide a virtual dipole having a length that is longer than that of the actual dipole length between two or more of, such as a pair of, of signal transmission elements. In certain aspects, the membrane is a structure that is positioned between the pair of signal transmission elements. The membrane may have a two-dimensional or three- dimensional configuration, and may have any convenient shape, such as square, disc, triangular, ovoid, irregular, etc., as developed in greater detail below. The length of the virtual dipole provided by the signal amplification element is, in certain instances, dependent on the particular shape of the signal amplification element. For example, where the signal amplification element has a disc configuration, as developed in greater detail below, the length of the virtual dipole is substantially the same as, if not identical to, the radius of the disc.

The pair of transmission elements are, in certain instances, a pair of electrochemical materials positioned on opposing sides of a solid support, e.g., where the solid support comprises an integrated circuit. For example, where the integrated circuit has an upper electrochemical material and lower electrochemical material on opposing sides or surfaces of an integrated circuit, the membrane may be an insulative material (or composite material) positioned between the upper and lower electrochemical materials. The outer edge of the membrane may or may not extend beyond the edge of the electrochemical materials, where examples of these differing aspects are reviewed in greater detail below.

FIG. 1A to provides a view of an aspect of an IEM according to the invention which has a membrane that extends beyond the outer edges of the membranes to provide a virtual dipole having a length that is longer than the actual dipole between the membrane. As shown in FIG. 1A, IEM 10 includes integrated circuit 2, having an upper electrochemical material 4 (which may comprise two distinct material layers) and a lower electrochemical material 6.

Also shown is disc shaped membrane 8. FIG. 1B provides an overhead view of the IEM shown in FIG. 1A, depicting the disc shape of upper electrochemical material 4 and the positioning of the upper electrochemical material in the center of disc shaped membrane 8. The distance that the edge of the membrane may extend beyond the edge of electrochemical materials may vary, and in certain aspects is 0.05 mm or more, e.g., 0.1 mm or more, including 1.0 mm or more, such as 5.0 mm or more and including 10 mm or more, where the distance may not exceed 100 mm in certain aspects.

As can be seen in the aspect depicted in FIGS. 1A to 1B, the upper and lower electrochemical materials are planar electrochemical materials, where these electrochemical materials may have any convenient shape, e.g., square, disc, etc. The disc shaped membrane or amplifier 18 is a planar disc structure, where the edge of the membrane extends beyond the edge of the planar upper and lower electrochemical materials. In the depicted aspect, the radius of the membrane is longer than the radius of the upper and lower electrochemical materials, e.g., by 1mm or more, such as by 10 mm or more.

Membranes may have "two-dimensional" or "three-dimensional" configurations. Membrane configurations of interest are further described in PCT application serial no. US2008/077753 published as WO2009/042812, as well as United States provisional application serial nos. 61/142,849 and 61/173,511; the disclosures of which are herein incorporated by reference. In some instances, IEMs of the invention include a membrane having a configuration that is chosen to provide for reduced susceptibility to signal-compromising events following contact with the target physiological site. One type of signal-compromising event that may occur is where the IEM adheres to a wall of the gastro-intestinal (GI) tract, such as the stomach wall, and thereby is prevented from interacting freely with fluid at the target physiological site. The membrane may be configured in a three-dimensional shape which discourages adhesion to a GI tract wall. One such configuration is shown in FIGS. 1C and 1D. FIG. 1C provides a cross-sectional view of an IEM 10 that includes an IEM circuitry component 12 and a membrane 14 that has opposing curved edges 16 and 18. FIGS. 1E and 1F provide views of additional types of membranes having a three-dimensional shape that discourages adherence to a GI tract wall. In FIG. 1E, IEM 10 includes IEM circuitry component 12 centrally positioned in membrane 14. Membrane 14

includes projections 15 which prevent the bottom side of the IEM circuitry component 12 from lying flat on a GI tract wall. In FIG. 1F, IEM 10 includes IEM circuitry component 12 centrally positioned on membrane 14, where membrane 14 has a concave configuration which prevents the bottom side of the IEM circuitry component from lying flat on a GI tract wall.

Alternatively, the membrane may include one or more deployable elements which serve to prevent the IEM from adhering to a GI tract wall. An example of such an IEM is shown in FIG. 2A, which depicts IEM 20 having IEM circuitry component 22 and membrane24. Also shown in FIG. 2A are deployable elements 26 and 28 having opposing configurations. As these elements are deployable, they are present in a first configuration prior to IEM ingestion and then deploy to a second position following ingestion. A deployable configuration is depicted in FIG. 2B, where IEM 20 of FIG. 2A is shown with the end 27 of arm 26 associated with the surface of the membrane 24, for example with a physiologically acceptable glue 25 that dissolves upon contact with an aqueous fluid. With respect to the IEM shown in FIG. 2B, upon contact with a target physiological fluid, such as stomach fluid, the glue dissolves to deploy the arms, such that the IEM assumes the configuration shown in FIG. 2A.

In yet another configuration of interest, the IEM circuitry component is non-centrically positioned relative to the membrane. An example of such an IEM is shown in FIG. 3, where IEM 30 includes IEM circuitry component 32 non-centrically positioned in the membrane 34.

Where desired, one or more components which promote movement of the IEM in a liquid environment, such as when present in stomach fluid, may be associated with the membrane. For example, an IEM may have a weight non-centrically associated with a membrane. An example of such a configuration is shown in FIG. 4. In FIG. 4, IEM 40 includes IEM circuitry component 42 and membrane 44. Also shown is weight 46 which is non-centrically associated with the membrane. Upon contact with a fluid, the weight serves to move the IEM in the direction of the arrow so that the IEM sinks into and becomes immersed in the fluid. In the aspect shown in FIG. 4, the weight has a density greater than that of stomach fluid and serves to pull the edge of the IEM with which the weight is associated down relative the opposite edge of the IEM. Instead of a weight, the IEM may have a swellable component non-centrically positioned on the

membrane which, upon contact with an aqueous fluid, swells in a manner such that its density decreases relative to stomach fluid and it lifts one edge of the IEM relative to the opposing edge. An example of such an IEM is shown in FIG. 5, wherein IEM 50 includes IEM circuitry component 52 and -membrane 54, as well as water-swellable component 56. Water-swellable component 56 swells under aqueous conditions to lift one edge of the IEM relative to the opposite edge, as indicated by the arrow.

To enhance movement of the IEM when present in a liquid environment, such as a target physiological fluid, effervescent structures that generate bubbles upon contact with the target physiological fluid may be associated with one or more locations of the membrane. One or more distinct effervescent structures may be associated with the membrane. Of interest are membranes that include two distinct effervescent structures associated with opposing sides of the membrane, such that a first effervescent structure is present on a first side of the membrane and a second effervescent structure is present on a second side of the membrane. In this orientation, the effervescent structures, upon generation of bubbles, force the IEM to rotate in a liquid environment as a result of opposing forces applied to the edges of the membrane. Representations of IEMs that include effervescent structures are shown in FIGS. 6A and 6B. FIG. 6A shows an IEM 60 having IEM circuitry component 62 that is centrically positioned in membrane 64. Also shown are effervescent structures 66 and 68 which generate bubbles upon contact with a physiological fluid, as shown. The bubbles apply opposing forces to the edges of the membrane, causing the IEM to rotate as indicated by the arrows. In FIG. 6B, IEM 63 is analogous to IEM 60 of FIG. 6A, with the exception that the membrane has curved edges 65 and 67. The effervescent structure may include any convenient effervescent material that is physiologically acceptable and generates gas bubbles upon contact with an aqueous fluid, such as stomach fluid. The effervescent material may generate a variety of gasses, such as carbon dioxide, hydrogen, oxygen, and the like. Of interest in some instances are effervescent materials that include magnesium, which generates hydrogen gas upon contact with an aqueous physiological fluid. Other effervescent materials of interest include acid sources, such as but not limited to food acids, acid and hydrite antacids such as, for example, citric, tartaric, amalic, fumeric, adipic, and succinic acids. Carbonate sources of

interest include, but are not limited to, dry solid carbonate and bicarbonate salt such as, sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and the like.

The membrane may be fabricated from a number of different materials, where the membrane may be made of a single material or be a composite of two or more different types of materials. In choosing a suitable material or materials, one characteristic of interest is mechanical strength. As indicated above, the membrane material may be a composite structure of two or more materials, e.g., an insulative material deposited on a metallic layer.

In certain instances, the membrane will have a mechanical strength sufficient to withstand the mechanical forces typical of the gastrointestinal (GI) tract without folding onto itself and losing its shape. This desired mechanical strength may be chosen to last for at least the duration of the communication, which may be 1 second or longer, such as at least 1 minute or longer, up to 6 hours or longer. In certain aspects, the desired mechanical strength is selected to least for a period of time ranging from 1 to 30 minutes. The desired mechanical strength can be achieved by proper selection of polymer or fillers, or mechanical design (e.g., lamination of multiple layers, or curvature of the amplifier surface) to increase the mechanical strength of the final structure.

Membranes of the invention are ones that are electrically insulating. As such, the materials from which the membranes are fabricated are electrically insulating materials. A given material is electrically insulating if it has a resistivity that is 2 times or greater than the medium in which the device operates (e.g., stomach fluid), such as 10 times or greater, including 100 times or greater than the medium in which the device operates.

Additional characteristics of interest for the membranes include ingestibility and low risk of blockage. It is desirable that the membrane be made of safe and ingestible material, such as food additives or pharmaceutical excipients. It may be further desirable to make the membrane in such a way to ensure low risk for blockage of the GI tract by one or more devices. This can be achieved via chemical or physical dissolution or digestion of the amplifier material, or mechanical breakdown of the membrane, or a combination of the two. For example, the membrane can contain one or more materials that chemically or physically dissolve in GI fluids after a certain amount of time. The material can

also be selected to become soluble upon reaching certain parts of the GI tract where the chemical environment is different, for example, a change in pH (e.g., from pH 1-2 in stomach to pH > 5 in intestine) or enzymatic components (such as enzymes present in the colon). The membrane may also be mechanically designed to have a weak point that dissolves and allows the entire structure to break up. The membrane may be constituted of several layers, for example an inner soluble or swelling layer and an outer layer that controls the dissolution rate of the inner layer; after a certain amount of time, the inner layer dissolves or swells, bursting apart the entire structure. The membrane does not need to be fully soluble or digestible to eliminate the risk of blockage; it is sufficient that the membrane becomes mechanically pliable or friable enough that it folds or breaks up under modest mechanical strain in the GI tract.

In certain aspects, the membrane may also serve as a reservoir of active pharmaceutical agents. The membrane will then serve the dual purpose of increase the dipole and serving as a drug depot. As summarized above, membranes of interest include an amount of a pharmaceutically active agent. The phrase "pharmaceutically active agent" (also referred to herein as drugs) refers to a compound or mixture of compounds which produces a physiological result, e.g., a beneficial or useful result, upon contact with a living organism, e.g., a mammal, such as a human. Pharmaceutically active agents are distinguishable from such components as excipients, carriers, diluents, lubricants, binders and other formulating aids, and encapsulating or otherwise protective components. The pharmaceutically active agent may be any molecule, as well as binding portion or fragment thereof, that is capable of modulating a biological process in a living subject. In certain aspects, the pharmaceutically active agent may be a substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication. In certain aspects, the pharmaceutically active agent may be a chemical substance, such as a narcotic or hallucinogen, which affects the central nervous system and causes changes in behavior.

The amount of pharmaceutically active agent that is present in the membrane may vary. In some instances, the amount of pharmaceutically active agent that is present in the membrane may range from 0.01 to 100% by weight. Specific pharmaceutically active agents of interest include, but are not limited to, those described and listed below.

Depending on the particular configuration of a membrane, the disposition of the pharmaceutically active agent in the membrane may vary. For example, the active agent may be homogeneously dispersed in the membrane. Alternatively, the active agent may be confined to a particular location or locations within the membrane, so that the membrane includes regions that have pharmaceutically active agent and regions that do not. An example of such a membrane is a membrane that is porous, where the pores of the membrane are filled with a pharmaceutically active agent. In such aspects, the porosity may range from 5 to 75% or more after swelling.

In some instances, the membrane is configured to provide for controlled release of the pharmaceutically active agent that is present in the membrane. By "controlled release" is meant that the membrane is configured such that the pharmaceutically active agent is released from the membrane upon contact with the target physiological site in a predetermined manner. In other words, pharmaceutically active agent is released from the membrane (upon contact with the target physiological site" in a way that has been predetermined, such as over an extended period of time, etc. As such, the pharmaceutically active agent is released from the membrane at predetermined intervals or gradually over a period of time.

The membrane can be configured to provide for controlled release of the pharmaceutically active agent using a variety of different approaches. For example, where the membrane is a homogenous structure, signal components or ingredients of the membrane may be chosen to provide for controlled release of the pharmaceutically active agent therefrom. Alternatively, where the membrane is porous, the porosity can be chosen to impart the desired controlled release characteristics to the membrane.

In yet other instances, one or more coating layers may be employed to impart controlled release characteristics to the membrane. In some instances, the release profile of the active agent from the membrane is controlled by a single coating applied to the membrane. In yet other aspects, a membrane may include two or more distinct coatings. In yet other instances, the coating layers may be fabricated from partly or entirely soluble polymer matrix materials which provide for a desired controlled release profile. Coatings of interest include those described in greater detail below.

In certain instances, the membrane has a multilayer configuration. Multilayered membrane configurations may be configured in a number of different ways. In some aspects, two or more of the different layers of the multilayered membrane may include the same active agent, where the multilayered configuration (for example where the two different layers have different compositions) provides for a desired controlled release profile of the active agent. In such aspects, the amount of active agent in each active agent comprising layer may be the same or different. In yet other aspects, two or more of the layers of a multilayered membrane may include different active agents.

Where desired, each layer of the multilayered membrane may include an IEM. In such instances, a given IEM will have a multilayered membrane where a distinct IEM is present in two or more layers of the multilayered membrane.

Where desired, the membrane may be configured such that the release of the active agent from the membrane is coupled to the activation of the event marker so that the IEM activation and communication coincides with active agent release, such as the precise start of the release of the active agent from the membrane.

As developed in further detail below, other components of the IEM may be configured to impart a controlled release profile to the active agent associated with the membrane, where these other components may be present instead of or in combination with membrane controlled release components, such as described above. For example, where the IEM includes a vehicle, such as a tablet or capsule, the vehicle may be configured to control release of the active agent from the membrane.

The membrane may be fabricated from various materials, categories of materials, and/or combinations of materials. Material categories of interest include, for example, but are not limited to: matrix materials; filler materials; soluble disintegrant materials; plasticizing agents; coatings; and wetting agents.

The surface of the membrane may also contain an anti-adhesion layer that prevents a transmitter from adhering to the stomach lining or getting blocked by objects in the GI tract such as food residue. An anti-adhesion film may also be used to prevent two or more devices from adhering to each other and blocking each other's communication.

In various aspects, the membrane may be fabricated from various materials, categories of materials, and/or combinations of materials. The categories include, for example, but are not limited to: film forming or binding / adhesive agents; fillers; soluble materials or disintegrants; plasticizing agents; coatings; and wetting agents.

The film forming or binding/adhesive agents include, for example, but are not limited to: agar; carageenan; cellulose acetate; chitosan; copovidone; ethyl cellulose; gelatin; gums (e.g., acacia, xanthan, guar, etc.); sugars (e.g., lactose, mannitol, xylitol, etc.); hydrogels (e.g., hydroxethyl cellulose, sodium alginate, urethane, etc.); acrylic acid polymers, cellulose acetate, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, carboxymethylcellulose, ethylcellulose, methacrylic acid copolymer, methyl hydroxyethylcellulose, polyethylene glycol, polyvinyl acetate phthalate, polyvinyl alcohol, povidone, starch, carbomers, dextrin, hypromellose, poly(methylvinyl ether/maleic anhydride), chitosan, glyceryl monooleate, polyethylene oxide, polycarbophil, acacia, ceretonia, confectioner's sugar, cottonseed oil, dextrates, dextrose, glyceryl behenate, hydrogenated vegetable oil, hydroxypropyl starch, inulin, lactose, glucose, magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, poloxamer, polycarbophil, polydextrose, polymethacrylates, stearic acid, sucrose, sunflower oil, zein, aluminum stearate, calcium silicate, colloidal silicon dioxide, glyceryl palmitostearate, pectin, polyethylene alkyl ethers, propylene carbonate, sodium ascorbate, zinc acetate, urethane, ammonium alginate, chlorpheniramine maleate, dibutyl phthalate, dibutyl sebacate, diethyl phthalate, dimethyl phthalate, ethyl lactate, vanillin, shellac, and the like.

The fillers include, for example, but are not limited to: oxides, e.g., titanium dioxide, magnesium oxide, etc.; silicates, e.g., magnesium silicate; phosphates, e.g., dicalcium phosphate; carbonates and bicarbonates; starches; cellulosic materials, e.g., microcrystalline cellulose; acacia, agar, alginic acid, carbomers, carboxymethylcellulose, carrageenan, cellulose acetate phthalate, ceratonia, chitosan, confectioner's sugar, copovidone, cottonseed oil, dextrates, dextrin, dextrose, ethylcellulose, gelatin, glyceryl behenate, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, hypromellose, inulin, lactose, glucose,

magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, microcrystalline cellulose, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, povidone, sodium alginate, starch, stearic acid, sucrose, sunflower oil, zein, bentonite, calcium stearate, carbomers, cellulose, colloidal silicon dioxide, kaolin, maltitol, sesame oil, sodium starch glycolate, sorbitan esters, tragacanth, xanthan gum, mannitol, ammonium alginate, calcium carbonate, calcium phosphate, calcium sulfate, cellulose, cellulose acetate, erythritol, fructose, fumaric acid, glyceryl palmitostearate, isomalt, kaolin, lactitol, magnesium carbonate, magnesium oxide, mannitol, simethicone, trehalose, xylitol, and the like.

The soluble materials or disintegrants include, for example, but are not limited to: alginates (e.g., sodium or calcium); crosscarmellose sodium, carbpoxymethyl cellulose sodium, crospovidone, hydroxypropyl, cellulose, hydroxypropyl methyl cellulose, hypromellose, lactose mannitol, polyvinyl alcohol, and salts such as sodium or potassium chloride, alginic acid, calcium alginate, carboxymethylcellulose, cellulose, chitosan, colloidal silicon dioxide, croscarmellose sodium, crospovidone, docusate sodium, guar gum, hydroxypropyl cellulose, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polacrilin potassium, povidone, sodium alginate, sodium starch glycolate, starch, and the like.

The plasticizing agents include, for example, but are not limited to dibutyl sebacate, triethyl citrate, andtriacetin, acetyltributyl citrate, acetyltriethyl citrate, benzyl benzoate, cellulose acetate phthalate, chlorbutanol, dextrin, dibutyl phthalate, dibutyl sebacate, diethyl phthalate, dimethyl phthalate, glycerin, glycerin monostearate, hypromellose phthalate, mannitol, mineral oil, lanolin alcohols, palmitic acid, polyethylene glycol, polymethacrylate, polyvinyl acetate phthalate, propylene glycol, 2-pyrolidone, sorbitol, stearic acid, triacetin, tributyl citrate, triethanolamine, triethyl citrate, and the like.

Coatings include, for example, but are not limited to polymethacrylates (pH sensitive) and polyvinyl acetate pthalate (pH sensitive), and hydroxypropyl methylcellulose (moisture barrier), acetyltributyl citrate, acetyltriethyl citrate, calcium carbonate, carboxymethylcellulose sodium, carnauba wax, cellulose acetate, cellulose acetate phthalate, cetyl alcohol, chitosan, ethylcellulose, fructose, gelatin, glycerin, glyceryl behenate, glyceryl palmitostearate,

hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hypromellose, hypromellose phthalate, isomalt, glucose, maltitol, maltodextrin, methylcellulose, microcrystalline wax, paraffin, poloxamer, polydextrose, polyethylene glycol, polyvinyl acetate phthalate, polyvinyl alcohol, povidone, shellac, sucrose, titanium oxide, tributyl citrate, triethyl citrate, vanillin, xylitol, zein, talc, triethanolamine, ammonium alginate, chlorpheniramine maleate, copovidone, ethyl lactate, and the like. When present, coating layers may range in thickness from .1 to 200 μm thick, such as 1 to 100 or 1 to 100 μm. Of interest are coating layers that modulate release of the pharmaceutically active agent from the membrane upon contact with a target physiological site.

Wetting agents include, for example, polyethylene glycol, docusate sodium, sodium lauryl sulfate, polyethylene oxide, lecithin, poloxamer, and povidone, benzalkonium chloride, benzethonium chloride, cethylpyridinium chloride, docusate sodium, hypromellose, poloxamer, polythethylene alkyl ethers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxoethylene sorbitan fatty acid esters, polyoxyethylene stearates, sodium lauryl sulfate, sorbitan esters, benzyl alcohol, benzyl benzoate, cetylpyridinium chloride, cyclodextrins, glycerin monostearate, lecithin, meglumine, poloxomer, povidone, sodium bicarbonate, stearic acid, sulfobutylether beta-cyclodextrin, and the like.

The surface of the membrane may also contain an anti-adhesion layer that prevents an IEM from adhering to the stomach lining or getting blocked by objects in the GI tract such as food residue. An anti-adhesion film may also be used to prevent two or more devices from adhering to each other and blocking each other's communication. In these aspects, materials of interest for use in anti-adhesion layers include, but are not limited to: ethyl cellulose, microcrystalline cellulose, cellulose derivative, silicates, e.g., magnesium silicates or aluminum silicates, oxides, e.g., titanium oxide, etc. As indicated above, mixtures of the above materials or materials analogous thereto may be employed.

Of interest in certain aspects are anti-adhesion layers. In these aspects, materials of interest for use in anti-adhesion layers include, but are not limited to: ethyl cellulose, microcrystalline cellulose, cellulose derivative, silicates, e.g.,

magnesium silicates or aluminum silicates, oxides, e.g., titanium oxide, etc. As indicated above, mixtures of the above materials or materials analogous thereto may be employed.

Membranes may be fabricated using any convenient protocol. Membrane fabrication protocols of interest include, but are not limited to, those described in PCT/US08/77753, the disclosure of which is herein incorporated by reference.

Vehicle

Ingestible event markers may further include a vehicle component with which the IEM and membrane are stably associated. The vehicle component may be any convenient physiologically acceptable carrier composition. By "physiologically acceptable carrier composition" is meant a composition which is ingestible, where the composition may be solid or fluid. Solid vehicle configurations of interest include tablet and capsule configurations. The vehicle component, when present, may be fabricated from a variety of different materials. Materials of interest can be found in Remington's Pharmaceutical Sciences, Mace Publishing Company, Philadelphia, Pa., 17th ed. (1985).

As summarized above, ingestible event markers of the invention may combine one or more IEM/membrane components with a vehicle, where the vehicle may be any convenient physiologically acceptable carrier component. In some instances, the vehicle component is configured to impart a controlled release profile to the pharmaceutically active agent that is associated with the membrane. For example, the IEM/membrane component may be present inside of a solid tablet vehicle, where the solid tablet breaks down after a certain period of time following contact of the IEM with the target physiological site, to allow any active agent present in the IEM to be released.

A vehicle may be present even in those aspects where an active agent is not administered. In some aspects, vehicles are present to enhance ingestibility of an IEM. By stably associating the IEM to a vehicle such as a tablet or capsule (which may be conventionally sized or smaller), adherence of the IEM to the mouth can be avoided. In some instances the vehicle is a small tablet (i.e., mini-tablet) that is adhered to the ingestible event marker, for example with a physiologically acceptable adhesive.

In some instances, IEMs are made up of an IEM stably associated with a solid vehicle component having a tablet configuration. In such instances, of interest are tablet vehicle components that are configured to promote contact of the electrochemical materials or IEM electrochemical materials with fluid upon contact of the IEM with the target physiological site. In such tablet configurations, the tablet may include one or more fluid passageways, such as grooves, channels, tubes or analogous structures, which serve to convey fluid from the environment of the IEM to an electrochemical material associated with a tablet vehicle. Passageway configurations of interest may also be configured to convey any bubbles generated at the electrochemical material component away from the electrochemical material component and/or to discourage formation of bubbles at the electrochemical material component. In such instances, the IEM is configured such that the electrochemical material is positioned relative to the passageway such that fluid in the passageway contacts the electrochemical material. An example of such an IEM is shown in FIG. 7. In FIG. 7, IEM 70 includes IEM 71 (made up of IEM circuitry component 72 and membrane 73) stably associated with the upper surface of tablet vehicle component 74. Also shown are channels 75 and 76 which are configured to provide a fluid passageway to the underside electrochemical material component of IEM circuitry component 72. FIG. 7B provides a cross-sectional view of IEM 70. In a given tablet configuration, the tablet may include one or more fluid passageways, where multiple fluid passageways may intersect, as desired to provide for desired movement gas bubbles. FIG. 8 provides an overhead view of another IEM 80 where tablet vehicle component 81 includes fluid passages ways 85, 86, 87 and 88 which intersect beneath the IEM 83 made up of IEM circuitry component 84 and membrane 82.

In these IEM configurations that include one or more fluid passageways, a given fluid passageway may be empty so as to provide uninhibited access of fluid to the electrochemical material component upon contact of the IEM with a fluid. Alternatively, the fluid passageway may be filled with a material that conveys the fluid from the environment to the electrochemical material component, such as material that wicks fluid from one location to another, a hydrogel material that absorbs fluid, and the like. Where desired, salts or other agents which control conductivity may be present.

Pharmaceutically Active Agent

Where desired, the IEM may include a pharmaceutically active agent. As indicated above, the pharmaceutically active agent, when present, may be present in the vehicle and/or membrane. As summarized above, membranes of the invention include an amount of an active agent, such as a pharmaceutically active agent or a diagnostic agent.

"Pharmaceutically Active agent" includes any compound or mixture of compounds which produces a physiological result, e.g., a beneficial or useful result, upon contact with a living organism, e.g., a mammal, such as a human. Pharmaceutically active agents (which may also be referred to herein as "drugs") are distinguishable from such components as excipients, carriers, diluents, lubricants, binders and other formulating aids, and encapsulating or otherwise protective components. The pharmaceutically active agent may be any molecule, as well as binding portion or fragment thereof, that is capable of modulating a biological process in a living subject. In certain aspects, the pharmaceutically active agent may be a substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication. In certain aspects, the pharmaceutically active agent may be a chemical substance, such as a narcotic or hallucinogen, which affects the central nervous system and causes changes in behavior.

The pharmaceutically active agent is capable of interacting with a target in a living subject. The target may be a number of different types of naturally occurring structures, where targets of interest include both intracellular and extracellular targets. Such targets may be proteins, phospholipids, nucleic acids and the like, where proteins are of particular interest. Specific proteinaceous targets of interest include, without limitation, enzymes, e.g., kinases, phosphatases, reductases, cyclooxygenases, proteases and the like, targets comprising domains involved in protein-protein interactions, such as the SH2, SH3, PTB and PDZ domains, structural proteins, e.g., actin, tubulin, etc., membrane receptors, immunoglobulins, e.g., IgE, cell adhesion receptors, such as integrins, etc., ion channels, transmembrane pumps, transcription factors, signaling proteins, and the like.

The pharmaceutically active agent may include one or more functional groups necessary for structural interaction with the target, e.g., groups necessary for hydrophobic, hydrophilic, electrostatic or even covalent interactions, depending on the particular drug and its intended target. Where the target is a protein, the pharmaceutically active agent may include functional groups necessary for structural interaction with proteins, such as hydrogen bonding, hydrophobic-hydrophobic interactions, electrostatic interactions, etc., and may include at least an amine, amide, sulfhydryl, carbonyl, hydroxyl or carboxyl group, such as at least two of the functional chemical groups.

Pharmaceutically active agents of interest may include cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Also of interest as pharmaceutically active agents are compounds having structures found among biomolecules, including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Such compounds may be screened to identify those of interest, where a variety of different screening protocols are known in the art.

The pharmaceutically active agent may be derived from a naturally occurring or synthetic compound that may be obtained from a wide variety of sources, including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including the preparation of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs.

As such, the pharmaceutically active agent may be obtained from a library of naturally occurring or synthetic molecules, including a library of compounds produced through combinatorial means, i.e., a compound diversity combinatorial library. When obtained from such libraries, the drug moiety employed will have

demonstrated some desirable activity in an appropriate screening assay for the activity. Combinatorial libraries, as well as methods for producing and screening such libraries, are known in the art and described in United States Patent Nos: 5,741,713; 5,734,018; 5,731,423; 5,721,099; 5,708,153; 5,698,673; 5,688,997; 5,688,696; 5,684,711; 5,641,862; 5,639,603; 5,593,853; 5,574,656; 5,571,698; 5,565,324; 5,549,974; 5,545,568; 5,541,061; 5,525,735; 5,463,564; 5,440,016; 5,438,119; 5,223,409, the disclosures of which are herein incorporated by reference.

Broad categories of active agents of interest include, but are not limited to: cardiovascular agents; pain-relief agents, e.g., analgesics, anesthetics, anti-inflammatory agents, etc.; nerve-acting agents; chemotherapeutic (e.g., anti-neoplastic) agents; neurological agents, e.g., anti-convulsants, etc.

Pharmaceutically active agents of interest include, but are not limited to: those listed in PCT application serial no. PCT/US2006/016370, the disclosure of which listed pharmaceutically active agents is incorporated herein by reference.

Salt

Where desired, a given IEM may include a non-active agent salt component, which component is made up of one or more non-active agent salts. In some instances, the amount of this salt component present in the IEM is chosen to be sufficient to enhance the strength of the communication generated by the IEM of the IEM when the IEM contacts the target physiological site, such as the stomach. The magnitude of communication strength enhancement may vary, where in some instances the magnitude of communication strength enhancement is 10X or more, such as 20X or more, including 50X or more, as compared to a suitable control (such as the strength of a communication generated by an analogous IEM which differs from the test IEM of interest solely by lack of the salt component). The amount of this non-active agent salt component is sufficient to provide for the desired communication strength enhancement. Non-active agent salts may vary, where non-active agent salts of interest include, but are not limited to: salts of physiologically acceptable electrolytes, such as but not limited to: sodium ion, chloride ion, potassium ion and calcium ion, magnesium ion, etc. Specific physiologically compatible salts of

interest include, but are not limited to: KCl, NaCl, $MgCl_2$, and the like. When present, this non-active agent salt may be part of one or more of: the membrane, the IEM and the vehicle.

Anti-foaming agent

Also of interest are anti-foaming agents, which agents decrease the surface tension of gas bubbles. Anti-foaming agents of interest include, but are not limited to: silicone oil-based agents, such as simethicone, sorbitan sesquoleate, etc. When present, the amount of anti-foaming agent present in the IEM may vary, ranging from 0.01 to 10 mg, such as 0.1 to 100 μg, and including 0.1 to 10 μg. When present, this anti-foaming agent may be part of one or more of: the membrane, the IEM and the vehicle.

Surfactants

In some instances, the IEM includes one or more surfactants. Surfactants of interest include, but are not limited to: ionic surfactants, such as anionic surfactants, cationic surfactants and zwitterionic surfactants, as well as nonionic surfactants and surface active biological modifiers. Surfactants of interest include, but are not limited to: castor oil derivatives, cholesterol, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polysorbates, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene compounds, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glycerol esters, polyglycerol fatty acid esters, SPAN™ surfactants, such as sorbitan esters), TWEEN™ surfactants, such as sucrose esters, glucose (dextrose) esters, alkali metal sulfates, quaternary ammonium compounds, amidoamines, and aminimides,

simethicone, lecithins, alcohols, phospholipids, and mixtures thereof. When present, the surfactant component may be 0.01 to 10%, such as 0.01 to 100 ppm, including 0.1 to 100 ppm of the IEM composition. When present, surfactants may be part of one or more of: the membrane, the IEM and the vehicle.

Disintegrants

In some instances, the IEM compositions include one or more disintegrants. By disintegrant is meant an agent that enhances break up of at least some portion of the IEM, such as the vehicle or membrane, upon contact with the target physiological site. As such, disintegrants may facilitate mechanical disruption of the IEM vehicle component, such as a tablet, when the IEM contacts a fluid, such as stomach fluid. Disintegrants of interest include, but are not limited to, those disintegrants listed above, such as microcrystalline cellulose, starch, sodium starch glycolate, crosslinked polyvinylpyrrolidone, crosslinked carboxymethylcellulose, alginic acid, etc. When present, the disintegrant component may range from about 0.01 to 15%, such as 0.01 to 100 ppm, including 0.1 to 10 ppm of the IEM composition. When present, disintegrants may be part of one or more of: the membrane, the IEM and the vehicle.

Antioxidants

The IEM compositions may also include one or more antioxidants which serve to enhance shelf-life stability of the IEM. Antioxidants of interest include, but are not limited to: tocopherol and derivatives, ascorbic acid and derivatives, butylated hydroxyanisole, butylated hydroxytoluene, fumaric acid, malic acid, propyl gallate, metabisulfates and derivatives. When present, antioxidants may range from 0.01 to 10%, such as 0.01 to 100 ppm and including 0.1 to 1 ppm. When present, anti-oxidants may be part of one or more of: the membrane, the IEM and the vehicle.

Preservatives

IEMs of the invention may further include preservatives such as, but not limited to, benzalkonium chloride and derivatives, benzoic acid, benzyl alcohol and derivatives, bronopol, parabens, centrimide, chlorhexidine, cresol and derivatives, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric salts, thimerosal, sorbic acid and derivatives. The preservative may be present from in amounts ranging from 0.01 to 10 mg, such as 0.1 to 100 μg and including 0.1 to 1 μg. When present, preservatives may be part of one or more of: the membrane, the IEM and the vehicle.

Micro-environment Modification Agents

IEMs of the invention may include one or more micro-environment modification agents that modify or control the micro-environment of an IEM upon contact with a target physiological site. Micro-environment modification agents of interest include but are not limited to surfactants, distintegrants, anti-oxidants, and preservatives. A given IEM may include one or more of these components as a micro-environment modification agent. Examples and amounts of each of these types of agents that may be present are provided above. When present, micro-environment modification agents may be part of one or more of: the membrane, the IEM and the vehicle.

Balanced Soluble/Insoluble Components

In some instances, IEM compositions of the invention are those in which the water insoluble and water soluble components of the vehicle are present in a ratio that is selected to provide for desired characteristics, such as dissolution of the vehicle, operations of the IEM, and the like. In some instances, the fraction of water insoluble components in the vehicle may range from 0.01 to 1, such as 0.1 to 0.9 and including 0.5 to 0.8. In some instances, the ingestible event marker has a fraction of soluble components up to 90% by weight.

Absorbent Component

An ingestible event marker may include a component that absorbs fluid, e.g., water, in order to increase the weight of the IEM (for example to ensure that the IEM sinks when it contacts fluid at a physiological site). This absorbent component may be the membrane, vehicle, or some distinct component of the IEM, such as an overlayer or coating, as desired. When present, this absorbent component may be fabricated from a variety of suitable materials, such as the hydrogel materials listed above.

Controlled Activation Element

IEMs of the invention may include a controlled activation element. The controlled activation element of the IEM that provides for controlled activation may be responsive to a variety of different types of stimuli. Stimuli of interest for which the controlled activation element can be configured to be responsive to include but are not limited to: liquid (wetting), time, pH, ionic strength, conductivity, biological molecules (e.g. specific proteins or enzymes that are present in the stomach, small intestine, colon), blood, temperature, specific auxiliary agents (foods ingredients such as fat, salt, or sugar, or other pharmaceuticals whose co-presence is clinically relevant), bacteria in the stomach, pressure, and light.

The controlled activation element is made up of one or more components that provides for the desired controlled activation functionality, such that the controlled activation element is responsive to the stimulus of interest. The nature of the component or components that make up the controlled activation element may vary. For example, where the stimulus of interest is temperature, the controlled activation element may be a barrier of a material, such as a film (e.g., a polymeric film) whose solubility is a function of temperature, specifically one that becomes soluble at or near body temperature. Such a film may be insoluble/ impermeable to water at room temperature but soluble/ permeable at 37°C. Materials of interest that may be used for such films include, but are not limited to the polymeric materials listed below. In those aspects where pressure is the

stimuli of interest, the controlled activation element may be a pressure sensitive material, e.g., a capsule or shell (for example, made of a cellulosic material), that has a specific mechanical strength such that at a pressure threshold above the threshold the element will be crushed and allow the higly reliable event marker to be activated and communicate. In other aspects of interest, the stimulus may be light. For example, the stimulus may be a fluorescent label which has been attached to a tumor. As the IEM passes by the tumor, the controlled activation element may include a component that provides light at a stimulating wavelength for the label and also a component that detects emitted light from the label. Any convenient light source and detector may be employed. When the detector component detects the emitted light, it will activate the IEM in a controlled activation manner.

In certain aspects, the one or more controlled activation components of the invention provide for controlled activation, i.e., activation in a manner that is substantially, if not completely, independent of target site environment, as reviewed above. In one aspect of interest, the controlled activation component includes a dried conductive medium that, upon combination with target site fluid, produces an ionic medium in the presence of the first and second dissimilar materials to activate the battery, e.g., as reviewed above. When present, the dried conductive medium precursor may be any of a variety of different types of compositions. Compositions of interest include, but are not limited to: salts of physiologically acceptable electrolytes, such as but not limited to: sodium ion, chloride ion, potassium ion and calcium ion, magnesium ion, etc. Specific physiologically compatible salts of interest include, but are not limited to: KCl, NaCl, $MgCl_2$, and the like. Aspects of the invention include the presence of a dried conductive medium precursor. When the precursor is a salt, e.g., as described above, the dried salt may be provided in any convenient format, such as a lyophilized salt composition.

Controlled activation elements of interest are further described in PCT application serial no. PCT/US2007/082563 published as WO 2008/052136; the disclosure of which is herein incorporated by reference.

IEM MANUFACTURE

A variety of manufacturing protocols may be employed to produce IEMs of the invention. Where the IEM does not include a vehicle, the IEM and membrane components may be produced as described above. Where the IEM further includes a vehicle, the IEM may be stably associated with the vehicle in some manner. By stably associated is meant that the IEM and the vehicle do not separate from each other, at least until administered to the subject in need thereof, e.g., by ingestion. The IEM may be stably associated with the vehicle in a number of different ways.

IEM fabrication protocols of interest include, but are not limited to, those described in PCT application serial nos. PCT/US2006/016370 and PCT/US08/77753; as well as in United States Provisional Application Serial No. 61/142,849; the disclosures of which are herein incorporated by reference.

SYSTEMS

Also provided are systems that include an IEM and a communication detection component, e.g., in the form of a receiver, sometimes referred to herein as a "detector". Receivers of interest are those that are configured to receive a signal from an IEM. The detection component may vary significantly depending on the nature of the communication that is generated by the IEM. As such, the receiver may be configured to receive a variety of different types of communications, including but not limited to: RF signals, magnetic signals, conductive (near field) signals, acoustic signals, etc. In certain aspects, the receiver is configured to receive a signal conductively from an IEM, such that the two components use the body of the patient as a communication medium. As such, the signal that is transferred between the IEM and the receiver travels through the body, and requires the body as the conduction medium. The IEM emitted signal may be transmitted through and received from the skin and other body tissues of the subject body in the form of electrical alternating current (a.c.) voltage signals that are conducted through the body tissues. As a result, such aspects do not require any additional cable or hard wire connection, or even a radio link connection for transmitting the sensor data from the autonomous

sensor units to the central transmitting and receiving unit and other components of the system, since the sensor data are directly exchanged via the skin and other body tissues of the subject. This communication protocol has the advantage that the receivers may be adaptably arranged at any desired location on the body of the subject, whereby the receivers are automatically connected to the required electrical conductor for achieving the communication, i.e., the communication is carried out through the electrical conductor provided by the skin and other body tissues of the subject.

The receiver may include a variety of different types of receiver elements, where the nature of the receiver element necessarily varies depending on the nature of the signal produced by the signal generation element. In certain aspects, the receiver may include one or more electrochemical materials (such as 2 or more electrochemical materials, 3 or more electrochemical materials, and/or includes multiple pairs of electrochemical materials, such as 2 or more, 3 or more, 4 or more pairs of electrochemical materials, etc., for detecting signal emitted by an IEM. In certain aspects, the receiver includes two or three electrochemical materials that are dispersed at a distance from each other, e.g., a distance that allows the electrochemical materials to detect a differential voltage. The distance between any two electrochemical materials may vary, and in certain aspects ranges from about 0.1 to about 5 cm, such as from about 0.5 to about 2.5 cm, e.g., about 1 cm.

In addition to receiving elements, such as electrodes electrochemical materials, receivers of the invention may include one or more integrated circuit components, one or more power components (such as power receivers or batteries), signal transmission components, housing components, etc.

The receivers of interest include both external and implantable receivers. In external aspects, the receiver is *ex vivo*, by which is meant that the receiver is present outside of the body during use. Where the receiver is implanted, the receiver is *in vivo*. The receiver is configured to be stably associated with the body, e.g., either *in vivo* or *ex vivo*, at least during the time that it receives the emitted signal from the IEM.

In certain aspects, the receiver is configured to provide data of a received signal to a location external to said subject. For example, the receiver may be configured to provide data to an external data receiver, e.g., which may be in the

form of a monitor (such as a bedside monitor), a computer, a personal digital assistant (PDA), phone, messaging device, smart phone, etc. The receiver may be configured to retransmit data of a received signal to the location external to said subject. Alternatively, the receiver may be configured to be interrogated by an external interrogation device to provide data of a received signal to an external location.

Receivers of interest include, but are not limited to, those receivers disclosed in: PCT application serial nos. PCT/US2006/016370 published as WO 2006/116718; PCT/US2008/52845 published as WO 2008/095183; PCT/ US2007/024225 published as WO 2008/063626 and PCT/ US2008/085048; as well as United States Provisional Application Serial No. 61/160,289; the disclosures of which applications (and particularly receiver components thereof) are herein incorporated by reference.

Systems of the invention may include an external device which is distinct from the receiver (which may be implanted or topically applied in certain aspects), where this external device provides a number of functionalities. Such an apparatus can include the capacity to provide feedback and appropriate clinical regulation to the patient. Such a device can take any of a number of forms. By example, the device can be configured to sit on the bed next to the patient, e.g., a bedside monitor. Other formats include, but are not limited to, PDAs, phones, such as smart phones, computers, etc. In some instances, the external device is configured to provide pharmacologic and physiologic information in a form that can be transmitted through a transmission medium, such as a telephone line, to a remote location such as a clinician or to a central monitoring agency. The external device can read out the information described in more detail in other sections of the subject patent application, both from pharmaceutical ingestion reporting and from physiological sensing devices, such as is produced internally by a pacemaker device or a dedicated implant for detection of the pill. The purpose of the external apparatus is to get the data out of the patient and into an external device. One feature of the external apparatus is its ability to provide pharmacologic and physiologic information in a form that can be transmitted through a transmission medium, such as a telephone line, to a remote location such as a clinician or to a central monitoring agency.

METHODS

Aspects of the invention further include methods of using IEMs, such as those described above. Methods of the invention generally include administering an IEM to a subject, e.g., by self-administration or via the assistance of another, such as a health care practitioner. Generally, methods of the invention will include placing the IEM in the mouth of a subject such that the subject swallows the IEM. In this manner, the subject ingests the IEM. IEMs may be employed with a variety of subjects. Generally such subjects are "mammals" or "mammalian," where these terms are used broadly to describe organisms which are within the class mammalia, including the orders carnivore (e.g., dogs and cats), rodentia (e.g., mice, guinea pigs, and rats), and primates (e.g., humans, chimpanzees, and monkeys). In certain aspects, the subjects will be humans.

Following ingestion, the methods include emitting one or more signals from the ingested IEM, for example when the IEM contacts the target physiological site. As reviewed above, the nature of the emitted signal may vary greatly. In some instances, the emitted signal is a conductively transmitted signal. Methods of the invention may also include receiving a signal emitted from an IEM, e.g., at a receiver, such as described above. In some instances, the received signal is a conductively transmitted signal.

IEMs may be employed in a variety of different applications, which applications may be both medical and non-medical in nature. Applications of interest include, but are not limited to: monitoring patient compliance with prescribed therapeutic regimens; tailoring therapeutic regimens based on patient compliance; monitoring patient compliance in clinical trials; monitoring usage of controlled substances; monitoring the occurrence of a personal event of interest, such as the onset of symptoms, etc., and the like. Applications of interest are further described in PCT application serial no. PCT/US2006/016370 published as WO/2006/116718; PCT application serial no. PCT/US2007/082563 published as WO/2008/052136; PCT application serial no. PCT/US2007/024225 published as WO/2008/063626; PCT application serial no. PCT/US2007/022257 published as WO/2008/066617; PCT application serial no. PCT/US2008/052845 published as WO/2008/095183; PCT application serial no. PCT/US2008/053999 published as WO/2008/101107; PCT application serial no. PCT/US2008/056296 published as

WO/2008/112577; PCT application serial no. PCT/US2008/056299 published as WO/2008/112578; and PCT application serial no. PCT/US2008/077753; the disclosures of which are herein incorporated by reference.

KITS

Also provided are kits that include one or more IEMs, such as described above. In those aspects having a plurality of IEMs, the IEMs may be packaged in a single container, e.g., a single tube, bottle, vial, and the like, or one or more dosage amounts may be individually packaged such that certain kits may have more than one container of IEMs. In certain aspects the kits may also include a receiver, such as reviewed above. In certain aspects, the kits may also include an external monitor device, e.g., as described above, which may provide for communication with a remote location, e.g., a doctor's office, a central facility etc., which obtains and processes data obtained about the usage of the composition.

The subject kits may also include instructions for how to practice the subject methods using the components of the kit. The instructions may be recorded on a suitable recording medium or substrate. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or sub-packaging) etc. In other aspects, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other aspects, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. An example of this aspect is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

Some or all components of the subject kits may be packaged in suitable packaging to maintain sterility. In many aspects of the subject kits, the components of the kit are packaged in a kit containment element to make a single, easily handled unit, where the kit containment element, e.g., box or

analogous structure, may or may not be an airtight container, e.g., to further preserve the sterility of some or all of the components of the kit.

It is to be understood that this invention is not limited to particular aspects described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, representative illustrative methods and materials are now described.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

It is noted that, as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly

dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual aspects described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several aspects without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and aspects of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary aspects shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

WHAT IS CLAIMED IS:

1. A highly reliable event marker comprising:

a support;

a control circuit physically associated with the support to control the highly reliable event marker;

a first electrochemical material physically associated with the support and electrically coupled to the control circuit;

a second electrochemical material electrically coupled to the control circuit and physically associated with the support at a location different from the location of the first material, such that the first and second electrochemical materials are electrically isolated from each other; and

a membrane physically associated to the support and positioned relative to the first electrochemical and second electrochemical materials to generate a virtual dipole length larger than an actual dipole length defined by the first and the second electrochemical materials.

2. The highly reliable event marker of Claim 1 wherein the control circuit controls the voltage between the first material and the second electrochemical materials.

3. The highly reliable ingestible event marker according to Claim 1 wherein the first and the second electrochemical materials are selected to provide a voltage potential difference when in contact with a conducting liquid at a target physiological site, wherein the potential difference provides power for communication.

4. The highly reliable ingestible event marker according to Claim 1 wherein the membrane is a planar structure having an outer edge that extends beyond the edge of the first and second electrochemical materials.

5. The highly reliable ingestible event marker according to Claim 1 wherein the membrane comprises at least one of multiple coatings and multiple layers

6. The highly reliable ingestible event marker of Claim 1 further comprising at least one controlled activation element.

7. The highly reliable ingestible event marker of Claim 1 further comprising at least one of a non-active agent salt, an anti-foaming agent, a micro-environment modification agent and a soluble component having a weight equal or greater to 90% of the overall weight of the highly reliable event marker.

8. The highly reliable ingestible event marker according to Claim 1 wherein the membrane has at least one of opposing curved edges, one or more projections, or one or more deployable elements.

9. The highly reliable ingestible event marker of Claim 1 further comprising a weight non-centrically associated with the membrane.

10. The highly reliable ingestible event marker of Claim 1 further comprising adding a water-swellable component non-centrically associated with the membrane.

11. The highly reliable ingestible event marker according to Claim 1, wherein the highly reliable event marker is physically associated with an active agent.

12. The highly reliable ingestible event marker according to Claim11, wherein the active agent is physically associated with the membrane.

13. The highly reliable ingestible event marker according to Claim 11, wherein the membrane releases the active agent in a phased manner.

14. The highly reliable ingestible event marker according to Claim 11, wherein the active agent comprises at least one fluid passageway.

15. A system comprising:

a highly reliable ingestible event marker comprising:

a support;

a control circuit physically associated with the support to control the highly reliable event marker;

a first electrochemical material physically associated with the support and electrically coupled to the control circuit;

a second electrochemical material electrically coupled to the control circuit and physically associated with the support at a location different from the location of the first material, such that the first and second electrochemical materials are electrically isolated from each other; and

a membrane physically associated to the support and positioned relative to the first electrochemical and second electrochemical materials to generate a virtual dipole length larger than an actual dipole length defined by the first and the second electrochemical materials.

16. The system of Claim 15 wherein the highly reliable ingestible event marker is associated with an active agent.

17. The system of Claim 15 wherein the active agent is physically associated with the membrane.

18. The system of Claim 15 wherein the highly reliable event marker further comprising at least one of a non-active agent salt, an anti-foaming agent, a micro-environment modification agent and a soluble component having a weight equal or greater to 90% of the overall weight of the highly reliable event marker.

19. The system of Claim 15 wherein the membrane is a planar structure having an outer edge that extends beyond the edge of the first and second electrochemical materials.

20. The system of Claim 15 wherein the membrane has at least one of opposing curved edges, one or more projections, or one or more deployable elements.