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(54) **ELECTRONIC MEDICATION COMPLIANCE MONITORING SYSTEM AND ASSOCIATED METHODS**

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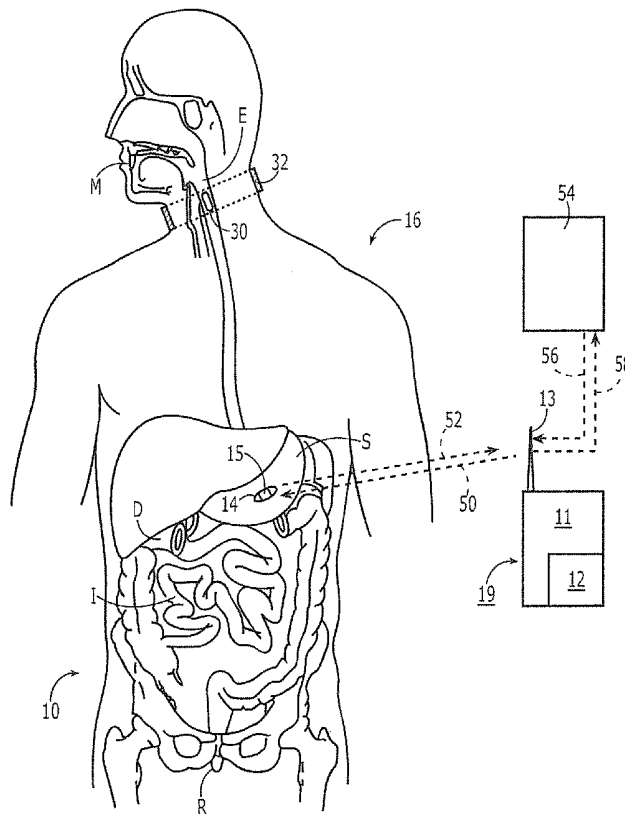
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Related U.S. Application Data

(63) Continuation-in-part of application No. 12/881,572, filed on Sep. 14, 2010, which is a continuation-in-part of application No. 11/458,815, filed on Jul. 20, 2006, now Pat. No. 7,796,043.
(60) Provisional application No. 61/789,077, filed on Mar. 15, 2013, provisional application No. 60/700,963, filed on Jul. 20, 2005, provisional application No.

(57) **ABSTRACT**

A method of monitoring a patient's compliance with a medication program includes transmitting a first signal from an electronic ingestible medication delivery device located within a patient's body, the signal including information about a physiological parameter of the patient. The signal is detected with an electronic reader located outside the patient's body. A second signal is provided to the reader from a different source than the delivery device. The second signal includes information about the same physiological parameter of the patient. Related systems are also described.



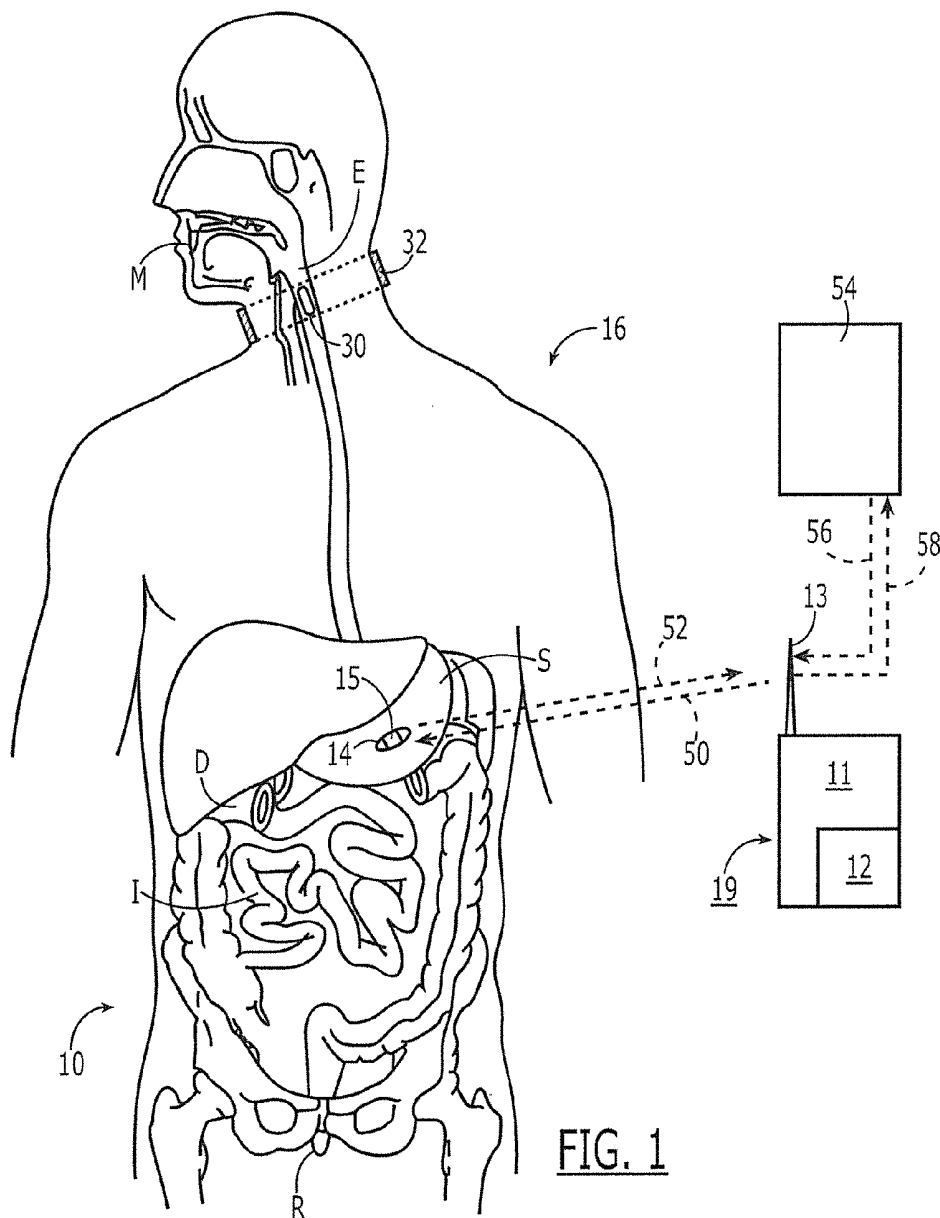
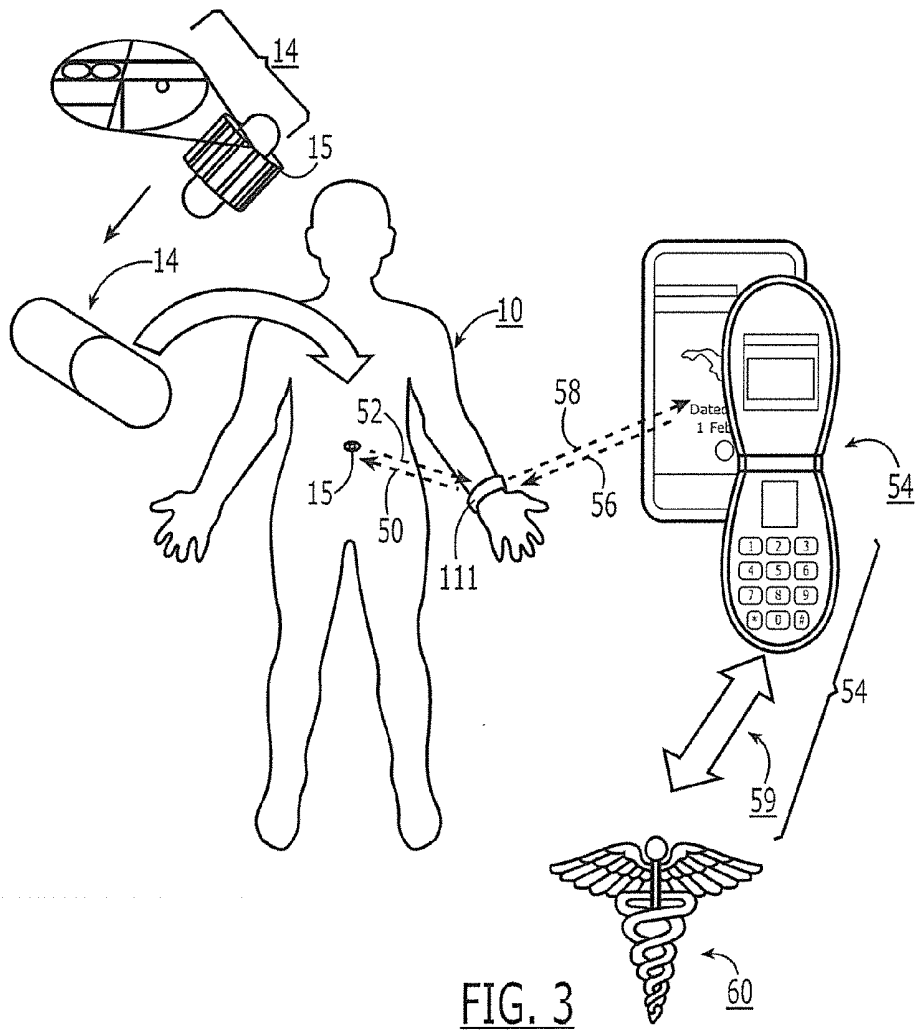
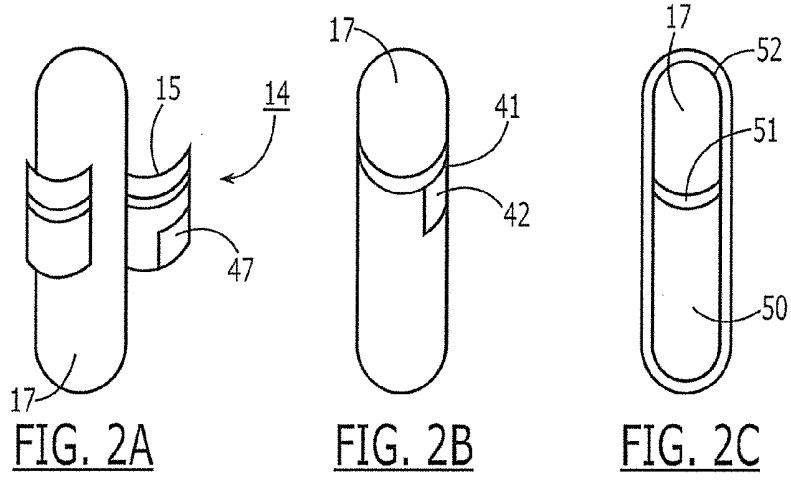


FIG. 1



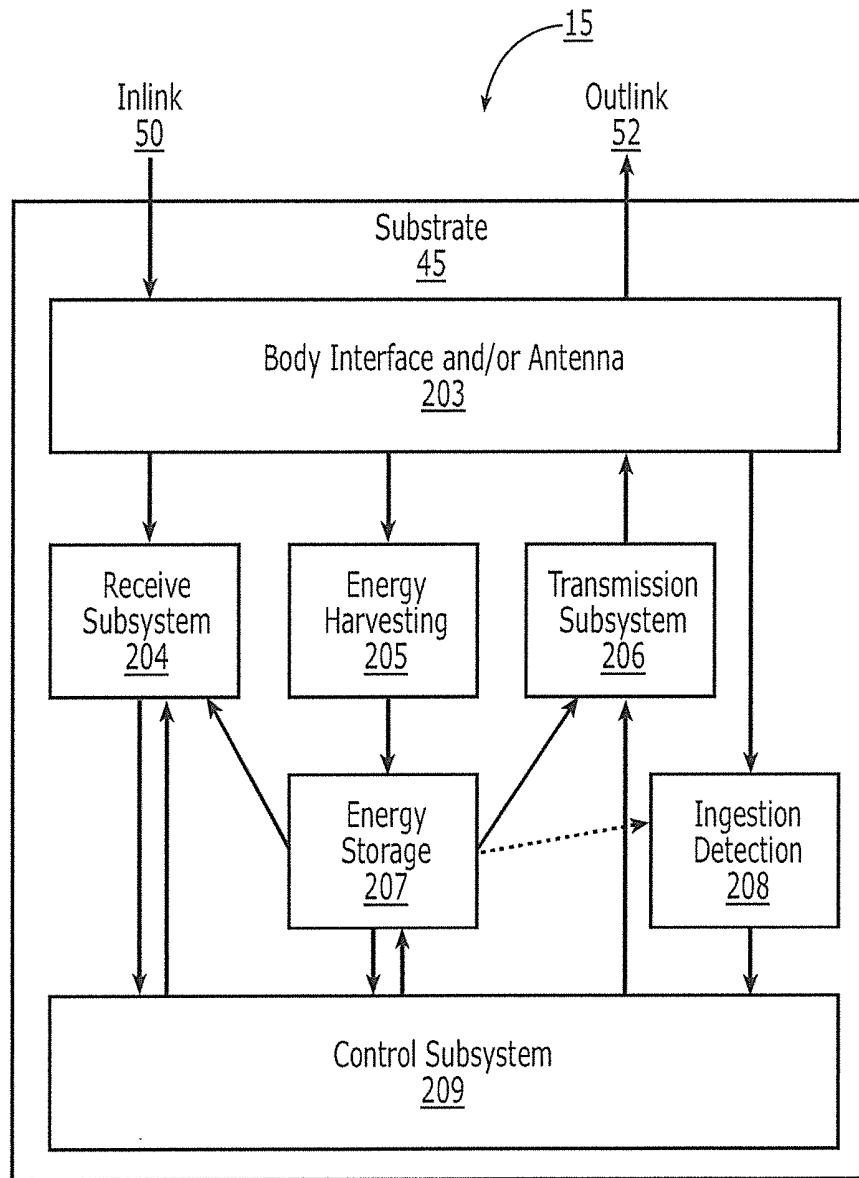
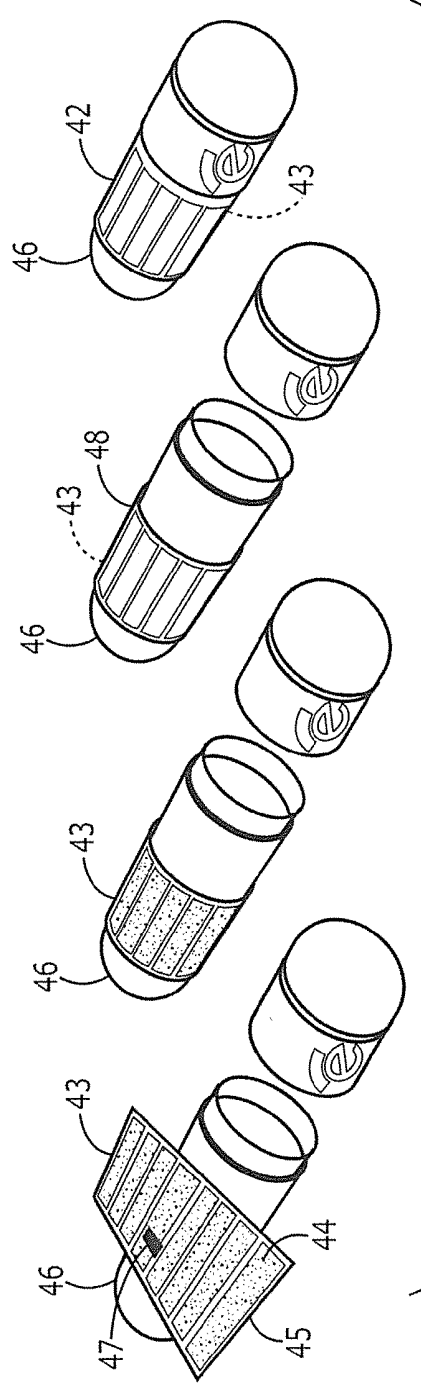
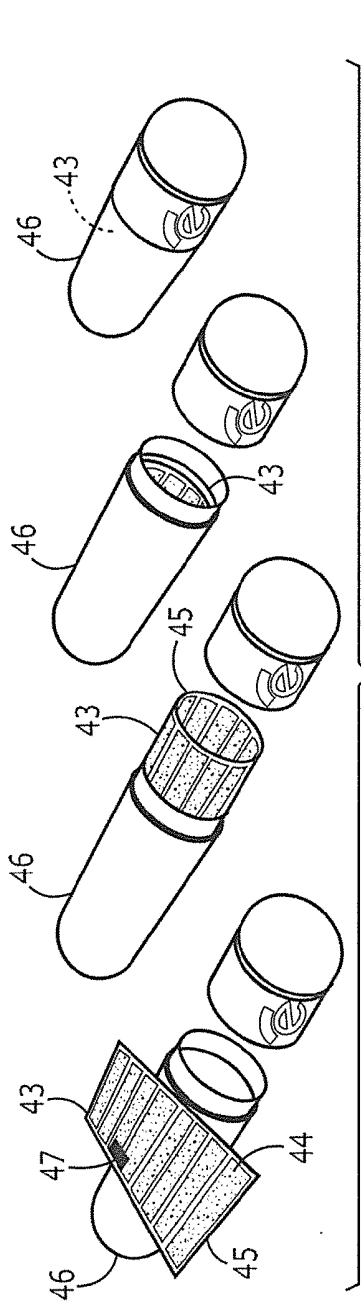


FIG. 4



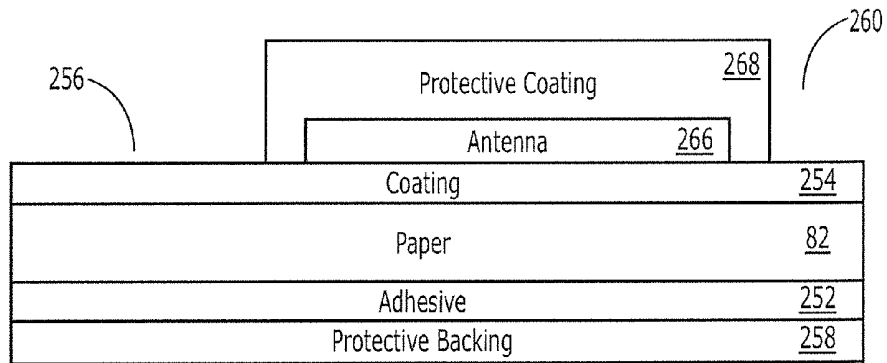


FIG. 6A

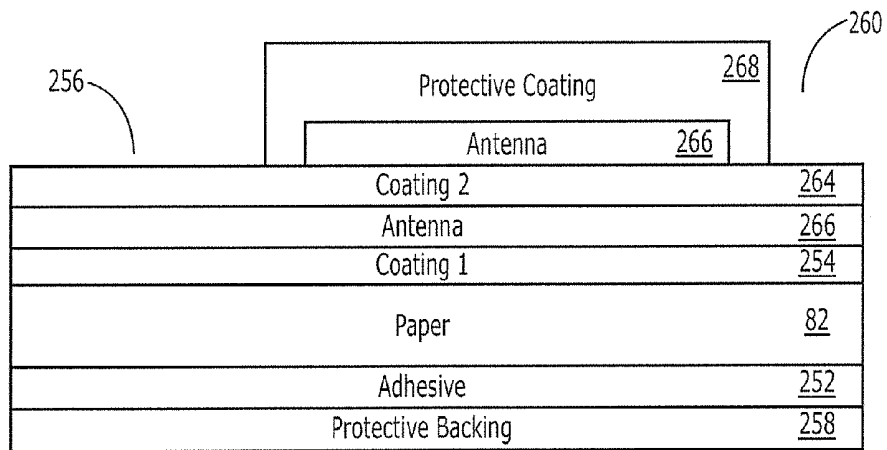


FIG. 6B

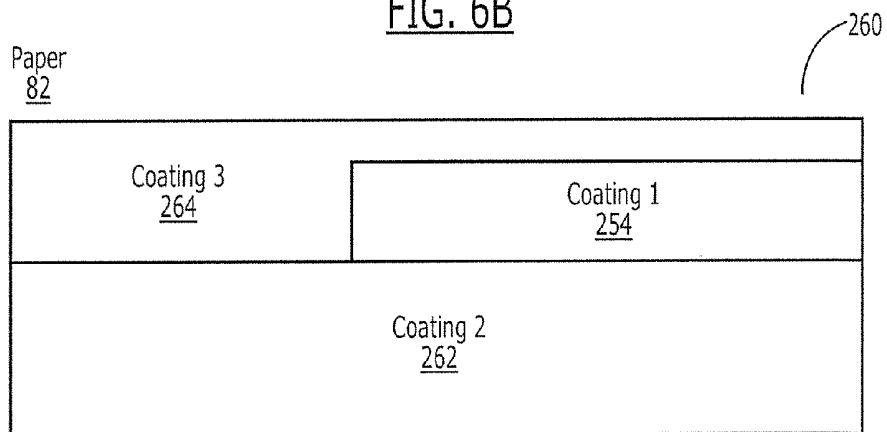
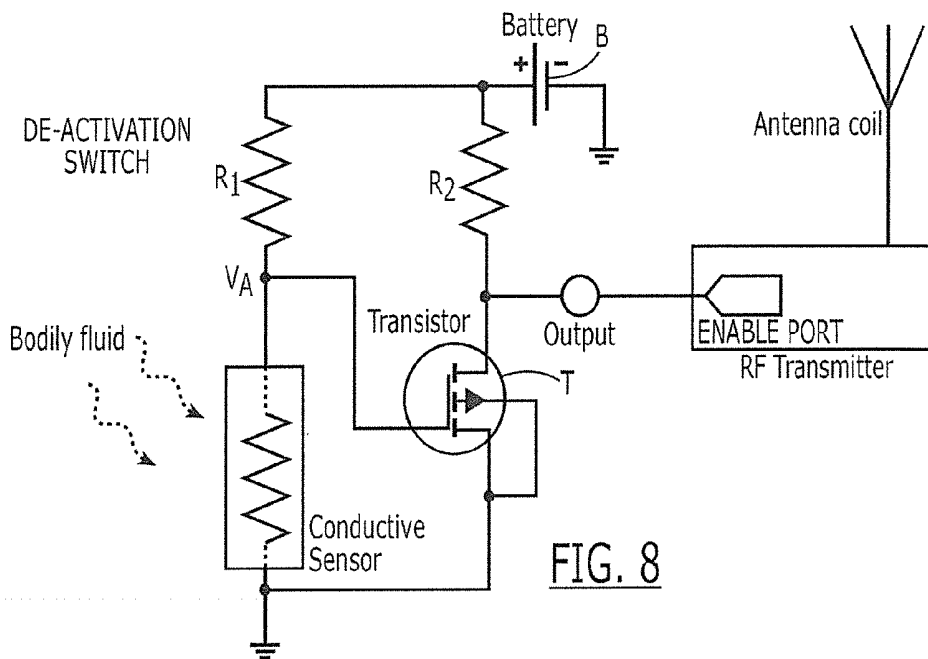
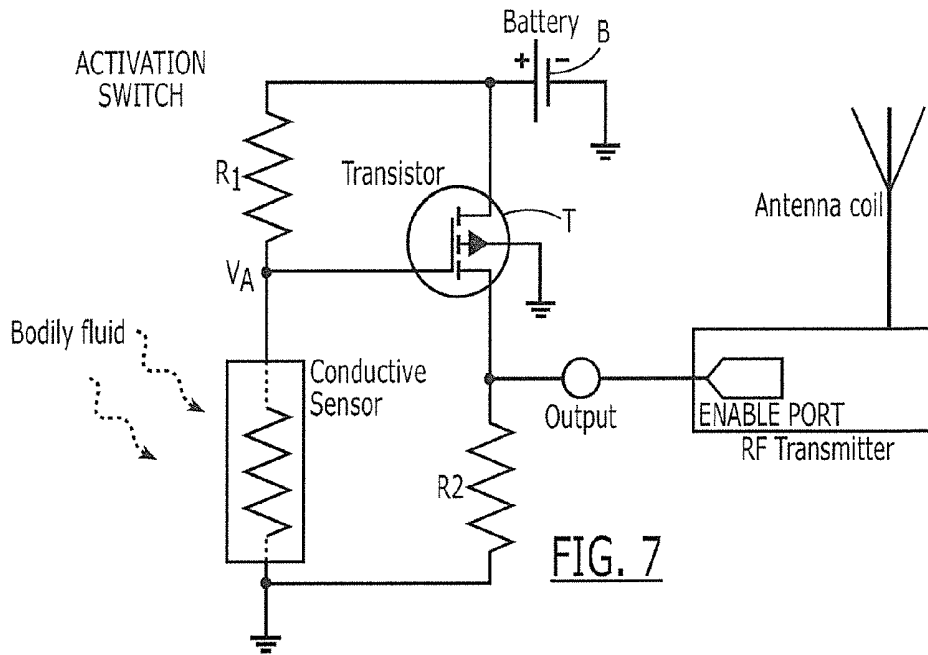


FIG. 6C



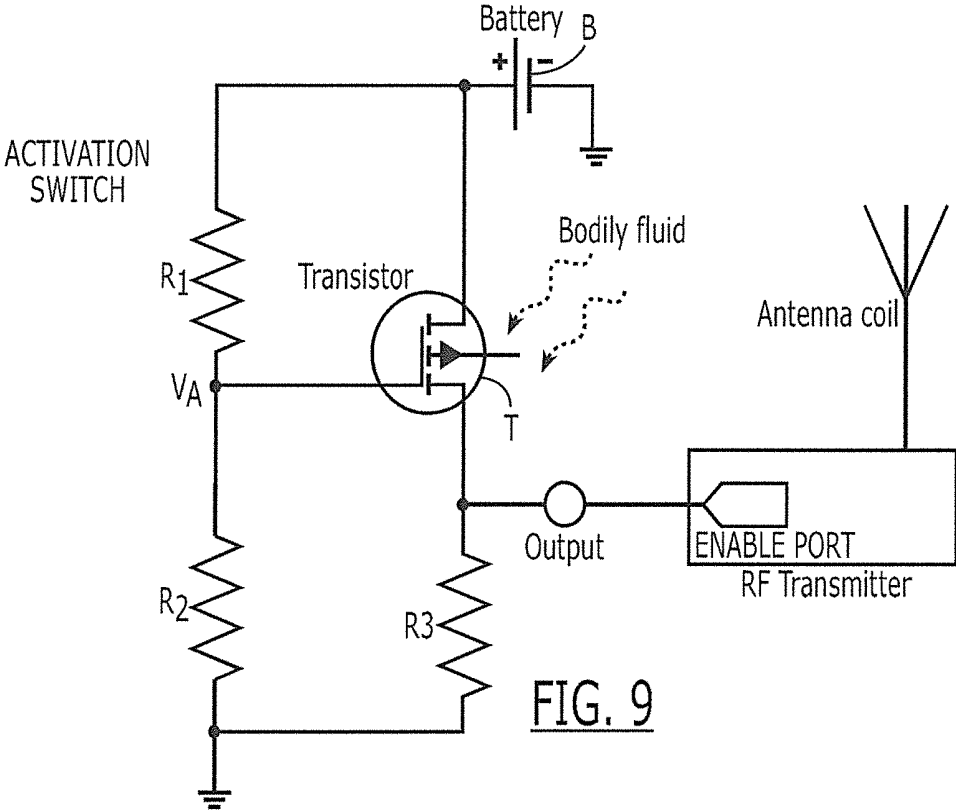
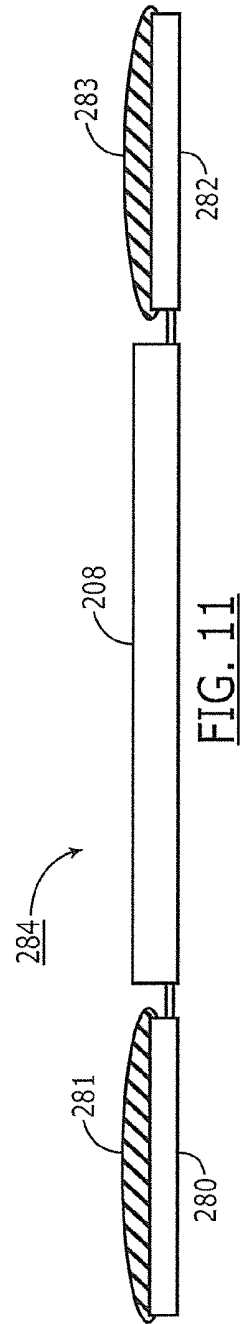
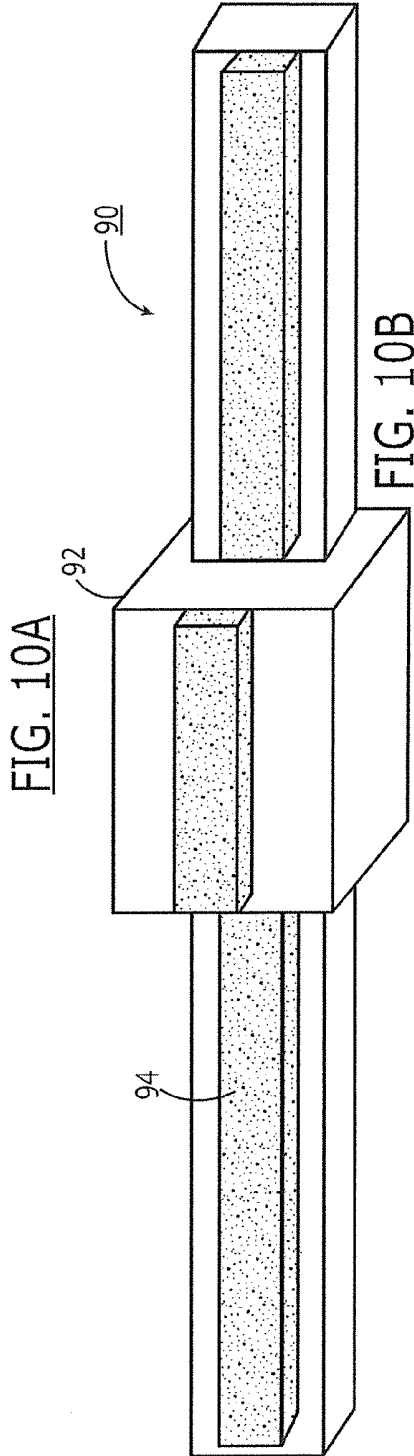
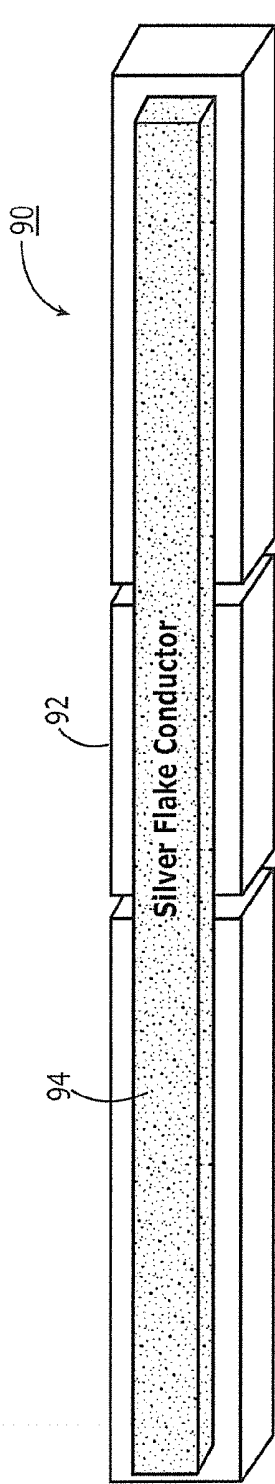


FIG. 9



Results

Electrode formation		20 kOhm load						1 kOhm load	
		5 s		10 s		15 s		5 s	10 s
time	Run	1	2	1	2	1	2	1	2
Test solution		Voltage							
Time (s)		(V)							
H2504	0	1.400	1.402	1.449	1.426	1.423	1.422	1.406	1.440
	30	1.209	1.180	1.368	1.419	1.389	1.415	0.980	1.403
	60	1.120	1.108	1.339	1.404	1.398	1.406	1.004	1.383
	90	1.099	1.090	1.320	1.398	1.411	1.405	1.012	1.376
	120	1.086	1.076	1.280	1.391	1.423	1.400	1.013	1.374
HCl	0	1.017	1.051	1.090	1.323	1.274	1.218	1.016	1.330
	30	1.050	1.029	1.052	1.097	1.053	0.994	1.007	1.013
	60	1.043	1.023	1.048	1.037	1.052	0.990	1.004	1.008
	90	1.035	1.018	1.045	1.030	1.045	0.984	1.001	1.001
	120	1.024	1.014	1.043	1.026	1.042	0.983	0.998	0.996
	15*					1.070	1.015		1.039

*15 s reading taken to show that the drop is dramatic within the first 15 s and not just 30 s

FIG. 12A

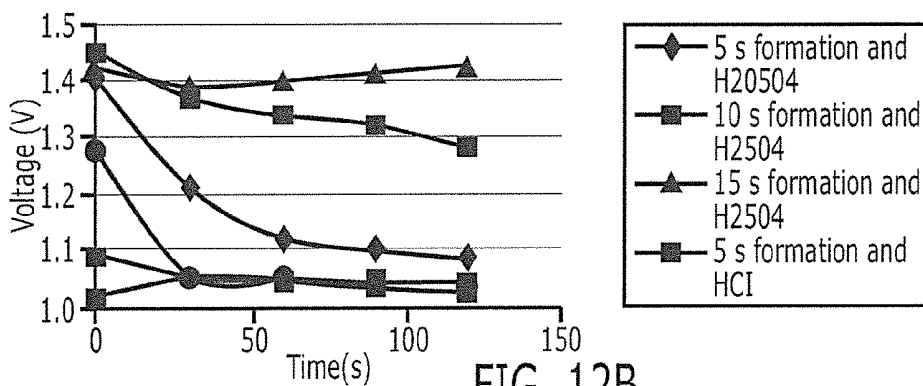


FIG. 12B

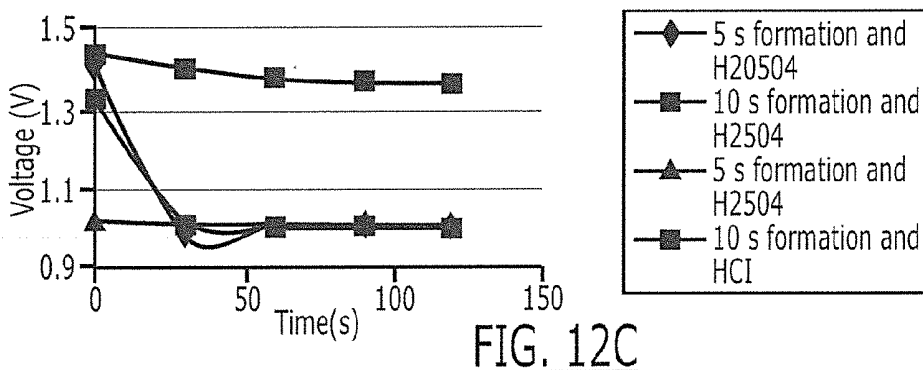


FIG. 12C

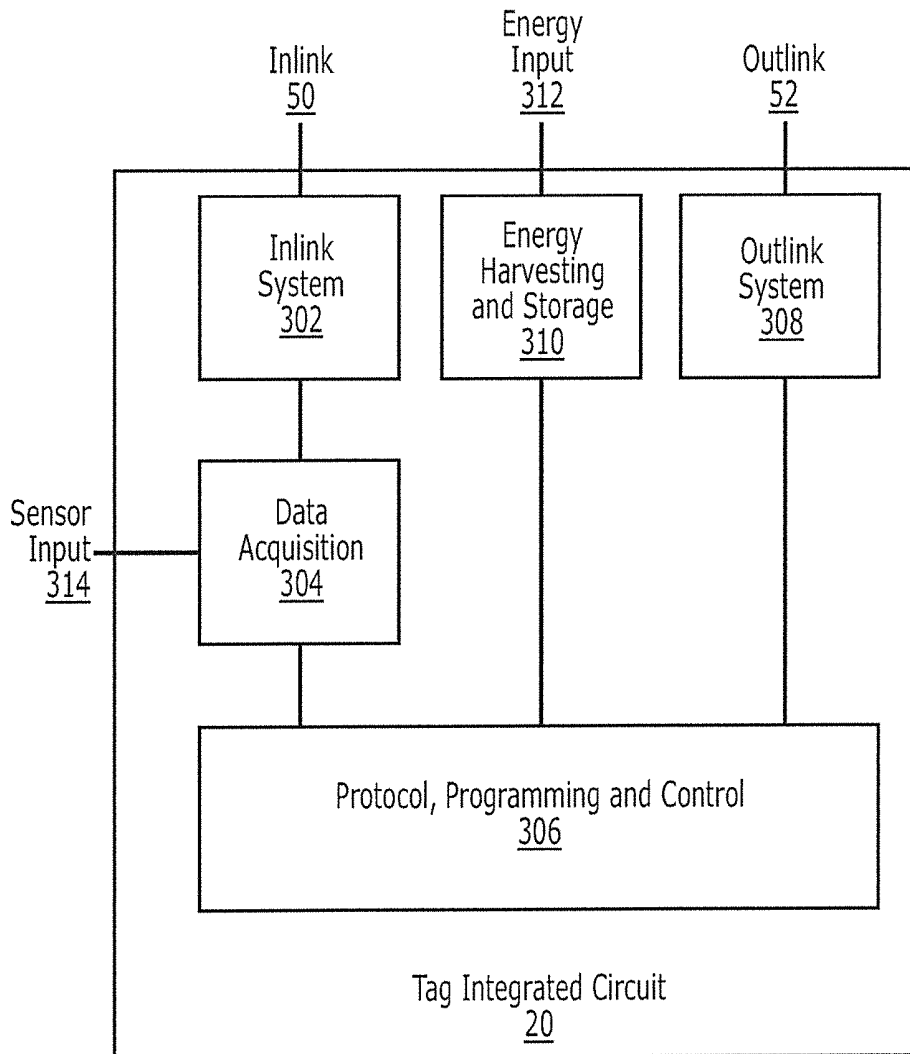


FIG. 13

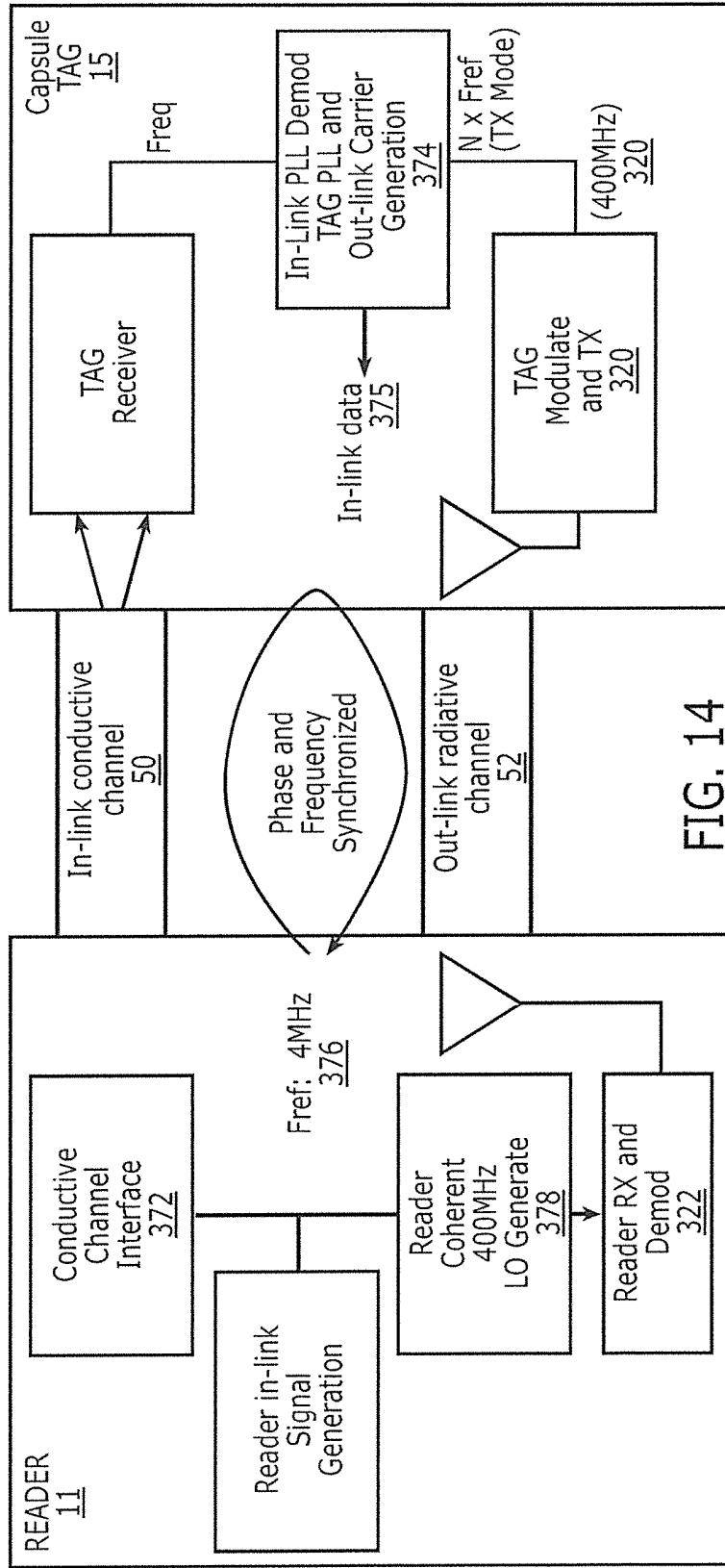


FIG. 14

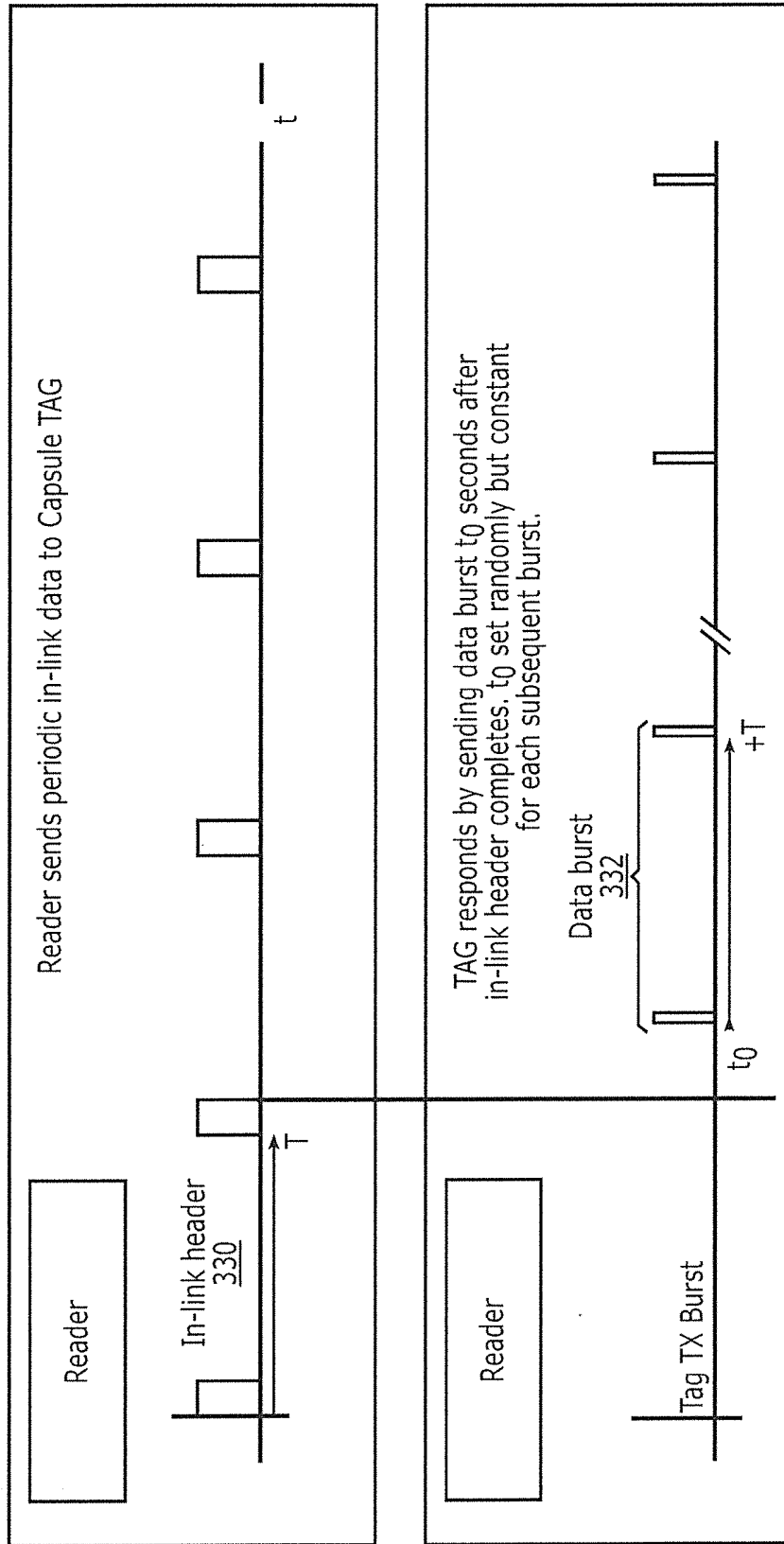


FIG. 15

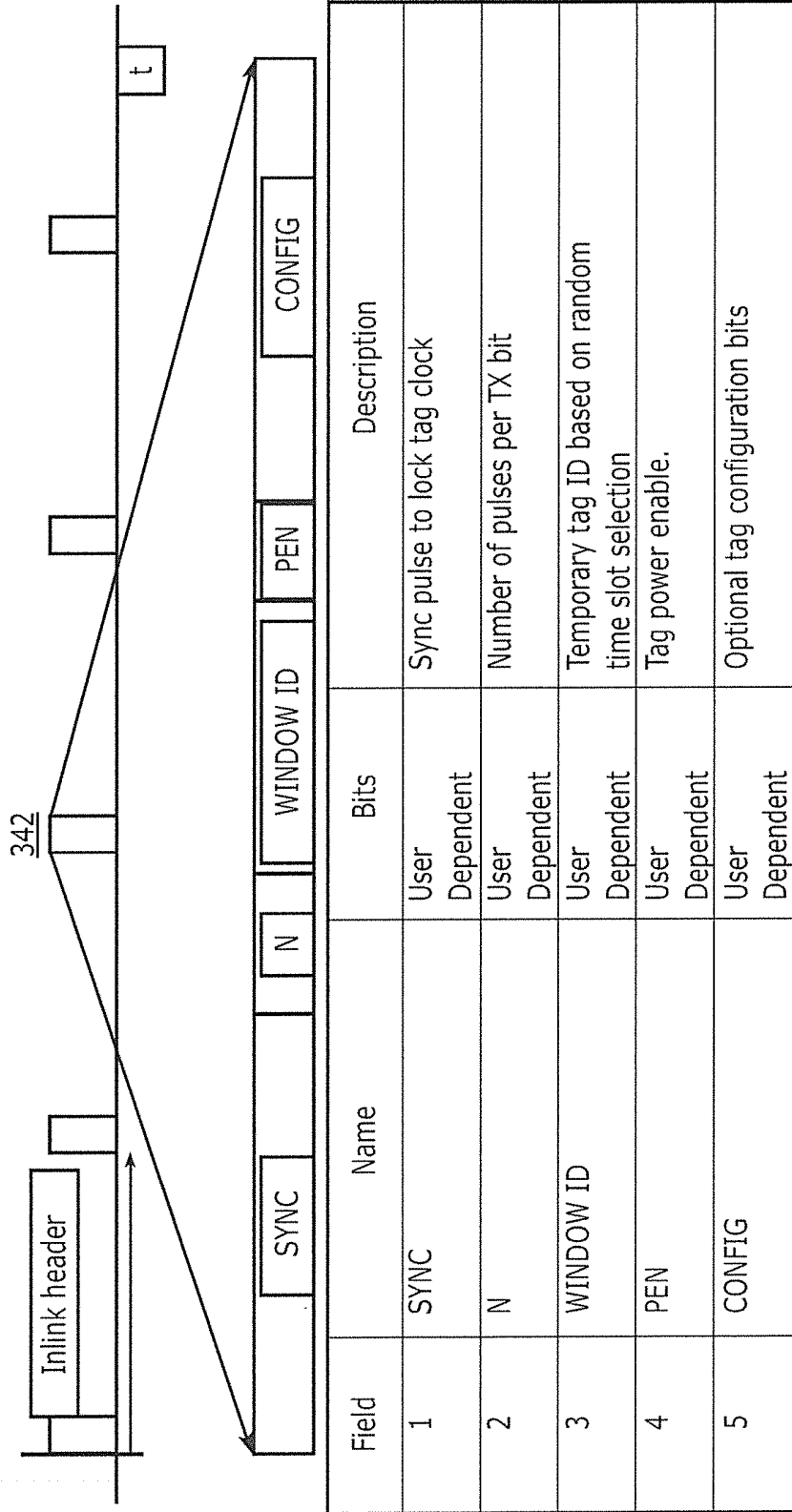
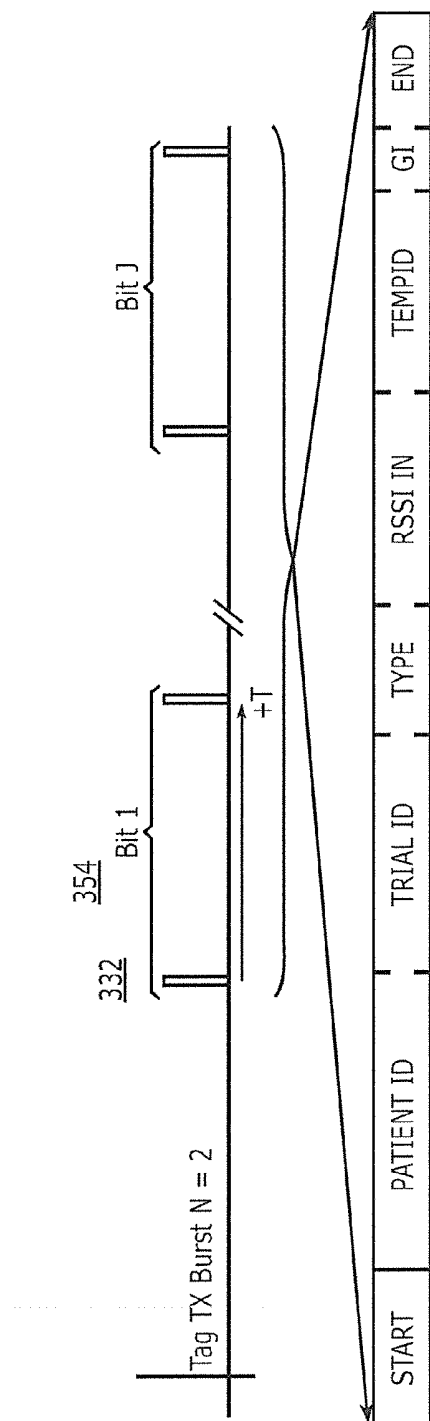


FIG. 16



Field	Name	Bits	Description
1	START	User set	Start sequence to calibrate receiver
2	PATIENT ID	User set	Patient ID programmed on tag
3	TRIAL ID	User set	Trial ID programmed on tag
4	TYPE	User set	Med type programmed on tag
5	RSSI IN	User set	In-link signal strength derived by tag
6	TEMP ID	User set	TX time slot defining the window ID
7	GI	User set	GI sensor data, Level proportional to time in GI tract
8	END	User set	End sequence to calibrate receiver

FIG. 17

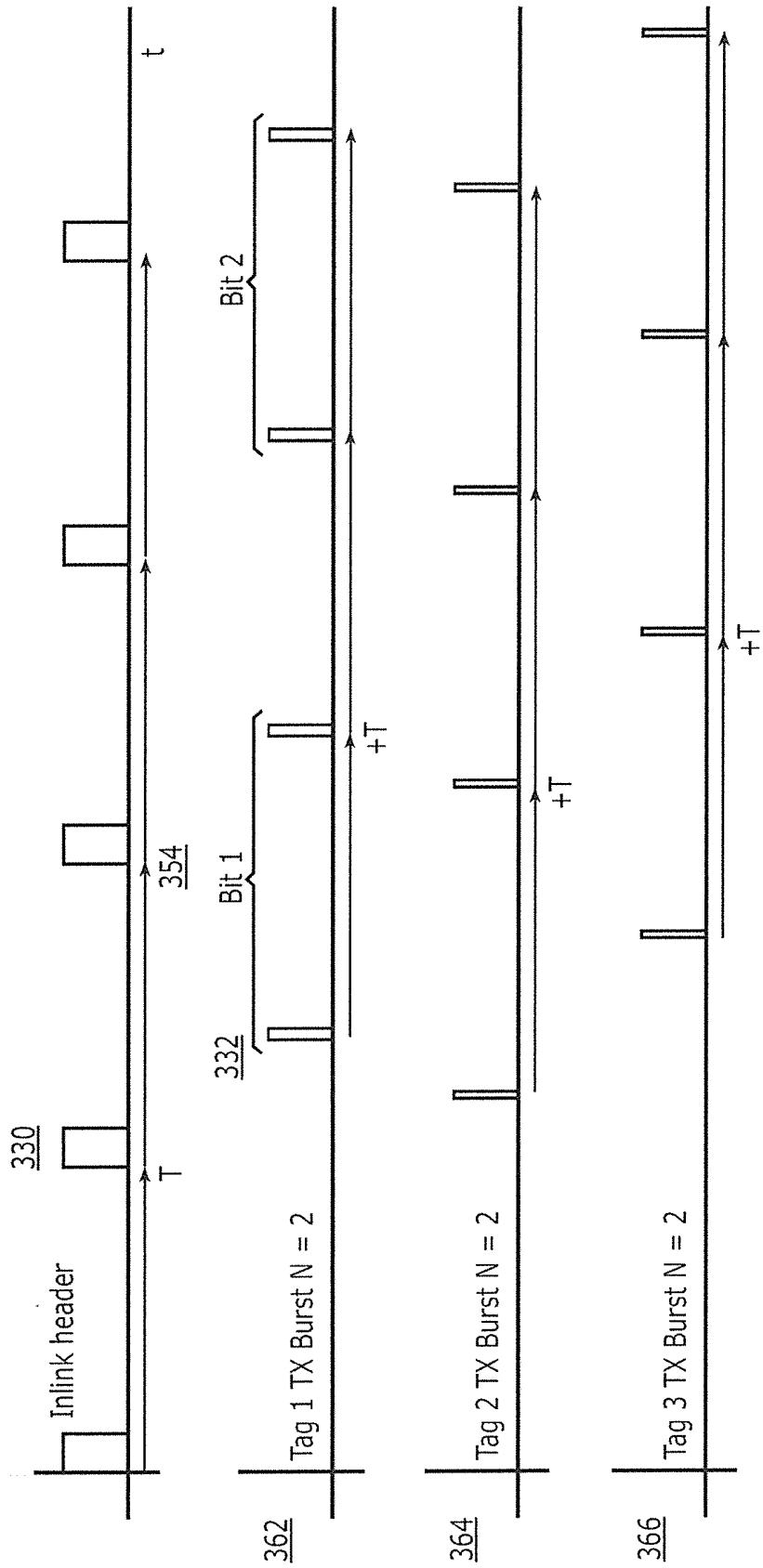


FIG. 18

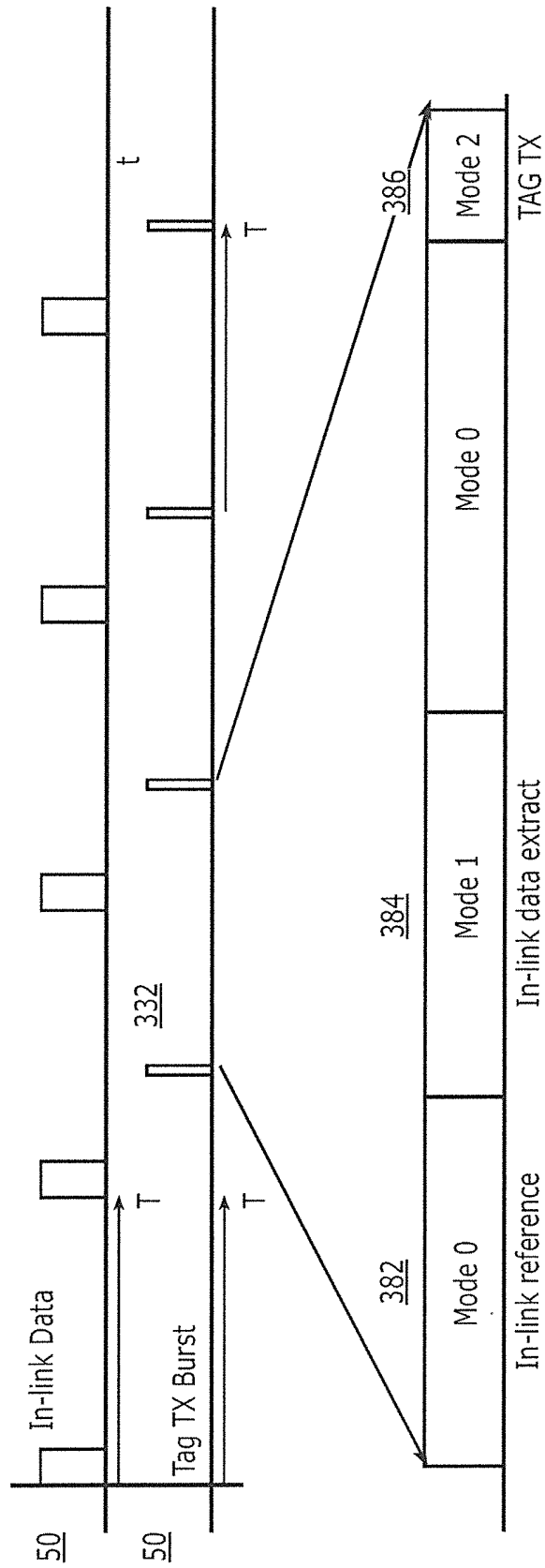


FIG. 19

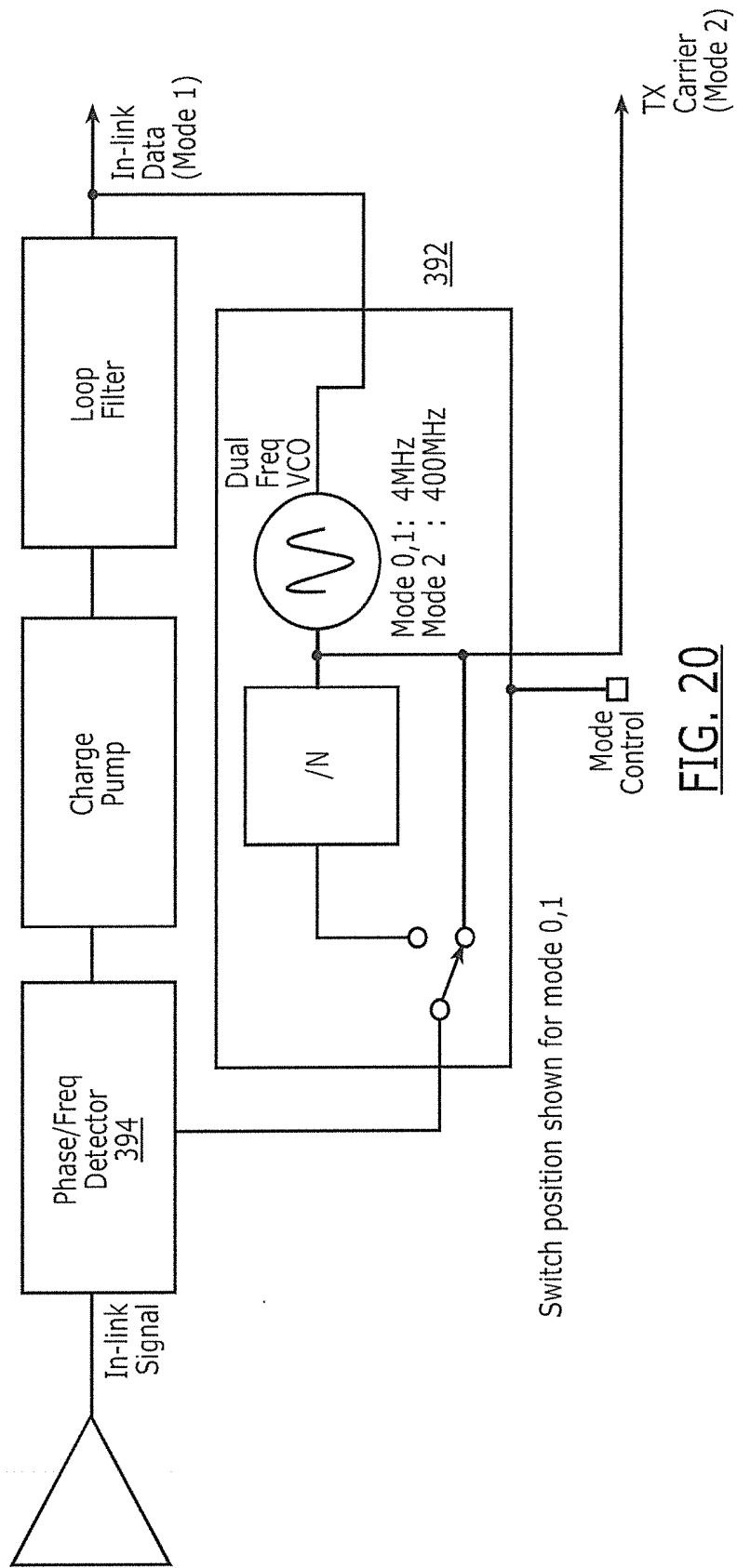
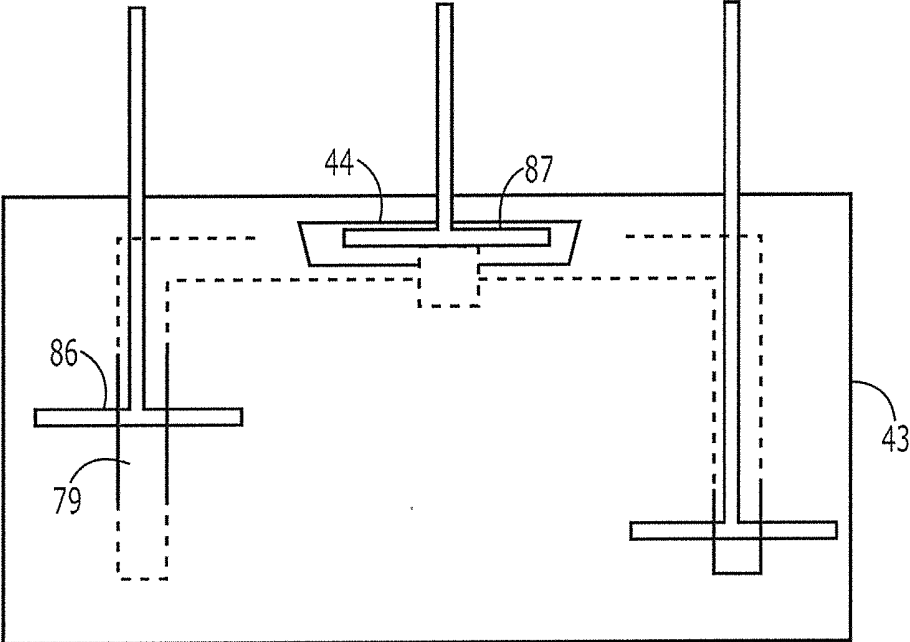
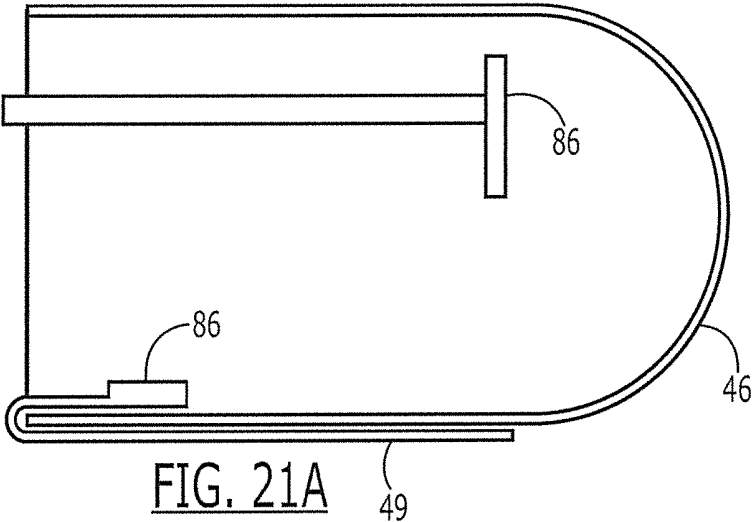


FIG. 20



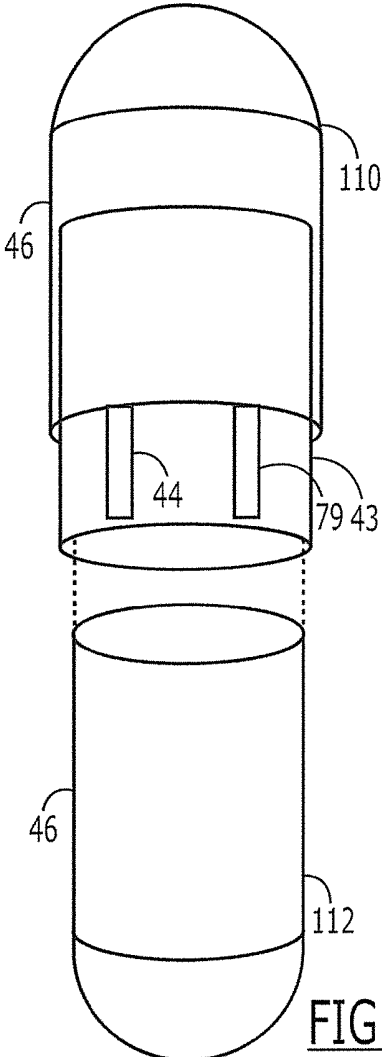


FIG. 22

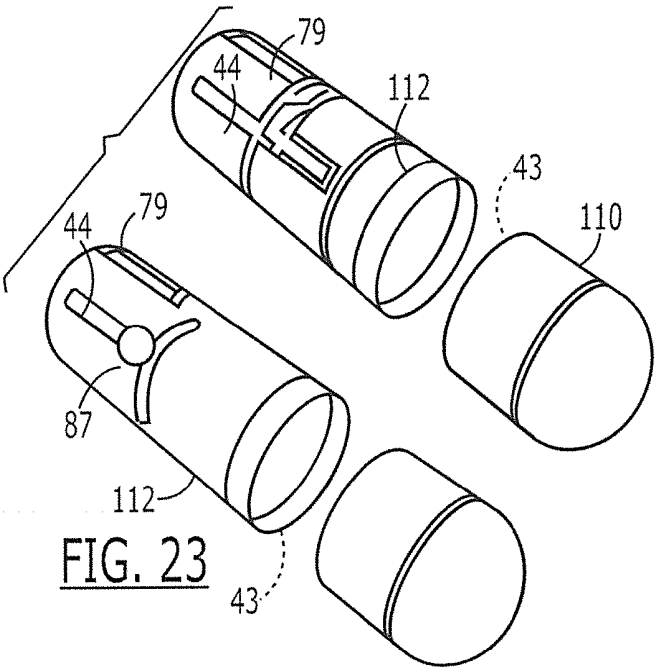


FIG. 23

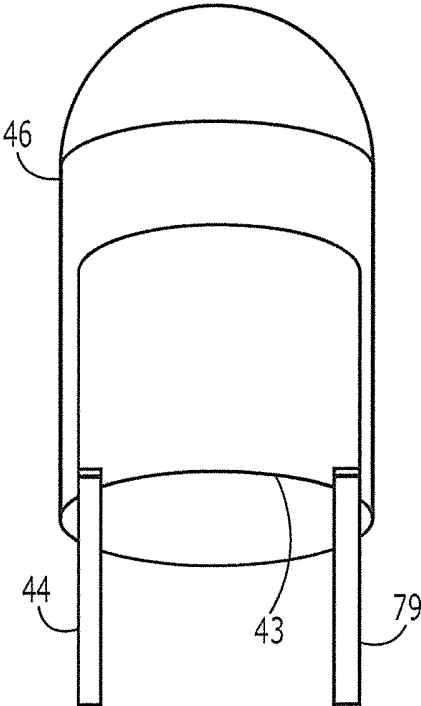


FIG. 24A

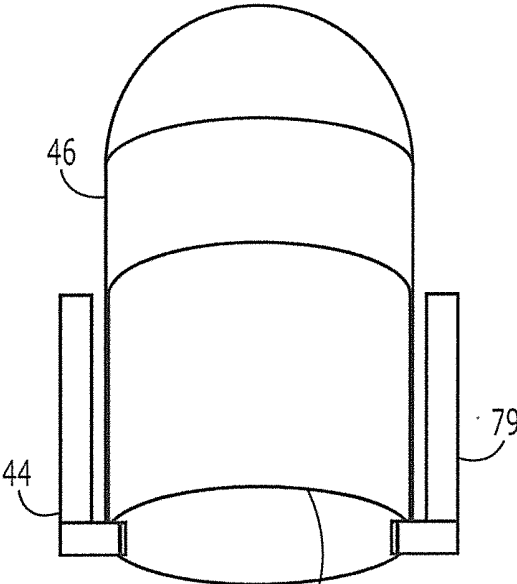


FIG. 24B

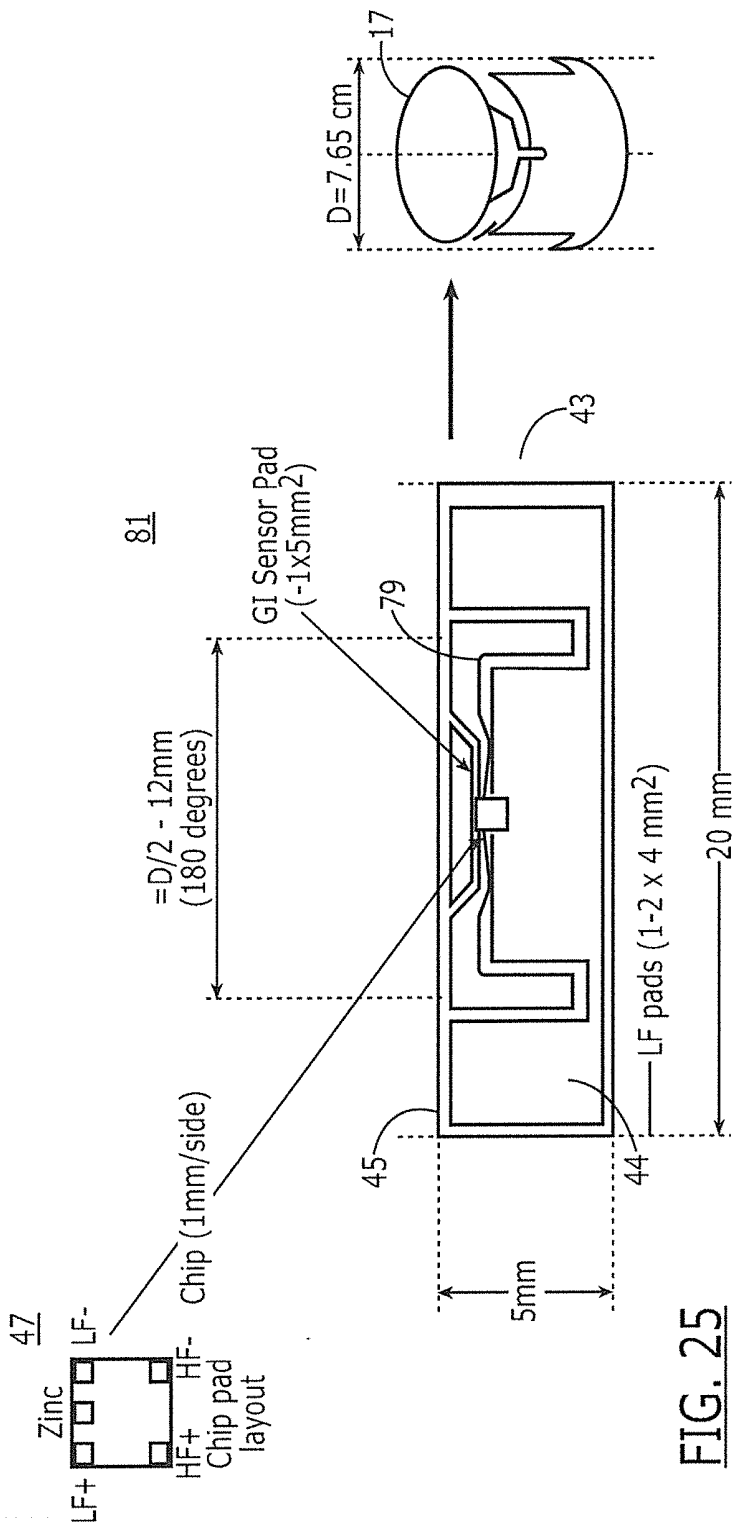


FIG. 25

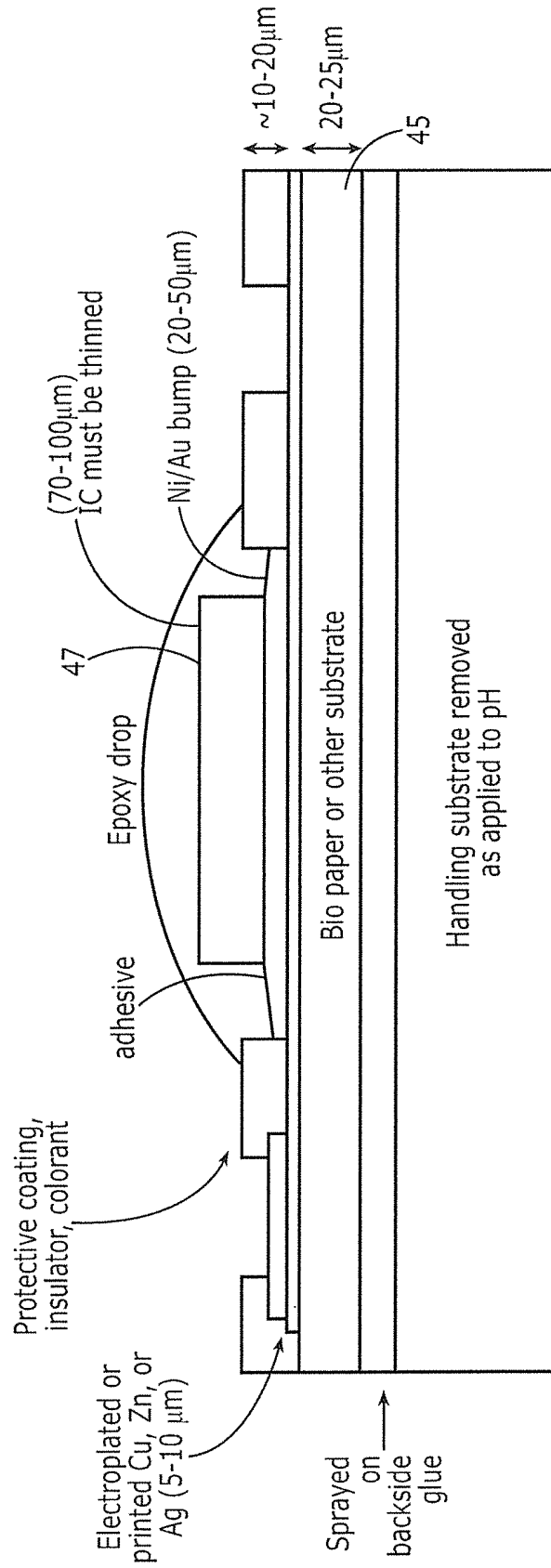
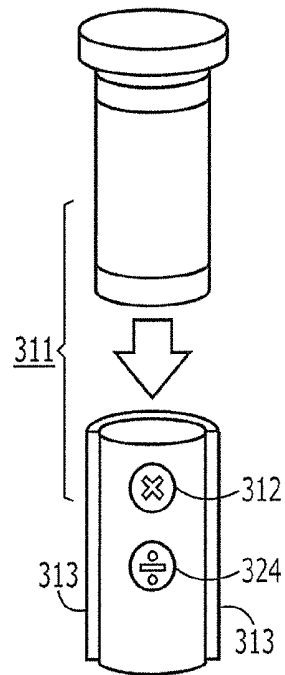
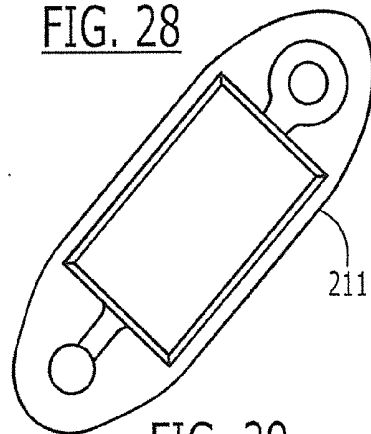
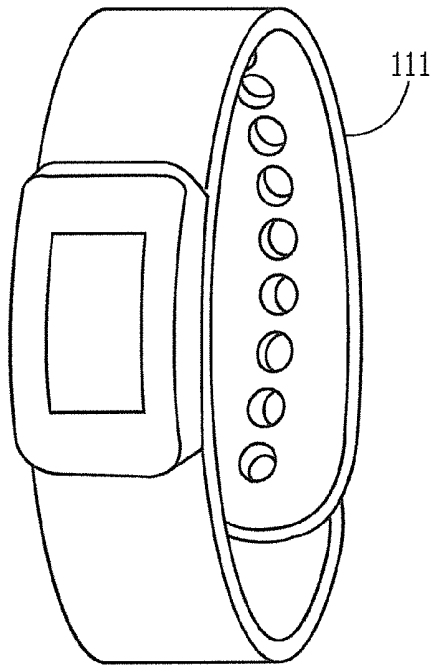
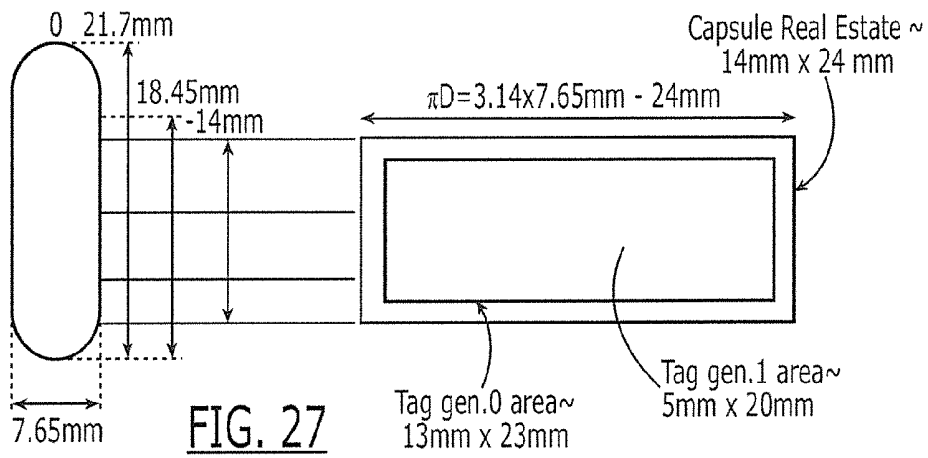


FIG. 26



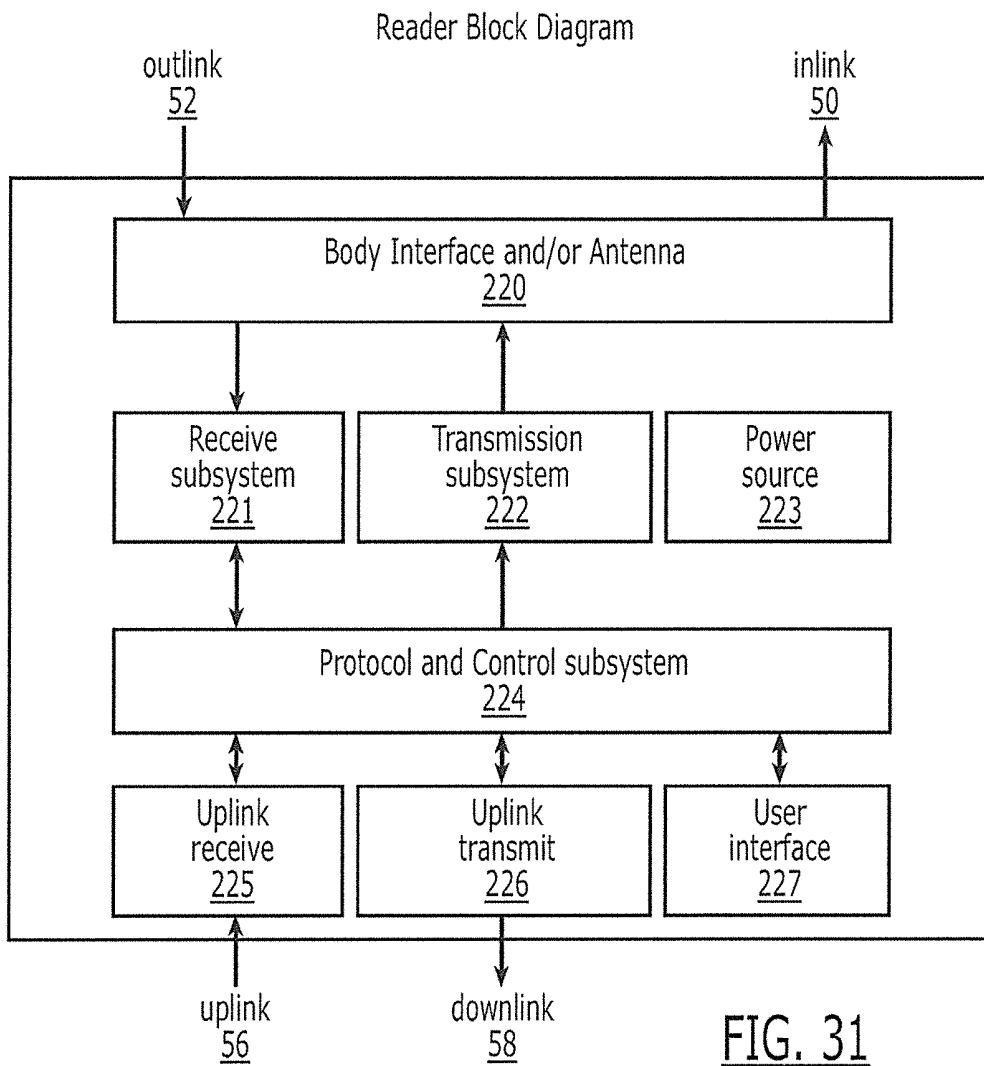


FIG. 31

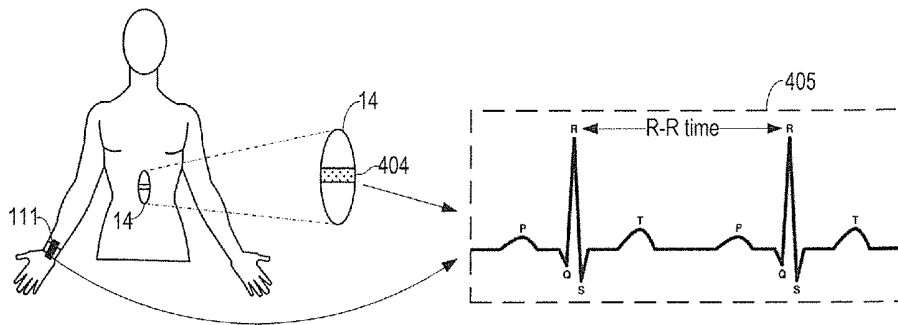


FIG. 32

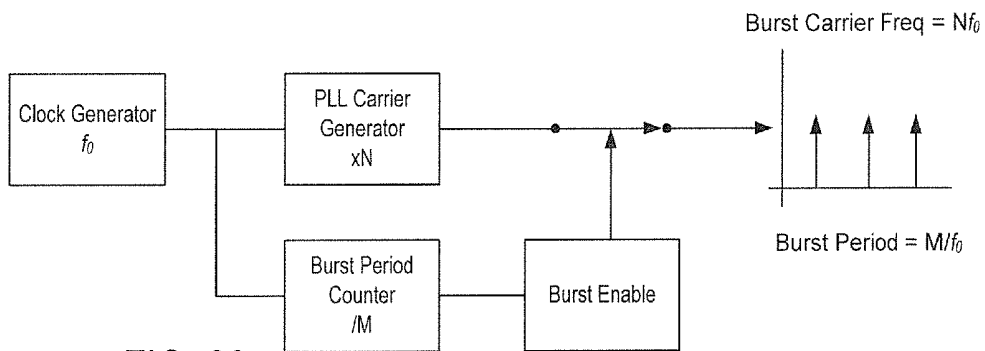


FIG. 33

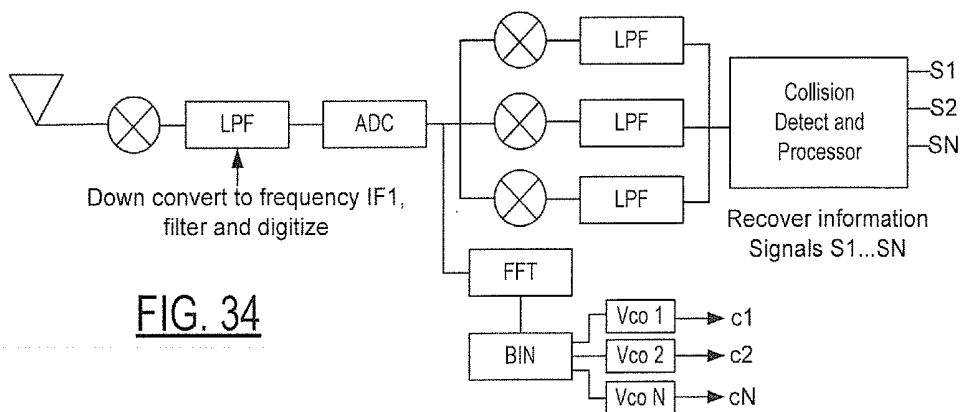


FIG. 34

ELECTRONIC MEDICATION COMPLIANCE MONITORING SYSTEM AND ASSOCIATED METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This claims priority to provisional application Ser. No. 61/789,077, filed Mar. 15, 2013 and is also a continuation-in-part of application Ser. No. 12/881,572, filed Sep. 14, 2010, which is a continuation-in-part of application Ser. No. 11/458,815, filed Jul. 20, 2006, which claims priority to provisional application Serial Nos. 60/700,963, 60/734,483 and 60/746,935, filed Jul. 20, 2005, Nov. 8, 2005 and May 10, 2006, respectively. The entire contents of these prior applications are incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention relates to electronic systems and methods for monitoring medication compliance.

BACKGROUND

[0003] Non-compliance of patients to drug regimens prescribed by physicians can cause a multiplicity of problems, including negative patient outcomes, higher healthcare costs and an increased risk of the spread of communicable diseases. Compliance monitoring is also critical in, for example, pharmaceutical clinical trials, geriatrics and mental health/addiction medicine. Poor medication compliance has a significant negative impact on patients, pharmaceutical manufacturers and the healthcare system in general. Non-compliant patients suffer from increased mortality, increased recurrence of chronic conditions and increased hospital and nursing home admissions. By some estimates, as much as 25% of all healthcare costs could be avoided if patients reliably took their prescribed medications.

[0004] Annual drug development spending has increased more than twelve times in inflation-adjusted dollars over the past three decades. Clinical trials consume a major portion of the development time and costs of introducing a new drug into the market. Knowing with certainty a patient's adherence significantly improves the understanding of the results from a clinical trial in terms of safety, efficacy, dose response relationship, pharmacodynamics, side effects and other results. For instance, in a beta-blocker heart attack trial the death rate was reported at 13.6% in subjects whose compliance was less than 75% compared to 5.6% in subjects whose compliance was over 75%. None of the existing methods of measuring adherence offer both a qualitative and a quantitative measure with proof-positive detection of ingestion of the medication. Accordingly, measuring medication regimen compliance continues to be a major problem. The only statistical recourse is to enroll large numbers of patients, which dramatically increases the cost of clinical drug trials that in turn increases the cost of the final marketed medication.

[0005] Compliance monitoring also provides significant benefits in market areas where patient adherence to a drug therapy protocol is vital to preventing or avoiding high-cost consequences for the patient or community. Strict regimen adherence is important for preventing emergence of drug-resistant strains of infectious diseases that can occur when proper dosing schedules are not followed. Such resistant

strains result in increased transmission, morbidity and mortality and are more expensive to treat or cure, often by one or two orders of magnitude.

[0006] A traditional method of increasing compliance is direct observance, but this is obviously difficult to administer and impractical on a large scale. Other techniques include blood sampling, urine sampling, biological marker detection, self-reporting, pill counting, electronic monitoring and prescription record review. These techniques are either invasive or prone to tampering.

[0007] In vivo biotelemetry and monitoring have been used for monitoring embedded oxygen, sensing glucose levels, fetal monitoring and hormone measuring. Passive radio-frequency identification (RFID) techniques have been suggested to provide biotelemetry by including external sensors into existing commercial systems. However, RFID was not designed to operate in vivo, and the transmission of electromagnetic signals from embedded or internal sensors is hampered by attenuation and reflections from the body.

[0008] Therefore, it would be beneficial to provide an active electronic device, system and method for non-invasively monitoring drug compliance in a facile manner.

SUMMARY

[0009] Our new medication compliance systems and methods address the drawbacks associated with transmitting RF signals through the body and/or with tampering.

[0010] A method of monitoring a patient's compliance with a medication program includes transmitting a first signal from an electronic ingestible medication delivery device located within a patient's body, the signal including information about a physiological parameter of the patient; detecting the signal with an electronic reader located outside the patient's body; and providing a second signal to the reader from different source than the delivery device, the second signal including information about the same physiological parameter of the patient.

[0011] A first system for monitoring a patient's compliance with a medication delivery program includes an electronic ingestible medication delivery device that, after ingestion by a patient, makes a first measurement of a physiological parameter of the patient and transmits a signal from within the patient's body, the signal including information from the first measurement. An electronic reader outside the patient's body reads the signal and makes a second measurement of the same physiological parameter of the patient. This system can help determine whether the delivery device and reader are operating on the same patient.

[0012] A second system for monitoring a patient's compliance with a medication program includes an ingestible medication delivery device carrying an electronic circuit that transmits an electromagnetic signal from within a patient's body to outside the patient's body. An electronic reader positioned outside the patient's body detects the electromagnetic signal. Here, transmission and detection of the electromagnetic signal are synchronized according to a physiological parameter measured from the patient. This synchronization provides better sensitivity for the transmitted signal.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 is a schematic diagram of the medication compliance system of the present invention.

[0014] FIG. 2A is one embodiment of a capsule having a planar substrate with an antenna and electronics wrapped about a portion of the capsule. FIG. 2B illustrates a capsule having a single-coil antenna wrapped about a portion of its periphery.

[0015] FIG. 2C illustrates a capsule having a digestible coating on its outer surface.

[0016] FIG. 3 is a schematic chart that illustrates the use of an electronic capsule with a wristband reader that is in communication with a cell phone, and which in turn can be used to forward information to a data collection center.

[0017] FIG. 4 is a block diagram illustrating the tag electronics and antenna fitted with an electronic pill or capsule like that shown in FIGS. 1, 2A-2C and 3.

[0018] FIGS. 5A and 5B illustrate techniques used to mate an electronic tag shown in FIGS. 1 and 3 with the inside surface of a capsule (FIG. 5A) or the outer surface (FIG. 5B).

[0019] FIGS. 6A, 6B and 6C are schematic side views illustrating the layers used to fabricate an electronic tag in accordance with different embodiments of this invention.

[0020] FIG. 7 is a circuit diagram for an exemplary activation switch circuit using a conductive sensor with a NMOS-FET transistor.

[0021] FIG. 8 is a circuit diagram for an exemplary deactivation switch circuit using a MOSFET transistor.

[0022] FIG. 9 is a circuit diagram for an exemplary MOS-FET sensor-based bio-switch.

[0023] FIG. 10A is a top perspective view of an ingestible switch in accordance with the present invention utilizing a hydrogel circuit breaker.

[0024] FIG. 10B depicts the switch of FIG. 10A, with a swollen hydrogel circuit breaker after exposure to gastrointestinal fluids.

[0025] FIG. 11 is a schematic side view of a galvanic gastric sensor for utilization with the electronic tag shown in FIGS. 1 and 3.

[0026] FIG. 12A is a summary of the results of testing of several phosphate electrodes at different modes.

[0027] FIGS. 12B and 12C are coded charts depicting the results set forth in FIG. 12A for a 20K Ohm load and a 1K Ohm, respectively.

[0028] FIG. 13 is a block diagram illustrating the electronics associated with the tag integrated circuit.

[0029] FIG. 14 is a block diagram illustrating the overall in-link and out-link communications between the electronic tag taken internally by a patient, and the external reader utilized to communicate with the tag illustrating a specific example of conductive transmissions from the reader to the tag at 4 MHz and radiative out-link transmissions from the tag to the reader at 400 MHz by way of example.

[0030] FIG. 15 is a timing chart illustrating the periodic transmissions from the reader to the tag and the data bursts from the tag to the reader.

[0031] FIG. 16 is a chart depicting the content of the in-link transmission from the reader to the tag.

[0032] FIG. 17 is a chart depicting the content of information contained in the data bursts from the tag to the reader.

[0033] FIG. 18 depicts a timing chart for out-link transmissions from multiple tags to the reader.

[0034] FIG. 19 is another timing diagram illustrating the operation of the system of the present invention.

[0035] FIG. 20 is a block diagram illustrating further aspects of the operation of the system.

[0036] FIGS. 21A and 21B are side views illustrating alternate constructions for the electronic capsule to permit a portion of the electronics to be carried within the capsule.

[0037] FIG. 22 depicts an alternate construction with the tag partially within the capsule and partially exposed.

[0038] FIGS. 23, FIGS. 24A and 24B depict exemplary constructions of a capsule with a tag in accordance with this invention.

[0039] FIG. 25 is an exploded illustration depicting, from left to right, the attachment of an integrated circuit chip to the tag connected to the low frequency and high frequency antenna areas, and the wrapping of the tag about a capsule (right hand side).

[0040] FIG. 26 is a cross-sectional side view of the tag, illustrating the various elements depicted in schematic form in FIGS. 6A and 6B.

[0041] FIG. 27 sets forth representative dimensions of the capsule and tag.

[0042] FIG. 28 is a top view of a wrist band reader feature shown in FIG. 3.

[0043] FIG. 29 depicts a patch reader wearable by a patient.

[0044] FIG. 30 depicts a pill container having an on-board reader.

[0045] FIG. 31 is a block diagram of the reader 19 in FIG. 1.

[0046] FIGS. 32 and 33 illustrate a biometric identification system using an electronic pill and an external reader worn by the patient to analyze a physiologic signal from the patient.

[0047] FIG. 34 is a block diagram of an external reader architecture for receiving and processing signals from the system of FIGS. 32 and 33.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0048] In the Summary and in the Detailed Description of The Preferred Embodiments, reference is made to particular features. Where a particular feature is disclosed in the context of a particular aspect or embodiment, that feature can also be used, to the extent possible, in combination with and/or in the context of other aspects and embodiments.

[0049] In this section, embodiments will be described more fully. These embodiments may, however, take many different forms and should not be construed as limited to those set forth herein.

[0050] A description of the preferred embodiments of the present invention will now be presented with reference to FIGS. 1-34.

[0051] Noting FIG. 1, a system 10 for monitoring medication compliance in a patient 16 comprises an electronic sensor, preferably in the form of an external wireless monitor or reader 11 that includes an RF transceiver 12 and one or more antennas 13. The antenna 13 can be external or internal to the reader 11 and can be implemented in a variety of ways as known in the art, including an on-chip antenna or simple pads or electrical contacts that function as an antenna. The reader 11 detects the presence of an electronic pill 14 in, for example, the gastrointestinal (GI) tract of the patient 16. As shown the electronic pill 14 has a tag 15 attached to or part of the pill 14. For purposes of this disclosure, the term "pill" can include a capsule or other form of medication administration or testing. The system 10 is designed to detect the pill 14 when located in the patient's mouth M, esophagus E, stomach S, duodenum D, intestines (including the colon) I or rectum R.

[0052] With continued reference to FIG. 1, the system 10 includes a tag 15 fixed with the pill 14, either internally or along the outer surface, or both. After ingestion of the pill 14, the tag 15 is made electronically active and begins communication with the external reader 11. The external reader 11 in one embodiment is in a housing 19 worn by or attached with the patient 16 so as to be comfortable and easy to wear continuously to ensure it is always with the patient.

[0053] The electronic pill 14 comprises an orally ingestible and biocompatible drug-transporting device with embedded or attached electronic circuits that communicates with the external wireless reader 16. As described in greater detail below, the electronic pill 14 uses, for example, a silicon-based integrated circuit and/or other passive components such as coil antennae and capacitors. The circuit can incorporate millions of transistors, patterned through various semiconductor processing steps, to provide an enormous amount of intelligence. For instance, the electronic pill 14 can store a patient's medical history in addition to detailed information about a drug being administered, provide a unique identification number, and implement advanced communication circuits and protocols to reliably transmit data to the external wireless reader 16.

[0054] Turning now to FIG. 2A, the electronic pill 14 preferably comprises a drug-transporting device, such as a capsule 17 that has associated therewith the electronic tag 15. Noting FIG. 1, a signal 18 received by the reader 11 from the electronic circuit 30 after ingestion of the capsule 17 is thus indicative of medication compliance. The term "drug-transporting device" is not intended as a limitation, and other compositions and devices for delivering medication are intended to be subsumed hereinto as known in the art. Alternatively, the capsule 17 may be devoid of medication to serve as a placebo during a drug trial.

[0055] Referring again to FIG. 2A, the electronic components of the electronic pill 14 are capable of wireless transmission and reception over short distances (i.e., in the range of 20-30 cm). The electronic components in the circuit 47 (i.e., antenna 21, power source 22, and silicon chip 23), once hermetically sealed and packaged, is small enough to fit either to the inside wall or on the outside wall of the capsule 17. This level of miniaturization is feasible owing to integration and circuit scaling trends associated with standard CMOS technologies.

[0056] With continued reference to FIG. 2A, a small chip or other electronics 47 is attached to the substrate 45 as well. This chip 47 provides a great deal of functionality including but not limited to two way communication and complex protocols, energy harvesting (mechanical, electrical, etc), sensing of conditions such as location of the tag, pH, chlorine content, encryption, and identification code storage and transmission.

[0057] Referring now to FIG. 3, the complete system is principally composed of a data reader 111 and multiple tags 15 attached to medication 14. Bidirectional data 50/52 is exchanged between the reader 111 and the tag 15. The reader 111 probes the one or more tags 15 inside the body 10 and coordinates the communication to allow multiple ingested tags to communicate simultaneously, sequentially, or in other ways to permit multiple communication pathways. The tags 15 communicate their unique identification data and whether they are in the GI tract. The reader 111 then provides output data 58 to a user interface 54 such as a laptop or smartphone enabling real-time upload 59 of medication events to a remote

database 60 or other location. The reader 111 receives information from the user interface 54 via the channel 56 indicating medication regimen status such as the time of the next scheduled medication event, confirmation of the event from the main database, or other information from the user interface 54 or the remote database or trial coordination center 60 via the wide area network (cell or wifi network) channel 59.

[0058] The data link from the reader 111 to tag 15 is defined as the "in-link" path 50. Preferentially, in-link data to the tag includes synchronization, signaling, address, and tag configuration information. The reader 111 preferentially transmits information by way of differential metallic skin contacts. The in-link signal 50 passes through the body 10 and is sensed by the tag 15 through a differential probe network.

[0059] The data link from the tag 15 to the reader 111 is defined as the "out-link" path 52. Preferentially, the out-link data to the reader includes GI sensing, pharmaceutical, adherence, signal level, and address information. The out-link channel 52 is a radio frequency signal traveling through both the body 10 and the free space between the body and the antenna of the reader 111. A small antenna 21 on the tag 15 radiates the out-link signal 52 which is received at the reader 111. The reader 111 is capable of receiving signals 52 from multiple tags 15 simultaneously.

[0060] All of these components work together to complete a system that can accurately detect a medication event, including the time of ingestion, the dosage, and specific identification of the medication. This information is then used to verify critical compliance with drug therapy. This data can also be used in combination with other patient data to improve adherence and treatment outcomes.

Tag Detail and Manufacturing

[0061] The following sections describe the detailed construction of the tag 15. Referring to FIG. 4, the tag 15 comprises a body interface and antenna 203 that allows for the in-link 50 and out-link 52 communication. The ingestion detection subsystem 208 utilizes the body interface and antenna system 203 to determine when the medication actually resides in the body 10 and in particular in the digestive tract M,E,S,D,L,R, and specifically which portion of the digestive tract. A receive subsystem 204 implements the in-link 50 communication and interfaces between the body interface and antenna subsystem 203 and a control subsystem 209. A transmission subsystem 206 implements the out-link 52 communication and interface between the control subsystem 209 and the body interface and antenna subsystem 203. An energy harvesting subsystem 205 captures energy from either the body interface 203 or from the environment that the tag 15 resides in, for example the motion or temperature of the device. The energy harvesting subsystem 205 provides energy which is stored in an energy storage system 207 and to the tag 15 in general to operate the components and provide sufficient power for out-link transmission. The control subsystem 209 coordinates and controls the differing components of the tag 15 and implements any communication protocol, sensor measurements, maintains tag memory for various identification information, and implements any other functionality required by the tag 15. The tag 15 can be attached to a pill 14 or capsule 17 in a variety of ways, either by being built into the medication, build onto the medication, being printed onto the medication, or by being attached onto the outside or inside of the medication carrier (i.e. a capsule). A preferred embodiment is to build the tag 15 on a biocom-

patible substrate **45** that can be built in high quantities and then later attached or built into a capsule **17**, for example.

Substrate (Printing and Tag)

[0062] Referring now to FIGS. **5A** and **5B**, in another embodiment of the tag **43**, the antenna **44** are printed on a flexible substrate **45** that is biodegradable and digestible, such as a flat sheet-like material, and includes an electronic chip **47** mounted on the substrate. This substrate **45** is then placed on or wrapped around the capsule **46**. The antenna **44** is preferably printed in a way that when the material **45** is wrapped around a capsule **46**, connections can be made from one end of the sheet **45** to the other, thus forming the antenna **44** as a continuous loop. Printing on both sides of the substrate **45** simplifies this process by using a technique similar to circuit board manufacturing with through-holes. Preferably, the substrate **45** should have sufficient rigidity for manufacturing and attachment, be easily and safely digested, be flexible for wrapping around a pill or capsule, and withstand temperatures required for manufacturing and sterilization.

[0063] There are relatively few materials for substrates **45** that are both easily and safely digested and can also withstand temperatures required for bonding the chips **47** to the antennae (up to 190° C.) or the sintering of metallic inks. In one embodiment, an enteric coating commonly used in colonic-targeted drug release, is utilized to create a flat and flexible substrate that meets these requirements and has been used in prototype tags.

[0064] Enteric coatings are commercial materials with good flexibility and proven biocompatibility. They are currently used in aspirin, acetaminophen and other drugs that upset the stomach, as they resist disintegration at low pH. Enteric coatings usually begin to disintegrate at a pH above 5.5 or higher, which is the typical pH of the duodenum and small intestine. Enteric coatings include but are not limited to polymethacrylate-polymethylmethacrylate (PMA-PMMA) copolymers and cellulose acetate phthalate (CAP), which are commercial coatings under names of "Eudragit" and "Aqua-coat CPD" that are readily available as pre-mixed solutions.

[0065] Referring now to FIG. **6A**, in another embodiment, the substrate **45** of FIGS. **5A**, **B** can be manufactured with a coated paper to create a biocompatible coated paper substrate system **260** to provide advantageous properties. A paper substrate **82** coated with a coating **254** provides improved mechanical properties, increased printing strength, reduced dissolution time, and allows for alternative printing methods, while maintaining biocompatibility. Enteric coated paper provides a smooth texture **256** for the paper **82** and allows for antenna patterns **266** to be easily transferred onto it. The paper **82** also breaks up rapidly once the coating **254** dissolves. Preferentially, the paper **82** is coated on all sides, but in some implementations coating only the top of the paper is required. In addition, a biocompatible adhesive **252** is applied to the bottom of the paper when the tag **15** will be applied to the outside of the medication. When adhesive **252** is included, a protective backing **258** is used to simplify handling and attachment to the medication.

[0066] The biocompatible coated paper system **260** of FIG. **6A** addresses manufacturing problems of electroplating/electroetching on biodegradable substrates. Preferentially, biocompatible paper **82** is a mixture of biodegradable materials distributed in impregnated and/or on coated the paper in a number of ways. Paper **82** can be any substance that can be used as a flexible and strong biocompatible substrate in the

dry state but weakens in the wet state. Rice papers, pulp papers, plant-based fiber papers including linen papers are all substrates that can be used with a biocompatible material coating or impregnation. The paper **82** itself is also biocompatible. The biocompatible substances **254** used for coating or impregnating the paper alter the dissolution properties, thermal properties, mechanical properties, biodegradation rates and other properties of the paper **82**. The biodegradable materials included in the construction of the biodegradable substrate **260** allow for digestion of the substrates **45** and prevents untoward effects such as lodging in the stomach of the substrate or pill itself, as may occur with non-degradable and smoothly-surfaced polymeric substrates.

[0067] The substrates **45** allow for the placement of a metallic trace for antennae **266**, chips **47** or other electronics via electro-plate, bonding, gluing, adhesive or printing. The antenna **266** may be covered in a protective coating **268** to prevent digestion, protect the antenna from handling, and dielectrically isolate the antenna from the environment. The paper **82** is superficially coated with the biodegradable substance such as polymethyl methacrylate-polymethacrylate, cellulose acetate phthalate, poly lactic acid, poly glycolic acid, various sugars, oils, waxes or proteins.

[0068] The biocompatible materials **254** added to the paper also allow for increased stability of paper materials in more extreme environments, including those of very high temperature and humidity, preventing the tag **15** from warping or deforming (and possibly fracturing the antenna **266**). Referring to FIG. **6B**, the substrate **45** is coated in a multi-layer or patterned method with multiple layers of coatings **254**, **264** such that various portions of the tag can be exposed or broken down in the body **16** at varying times or locations. At different times or locations in the body, different coatings may dissolve exposing different types or portions of the antenna **266** or sensors to the body **16**. These varying conditions provide information to the system allowing for determination of ingestion time or tag **15** location. Referring to FIG. **6C**, a cross-sectional side view of an alternate form of the system **260A**, the coatings can be patterned such that different portions of the paper **82** are coated with different coatings. This multi-layer or multi-coated system **260A** tracks the progress of the substrates as they pass through the digestive tract M,E, S,D,I,R or encounter different solutions in the body **16**. In a preferred embodiment, each coating **254**, **264** is an enteric coating that is formulated to dissolve in specific areas of the human body **16**. In combination with a multi-level electronic sensor and in the form of an electronic pill, the location of the medication is tracked through the human body. As each layer of the substrate **254,264** dissolves in its pH or chemically sensitive environment, a new electronic sensor, which by way of example can be a galvanic cell is exposed. In addition to exposing different sensors or probes in different portions of the body **16**, the selective dissolution of the coatings in different parts of the body **16** alters the transmission properties of the antenna **266** or system **260A** in general, thus making the location of the tag **15** in the body detectable without separate sensors.

[0069] Various bodily chemicals and even organisms (and their respective chemicals) can cause the degradation of the materials used with the systems **260** and **260A**. Enzymes, hormones, cells (blood cells), proteins, acids, ions, bacteria, and so forth can contribute to the degradation of the substrates or any of the substrate layers.

[0070] Furthermore, in another embodiment, the system 10 is triggered to dissolve in the patient's body 16 in the presence of both a bodily chemical and an external impulse for additional control. For example, the sensitivity of chemical breakdown is enhanced by the application of RF energy to the substrates 260, 260A (producing heat or otherwise) from an outside RF source.

[0071] The system 10 may also be loaded with various degradation control chemicals that can delay or hasten degradation rates. This is useful if the processing of substrate layers that require extra-thick amounts of a certain layer to be mechanically stable or if a layer requires another chemical in addition to the ones found in the human body 16 to begin degrading appreciably.

Antennas and Coatings

[0072] Pills 14 or capsules 17 are typically printed with edible inks of pharmaceutical grade to uniquely identify the product and provide additional information such as company logo, brand name, and dosage information. In accordance with this invention, these edible inks are replaced with conductive and biocompatible silver inks to pattern small antennas 266 (FIG. 6A), coils 41 (FIG. 20) or deposited conductive pattern 44 (FIGS. 5A, 5B) directly on the capsule 14, 17. Other compositions known in the art are also contemplated such as but not limited to carbon black, iron, gold, copper, zinc, and conducting polymers.

[0073] Thus, by way of printing, etching, or electroplating, miniature antennae 266 are made of silver, carbon black, copper, or other biocompatible coatings. Silver, copper, zinc and other metals are substantially biologically inert, and when ingested in small amounts, are nontoxic to humans and pass through the body without being absorbed into tissues. Furthermore, the conductivity of most of these metals is very high, making them excellent conductors. Therefore, the antenna 266 performance not only depends on physical size constraints, but also on the total usable concentration of conductive material.

[0074] Coatings.

[0075] Referring again to FIGS. 6A and 6B, it is preferred to encapsulate the components of the tag with a coating 268 for multiple reasons, including but not limited to: electrical isolation from the conductive fluids of the GI-tract M,E,S,D, I,R, prevention of dissolution or exposure to the body for safety, and selective dissolution at different locations in the body 16. For example, the coating 268 prevents contact with the body, limiting exposure of the materials to the patient 16. Certain coatings can be utilized that are pH or otherwise selectively dissolved in different portions of the GI tract. In a preferred embodiment, enteric coatings that do not dissolve until they reach the intestine I or other locations, where very little digestion occurs. This allows the material to break up before excretion but not leach materials into the blood stream. It is also desirable to activate the tagging system only after the patient has ingested the pill 14. Once ingested, the pill 14 or capsules 17, 46 are exposed to stomach acids that eat away coatings 268 on the surface of the capsule 17, 46. Coatings 52 (or 268) may be applied or selectively applied to cover parts of the tag or capsule/pill. In one embodiment, these coatings 268 are applied selectively to cover certain portions of the tag and capsule but allow other portions of the tag and capsule to break down. This allows the tag to change shape or break down in such a way that it easily passes through the digestive tract while still protecting sensitive materials from digestion.

[0076] In another embodiment, the conductive layers of the antenna 266 on the tag 15 are made by incorporating a metal that can dissolve, such as iron filings under a temporary protective layer 268 such as polyglycolic acid or by incorporating particles that are nontoxic by virtue of being non-absorbable (e.g., silver or carbon). Degradation of the matrix releases particles that move through the digestive system of the patient without absorption. Such particles are present above a percolation threshold for conductive "contact" (within 1000 Å), and reside in a degradable matrix such as polylactic/glycolic acid or starch. The degree of conductivity is adjusted by the degree of close contact and by the number of contact points (volume fraction). Particles that are not spherical can be added at lower levels to get good conduction. Hence, graphitic carbon plates can reach a percolation threshold at lower levels, and silver can be used as planar particles as well.

[0077] In a preferred embodiment, the integrated circuit 47 is encapsulated or coated in a protective coating such that it is not exposed to the body 16 and its digestive process. Packaging preferably does not interfere with the RF communication but provides enough safety for human studies. Methods of use allow access to the aqueous environment for sensors while still ensuring safety.

Energy Harvesting

[0078] Power sources for body-powered electronic pills must be biocompatible, small in size with the appropriate form factor, capable of delivering high power with good maximum discharge current characteristics and low self-discharge, and provide long calendar life. Referring again to FIG. 4, many techniques exist for harvesting power 205 and storing the power 207 within the circuit 47 for use with the tag 15. For example, a capacitor can be used to store the energy at block 207 owing to the short duration of the active nature of these devices (less than 1 minute). In one embodiment, the capacitor is embedded into the pill electronics and charged from block 205 by a handheld device via a magnetic field or other mechanism before being swallowed by the patient 16. The capacitor holds this charge until activated by a triggering mechanism, such as the dissolving of a specially coated switch by stomach acid.

[0079] In another embodiment of the energy harvesting block 205 in FIG. 4, the chemical energy of the stomach contents is converted into electrical energy. For instance, the chemical reaction between the stomach acid and a zinc electrode oxidizes the zinc, creating an electric current via a metal electrode making the return path. In another embodiment, the system converts mechanical motion (e.g., peristaltic and other motion common in the digestive tract) into electrical energy.

[0080] In yet another embodiment, the energy harvesting system 205 of FIG. 4, harvests the energy of the in-link channel 50, stores the energy in block 207 and uses this energy to power the tag 15 and transmit data via the radiative out-link 52. Harvesting of the energy from the reader's in-link 50 is sufficient to power the tag 15 and its transmission of the out-link channel 52. In all of these embodiments, the tag 15 harvests the energy until it obtains sufficient energy to transmit a signal to the external reader 11 along the out-link channel 52. As illustrated in FIG. 15, this harvesting process typically is substantially longer than the duration of the burst information sent out by the tag 15, thus allowing for amplification of the out-link channel 52 with respect to the instan-

taneous power harvested, for instance from the in-link channel 50. For example, if the in-link channel 50 is harvested for 100 ms and the out-link burst of information is 1 ms in duration, the out-link power transmission 52 may be 100 times larger than the instantaneous power harvested by the pill 14 or capsule 17 from the in-link signal 50.

Ingestion Detection

[0081] An important aspect in successful detection of the ingested electronic pills 14 or capsules 17, 46 is to positively identify the origin of the transmission, that is, whether the pill or capsule is transmitting from inside the patient's body 16. Knowledge of transmission origin is necessary to detect a patient who might intentionally spoof the system into registering a positive compliance. Multiple methodologies can be implemented for ingestion detection with element 208 (FIG. 4). Noting FIG. 17, multiple techniques exist for "triggering" the system to respond only after reaching the stomach. The trigger can be activated by the dissolving of material that opens (or closes) a switch. The trigger can be based on electrical, chemical, or mechanical detection of stomach or GI tract contents (e.g., pH sensor, ISFET, temperature sensor, three electrode electrochemical cell, microelectro-mechanical systems (MEMS), microfluidics, miniaturized or nanoscale lab-on-a-chip, biomarker targeting, biosensors, optical sensor, sound transducers, bio- or chemi-luminescent sensor, or the like). When spoofing is not an issue, the trigger can be activated just before ingestion or by the reader 11. Additionally, one also simultaneously measures changes in material properties such as physical size (swelling), magnetism, polarizability/polarization, phase (solid-solid, solid-liquid, liquid-liquid, etc.), viscosity, chemical/molecular makeup, optical clarity, thermal conduction, state of charge and so forth. For example, the sensor may sense changes in the outer walls of a capsule, such as temperature or conductivity before it comes in contact with the outer environment.

[0082] The ingestion detection system using the galvanic gastric sensor 284 (FIG. 11) with sensor 208 communicates with the control subsystem 209 of FIG. 4. The control subsystem 209 is then either programmed to process the data it receives to determine if the tag 15 is in the proper location, or passes the data through the transmission subsystem 206 for analysis by the external components, for example the reader 11 (FIG. 1) or 111, external device 54, or central database system or healthcare provider 60 (FIG. 3). In another embodiment, the tag 15 does not respond to queries from the reader 111 or 11 until the ingestion detection system 208 indicates that the tag 15 is in the proper location, such as the stomach S.

[0083] Additionally, the presence of specific features in the received signal from inside the body may be sufficient to determine the transmission origin. For instance, signal strength in out-link 52 coming from inside the body 16 is lower compared with that from outside the body due to attenuation from tissue, blood, and bones. It is also reasonable to expect a shift in the resonant frequency or a unique characteristic of the frequency spread or content when a signal propagates through tissue, which is absent when the transmission is outside the body 16.

[0084] Additional techniques for detecting the origin of the transmission of tag 15 include the following examples. The dynamics of pill motion in the esophagus E (e.g., speed of pill travel, orientation of magnet, and path of travel) and or stomach S may provide subtle discriminating differences between the in-link signal 52 received from tag 15 inside the body 16

and a tag 15 that is outside the body 16. The peristaltic motion of the esophagus and the tossing and turning in the stomach may produce pill motion that affects the signals received due to the natural or purposely modified directionality of the fields generated by tag transmission. Additionally, there is a normal progression from mouth M to esophagus E to stomach S that will produce a difference in motions that must be obtained sequentially to validate the location of the pill 14.

[0085] Transmission of Unique Codes Based on a Variety of Potential Sensors Attached to the Tag 15.

[0086] In one embodiment, body temperature and/or pH sensors are included in the ingestion detection system 208 and either processed or relayed by the control system 209 to the transmission subsystem 206. The control subsystem 209 can transmit either raw sensor back to the reader 11 or 111 for analysis of the patterns, or process the data itself and transmit back to the reader 11 (FIG. 1) or 111 (FIG. 3) an indication of its location.

[0087] Ensuring that the tag 15 is only active inside the patient's body 16. For instance, the tag 15 is inert when dispensed and is activated upon contact with saliva and/or other bodily agent.

[0088] Alternatively, the tag 15 is activated outside the body 16, prior to ingestion, and deactivated inside the body 16 after coming in contact with bodily fluid.

[0089] The activation/deactivation process can be carried out using, for example: selectively coated sensors that exhibit change in properties in the presence of specific chemical compounds, biodegradable switches based on proteins that are broken down when exposed to digestive enzymes in the stomach, and/or unique GI fluid sensors based on the properties of the GI fluid.

[0090] Conductive Sensors.

[0091] One implementation strategy of a bio-switch is to interface the conductive sensor with a transistor (e.g., MOSFET, FET, BJT, etc.), as shown in FIG. 7. A conducting sensor in series with resistor R1 acts as a simple resistor divider and provides the necessary biasing voltage the transistor gate. The output of the bio-switch is taken from the transistor drain and fed to the enable port of the RF transmitter (an RF transmitter is used as an example, but can be any electronic device that requires activation). A power source provides necessary power to drive the transistor and activation voltage. When the bio-switch is outside the body, the resistance of the conductive sensor is small compared to R1; thus the activation voltage (VA) will be below the gate threshold voltage. When the gate voltage is below the threshold, the transistor is turned off and the voltage at output equals zero. When the bio-switch comes in contact with a bodily fluid, select chemical molecules will bind to the conductive sensor and increase its resistance, thereby also increasing the activation voltage. When the activation voltage increases beyond the gate threshold voltage, the transistor turns on, and voltage at output equals that of the battery. A large voltage at the output in turn enables the RF transmitter and readies it for transmission.

[0092] An alternative implementation is shown in FIG. 8, where the circuit configuration yields a deactivation circuit. When the bio-switch is outside the body, the voltage at output equals that of the battery; that is, the RF transmitter is enabled. When the conductive sensor comes in contact with a bodily fluid, the transistor is turned on and voltage at output equals zero, thereby disabling the RF transmitter.

[0093] A bio-switch implementation using a conductive sensor is not limited to the above examples. Variations in

transistor type, substrate type, biasing schemes, selection of power, etc., can yield several different implementation options. An exemplary concept here is the utilization of a conductive sensor to drive a switching mechanism. In the above examples a battery was used to drive the transistor and circuitry, but instead a charged capacitor can easily replace the battery. The switch can also be used to modify the frequency of the signal transmitted or detected externally (e.g., changing the frequency response of the pill/antenna). The capacitor can be charged before a pill is dispensed or can be charged by RF induction as is done in RFID techniques. One positive aspect of using a capacitor is that over time the capacitor will discharge and the entire system will become inert, meaning the subject must take the pill within a given time frame, thereby increasing the robustness of the system to spoofing.

[0094] MOSFET Sensor.

[0095] Another implementation of the bio-switch is to use a MOSFET e-nose sensor instead of a conductive sensor. A bio-switch with a MOSFET e-nose sensor can be implemented with much simpler supporting circuitry since the transistor does both sensing and switching. An example is shown in FIG. 9. The resistor divider of R1 and R2 provides a fixed activation voltage to the transistor gate. When the bio-switch is outside the body, the activation voltage is just below the gate threshold voltage; therefore, the transistor is off. When the MOSFET sensor comes in contact with a body fluid, a catalytic reaction takes place at the transistor gate and changes the channel conductivity; i.e., the gate threshold voltage is lowered so that the activation voltage is now above the threshold voltage. Therefore, the transistor turns on, and the voltage at output equals that of the battery. Again, this illustration is just one possible implementation scheme, and variations can be constructed with different types of substrate (e.g., n-type and p-type) and supporting circuitry.

[0096] An additional embodiment utilizes biodegradable switches that undergo significant changes in conductivity when exposed to the digestive enzymes of the stomach. One can mix a conductive substance (e.g., carbon) with a non-conductive substance (e.g., protein). A conductive substance doped with a non-conductive substance will tend to have lower conductivity (high resistance) than a pure or even semi-doped material. When the doped material comes in contact with digestive enzymes, the non-conducting material is broken down or dissolved by the enzymes, leaving behind just the conductive material. One possible switch implementation can be based on a composition of carbon and albumin. The albumin protein is broken down by pepsin, an enzyme that is naturally present in the stomach. When the switch composition is devoid of albumin, the conductivity of the switch increases and bridges a gap in the circuit to complete the circuit. A number of possibilities exist in selecting a conducting material and a protein. Furthermore, it is also possible to incorporate multiple non-conducting materials to yield switches that are extremely selective to activation.

[0097] In the embodiment shown in FIG. 4, the in-link 50 signal is used for energy harvesting 205 and is sufficiently low in frequency such that most of the energy is transferred conductively through the body of the patient 11. Thus, the tag 15 is only easily powered when the tag 15 is in contact with the body of the patient 11 since the in-link signal is significantly attenuated in the air. As such, the tag 15 will not respond to queries from the reader 11 until such time as the pill is being

touched or ingested by the patient 11. This provides a level of spoofing prevention with virtually no additional complexity added to the system.

[0098] Noting FIGS. 10A and 10B, in order to ensure that the pill is ingested, the antenna system can be disabled by electrically "shorting" the antenna through the use of an ingestible switch 90 that contains a circuit breaker 92 that becomes modified in the presence of gastric juice. An embodiment of this concept includes a method of breaking a circuit via the swelling of the breaker material in the presence of stomach fluid. The switch 90 comprises a thin layer of hydrogel 92 partially coated with a conductive trace 94 such as metal flake or micro-thin metal foil. When the hydrogel is exposed to low pH liquid, it swells to about sixteen times its normal size and breaks the conductive trace 94. This mixture is then coated with an albumin-based layer that will prevent exposure of the hydrogel to fluids until the albumin is selectively broken down in the GI tract by either pepsin or trypsin. The preferred mechanism for deactivating the system using an ingestible switch is to electrically connect the two pads of an antenna 13, creating an electrical "short". The lower the resistance, the more power is diverted from the signaling antenna. By way of example, a five ohm resistance is sufficient to reduce the input power from the antenna by 95+%. A resistance of 10K ohms will reduce the input power to the signaling chip by only 10% or less. In the case where the in-link 50 is separate from the out-link 52, either antenna can be shorted by this technique, essentially crippling the tag 15. The preferred embodiment is to short the in-link antenna in a system that utilizes the in-link to power the system.

[0099] Sensor such as pH sensors and other chemical sensors are fairly complex devices. Noting FIG. 11, to avoid a requirement to embed such a complex device into the tag 15 or integrated circuit 20, the preferred embodiment of a gastric sensor 208 utilizes a galvanic couple 208 that is placed in various bodily fluids (stomach fluid, esophageal fluid, GI fluid, etc.) to create a measurable change in electrical properties such as current, voltage, and/or resistance and allow ingestible electronics to evaluate the location of a tag 15 in the human body 16. In one embodiment, the sensor 208 senses changes in the outer walls of a pill 14, such as temperature or conductivity before it comes in contact with the outer environment. In the preferred embodiment, the galvanic couple can provide discrimination of location as well as providing electrical power to the system. The ingestion detection system 208 on the tag 15 works either outside or inside a pill 14. Inside the pill, the detection system 208 operates when the GI fluids permeate the pill or dissolve any external layers. The tag 15 begins generating power and voltage as soon as it is wetted by ingestion and allows the tag 15 to begin communicating with the reader 111. As the tag moves through the GI tract M,E,S,D,I,R, the sensor or voltage information is communicated or processed by the control logic 209 such that location information can be determined by the reader 111 or other external system. FIG. 11 shows the GI sensor/energy cell connected to control logic 208. The GI sensor requires two electrodes for operation and one or both of these electrodes may also function as antennas. In the preferred embodiment, one of the electrodes for the GI sensor comprises a small strip of metallic zinc while the second electrode consists of a specially coated silver electrode that is shared with the in-link antenna.

[0100] In one embodiment, the galvanic couple 284 is constructed of two differing metals 280, 282 or compounds that,

when placed in a bath of any number of solutions, produces an electric voltage and subsequent current and is measured by the control system **208**. Metals used for a galvanic gastric sensor **284** are transformed by a number of chemical reactions to produce a new chemical compound. The new compound changes the differential voltage. Upon immersion in a target fluid, the compound transforms into a different compound and accompanying the transformation is a change in voltage. Other changes in the galvanic cell materials can be phase transitions, state transitions, amount of the chemical compound (causing a natural change in differential voltage based on the degree of material available to sustain such a voltage), and other materials transitions that cause a change in the electrical output of the galvanic cell. In the preferred embodiment, the GI sensor creates varying degrees of current or voltage depending on the nature of the fluids in which it is immersed. Thus, the GI sensor not only gives true/false data about the environment, but may also senses the chemical/electrical/thermal/etc. makeup of the environment and give a signal corresponding to the state.

[0101] The metals or compounds are connected to a measurement means in the control logic **208** (FIG. **11**) and can be a voltmeter, potentiostat/galvanostat, electronic switch or other means to measure or gauge the voltage and report if and/or when the target electronic reading is reached in the target solution. If the sensor **284** is not in the target solution, the voltage will not change appreciably as no chemical transformation will proceed. Thus, the voltages or an indicator of location can be transmitted via the tag **15** to the reader **11** or **111** to confirm the location of the pill **14** or capsule **17, 46**. Such chemical transformations include silver phosphate and other silver compounds, including silver chloride, silver sulfate, silver carbonate, or even silver metal itself. Transformation can occur on the anode or cathode of the galvanic cell. In the preferred embodiment of FIG. **11**, a silver phosphate electrode **280** is attached to a zinc electrode **282**, and the silver phosphate transforms to silver chloride and silver metal while the zinc oxidizes to zinc metal or forms a zinc compound with anions in solution. Accompanying the silver materials transformation is a voltage differential (from high-to-low or low-to-high state). The voltage/current differential is affected by the selection of the two metals or compounds (or mix thereof), whereby a silver phosphate-zinc system differs in output voltage/current from that of a silver-phosphate-copper or silver sulfate-zinc system. Furthermore, a dissolvable or protective coating **281, 283** may be applied to the electrodes **280, 282** such that the electrodes are not exposed to the fluid until a certain external condition exists, such as when the tag **15** is exposed to the high chlorine content of the stomach. Coatings on each electrode **281, 283** can be the same or different, providing flexibility in the voltages and currents produced in different transit times and locations in the body **16**.

[0102] FIG. **12A** is a chart describing the voltages measured from the silver phosphate electrode **280** of FIG. **11** formed by applying 9V to a silver chloride electrode in KH_2PO_4 solution with a silver electrode return path **282**. The silver phosphate electrode **280** was tested at loads of 20 kOhm and 1 kOhm. The charts in FIGS. **12A, 12B** and **12C** show the time course of voltages of the electrodes with differing amounts of phosphate (exposure time to the KH_2PO_4 solution), differing loads, and differing solutions. The gastric

sensor **284** has a substantially different voltage in HCl, the primary component of stomach fluid, versus sulfuric acid solution.

[0103] In alternate embodiments, the tag **15** is modified to include sensors to measure various attributes of the pill's surroundings. For instance, the tag **15** can have a pH monitor, temperature probe, or other sensors **42** (FIG. **2C**) to verify compliance. In addition, it may be beneficial to use a system that can also provide a readout of the in-link signal strength. This signal strength is beneficial for optimizing the communication protocol dynamically as well as providing potentially discriminating information relating to the location of the tag **15**.

Biometrics

[0104] In addition to determining when the pill **14** or capsule **17, 46** is ingested and where it resides, it is important to detect that the pill is ingested by the appropriate person. As such, a variety of biometrics are utilized to detect that the reader **11** or **111** and pill **14** or capsule **17, 46** are located on or in the correct person **16**.

[0105] In one embodiment, an electronic pill monitors physiologic signals inside the body **16** that are typically difficult to mimic outside the body. For example, the patient's electrocardiogram (ECG) is detected and measured by the electrical contacts or antenna of the tag **15**. The tag **15** either processes the signal or passes the signal via the out-link **52** to the reader **11** for further processing. Detecting the presence of a valid ECG signal indicates that the tag **15** is inside the body **11**. Detection of a periodic pulse between 30 and 120 BPM is sufficient to detect that the tag **15** is inside the body. Furthermore, a wide variety of parameters can be extracted from the physiologic signals detectable inside the body **16**. In a preferred embodiment, the processing system (either in the tag **15**, reader **11**, or elsewhere downstream) detects parameters of the electrical characteristics of signals received inside the body **16** including but not limited to: periodicity, amplitude, signal shape (including peak geometry, relative height), and signal to noise ratio. In addition, the signal detected inside the body can be transmitted to the reader **11** and verified against a preloaded signature of the ECG or other physiologic signal recorded earlier, for example, during the initial administration of the system **10**. Additionally, the reader **11** can record the same signal outside the body **16** and ensure that the tag **15** is in the same person **11** that is wearing the reader and also checked against the stored signature. These features of the ECG and other physiologic signals measured at the tag **15** or reader **11** are also capable of biometric identification.

[0106] These physiologic features and their dynamic features (changes in the signals over time) are useful to identify the patient **16**, ensure ingestion, or determine the location of the tag **15** in the digestive tract M,E,S,D,I,R. The dynamic features include but are not limited to heart rate variability, changes in signal strength as the tag moves through the body **16** and muscle activity in different parts of the body. For example, the ECG will be quite strong as the pill passes the heart in the esophagus E and then gradually get weaker as it moves farther from the heart in the GI tract S,D,I,R.

[0107] In an embodiment, the external reader **11** is used to monitor and assess a given patient's **16** ECG output (periodicity, peak geometry). This information is used for a first calibration step and recorded as the baseline ECG output. The later measurement of the ECG by the reader **11** validates that the same person is using the reader. Additionally, the measure-

ment by the tag **15** can be checked against this calibration to ensure that the proper person is taking the medication. In this case, if either the medication or the external reader is switched to a different person **16**, the results can be checked against the calibration data. Calibration can take place in the presence of proper supervising personnel, including doctors, nurses, etc., and the calibration can be locked to those who either have calibration codes or calibration devices.

[0108] These biometric capabilities can also be used to help guard against improper medication (type or dose) being taken. Each tag **15** can be programmed to be taken by a specific patient. The patient specificity will be recorded by certain physiologic signals that can identify individual patients, such as parameters of the ECG. The reader **11** or interface **54** can first be programmed to register the kind and frequency of medication to be taken for a given patient ECG. The reader **11** or interface **54** then alerts the patient or proper personnel if the medication taken was given to the wrong person (pill ECG does not match reader ECG) or if the medication was taken at improper time intervals (over- or under-medication).

Control Logic/IC Design

[0109] Maximizing power efficiency is of utmost importance to maximize the reading distance between the reader **11** and the tag as well as power output and detectability. Advanced low-voltage and low-power circuit design topologies and a suitable process technology are required to achieve operation with small input power levels from radiated electromagnetic fields.

[0110] Referring to FIG. **13**, the preferred embodiment of the integrated circuit **20** for the tag **15** includes: protocol logic **306** having a random bit generator for robust two-way communication and control, data acquisition subsystem **304** and sensor **314** to determine the strength of the in-link signal **50**, in-link subsystem **302**, out-link subsystem **308**, and energy harvesting and storage system **310**. The IC **20** is designed with fallback operating modes, including a chirp mode and a beacon mode. In the chirp mode, the protocol is suspended and the IC **20** transmits data whenever it has sufficient power from the energy harvesting and storage system **310**. In beacon mode, the IC **20** transmits a periodic burst pattern with no data (bypassing all digital logic). In one embodiment, the energy harvesting and storage system **310** extracts power from induced currents generated from the external reader **11** via the in-link subsystem **302** or directly via the in-link antennas **50**. In a second embodiment, a galvanic cell, GI sensor, thermocouple, or other method of generating power from the digestive tract M,E,S,D,I,R or motion through it provides primary or supplemental power via the energy harvesting subsystem **310** to enable the IC **20**. The out-link subsystem **308** drives the out-link signal **52** under control of the protocol logic and control subsystem **306**. The protocol and control system **306** contains all the logic to control the IC, the communications protocol, the data acquisition, synchronization, and data storage and output, including the preprogrammed information about the medication, patient, study and other information. Minimizing the power usage of all these subsystems and in particular the out-link subsystem **308** is of utmost importance.

[0111] Preferably, the IC **20** is fabricated using industry standard CMOS manufacturing processes in class **10** or better clean rooms. The physical dimensions of the IC **20** are expected to be very small, less than 1 mm×1 mm×0.1 mm.

When affixed to the tag **15**, the IC **20** is encapsulated in biocompatible epoxy to cover any hard edges and to prevent interaction between the IC **20** and the patient's body **16**. The preferred IC **20** is a custom designed microchip that stores the medication information, reads the GI sensor, and implements the signaling and communications protocol. The IC is designed to operate with extremely low power and to provide reliable deep in vivo communications.

[0112] In addition to integrated circuit implementations for the various logic and systems of the tag **15**, another embodiment includes printed electronic circuits created with various inks including metallic, dielectric, and organic materials. The creation of complex printed electronics requires the creation of multilayer electronic devices such as transistors and capacitors, silver conductive ink and dielectric materials are typically loaded into separate ink cartridges. For example, in the case of capacitors, fabrication can be achieved by first printing a single line of nanoparticles onto a substrate that is heated until the inks are metalized. Next, a dielectric of polymer is printed directly over the line. Finally, a second conductive line is printed perpendicular to the original conductive line. In this way, the overlapping cross-section of the two conductive lines—with a dielectric between them—creates a capacitor whose capacitance is defined by the overlap area and the dielectric material and thickness. Thus, if an antenna is printed simultaneously and attached to each conductive line, a simple 3-step inking procedure is enough to begin creating simple inductor-capacitor antennas that can resonate at a tuned frequency.

[0113] Many generally recognized as safe (GRAS) materials are available for use as dielectrics, for example polytetrafluoroethylene (PTFE), polyimide (from precursors) and PVP. In the preferred embodiment, enteric coatings are used as a dielectric material.

Communication Links and Protocol

[0114] Transponder Antenna Size and Efficiency.

[0115] The radiation efficiency of a typical loop antenna increases with loop area and is inversely proportional to the excitation signal wavelength. Since the loop area is limited, it is desirable to operate at higher frequencies to improve the antenna efficiency. In typical RF applications, operating at higher frequencies can improve the aperture efficiencies of small antennae to maximize the received power. However, in biological systems, the operating frequency is a tradeoff between increased path loss in tissue and antenna efficiency. Indeed, RF signal attenuation behavior of the in-link **50** and out-link **52** in bodily fluids and body tissue to and from an ingested tag **15** is complex and difficult to model.

[0116] The tag **15** may be coded with a variety of information including but not limited to data about medication, the patient **16**, the reader **11**, or the drug trial the patient is participating in. Additionally, the tag **15** can have a unique ID that is utilized with a database of other information tagged to each tag ID to obtain similar information without storing it on the tag **15**. Upon detecting the tag **15**, any of the readers **11**, **111**, **211** or **311** can store a time-stamped reading of a medication event. If the tag **15** is not detected, failed compliance can be signaled, for example, to the patient **16** and/or to a second party such as a health care provider or other agency **54** via input and output signals **56**, **58**.

[0117] It is preferred that the communication between each reader **11**, **111**, **211** or **311** and the tag **15** provides two way communication, with the communication from the reader to

the tag 15 being preferably through a conductive in-link channel 50 and the communication from the tag 15 to the reader being preferably through a radiative out-link channel 52. The in-link channel 50 is preferentially in the range of 1-20 MHz; this frequency range produces efficient data transfer from outside the body to deep inside the body 16 and can travel through the body conductively, requiring very small antennas or pads only to receive the signal. Because the in-link transmissions 50 travel conductively, the signaling attenuates very rapidly outside the body 16 thus providing for increased privacy for the in-link channel 50. Skin surface contacts with the reader, as readers 111, 211 and 311, maximizes the efficiency of the in-link transmission 50 from the reader. The in-link channel 50 communicates a variety of information to the tag 15, including but not limited to querying for the presence of the tag 15, turning the tag's transmitter on or off, collision avoidance, and various other protocol-based communications. The in-link channel 50 also provides synchronization signals between the reader and tag 15. Synchronization between the reader 11 and tag are particularly important when the out-link signal 52 is very small (as is expected when coming from inside the body) and/or when the out-link signal is transmitted in very short bursts for better energy efficiency.

[0118] In an embodiment, the tag 15 is powered using the RF energy received by its coil or antenna or in another embodiment where power is generated by energy harvesting means. As described previously, this power can be stored temporarily and then used to transmit a pulse or signal to the reader 11. Storing the energy internally in the tag 15 helps alleviate two distinct problems. First, it allows for the storage and amplification of the instantaneous power received from the in-link 50 or energy input 312 to create higher powered but shorter bursts of out-link transmissions 52. Second, when transmitting into the body 16, the external powering signal (in-link 50) creates significant noise that may make detection of the out-link signal 52 from the tag 15 very difficult.

[0119] One method to create more detectable signals for out-link signal 52 is to utilize different frequencies for power transmission and data signaling. This allows the external receiver 12 of the reader 11 to be frequency-isolated from its transmitter. A frequency selective filter may then remove the noise from the transmitter to allow for high quality reception of the data signal. Lower frequency signals typically have lower losses in the human body. As such, the power transmission signal 50 may necessarily be lower in frequency than the data transmission signal 52 which can be much lower in power.

[0120] Another method involves the use of dual antennas on one or both of the tag 15 and receiver 12; that is one antenna or set of probes/contacts for the transmission/reception of the in-link or power transmission, the other for transmission/reception of the out-link signal.

[0121] As discussed in greater detail below with reference to FIGS. 15-18, another method involves the time multiplexing of the signals such that the power transmission ceases during predefined time periods to allow tag 15 to start transmitting data. The circuitry of tag 15 can be designed to utilize this cessation of power transmission as a marker to determine when to start transmitting data. Additionally, that circuitry may store the power during the "power cycle" for a period of time typically longer than the transmission cycle to provide a power multiplication to improve the signal strength of the data transmission.

[0122] It is preferred that the communications to and from the tag 15 and to and from the readers 11, 111, . . . are protected, encrypted, encoded, or made secure in a way to prevent interpretation by other devices and have software and/or hardware required to protect the data and support privacy or data security requirements of the communication system.

[0123] Many of the tag 15 embodiments support IDs and other stored data that can be transmitted back to the reader 11 via the out-link channel 52. IDs and other data can be transmitted via pulsatile signals (information in the pulse duration, pulse spacing, pulse frequency, etc.) or via digital encoding. To increase signal-to-noise ratio, it is preferable to have a transmit/receive event wherein the tag 15 responds to a request from the reader 11 with a predetermined signal. This signal is repeated and then synchronously averaged over multiple transmit/receive events to produce a better signal-to-noise ratio. Synchronization of the transmissions from and to the reader 11 and tag 15 also improves the ability of the reader 11 to detect faint signals 52 from the tag 15 in the body 16.

[0124] An embodiment of an efficient communication and protocol approach is demonstrated in FIG. 14. The approach is based on a unique communication path between the tag 15 and the associated reader 11. The reader 11 transmits data to the tag 15 by way of the conductive in-link 50 communication channel. The tag 15 transmits data to the reader 11 through the out-link radiative channel 52. An electromagnetic transmitter block 320 provides the interface to the radiative channel 52 at the tag 15 and a corresponding reader RX 322 extracts the signal at the reader 11. A tag 15 for a patient 16 is linked directly to the patient reader 11 similar to a key and lock. Only data with the proper key or data word are recognized by the reader 11 as valid patient data. As an extra measure of protection, the out-link TX carrier 320 is phase locked to the reader in-link signal 50 to provide means for synchronization of data. Phase lock also allows coherent detection of the tag data at the reader 11, thereby enabling use of phase modulation and reduced error rates. Since the in-link signal 50 is propagated by direct body contact (in-link conductive channel), only the reader 11 attached to the patient's body 16 can properly demodulate the return tag out-link 52 data. This feature makes external eavesdropping of the data very difficult. Hence, this approach enhances security of the data. As will be appreciated, this communication protocol also allows several tags to be consumed and data read without the need for individual tag identification bits, thus reducing significantly the amount of data that needs to be stored.

[0125] The protocol is composed of the communication link timing and the associated in-link 50 and out-link 52 data fields. FIG. 15 depicts the relative communication link timing of the data for the in-link 50 and out-link 52. The process begins with the reader 11 sending an FM modulated signal, or "in-link header" 330 to the tag 15 with information necessary for proper tag operation. The header is sent periodically every T seconds. On ingestion, a random bit generator in the circuit 20 for the tag 15 begins operation. On completion of the in-link header field 330, the value of the random bit generator is latched. This latched value is used to set the time, t_r , at which the tag 15 responds to the reader 11 by sending a data burst 332. The data burst 332 contains a subset of the data stored on the tag 15 to be sent to the reader 11. Several bursts 332 in sequence make up the full data transmission through out-link 52. The latched random generator value becomes the pill ID or address for this specific tag. Since the ID is random, each

tag swallowed will have a unique ID. As will be appreciated by those skilled in the art, the algorithm may be as simple or complex as necessary to assure no two tags randomly end up with the same address. Each tag swallowed will send a pulse **332** delayed in time from the end of the header **330** proportional to the value of the random address. In this fashion, no two tags **15** can transmit at the same time, thus preventing interference but also allowing multiple ingestion of tags. Also, since the tag address is set randomly, there is less need for special tag identification bits to be stored on each tag, thus reducing significantly the number of bits of memory required on the tag **15**. This reduces cost and complexity of the tag **15** significantly.

[0126] Referring to FIG. 16, a representative efficient in-link data field **342** and corresponding definitions are shown. Field selection can be used to improve the robustness of the communications between the reader **11** and the tag **15**. For example, the field **N** defines the number of data bursts **332** that the tag **15** uses to define a single tag information bit. Thus, it is appropriate to use a mechanism by which the system **10** assigns more data bursts **332** per bit for situations where the signal to noise ratio may be poor (very large patients for example). This allows for more integration time and improved reliability. Such a system is adaptable for broader utility.

[0127] Referring to FIG. 17, a representative efficient out-link data field **352** is configured to allot two data bursts **332** for a single bit **354**. Depending on the total number of bits **J** of information transmitted, $N \times J$ data bursts are generated. For example, if the total number of bits **354** is $J=16$ and $N=2$, then 32 data bursts **332** are transmitted. As a further example of the utility of this protocol, the reader **11** may be preprogrammed to only accept out-link data with the proper patient ID. This along with the fact that the data is coherently linked to the reader essentially reduces the likelihood of data not associated with this patient **16** being received as valid data.

[0128] FIG. 18 shows the timing for the case of three tags taken together to further illustrate the efficiency of the protocol. Tag 1 **362** transmits at a random slot after the in-link header **330** and transmits multiple bursts **332** per bit **354**. Similarly, Tag 2 **364** and Tag 3 **366** transmit their multiburst per bit transmission in different time slots after the in-link header **330**.

[0129] As has been previously discussed, a communication network utilizing a phase based modulation scheme is known to have advantages of reduced bit error rate (BER) for the same transmission power compared to simple modulation schemes such as Amplitude Shift Keying (ASK). Since power is extremely limited in in-vivo communication systems, minimizing BER is a challenge. Implementing a phase-based modulation scheme requires that the reader **11** be able to coherently demodulate the signal **52** for each tag **15**. This normally requires that the frequency stability of each tag **15** be within a tight tolerance (20-40 ppm) to permit the reader **11** to phase lock and demodulate the received signal. Such frequency tolerance requires that the tag **15** transmit frequency be based on a crystal reference. Size and safety constraints prohibit the use of crystals to generate the transmit signal for the tag **15**. Further, since the tag transmission burst is short in duration, there may be issues in proper settling which may cause demodulation errors. Another solution is for the reader **11** to have an independent receiver for each tag **15** and preferably use a phase lock loop based approach to lock to the incoming signal. There are issues with this approach as well.

First, the burst durations are short making the design of such a receiver extremely difficult. Second, the tag **15** still requires some measure of frequency tolerance to assure regulatory or system specifications are achieved. This may require the need for tag frequency trimming which adds to the manufacturing and test costs of each tag **15**. Hence, a method is required to eliminate the need for a tight frequency tolerance on the tag **15** as well as a complex reader **11** receiver design.

[0130] A preferred approach takes advantage of the fact that the reader **11** is connected via the conductive in-link **50** communication channel to each tag **15**. Hence, by using the reader **11** as the initial frequency reference and locking each tag **15** to the reference signal for reader **11**, a self-synchronized coherent communication system is realized. FIG. 14 illustrates this concept in detail. First, the reader **11** generates a reference signal (shown here for example with frequency of 4 MHz). This signal is passed to the conductive channel **50** through an interface circuit **372** and propagated to any tag **15** within the channel. At the same time, the 4 MHz reference **376** is frequency multiplied within the reader **11** to the tag **15** burst frequency (400 MHz by way of example). This signal is ultimately used to coherently demodulate data from any tag **15**. In the tag **15**, the 4 MHz reference frequency is extracted, amplified and passed to the input of a PLL demodulator and TX carrier generation circuit (Tag PLL) **374**. This circuit has several modes of operation including the tag burst mode. During the tag burst mode, the signal is frequency multiplied to the TX frequency of 400 MHz. This signal is subsequently passed through the out-link **52** channel where it is extracted at the reader **11**. The reader local oscillator **378** derived from the original 4 MHz reference is used to demodulate the received tag signal **52**. The system is self coherent. Thus, the tag **15** achieves a tight transmission frequency tolerance by virtue of the phase lock loop **374** and does not require any internal crystal reference.

[0131] Other advantages of this embodiment may be seen by referring to FIG. 19. This figure shows the timing relationship between the in-link **50** and out-link **52** burst signal and defines the three modes of operation of the tag PLL **374** network. The in-link data is sent at a periodic rate of T seconds, typically on the order of 1 ms. As described earlier, the tag **15** responds some time later (less than 1 ms) with a TX burst. The TX burst also repeats at the same 1 ms interval. A single period is expanded in FIG. 20 to further highlight the modes of operation of the tag PLL. The tag PLL operates continuously. During mode 0 **382**, the reader sends a fixed reference signal of frequency f_{ref} (4 MHz). The tag PLL locks to this frequency and remains locked until progressing to mode 1 **384**. During mode 1, the tag PLL remains locked; also during mode 1, the reader **11** frequency modulates the 4 MHz reference signal with any required information or configuration data for the tag **15**. Since the tag PLL is still locked to the reader signal, the modulated data can directly be extracted from the VCO control voltage **375** on the tag PLL. Hence, during mode 1 **384**, the tag PLL is acting as a demodulation block. The tag PLL then returns to mode 0 **382** and stabilizes. Finally, during mode 2 **386**, the PLL is given the command to frequency multiply the 4 MHz reference signal, generating the 400 MHz TX burst signal. This is an efficient realization using the same circuitry for both in-link demodulation and TX carrier generation.

[0132] FIG. 20 shows more detail of the tag PLL **374**. One key to its operation is the dual frequency VCO **392**. During modes 0 and 1, the VCO **392** operates at 4 MHz. During mode

2 the VCO 392 is switched to 400 MHz (with VCO gain parameters changed accordingly) at the same time a divide by N (100 for this example) is enabled within the loop. The frequency of the phase detector 394 remains unchanged and the loop dynamics remain the same. As a result the loop quickly settles to a precise 400 MHz and the TX burst is transmitted. Once the TX burst 332 is sent, the PLL 374 is returned to mode 0 and the process repeats.

[0133] It will be appreciated by those skilled in the art that this implementation has several advantages. Using fine lithography integrated circuit technology, the power requirements for the VCO 392 during mode 0 and 1 are very minimal. Simple ring oscillator approaches may be used for the VCO 392 requiring just a few micro-amps of current. This allows the tag PLL 374 to operate continuously which then permits a very frequency tolerant transmission burst. The tag PLL 374 will stabilize with each subsequent burst. The same circuitry is used for both transmit and receive and area requirements are very small leading to a low cost solution.

Attachment

[0134] Wrapped tag embodiments are shown in FIGS. 5A and 5B. Noting FIG. 5B, the wrapping process is typically partially around or completely around the outer surface of capsule 46, soft gelcap, or other medication carrying device as shown in FIG. 5B. The recent invention includes the method of attaching the tag 43 to the inside surface of the capsule 46 as shown in FIG. 5A.

[0135] Referring again to FIG. 5B, to avoid the accidental or purposeful removal of the tag 43 from the outside of the capsule 46, prevent tampering, avoid damage to the tag 43, substrate 45, chip 47, or antennas 44 from handling and environmental issues and to increase the aesthetic appeal of capsules (and minimize patient hesitation in taking an electronically-tagged medication), it is prudent to conceal and protect all electronic devices, including antenna 44 and chip 47, under a protective coating 48. The protective coating 48 can be colored to match the capsule 46 or an additional layer 42 can be included to cover the tag 43 or the entire capsule 46 to further obscure the presence of the tag.

[0136] Now noting FIG. 5A, placing the tag 43 inside the capsule 46 obscures the tag from view, prevents tampering, and also provides protection to the tag as the capsule 46 must dissolve or be disassembled before the tag is exposed. Placing the tag 43 inside the capsule 46 also maintains a minimal change in capsule volume, and simplifies tag attachment and functionality. When the pill 14 is in the form of capsule 46 and the tag is inserted into the capsule 46, the tag 43 operates similar to when the tag 43 is placed on the outside of the pill. As the capsule 46 begins to absorb fluids or the capsule begins to dissolve, the tag 43 will come in contact with the GI fluids and begin to operate normally. A tag 43 using leads that make contact with the interior wall of the gelatin capsule 46 and activates upon wetting of the capsule can react with the environment to identify location, chemistry, or otherwise. The tag 43 can then use the gelatin capsule itself as a protective system in non-aqueous environments. The diffusion time of fluid through the capsule wall is the limiting factor for detection of body fluids or transmission/reception of conductive signaling within the body itself. To make contact with the outside environment in an expedient manner, however, the receiving pads must be in direct contact with the capsule as some pills swell outwardly when exposed to fluid. Thus, for

this approach an adhesive for attaching the tag 43 to the inside wall of the capsule 46 is required.

[0137] In many cases, placing the tag 43 inside the capsule 46 works well. In some cases, the delay between ingestion and activation of the sensor system on the tag 43 may be problematic. Fitting the tag 43 with external exposed sensor or pads would be advantageous for quick analysis of the body environment and for advanced location discernment. Transit from mouth to stomach typically takes place in less than 8 seconds, which is faster than most gelatin capsules can absorb fluid and begin to break down. Having an external lead or sensor minimizes this delay in sensing time for an internally-placed tag 43. The number of pads that need to be exposed can be as few as one, depending on configuration.

[0138] Referring to FIGS. 21A and B, a trace or foil 49 that runs from inside the gelatin capsule to its exterior allows for electronic transmission from within a capsule or power harvesting from outside the capsule. Certain portions of the antennas or leads remain exposed 79, 44 on the tag 43 allowing for electrical contact between the tag on inside of the capsule and the interior-exterior lead 49 on the capsule 43. The interior-exterior lead 49 is preferably constructed such that an elongated pad 86,87 is included to make contact with the antennas or leads 79,44,81 of the tag 43. The tags 43 are constructed with coatings such that only the leads or antennas that need to be connected to the interior-exterior leads are exposed while all other electrical components and antennas are coated in a protective and/or dielectric substance. The elongated pads 79,87 and the design of the exposed areas of the antennas or leads 44,79 allow for easy alignment of the tag 43 and the internal/external leads 49. For example, in FIGS. 21A and 21B each elongated pad 86,87 and exposed pad 44, 79 has a distinct depth inside the capsule which provides for very simple alignment of the tag 43 and leads 49. To make the interior-exterior connection, the metal film 49 is thin enough to allow a 2-part gelatin capsule to still snap together. The tag 43 itself, being composed only of thin components (antenna, chip, substrate, etc.), takes up a minimal amount of volume within the capsule 46 and should not impair drug loading amounts.

[0139] Referring to FIG. 22, in one embodiment, the tag 43 is inserted partially into the cap 110 of the capsule 46 and is partially exposed as the capsule body 112 is inserted into the cap 110 but under the tag 43. The leads 44, 79 are thus exposed to the outside of the capsule and can be made to appear innocuous. Likewise, the tag 43 can be attached to the outside of the body 112 and partially covered once the cap 110 is placed on top of the body/tag combination. Again, leaving leads 44,79 exposed for proper sensing and/or power generation. Referring to the top portion of FIG. 23, the tag 43 is inserted into the cap 110 and external leads are printed, built into, or attached via a second printed antenna substrate on the capsule body 112. When the cap 110 and tag 43 combination are inserted on top of the body 112 with external antennas, 44,79, electrical contact is made between the internal tag 43 and the external leads 44,79. This embodiment also allows for "hot-swapping" of internal and external components of the tag 70. Different geometric designs of an external antenna can be accommodated by a single or few internal tags by creating a system that simply needs alignment of antennas with external traces. This way, a number of antennas/sensor probes can be produced that have specific applications (frequency, power transmission properties, size, complexity) for a specific drug, creating a modular design that can have certain unique or

complex components placed on the exterior of the capsule and maintain a communication pathway. This embodiment also makes the process of creating multi-metal antennas or sensors simpler as only small strips of material need be placed on the outside of the capsule 70.

[0140] Referring to the bottom portion of FIG. 23, the tag 43 is inserted into the body of the capsule 112 and the external leads 44, 79 are attached, built-into, or printed on the outside of the capsule body 112. Vias, 87 or other methods are then used to connect the tag 43 to the external leads 44, 79.

[0141] FIGS. 24A and B illustrate an alternative embodiment where the tag 43 substrate is built with elongated portions that contain external antenna or lead components 44, 79 such that when the tag 43 is inserted into one end of the capsule 46 the elongated portions can be folded back and adhered to the outside of the capsule 46.

Tag Construction

[0142] Referring to FIG. 25, in the preferred embodiment, the main components of the tag 15 are a very small integrated circuit (IC) 47, a metal antenna 44, a gastrointestinal (GI) sensor/energy cell composed of a specially coated GI sensor pad that doubles as an in-link antenna 79 and a second metallic GI sensor pad 81, and a substrate 45.

[0143] The substrate 45 is composed of a specially coated paper. Non-whitened, low-weight papers are non-toxic and become softened in the GI tract M,E,S,D,I,R to allow for easy passage without risk of lodging as it passes. These papers will then be coated with a pharmaceutical enteric coating known as "Eudragit", which provides a smooth surface to allow printing of antennas. Eudragit is also a pH-sensitive material that will dissolve in the colon I, allowing the tag 15 to remain active long enough to be detected before disintegrating.

[0144] The biocompatible antennas 44, 79 are printed on the substrate and preferentially coated with Eudragit as described above to protect the antenna and prevent interaction with the antenna materials until the tag passes into the colon I where it begins to disintegrate.

[0145] The GI sensor/energy cell includes the use of a zinc electrode 81 and silver electrode 79 with special coatings as described previously. The GI sensor is designed to restrict the bioavailability of the materials to levels far below FDA, EPA, and/or recommended daily intakes. The simple GI sensor produces induced voltages from the voltaic battery when different metals interact with the acidic GI fluids. Zinc foil is preferably used for small scale production and is bonded to the tag 15 using a conductive adhesive. An analog to digital converter within data acquisition block 304 in the chip 20 is used to uniquely detect the sensor's response to GI fluid.

[0146] FIGS. 25 and 26 show the preferred embodiment of the tag, its size, and its approximate location of features. The tag 15 consists of four logical components: the in-link antenna system 79, the GI sensor 85, the tag integrated circuit (IC) 47, and the out-link TX antenna 44. The in-link antenna system 79 includes two in-link 50 pads (body contact pads) that are 1-2 mm by 4 mm. The GI sensor includes a pad 81 that is approximately 1 mmx5 mm. The out-link antenna 44 utilizes the rest of the available space. The tag IC 47 is shown in the inlay of the figure. On the right of FIG. 23 is a diagram of the tag 15 after it is wrapped around a cylindrical object. The in-link antenna pads are separated by the maximum available distance, which is 180 degrees across the capsule once the tag is wrapped around it. The out-link antenna is optimized for the required three dimensional geometry of the capsule (or

pill) after attachment. The tag 15 materials and construction conforms to all safety, regulatory, and manufacturing requirements. The physical structure of the tag 15 and its relationship to a medication capsule is shown in FIG. 27. Target Tag sizes are shown such as to conform to a size 0 capsule. Future generations are expected to support smaller capsule geometries and tablets.

Reader

[0147] To minimize the size and power requirements of the external reader 11, in one embodiment it may not include the capabilities to transmit information via a cell system, wi-fi, or other wireless network. However, in another embodiment, the reader 11 can transmit data to a standard cell phone, pager, or other device as shown in FIG. 1 and as described below with reference to FIG. 3, to allow for real-time updating of patient compliance and monitoring. Using a two part reader system allows for a miniaturized on-body receiver 19 and a more powerful mobile device 54 with a more sophisticated user interface for messaging and transmission to a global database. In such a two-part reader system, an on-body reader 11 has two communication systems, one 50, 52 to communicate with the tag 15 and one 56, to communicate with the mobile device (for example a bluetooth; see FIGS. 3 and 30 and discussion below). In such a system, the mobile device only requires special software to operate as both a standard mobile device and a front-end user interface and wide area network (WAN) transmission interface.

[0148] The external reader 11 can be embodied in several forms. For example, the reader can be the wristband 111 of FIG. 28, or the patch 211 of FIG. 29 that can be adhered to the skin like a bandage, an arm band, a handheld device or the like. In some embodiments, it is advantageous for the reader to have contact with the skin during a medication event. It is also advantageous to design the reader to be readily available and/or worn to ensure it is present with the patient 16 for all medication events. Another form is the pill container 311 shown in FIG. 30 with contacts 313 on the bottle holder 311 for skin contact during the ingestion of the medication. A minimal user interface exists on the bottle holder 311 with a button to indicate ingestion has taken place 312 and an indicator 313 to determine when the pill was detected. The patient 16 removes the medication from the container 311, ingests it, presses button 312 and holds the pill container 311 against the skin until the ingestion event is detected at the contacts 313 and the indicator 314 confirms that the tag 15 was detected in the body 16. In other forms, the reader is also built into a mobile device such as a cell phone, PDA, wrist watch, or into a memory card, dongle, or other add-on device that can be attached or inserted into a mobile unit.

[0149] Noting FIG. 30, each reader 11, 111, 211 and 311 has a small user interface 227 that presents indicators of ingested medication being detected and/or the capabilities to indicate when medication should be ingested. The readers are disposable or reusable, or contains portions that are disposable and reusable. The readers also preferably contain means for storing the recorded data for downloading via USB or other means directly to a PC or other computing device. The readers are also preferentially rechargeable. In addition, for those applications where the readers do not need to be mobile, they may be built into a dongle or other means into a standard computer or laptop.

[0150] Continuing with FIG. 31, the reader comprises several RF/analog front-end components interconnected with a

digital processing core to handle the communication protocols. The body interface or antenna subsystem 220 interfaces with the body 16 or media surrounding the body (e.g. air). It contains the antenna and/or contact points to transmit the in-link 50 data to the tag 15 and receive the out-link 52 data from the tag 15. In addition, the body interface subsystem 220 includes the sensors, contacts, or antennas necessary to acquire physiologic or biometric data required to ensure the reader 11 is on the right patient 16 and the tag 15 has been ingested by the right patient. The receive subsystem 221 and transmission subsystem 222 contains the electronics to drive the antennas and/or receive data from the body interface and antenna subsystem 220. The uplink receive 225 and uplink transmit 226 subsystems transmit data to and from an either a mobile device for wide area communication or directly to a wide area communication system such as cell phone, wifi, or paging networks. The protocol and control subsystem 224 manages the communications of the out-link 52, in-link 50, uplink 56, and downlink 58 transmissions, controls the user interface 227 and processes all data coming in and out of the reader 11. The user interface system 227 provides information to the patient about when a tag 15 has been detected, allows the patient 16 to initiate a manual detection, provides indicators of when the pill 14 should be taken, and provides other information to the patient.

[0151] The transmission subsystem 220 consists of a multiple modules. The first module contains a high voltage modulator stage with a programmable low frequency carrier to conductively couple RF signals into the body 16. The supply voltage of the modulator can be dynamically varied to superimpose in-link telemetry data to communicate with the tag on the pill. Digital input signals will be derived from the protocol and control subsystem 224 tasked to handle communication protocols to and from the tag and also to and from an uplink/downlink transceiver 225, 226 that wirelessly interconnects mobile devices to the reader 11. The second module is a UHF receiver chipset used to demodulate out-link 52 data from the tag 15. The receiver is used to downconvert the detected out-link RF signals 52 for data extraction by the baseband processor. Preferably, all communication protocols between reader 11, tag 15 and mobile devices 54 are be synchronized to a master clock generation module to ensure proper timing control.

Software System

[0152] True adherence improvement is likely to only be achieved when the patient 16 is motivated to follow the prescribed regimen. By connecting the patient with the medication, the pharmacodynamics (PD) and pharmacokinetics (PK), dose/response data, and their own reaction to the medications, patients become more interested in their regimen and become more adherent. The software system is preferentially implemented in a smart phone application that is linked to the reader 11 and the information provided by the uplink/downlink data. In a preferred embodiment, the software shows estimated blood levels of the drug of interest based on the known patient information and medical information stored in the system, as well as the exact timing and doses of the medication taken by the patient. The software shows the patients how missing doses or improperly taking their medication affects their simulated blood levels, drug effectiveness, and how it changes their physical responses to the medication.

[0153] Other embodiments include personalized calendars that a list each medication and dosage listed under the following four time periods: Morning, Noon, Evening, and Bedtime. If a patient does not take their medicine, they are asked to write the reason. It also lists any special instructions to help prevent adverse effects resulting in decreased medication adherence. The software also contains a list of abbreviated instructions on how to use and monitor each drug so that the patient understands the benefit and risk of each drug. The software also allows the pharmacist to enter how many days late the patient comes to the pharmacy for a refill of chronically taken medication. If the adherence rate is unsatisfactory, the pharmacist is presented with various options on how to enhance adherence through patient education programs designed from well documented motivational interview techniques.

[0154] The Personalized Medication Adherence Registry (PMAR) is a mobile software system that receives medication adherence data from the patient and device links, then presents it to the patient and healthcare providers in an extremely quick and easy to understand format. The largest group that will benefit from PMAR are those patients taking multiple chronically administered medications that are essential to wellness. Another important population are patients who are receiving medications that create frequent or severe adverse drug reactions (ADRs). Typical examples of healthcare providers are all physicians, pharmacists, nurse practitioners, physician assistants, clinical trial personnel, and any other health related professions who advise, monitor or treat patients with medications.

[0155] When patients visit their physician or other health care providers, they are usually asked to produce a comprehensive, up-to-date, and accurate list of all their medications including the name of the drug, the dosage strength, and the directions for use. This list can become extremely complex very quickly and difficult to recall. This list is immensely valuable when a patient is traveling and in an accident. It may be life saving if this medication list can be produced as quickly as possible with all the required details. Having an electronic copy immediately available can save the patient time and money while improving their health and possibly preventing an inappropriate drug related catastrophe. A common example is when one of over 20 million Americans with diabetes becomes extremely weak in a public place. If he/she has recently taken his blood sugar lowering agent, a liquid with concentrated sugar e.g. a soft drink or orange drink may save their life. The patient must provide their username and password to allow others access to this encrypted information. Since this protected information resides on their cell phone, access to cellular service is not required. A back-up of all this protected information can also be accessed by the patient and any healthcare provider, family member or close friend who has access.

[0156] If the patient has access to the Internet via their cell phone or personal computer, they will be able to click a drug from their drug list and be linked to drug-specific information in Wikipedia. They will be reminded to print the information and have it validated for its accuracy and personalized application to their situation based upon various factors that are relevant, e.g., all their existing disease stated, medication list, age, sex, weight, diet, and exercise program.

Medication and Refill Reminders

[0157] The Reminder feature of PMAR provides a timely visual and auditory notice to the patient via their mobile phone allowing the customer to be alerted for each of their scheduled medications. PMAR is easily customizable as to each patient's preference as to how they are to be reminded and the sound/vibrate/visual notification rules governing the reminder system. They can be reminded to take all their prescription medications (Rx's), OTCs, herbal medications, and nutritional supplements. This information is stored in their cell phone calendar and also does not require access to a cellular network.

[0158] PMAR will also remind the patient several days prior to completing their medication that it is time to obtain a new refill or if they are probably almost out of their OTC, herbal, and nutrition supplement. This prevents one of the leading causes of proper medication adherence. These reminders are based upon the date of the last refill and whether they received a weekly, monthly, or quarterly refill.

[0159] Although reminder systems are not uncommon, when coupled to compliance monitoring systems, additional features become possible. For example, if medications are not ingested when requested, a series of reminders or alerts can be sent starting with the patient and following up with family, care givers, doctors, pharmacists, drug trial monitors and administrators. If necessary, the system or support personnel can call or visit the patient to ensure that there are no problems and that the patient is taking the medication regularly.

[0160] In addition, various advantageous patient reward systems can be included in PMAR since medication adherence is positively recorded by the system. For example, when patient's take their medication according to their regimen, they may be provided with coupons for free or discounted services or products. These coupons could be funded by any number of parties with a vested interest in ensuring medication adherence, including the pharmacy, the pharmaceutical company, the insurance company or government agency. For children and young adults, gaming coupons or online money or points for online games, music downloads, etc. can be provided for good or improving adherence.

Adverse Drug Reaction Report (ADR)

[0161] When the patient is reminded to take their medication, one of their options will be to choose from a list of common side effects and ADRs to document if they have experienced a recent ADR and if they stopped taking their medication secondary to the ADR. This often happens without the pharmacist or physician being aware. This will assist healthcare providers in determining the cause of patient non-adherence and prompt them to possibly decrease the dose or select an alternative medication. This feature alone can help decrease many avoidable hospitalizations.

Neck Sensor

[0162] Referring again to FIG. 1, as an alternate to detection of the pill in the gastrointestinal system, it is also possible to detect a pill 30 as it passes through the esophagus E using a sensor 32 designed to fit around the neck 33. Preferably, this sensor 32 takes the form of a complete circle around the neck 33, a partial, horseshoe-like enclosure, or a simple device held against the neck 33. The sensor 32 detects all embodiments of the pill 30 described elsewhere as it passes through the esophagus E into the stomach S. The embodiments in which

the sensor 32 forms a semi- or full circle around the neck 33 also improve the signal-to-noise ratio over a sensor that is simply held in front of the patient. There is also less dependence on digestive mechanisms, providing less design restrictions on the pill itself.

[0163] The neck sensor operates in all the same ways as the gastrointestinal reader 11, but also allows for other, possibly advantageous, protocols. For the case in which multiple pills must be detected, a protocol in which the patient takes one pill at a time can be employed. In this approach, only one pill will occupy the esophagus E at any time, which improves the sensor's capability to identify and tally dosage.

Biometric Identification and Compliance Monitoring with Physiological Signal

[0164] A biometric identification aspect of the invention is now described with reference to FIGS. 31-33. In some instances, it is important to know that the electronic pill 14 is inside the body of the person wearing the reader device 111. In an embodiment, this is accomplished by both the pill 14 and reader 111 measuring a known physiologic signal and communicating attributes of this signal between them. The knowledge that the reader 111 and pill 14 devices are measuring the same physiologic signal indicates that the pill 14 is inside the same person that the reader 111 is attached to.

[0165] The pill 14 includes a compliance monitoring device 404 attached or inside. This compliance monitoring device 404 measures a biometric signal such as the patient's ECG 405 after being ingested and sends a signal corresponding to the ECG signal 405 to the reader 111 attached to the patient. The reader 111 also measures the ECG signal 405 of the patient and can compare its signal to that measured by the compliance monitoring device 404. If the two signals match, the pill 14 is confirmed to have been ingested by the person wearing the reader 111.

[0166] In a preferred embodiment, in order to reduce the amount of information that needs to be transmitted, certain characteristics of the ECG signal are calculated and transmitted between the pill 14 and reader 111. Many characteristics are possible, but a preferred characteristic is the timing of the peaks in the ECG signal 405. This timing, sometimes called the R-R time because the peak of the ECG 405 is often described by the letters QRS, can be easily calculated at both the pill 14 and reader 111 and compared, without the need to transmit the entire ECG signal 405. Other characteristics of the ECG that can be measured include: heart rate, ratio of P to QRS or T to QRS amplitudes, duration P-R or R-T timing, QRS duration, and others that are known.

[0167] In addition to ECG, other physiologic signals may be used, including but not limited to breath rate, muscle activity, acoustic information, and blood flow measurements such as pulse oximetry, or body movements read with an accelerometer or similar sensors.

[0168] In certain communication schemes, synchronizing the transmitter and receiver provides advantages including but not limited to higher signal to noise ratios, lower power transmission, and better reception. The use of the physiologic signal to synchronize the in vivo and ex vivo transmitter and receiver provides both a mechanism for synchronization and also ensuring that only pills ingested by the person wearing the reader 111 are detected. If a person other than the person wearing the reader 111 ingests the pill 14, the physiologic synchronization cannot take place since each device will have a different synchronization signal. Only if the same person who is wearing the ex vivo reader 111 also ingests the pill 14

can the two devices properly synchronize. In addition to this advantage, synchronizing to the physiologic signal prevents the need for either device to broadcast a synchronization signal, thus saving power in the communication system.

[0169] Another use of monitoring the physiologic signal is biometric identification. By measuring attributes of the ECG or other physiologic signal of the patient, identification of the person actually wearing the watch can be done. In a preferred embodiment, the physiologic signal is measured by the compliance monitoring device **404** or reader **111** when the pill **14** is first provisioned. Thus, the device records the important attributes of the physiologic signal and then continuously compares the attributes of the physiologic signal throughout the use of the devices.

[0170] If the attributes change significantly, this indicates that the person wearing the reader **111** is not the same as the person who was originally provisioned the reader **111**. This prevents people from swapping readers **111** or having other people take their pills **14** for them.

[0171] Principal component analysis (PCA) is used for feature extraction from the vector of data points representing a single pulse of ECG. For this algorithm, the fiduciary points are projected with PCA into a subset of features. For the classifier portion of the biometric, a linear model is used to match the PCA features to each person. In our experimental trials, this method achieved an identification rate of 93% with ECG data sets from sixty different people.

[0172] A new algorithm was developed that averages the individual pulses and then applies a similarity measure that compares the vector of PCA features from one subject to the vector of PCA features of other subjects. The similarity metric (for example mean squared error or Mahalanobis distance) calculates the distance between the vector under study and the average vectors from each subject in the database. For example, individual beats are aggregated and pruned for training the model. Pruning is determined by the similarity between beats. The similarity is calculated as follows:

$$\frac{n \sum x_i y_i - \sum x_i \sum y_i}{\sqrt{n \sum x_i^2 - (\sum x_i)^2} \sqrt{n \sum y_i^2 - (\sum y_i)^2}}$$

[0173] This similarity measure is also used to determine patient X's distance with respect to either patient Y or a model that represents the world (averaged across all other patients) i.e. a cohort vs World model. In experimental trials, this model was able to correctly identify 98.67% of the patients (including the multi-day recordings).

[0174] The use of continuous data available on a reader **111** that is worn for extended periods of time provides a methodology for a much more robust biometric identification. Methods to remove noisy data during motion or other artifacts while still matching only the clean signals provides great flexibility in the identification system. In addition, the ability to detect when the signals are lost can be useful in determining when the reader **111** is removed and replaced on the body. As long as the signal does not change dramatically or cease to be collected, it can be assumed that the same person is wearing the reader **111**.

[0175] When multiple pills **14** are ingested it is desirable for the reader **111** to be able to detect each device independently. In cases where the pills **14** are not in communication

or synchronized by some other means, it is desirable to have a communication telemetry system that may operate asynchronously. Pills **14** provide telemetry data by sending amplitude based bursts of radio frequency (RF) energy at a frequency of f_c Hz. These bursts are separated by a period of TB seconds. For multiple devices the frequency f_c may be different for each device, either by design or due to process variations. Similarly, the period of bursts will be different for each device.

[0176] Asynchronous operation may be used to assure a relationship between the burst separation period and the burst frequency. The reader **111** may then perform frequency analysis on the incoming pulse stream and sift out the individual pieces of telemetry from each communication device.

[0177] By way of example, consider FIG. **33**. Here, an individual communication device generates a burst separation and carrier frequency from a common clock generator. By determining the burst separation period at the reader **111**, the burst frequency may be easily calculated.

[0178] FIG. **34** shows a reader **111** receive architecture which accomplishes this. The input signal to the receiver includes bursts from up to N individual communication devices. The bursts contain information from each device **1** through N represented by signals S1, S2, . . . SN. The ensemble burst telemetry is down-converted and filtered to a first Intermediate frequency, IF1. This signal is digitized by the analog to digital converter (ADC). A Fast Fourier Transform (FFT) is carried out which finds the periodicity of the pulse period for each communication device. Because the pulse period is directly related to the carrier frequency, this information is binned and used to digitally control oscillator blocks that generate local down conversion signals to bring each individual in-vivo signal to baseband. The converted signal is optimally filtered and passed to a signal processing block that extracts the information signals S1 . . . SN.

[0179] An alternative approach is to use fixed oscillator signals for c_1 . . . c_N and down-convert directly.

Power Source on the Back Side of a Die

[0180] Two forms of creating one half of a galvanic cell on the backside of a semiconductor die are now described. These metallizations are used as a power source for the die upon immersion of the device in a fluid and when paired with an appropriate cathode/anode.

[0181] In each case, a metallization is formed to connect the front side of the die where the bond pads have been created to the typically bare backside of the die which is metallized with the appropriate cathode/anode material.

[0182] An alternative embodiment includes both the cathode and anode material deposited on the backside with a physical space between them that may or may not be filled with a solid material.

[0183] Backside metallizations may be sputtered, vapor deposited, laser deposited, bombarded, condensed, or physically attached/adhered/secured/melted.

[0184] Various modifications of the embodiments described here can be made without departing from the spirit and scope of the invention as described above.

1. A system for monitoring a patient's compliance with a medication delivery program, the system comprising:

an electronic ingestible medication delivery device that, after ingestion by a patient, makes a first measurement of a physiological parameter of the patient and transmits a

- signal from within the patient's body, the signal including information from the first measurement; and an electronic reader outside the patient's body that reads the signal and makes a second measurement of the same physiological parameter of the patient.
2. The system of claim 1, wherein the physiological parameter of the patient is the patient's ECG.
 3. The system of claim 2, wherein the information from the first measurement is a time component selected from the patient's ECG, the time component being a time between successive peaks in the patient's ECG.
 4. The system of claim 2, wherein the information from the first measurement is a time component selected from the patient's ECG, the time component being a time between successive R peaks in the patient's ECG.
 5. The system of claim 1, wherein the reader is wearable by the patient.
 6. The system of claim 1, wherein the reader reads the signal within a time-frame defined by the physiological parameter.
 7. A system for monitoring a patient's compliance with a medication program, the system comprising:
 - an ingestible medication delivery device carrying an electronic circuit that transmits an electromagnetic signal from within a patient's body to outside the patient's body; and
 - an electronic reader positioned outside the patient's body that detects the electromagnetic signal; and
 - wherein transmission and detection of the electromagnetic signal are synchronized according to a physiological parameter measured from the patient.
 8. The system of claim 7, wherein the physiological parameter is measured by the delivery device, the reader, or both.
 9. The system of claim 7, wherein the physiological parameter is the patient's ECG.
 10. The system of claim 9, wherein the transmitted signal includes a time component selected from the patient's ECG, the time component being a time between successive R peaks in the patient's ECG.
 11. The system of claim 7, wherein the reader is wearable by the patient.
 12. A method of monitoring a patient's compliance with a medication program, the method comprising:
 - transmitting a first signal from an electronic ingestible medication delivery device located within a patient's body, the signal including information about a physiological parameter of the patient;
 - detecting the signal with an electronic reader located outside the patient's body; and
 - providing a second signal to the reader from a different source than the delivery device, the second signal including information about the same physiological parameter of the patient.
 13. The method of claim 12, further comprising comparing the first and second signals to determine whether both the first and second signals are from the patient.
 14. The method of claim 12, further comprising synchronizing transmission by the delivery device and detection of the first signal by the reader with a time component of the physiological parameter.
 15. The method of claim 12, wherein the physiological parameter is measured by the delivery device, the reader, or both.
 16. The method of claim 12, wherein the physiological parameter is the patient's ECG.
 17. The method of claim 12, further comprising the step of providing the first signal with a time component selected from the patient's ECG, the time component being a time between successive R peaks in the patient's ECG.
 18. The method of claim 12, wherein the reader is worn by the patient during the detecting step.
 19. The method of claim 12, wherein the transmitting and detecting steps occur during a plurality of times while the delivery device is within the patient's body.
 20. The method of claim 12, further comprising applying a principal component analysis algorithm to the first signal.

* * * * *

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摘要(译)

监测患者对药物程序的依从性的方法包括从位于患者体内的电子可摄入药物输送装置发送第一信号，该信号包括关于患者的生理参数的信息。使用位于患者体外的电子阅读器检测信号。从与递送装置不同的来源向读取器提供第二信号。第二信号包括关于患者的相同生理参数的信息。还描述了相关系统。

