Title: TRANSDERMAL THERAPEUTIC SYSTEM AND METHOD

Abstract: A system (200) for monitoring compliance with a medication regimen comprises a transdermal therapeutic patch (201) for administering a medication to a user, the transdermal therapeutic patch comprising: an antenna (404); and control electronics (402) configured to cause the antenna to transmit an identifier.
Transdermal Therapeutic System and Method

Technical Field

The disclosure relates to a patient care system and method, and in some embodiments relate to a transdermal therapeutic system and method. Embodiments further relate to a patient care system for patients with neurological disorders such as Alzheimer's disease.

Background

A number of diseases or conditions are known which exhibit neurological effects, and/or which affect or impact elements of a patient's motion, such as gait and/or balance or some aspect of movement. Parkinson's disease, Lou Gehrig's Disease (ALS), cerebral palsy, Autism, schizophrenia and Alzheimer's disease are well known examples.

In some cases, a disease or condition may affect a patient's activity level, which can lead to the patient inadvertently harming himself or herself, and/or impede or prevent the patient from self-dosing with a medication which can otherwise alleviate or mitigate the such effects of the disease or condition. Diseases or conditions, such as Alzheimer's, which exhibit neurological effects are particularly significant in this regard. As Alzheimer's affects the elderly, such patients are prone to other age-related consequences, such as injury from falling or running into objects, and can become lost or disorientated.

Neurologically-impaired patients, for example, Alzheimer's patients, may therefore be unable to administer medications for their condition. Such patients further are very susceptible to injury, such as from falling, as they move about. Moreover, the neurological effects of such diseases often result in a loss of self-awareness as to location and activity.

Alzheimer's patients may be treated with medications, for example, cholinesterase inhibitors such as donepezil and rivastigmine. Such medications are often suitably administered via a transdermal therapeutic system, or "patch". In many cases, such transdermal therapeutic systems must be applied by a caregiver. In many cases, such transdermal therapeutic systems must be applied daily. However, in patients with neurological impairment, the applied transdermal therapeutic system may be inadvertently or purposefully removed by the patient who does not otherwise appreciate the purpose of the transdermal therapeutic system. Additionally, multiple patches may be inadvertently
applied at the same time, either by the patient or the caregiver, thereby exposing the patient to a risk of overdosing.

Moreover, such patients suffering from neurological impairment may, from time to time, wander away from their familiar surroundings, or may become lost or disoriented while traveling or moving about. As noted above, elderly patients suffer from fall-related injuries, and can become disoriented or lost, with disastrous consequences.

Accordingly, embodiments of the invention provide a transdermal therapeutic system which can be monitored by the patient and/or remotely by a caregiver or family member, to ensure that they are being properly used by the patient (or user). Embodiments of the invention thus comprise therapeutic transdermal systems which further comprises patient compliance monitoring components. Such monitoring can verify that the system is in place on the user, and/or that only a single system is in place on the user, and/or that the drug remains efficacious (is not expired) and/or that the particular transdermal therapeutic system is correct for a given time period, such as a correct transdermal therapeutic system for each day, or a correct transdermal therapeutic system for a given week.

Brief Description of the Drawings

The present disclosure and the embodiments set out herein can be better understood with reference to the description of the embodiments set out below, in conjunction with the appended drawings which are:

Fig 1 is a schematic drawing of a known transdermal therapeutic patch.

Fig 2 is a schematic drawing of a system according to an embodiment of the invention.

Fig 3 is a flow diagram showing an exemplary method of operating the system of Fig 2.

Fig 4a is a top-view schematic of an eLabel according to an embodiment of the invention.

Fig 4b is a side-view schematic of the eLabel of Fig 4a.

Fig 5 is an exemplary schematic of a circuit design for implementing the electronic components of the eLabel of Figs 4a and 4b.
Fig 6 is a flow diagram showing an exemplary mode of operation of the telemetry circuitry of the eLabel of Fig 5.

Fig 7 is a schematic of a user-wearable device according to an embodiment of the invention.

Fig 8 illustrates an exemplary user-wearable device according to an embodiment of the invention.

Fig 9 is a block diagram of an exemplary computing system according to an embodiment of the invention.

Summary

In embodiments of the invention, a transdermal therapeutic patch is provided, the patch comprising: an antenna; and control electronics configured to cause the antenna to transmit an identifier using magnetic induction; wherein the antenna and the control electronics are affixed to the patch, and the patch is configured to be removably attachable to a user.

The antenna may be configured to transmit the identifier over a maximum range of 1.1 to 1.25 metres and/or be configured to operate at a frequency in the range of 12.8 to 13.2 MHz.

The antenna may be a double-sided coil antenna. Such an antenna configuration advantageously reduces the space occupied by the antenna on the patch.

The patch may further comprise a power supply configured to power the antenna transmission for a period in the range of 24 to 72 hours. The power supply may be a 1.5 printed battery, thereby reducing the space occupied by the power supply.

The control electronics may be configured to cause the antenna to transmit the identifier periodically.

The patch may further comprise an activation switch configured so that triggering the switch activates the control electronics to cause the antenna to transmit the label identifier.
The control electronics may be further configured to: determine whether the patch is attached to a user; and if the control electronics determine that the label is not attached to a user, to cause the antenna to cease transmission of the identifier. In this manner, accidental activation of the switch does not result in discharge of the power supply.

The patch may comprise a medication or active ingredient for administering to the user. For example, the patch may comprise rivastigmine medication.

In embodiments of the invention, a system is provided for monitoring drug administration, the system comprising: a transdermal therapeutic patch comprising an antenna and control electronics configured to cause the antenna to transmit an identifier using magnetic induction; and a user-wearable receiver configured to receive the label identifier transmitted by the patch antenna.

The user-wearable receiver may comprise a rechargeable power supply. Additionally or alternatively, the user-wearable receiver may be configured to: determine whether an identifier has been received from the patch antenna; and responsive to the determination, to cause the transmitter to transmit data to a remote data processing unit.

The user-wearable receiver may further comprise one or more of: a motion sensor; a fall detection sensor; a temperature sensor; a location sensor; and a user-activatable alert.

The system may further comprise a memory in communication with the user-wearable receiver. In this manner, data or measurements detected or received by the user-wearable receiver can be stored for analysis.

In embodiments of the invention a method of transmitting data from a transdermal therapeutic patch is provided, the method comprising: (a) detecting activation of the patch; (b) determining whether the transdermal therapeutic patch is affixed to a user, and if so: causing an antenna coil to transmit an identifier associated with the patch using magnetic induction.

If the transdermal therapeutic patch is determined not to be affixed to a user, the method may further comprise: (c) determining an elapsed period since the activation of the patch was detected; (d) if the elapsed period is less than or equal to a predefined threshold, repeating step (b); and (e) if the elapsed period is greater than the predefined threshold, deactivating the patch.
In embodiments of the invention a system for monitoring compliance with a medication regimen is provided, the system comprising: a transdermal therapeutic patch for administering a medication to a user, the transdermal therapeutic patch comprising: an antenna; and control electronics configured to cause the antenna to transmit an identifier.

The system may further comprise a user-wearable receiver configured to receive transmissions from the antenna.

The control electronics of the system may be configured to cause the antenna to transmit the identifier using one of magnetic induction.

Alternatively, the control electronics of the system may be configured to cause the antenna to transmit the identifier using radio frequency transmission. In this case, the control electronics may be configured to cause the antenna to transmit the identifier using either active or passive RFID transmission.

If the control electronics are configured to cause the antenna to transmit the identifier using passive RFID transmission, the user-wearable receiver may be configured to transmit an interrogation signal, responsive to which the antenna transmits the identifier.

In embodiments of the invention a kit for medication delivery is provided, the kit comprising: a plurality of the above-described patches and/or a plurality of the above-described systems; and a user-wearable receiver configured to receive transmissions from the antenna.

In embodiments of the invention a patient management system is provided, the system comprising: a transdermal therapeutic patch comprising: an antenna; and control electronics configured to cause the antenna to transmit an identifier using magnetic induction; wherein the antenna and the control electronics are affixed to the patch, and the patch is configured to be removably attachable to a user; and a user-wearable receiver configured to receive transmissions from the antenna.

A method for monitoring compliance with a medication regimen is provided, the method comprising: providing the above-described patient management system; receiving, at the user-wearable receiver, data transmissions from the patch antenna; and outputting data in accordance with the received transmissions.
Outputting data in accordance with the received transmissions may comprise outputting, at
the user-wearable receiver, audio and/or visual data.

Additionally or alternatively, outputting data in accordance with the received transmissions
comprises transmitting data to a remote processing unit. In this case, the remote
processing unit may be operated to output an alert based on the data received from the
receiver.

A further aspect of the present invention comprises any two or more of the aspects, embodiments or features described herein.

Throughout this specification and in the claims that follow, unless the context requires
otherwise, the word "comprise", or variations such as "comprises" or "comprising", should
be understood to imply the inclusion of a stated integer or step or group of integers or
steps but not the exclusion of any other integer or step or group of integers or steps.

The use of the term "about" to qualify a numerical range, qualifies all numbers within the
range, unless the context indicates otherwise.

The entire disclosure of each United States and International patent or patent application
mentioned in this patent specification is fully incorporated by reference herein for all
purposes.

**Detailed Description**

The following description is presented to enable a person of ordinary skill in the art to
make and use the various embodiments. Descriptions of specific devices, techniques, and
applications are provided only as examples. Various modifications to the examples
described herein will be readily apparent to those of ordinary skill in the art, and the
general principles defined herein may be applied to other examples and applications
without departing from the spirit and scope of the various embodiments. Thus, the various
embodiments are not intended to be limited to the examples described herein and shown,
but are to be accorded the scope consistent with the claims.

In embodiments of the present invention, there is provided an apparatus, system and/or
method of treatment comprising a transdermal system having monitoring capabilities. In
embodiments of the present invention, there is provided an apparatus, system and method of treatment and controlled-release formulation(s) comprising a transdermal therapeutic system having monitoring capabilities. Monitoring capabilities comprise compliance monitoring, patient self-monitoring, caregiver-monitoring, remote monitoring, and combinations thereof.

Transdermal therapeutic patches and their manufacture are generally known in the art. US 6316023 and US 6335031 disclose a transdermal therapeutic patch containing rivastigmine and an antioxidant. US 5602176 discloses a transdermal therapeutic patch containing rivastigmine and a hydrophilic polymer. This transdermal therapeutic patch provides the benefit of having substantially less inter-individual variation with regard to plasma concentrations of rivastigmine required to produce a therapeutic benefit without unacceptable side effects.

In embodiments of the invention there is provided a system for monitoring compliance with a medication regimen, the system comprising a transdermal therapeutic system, comprising an adherent substrate and a medication, wherein the transdermal therapeutic system is adhered or affixed to a label comprising an antenna and control electronics. The adherent substrate is configured to be removably attachable to a user's body thereby allowing administration of the medication; the label antenna is configured to transmit data. It will be appreciated that the user may be human. Alternatively, the user may be an animal.

The data transmitted by the antenna may comprise any information representative of, or associated with, the system or user. In an exemplary embodiment, the data may comprise a unique or quasi-unique identifier of the transdermal therapeutic patch, the transdermal therapeutic system and/or the formulation comprised within the patch.

In embodiments of the invention, the data may be transmitted using magnetic induction.

Embodiments of the invention comprise a monitoring system comprising a label comprising an antenna and control electronics, and the label antenna is configured to transmit data. The label may be affixed or attached to an adherent patch, or may be affixed or attached to an alternative substrate or device, which itself may be attached to the body. In such embodiments, the data may be transmitted using magnetic induction.
In embodiments of the invention, the data may be transmitted using Radio Frequency (RF) transmission. For example, the antenna may be a Radio Frequency Identification (RFID) transponder comprised within an RFID tag affixed to, or embedded within, the transdermal therapeutic system.

The antenna may, for example, be configured to transmit the data periodically or aperiodically. Alternatively, the antenna may be configured to transmit the data continuously over a predefined period.

The system further comprises a user-wearable device, hub or apparatus comprising a receiver configured to receive the data transmitted by the antenna. The user-wearable hub may further comprise an output device or interface for outputting data in accordance with the received data. The output device may, for example, comprise a transmitter configured to communicate with a remote data processing unit. Additionally or alternatively, the output device may comprise audio, display, or video means for outputting a user-perceptable audio and/or visual signal in accordance with the data received from the antenna.

In embodiments of the invention the monitoring system may be used for monitoring the administration of any active agent. Active agent(s) comprise any suitable medication, biological marker, indicator, tracer, drug, pro-drug, pharmaceutical or nutraceutical which may be useful or beneficial to administer. Embodiments of the invention comprising the monitoring system may be used with transdermal therapeutic systems for treating neurological impairments such as Alzheimer's, in which case the medication may be a cholinesterase inhibitor such as rivastigmine. In such embodiments, the data transmitted by the antenna may comprise an identifier associated with, or indicative of, an active agent.

In embodiments of the invention the monitoring system may be used for monitoring the presence of a patch comprising an adherent substrate, wherein the patch further comprises physical, chemical, or electrical means to monitor and/or record one or more physical, physiological or metabolic aspect(s) of the user to whom/which the patch is adhered. In such embodiments, the patch may optionally administer one or more active agents, medicaments or drugs.

Fig 1 is a schematic drawing of a known transdermal therapeutic patch 100. It will be appreciated that the patch 100 is one example of a transdermal therapeutic patch that can
be used with a system in accordance with embodiments of the invention. However, the invention is not limited to use with the patch 100 and may instead be used with any suitable transdermal patch. For example, a transdermal therapeutic patch incorporating any one of the herein-described active ingredients, may be used. Active ingredients are suitably any which supply a therapeutic or nutraceutical effect, for example those described herein.

In the example depicted in Fig 1, the patch 100 is a thin, opaque, plastic patch configured to be adhered or affixed to a patient or user's skin. The surface area of the patch 100 may be one of 5cm², 10cm² or 15cm² and the patch may have a thickness of approximately 0.25mm. In various embodiments of the invention, the patch 100 may be of any shape or size as dictated by the purpose of the patch.

The patch 100 may be comprised of four layers 101-104. For example, the first layer 101 may be a backing layer; the second layer 102 may be a reservoir layer comprising at least one active ingredient and a polymer of Acrylic matrix; the third layer 103 may be an adhesive layer comprising a silicone polymer and a tackifier; and the fourth layer 104 may be the detachable protective layer or release liner, which is removed before affixing the patch 100 to the user.

Embodiments of the present invention comprise application of a transdermal therapeutic patch having a surface area in the range of 2 to 60 cm². Embodiments of the present invention comprise a transdermal therapeutic patch comprising one or more of: a mean maximum plasma concentration of about 1 to 30 ng/mL from a mean of about 2 to 16 hours after application and an AUC24h, of about 25 to 450 ngh/mL after repeated "QD" (i.e., once daily) administration. Embodiments of the invention comprise a transdermal therapeutic patch comprising rivastigmine as the medication, and one or more of a mean maximum plasma concentration of about 1 to 30 ng/mL from a mean of about 2 to 16 hours after application and an AUC24h, of about 25 to 450 ngh/mL after repeated "QD" (i.e., once daily) administration.

The patch 100 may be configured to be affixed, attached, or adhered to the user by applying the adhesive layer 103 to skin, preferably clean, dry hairless, intact, healthy skin in a place that will not be rubbed against by tight clothing. The upper or lower back is recommended as the site of application because the patch is less likely to be removed by the user. However, the patch 100 may also be applied to the upper arm or chest, or other
suitable location. The patch 100 should preferably not be applied to skin that is red, irritated or cut.

Once adhered to the user's skin, the drug product present in the second layer 102 is administered to the user via the adhesive layer 103. Example patches comprise sufficient drug product for administration of the drug over a period of 24 hours. Such patches should be replaced with a new patch every 24 hours. In this dosing regimen, only one patch should be used at any given time to ensure that a correct amount of the drug is administered to the user. Other patch dosages are within the scope of the invention, such as those which supply a drug for 24, 36, or 72 hours, or 7 days, or any desired time period.

Unless indicated otherwise, the expressions used in this invention have the following meaning:

The term "transdermal therapeutic patch" denotes any device that is capable of releasing a pharmaceutically active ingredient through the skin. This includes particularly self-adhesive patches.

The term "backing layer" denotes the layer remote from the skin. This layer is preferably active ingredient-impermeable. Any suitable material or combination of materials may be used.

The term "reservoir layer" denotes a layer containing one or more active ingredients in connection with one or more polymers. In an exemplary embodiment, the reservoir layer comprises an active ingredient or drug product in the form of a polymer matrix, for example an Acrylic matrix.

The term "adhesive layer" denotes the layer facing the skin. This layer comprises a silicon polymer and a tackifier.

The term "detachable protective layer" denotes the layer remote from the patch prior to its application to the skin. This layer is preferably active ingredient-impermeable. Any suitable material or combination of materials may be used. For example, siliconized PET, siliconized Polypropylene, siliconized Polyethylene, fluor-polymer coated PET, fluor-polymer coated Polypropylene, Fluor-polymer coated Polyethylene, etc. may be employed.
The term "active ingredient" denotes any active ingredient, or drug product, suitable for transdermal administration. In embodiments of the invention active ingredients include water-soluble and also water-insoluble, pharmaceutical active ingredients, which may be inorganic, organic or biological substances. In embodiments of the invention actives are organic substances. The active ingredients are to be used in accordance with their indication as analgesics, antipyretics, antirheumatics, sedatives, hypnotic agents, anti-epileptics, antidepressants and stimulants, anaesthetics, neuroleptic analgesics, opioid analgesics, antihistamines, antihypertensive agents, anticoagulants, antithrombotic agents, psychopharmacological agents, psycholeptics, chemotherapeutic agents, for example, antibiotics, anti-infectives, anti-virals, sulphonamides, antituberculosis agents (tuberculostatic agents) or also chemotherapeutic agents against tropical infections, diuretics, spasmyotics, cardiovascular agents, for example, sympathomimetics, antihypertensive agents, cardiac stimulants, for example, cardiac glycosides and digitaloids, parenteral sugar therapeutics, analeptics acting on the central nervous system, geriatric agents, tonolytics (of striated muscles), anti-Parkinson agents, cytostatic agents, immunosuppressants, tonics, vitamins and vaccines.

In embodiments of the invention active ingredients are selected from the group consisting of alpha-adrenoreceptor agonists, beta-adrenoreceptor agonists, alpha-adrenoreceptor blockers, anesthetic analgetics, non-anesthetic analgetics, androgens, anesthetics, antiallergics, antiandrogens, antianginals, antiarrhythmics, penicillins, antidiabetics, antihistaminics, antimigraine agents, hydrated ergot alkaloids, Ca++ antagonists, serotonin antagonists, platelet aggregation inhibitors, antidepressants, broncholytics, estrogens, estradiols, gestagens, vasodilators, hormones, anti-dementia drugs (including cholinesterase inhibitors).

In embodiments of the invention antibiotics include penicillin, tetracycline, chlorotetracycline, bacitracin, nystatin, streptomycin, neomycin, polymixin, gramicidin, oxytetracyclin, chloramphenicol, erythromycin, rifampicin, cefazolin, cefoxitin, cefsulodin, cefotiam and mefoxin. Suitable chemotherapeutic agents include sulfamethazine, sulfamerazine, sultamethizole and sulfisoxazole. Sedatives and hypnotic agents include chloral hydrate, pentobarbital, phenobarbital, secobarbital, codeine and carbrom. Cardiac glycosides and digitaloids include digitoxin and digoxin. Sympathomimetics include epinephrine. Anti-Parkinson's medications may include rigotine. Parasympathomimetics include nicotine.
In embodiments of the invention, antipyretics, analgesics and antirheumatics may be used as the active ingredient in the presentation according to the invention in suitable water-soluble form or water-insoluble form, for example, fentanyl, buprenorphine, propyphenazone, aminophenazone, aspirin (ASA), antipyrene, methyl nifenazine, melaminsulfone, sulfanazone, phenacetin, pentazocine, lactophenin, paracetamol, quinine, flufenamic acid, mefenamic acid, tolfenamic acid, niflumic acid, clonixin or clonixidin, flunixin, ibuprofen, suprofen, ketoprofen, pirprofen, diclofenac, ibufenac, procticic acid, naproxen, cicloprofen, tolmetin, clopirac, tiaprofenic acid, oxaprozin, fenclozic acid, fentiazac, clidanac, fenclonac, fenoprofen, flurbiprofen, carprofen, sulindac, cinmetacin, fenbuten, etodolac, and butifufen.

In embodiments of the invention psychopharmacological agents include neuroleptics, antidepressants, thymoleptics, thymoethical drugs and tranquilisers such as methylphenidate, selegeline, thioridazine, imipramine, desimipramine, clomipramine, ketimipramine, opipramol, amitriptyline, nortriptyline, reserpine, aromazine, chlorpromazine, fluopromazine, methopromazine, trimeprazine, diethazine, promethazine, aminpromazine, mepazine, pipamazine, maprotiline and memantine.

In embodiments of the invention, antihypertensive agents include oxprenolol and metoprolol.

In embodiments of the invention the transdermal therapeutic patch comprises two or more drugs or actives. In embodiments of the invention adjuncts such as anti-oxidants, stabilizers, potentiators and the like may be formulated with the active and/or are present in or associated with the transdermal therapeutic patch

In embodiments of the invention, active ingredients are selected from the group of anti-dementia drugs, such as rivastigmine, donepezil, galantamine, memantine and the pharmacologically acceptable salts of said active ingredients.

In embodiments of the invention, cholinesterase inhibitors include tacrine, rivastigmine, donepezil, galantamine, physostigmine, huperzine A and pharmacologically acceptable salts thereof. A combination of rivastigmine and Memantine as active ingredients are present in some embodiments.

In embodiments of the invention, active ingredients are chosen from rivastigmine and rivastigmine hydrogentartrate. Rivastigmine (Exelon® RTM) is useful in the treatment of
patients with mild to moderately severe dementia of the Alzheimer type (also known as Alzheimer's Disease), dementia associated with Parkinson's disease and symptoms of traumatic brain injury.

The term "polymers", when used in connection with the reservoir layer of the active ingredient, denotes a polymer selected from the group consisting of polydimethylsiloxanes, poly-acrylates, poly-isobutene, polybutenes and styrene-isoprene-styrene block copolymers or mixtures thereof, respectively combined with resins.

In embodiments of the invention, polymers to be used within the reservoir layer are selected from the group consisting of polyacrylates, for example, Durotak 2353 from National Starch.

The term "silicon polymer" denotes polydimethylsiloxane based polymers, for example, the aminincompatible Bio-PSA Q7-4302 from Dow Corning.

The term "tackifier" denotes a substance which is increasing the adhesivity/tackiness of the transdermal formulation. Preferred tackifiers are selected from the group consisting of Silicone oils, glycerine esters of hydrogenated resin acids, hydroabietyl alcohol, resin esters, Hydrogenated Methyl Ester of Wood Rosin, Ester of Partially Hydrogenated Wood Rosin, Esters of Rosin, etc. and combinations of those. As appreciated by the skilled person, transdermal therapeutic patch are made out of several layers having specific characteristics. These layers may vary with respect to the individual composition and to the thickness of the separate layers.

In embodiments of the invention, the active ingredients used have low saturation solubility in the silicone adhesive. The saturation solubility of the active ingredient in the silicone adhesive is, for example, less than 15%-wt., such as less than 10%-wt., and such as between 2 and 8%-wt.

The silicone adhesive layer may reduce the active ingredient permeation from the reservoir layer through the skin by no more than 40%, such as by no more than 20% or by no more than 10%.

The weight per unit area of the silicone adhesive layer is, for example, in the range of 5 to 60 g/m², preferably in the range of 10 to 30 g/m².
The composition according to the invention may be used for administrating a wide variety of agents. Suitable active ingredient agents include, but are not limited to those identified above. An agent may also comprise a placebo, or agent that itself is pharmaceutically inactive. In embodiments of the invention, the composition may comprise pharmacologically appropriate combinations of actives.

In embodiments of the invention, the reservoir layer further comprises auxiliaries such as fillers, antioxidants, colorants, skin penetration promoters and/or preservatives. In a preferred embodiment, the reservoir layer contains an antioxidant, such as alphatocopherol, Ascorbyl palmitate or butylated hydroxytoluene (BHT).

In embodiments of the invention, the reservoir layer contains a skin penetration promoter such as Transcutol, Glycerine, Glycerine-esters, Fatty-acids, Salts of Fatty-acids, Azone, Diethyl-toluolamide, Propylengylcol, Propylenglycol-esters, Butandiol, Isopropyl-esters, Urea, etc.

In embodiments of the invention, the ratio of thickness of reservoir layer: adhesive layer is between 5:1 and 1:2; such as between 2:1 to 1:1.

In embodiments of the invention, the transdermal therapeutic patch has an adhesive force greater than 5 N/10 cm², preferably greater than 10 N/10 cm².

Alternatively, the transdermal therapeutic patch may have an adhesive force less than 1 N/10 cm², for example less than 50 N/10 cm². The adhesive force is determined according to standard procedures, for example, as described in the examples.

In embodiments of the invention, the transdermal therapeutic patch has a size range of 2 to 60 cm², particularly preferred 5 to 20 cm².

In embodiments of the invention, the transdermal therapeutic patch provides one or more of a mean maximum plasma concentration of rivastigmine of 1 to 30 ng/mL from a mean of 2 to 16 hours after application with an AUC24h of 25 to 450 ngh/mL. In embodiments of the invention, the transdermal therapeutic patch provides one or more of a mean maximum plasma concentration of rivastigmine of 2.5 to 20 ng/mL from a mean of 4 to 12 hours after application with an AUC24h of 45 to 340 ng-h/mL.
In embodiments of the invention, not only the polymer matrix contains the active ingredient(s) but also the silicone adhesive layer.

The transdermal therapeutic patch may, for example, comprise as active agent a cholinesterase inhibitor in free or pharmaceutically acceptable salt form, for use in the prevention, treatment or delay of progression of dementia.

Alternatively, the transdermal therapeutic patch may comprise as active agent, a cholinesterase inhibitor in free or pharmaceutically acceptable salt form for the treatment, or delay of progression of, Parkinson's disease.

In a further alternative, the transdermal therapeutic patch may comprise, as active agent, a cholinesterase inhibitor in free or pharmaceutically acceptable salt form for the treatment, or delay of progression of, Alzheimer's disease.

The manufacturing of a transdermal therapeutic system according to the invention may be accomplished in any method known to the skilled person. One such method is described in US Patent Application Publication US 2007/0128263, the full disclosure of which is incorporated herein by reference for all purposes.

In addition or alternatively, embodiments of the invention may provide a transdermal therapeutic patch comprising, as an active ingredient, rivastigmine in free base or pharmaceutically acceptable salt form and providing specific plasma concentrations. For example, the rivastigmine may have a mean maximum plasma concentration of about 1 to 30 ng/ml from a mean of about 2 to 16 hours after application.

In embodiments of the invention, the rivastigmine may additionally have an AUC24h of about 25 to 450 ng-h/mL after repeated “QD” (i.e., once daily) administration.

In embodiments of the invention, the transdermal therapeutic patch may comprise a user-wearable substrate which provides for controlled delivery of a therapeutic agent, for example rivastigmine, over a period of greater than one day, such as 2, 3, 4, 5, 6 or 7 days.

Fig 2 is a schematic drawing of an exemplary system 200 according to an embodiment of the invention. The system 200 comprises a SmartPatch 201 comprised of an eLabel 202 affixed to a patch 100 via an adhesive layer. It will be appreciated that the patch 100 may
be the patch described in relation to Fig 1. Alternatively, the patch may be any other user adherent patch, such as a transdermal patch.

The system 200 also comprises a receiver or reader 204. As discussed in detail in relation to Fig 7, the receiver 204 may be comprised within a device or hub that is configured to be worn by the user of the patch 100. For example, the receiver 204 may be comprised within a body-wearable hub configured to be worn around the user's wrist or elsewhere, such as on or near any appendage of the user's body, or associated with any article of clothing, ornament or jewelry of the user.

The receiver 204 may be configured to receive data transmitted by the eLabel 202. In this way, the eLabel 202 can communicate its presence to the receiver 204. The data transmitted by the eLabel 202 may comprise a unique or quasi-unique identifier. The identifier may be any suitable data for identifying the eLabel 202 and distinguishing one eLabel from other eLabels. For example, the identifier may comprise a sequence of numbers and/or characters assigned to, or associated with, the eLabel 202 during manufacture. As discussed above, the eLabel 202 identifier may additionally or alternatively comprise an identifier of, or associated with, the transdermal patch 100.

This communication between the eLabel 202 and the receiver 204 enables the use of the patch 100 to be monitored, for example, to facilitate compliance with one or more of the following: that the patch 100 is replaced daily; that only a single patch 100 is used at any given time; that the patch 100 remains attached to the user for the required period; and that the active ingredient comprised within the patch 100 has not passed its expiry date.

In embodiments of the invention, the receiver 204 may be communicably coupled to a memory 203. It will be appreciated that in embodiments of the invention, both the memory 203 and the receiver 204 may be comprised within the user-wearable device. Additionally, or alternatively, the receiver 204 may be configured to communicate with the memory 203 via any suitable wired or wireless connection.

In embodiments of the invention, the system 200 may further comprise a remote data processing unit 206 with which the user wearable device is configured to communicate via a suitable connection, such as a wired or wireless connection.

Operation of the system 200 in accordance with embodiments of the invention will now be described with reference to the method 300 of Fig 3. At block 302, the eLabel 202 is
activated, or switched to an operational state. Activation of the eLabel 202 is discussed in more detail with respect to Figs 4 and 5.

After activation of the eLabel 202, operation of the system 200 continues at block 304, at which the eLabel 202 transmits the identifier to the receiver 204 comprised within the user-wearable device. As will be discussed in more detail with respect to Figs 4 and 5, in embodiments of the invention the eLabel 202 may transmit data comprising the eLabel identifier whilst the SmartPatch 201 is affixed to the user's skin. The eLabel 202 may transmit the data by any suitable means, for example, the eLabel 202 may transmit data packets comprising the eLabel identifier. The eLabel 202 may transmit the data in any suitable manner, for example, the data may be transmitted continuously over a predefined period; periodically, randomly or at any other suitable interval. On detachment of the SmartPatch 201 from the user's skin, the eLabel 202 may be deactivated and transmission of the identifier may cease.

At block 304, the receiver 204 receives the identifier transmitted by the eLabel 202. As will be discussed in more detail with respect to Fig 7, on determining that a communication has been received, the user wearable device may communicate with the remote data processing unit 206.

Additionally or alternatively, the user wearable device may compare the received identifier to a value stored in the memory 203. Responsive to the outcome of this comparison the user wearable device may initiate communication with the remote data processing unit 206.

Fig 4a is a top-view schematic of a SmartPatch 201 according to embodiments of the invention. Fig 4b is a side-view schematic of the SmartPatch 201 depicted in Fig 4a. In the exemplary embodiments depicted in Figs 4a and 4b, the SmartPatch 201 comprises a patch 100 with the eLabel 202 adhered thereto. The eLabel 202 may be manufactured and supplied distinctly from the patch 100. The eLabel 202 may then be adhered to the patch 100 (or the patch 100 may be adhered to the eLabel 202) as a separate processing step. In this manner, multiple types of transdermal therapeutic patches may be used with a given type of eLabel 202.

It will be appreciated that, in alternative embodiments, the SmartPatch 201 may be a unitary patch comprising both the above-described components of the patch 100 and the
above-described components of the eLabel 202. It will be further appreciated that the 
eLabel 201 may be independent of the patch 100.

In the embodiments of Figs 4a and 4b, the eLabel 202 comprises a printed circuit board 
(PCB) 406 which typically is encapsulated with encapsulation 412 for protection. The PCB 
406 comprises three general regions: the battery 408 which sits on top of an activation 
switch 410; electronic components 402; and an antenna 404. The PCB 406 also 
comprises a 0V, or ground, plane (not shown) located under at least part of the electronics 
components 402.

As discussed in detail with respect to Fig 5, the electronic components 402 may comprise 
one or more of telemetry (or communications) circuitry components; activation circuitry 
components; and skin sensing circuitry components.

In embodiments of the invention, the activation switch 410 is configured to switch the 
eLabel 202 to an operational state. Once the eLabel 202 is in the operational state, the 
battery 408 provides a power source for electronics components 402 via battery terminals 
409. In certain embodiments, the battery 408 is a printed 1.5V battery. In this manner, the 
battery 408 can be made to fit the dimensions of the eLabel 202, allowing for optimization 
of the battery volume for a given dimension of the eLabel 202.

In embodiments of the invention, the electronics components 402, powered by the battery 
408, may determine whether the SmartPatch 201 is in contact with, attached, affixed, or 
adhered to a user’s skin. If the electronics components 402 determine that the 
SmartPatch 201 is attached to a user, then the electronics components 402 may operate 
to cause the antenna 404 to transmit data comprising the eLabel identifier, such as in one 
or more of the above-described manners.

In embodiments of the invention, the antenna 404 may be a coil antenna located around 
the periphery of the PCB 406. For example, the coil antenna may be double-sided (i.e., on 
both sides of the PCB 406). In this manner, electronic components 402 and tracks can be 
kept as far from the antenna 404 as practicably possible. This arrangement reduces 
interference between the antenna 404 and the electronic components 402.

As discussed in relation to Fig 2, the antenna 404 may be configured to transmit the 
eLabel identifier to the receiver 204 which may, for example, be comprised within a user-
wearable device, such as one configured to be worn around the user’s wrist. Accordingly,
the antenna 404 should be capable of transmitting the identifier a sufficient range through
the body for it to be received by the receiver 204. The range of transmission of the
antenna 404 should also be limited to avoid a receiver 204 receiving transmissions from
eLabels 202 worn by other users. Hence, accurate control of the antenna transmission
range is desirable.

In embodiments of the invention, the antenna 404 uses magnetic induction to transmit the
identifier using a modulated magnetic field. As is known in the art, magnetic induction can
be used to transmit data by modulating a time-varying magnetic field. The antenna 404
may be configured to transmit the data in a predetermined direction only, i.e., directional
transmission. For example, the antenna 404 may comprise a single magnetic coil across
which a varying voltage is applied. The transmitted signal can then be received by a
receiver configured to receive data from this direction of transmission.

Alternatively, the antenna 404 may be an 'omni-directional' antenna, i.e., configured to
transmit data in multiple directions. In this case, the antenna 404 may comprise multiple
coils across which a time varying voltage is applied. The receiver 204 can then receive
the transmitted data if the receiver is configured to receive data from any one of the
multiple directions of transmission.

Magnetic induction transmission demonstrates a steep roll-off with distance and angle.
These characteristics of magnetic induction allow control of the transmission range of the
antenna 404 to ensure that the user-wearable receiver 204 worn by the user wearing the
eLabel 202 can receive the identifier, whilst also preventing the user-wearable receiver
204 from receiving transmissions from other eLabels, for example eLabels worn by
passers-by or by multiple users in close proximity.

The range over which the antenna 404 can transmit the identifier through the body is less
than the range achievable in open (or free) air. In an exemplary embodiment, the antenna
404 is configured to transmit data over a maximum range in the region of 1.1 to 1.25
metres through the user's body, which corresponds broadly to a transmission range of 1.2
to 1.3 metres in open air. The transmission range of the antenna 404 may be improved by
providing slots in the 0V plane of the PCB 406 and the skin sensing circuitry components
of the PCB 406. These slots reduce the effect of eddy-current induced reaction fields on
the telemetry circuitry of the electronics components 402.
In embodiments of the invention, the antenna 404 is configured for resonance at a frequency in the range of 12.8 to 13.2 MHz, and preferably in the range of 12.814MHz or 12.963MHz, with an inductance in the region of 2.5 μH and a resistance in the region of 4.10 Ohms. It will be appreciated that operation in this frequency range allows for low power consumption, resulting in prolonged battery life for a given battery volume. In some embodiments, the transmission bandwidth will be in the range of 149 kHz or 298 kHz. It will be appreciated that the frequency of resonance may be selected in accordance with available frequencies as defined by regulatory authorities.

In other embodiments of the invention, the antenna 404 is an RFID transponder configured to transmit the identifier using RF electromagnetic fields to transfer the identifier. The RFID transponder may be mounted on a substrate as an RFID tag, or can be sandwiched between layers of material. The RFID tag may be adhered/affixed/attached to, or embedded in, the eLabel 202 or the patch 100. Alternatively, the eLabel 202 may comprise, or consist of, the RFID tag.

The RFID transponder may operate at any frequency allocated for such systems, for example, low-frequency (generally in a range of 120-150 kHz), high-frequency (generally in a range of 10-20 MHz) or ultra-high frequency (generally in a range of 2-10 GHz).

In certain embodiments of the invention, the RFID transponder may be a passive RFID transponder, meaning that the RFID transponder does not require a local power source. In this case, the battery 408 and the activation switch 410 may not be required and the eLabel 202 may comprise no battery or power source. Instead, the RFID transponder may operate by propagation coupling or by inductive coupling.

In addition to the receiver 204, the user-wearable device may comprise a transmitter that is operable to emit an electromagnetic induction signal for interrogating the RFID transponder. The interrogation signal may be transmitted continuously, or periodically, or randomly, or at any other suitable intervals, or combinations thereof, over a predefined period.

For example, the transmitter comprised within the user-wearable device may emit, via an antenna, an interrogation signal comprising electromagnetic energy in the form of radio waves. The RFID transponder may then receive the interrogation signal and uses the energy contained therein to change the load on the transponder and reflect back an altered signal. In this manner, the RFID transponder may be powered and read by the
interrogation signal emitted by the receiver 204. The signal reflected back by the RFID transponder comprises the identifier and therefore provides a confirmation that a specific patch 100 is in use.

Alternatively, the RFID transponder may be an active or semi-active RFID transponder, in which case the RFID transponder is powered by a local power source. In this case, the battery 408 may provide the RFID transponder with the necessary power to transmit the identifier using radio waves, i.e., by emitting electromagnetic radiation at radio frequencies.

Regardless of the type of transmission used (e.g., magnetic induction, or passive, active or semi-active RFID transmission) the antenna 404 may be configured to encode the data transmitted. Such encoding can be accomplished by a signal modulation scheme as known in the art, including amplitude/phase/frequency modulation. The antenna 404 may additionally include circuitry configured to encode additional data or instructions and communicate with the receiver.

For any of the above-described types of transmission, the antenna 404 may include, or be coupled to, one or more of additional logic, memory and a processor. In such embodiments, an integrated circuit can be configured to store one or more of data, instructions, and information associated with the SmartPatch 201, the eLabel 202 and/or the patch 100 in the memory. Some or all of the stored information stored may be transmitted by the antenna 404 to the receiver 204. Based on this information, the receiver 204 and/or the remote processing unit 206 may determine a compliance profile and/or output an alert.

Additionally or alternatively, the integrated circuit may be configured to perform any other desirable functions. For example, the integrated circuit may be configured to process or manage data and information and/or modulate and demodulate a radio signal.

In embodiments of the invention, the eLabel 202 may be affixed to the patch 100 with an eLabel adhesive 414. The adhesive 414 may comprise a non-sensitizing polyacrylic pressure sensitive adhesive, for example, Durotak 387-2353 (Henkel). Assuming a 30gsm loading from both the patch 100 and the eLabel 202, the eLabel 202 comprises 21mg of the adhesive 414.

Fig 5 shows an exemplary schematic of the electronic components 402 according to embodiments of the invention. In these embodiments, the electronics components can
broadly be divided into four inter-connected subsystems (or circuits): an activation subsystem 501; a conditioning subsystem 502; a telemetry subsystem 503 which is in communication with the antenna coil 404; and a skin sensing subsystem 504.

The activation subsystem 501 causes the battery 408 to supply power to the telemetry subsystem 503 when an activation trigger is received from the activation switch 410, thereby placing the eLabel 202 in an operational state.

The conditioning subsystem 502 is configured to reduce electrical noise and maintain voltage levels in the telemetry subsystem 503 by decoupling capacitors in the telemetry subsystem 503. The capacitors provide a small but local energy store, which in the absence of the conditioning subsystem 502 may cause noise or variance in voltage levels, resulting in performance degradation.

When the eLabel 202 is in an operational state, the telemetry subsystem 503 is powered by the battery 408 and causes the antenna 404 to transmit data packets comprising the identifier of the eLabel 202 to the receiver 204. As discussed above, in embodiments of the invention the identifier may be transmitted via magnetic induction radio transmission. Alternatively, in further embodiments of the invention, the identifier may be transmitted via any wireless mode and/or standard and/or protocol of data communication, such as RF transmission, employing any known frequency band and modulation scheme. Exemplary standards include Bluetooth, Zigbee, WiFi or any other suitable transmission means.

The electronics components 402 may be configured to cause the antenna 404 to transmit the data packets in any suitable manner. For example, the antenna 404 may transmit the data packets continuously, periodically, or at random intervals whilst the eLabel 202 is in an operational state.

In embodiments of the invention, the telemetry subsystem 503 may be implemented using an ASIC. Alternatively, the telemetry subsystem 503 may be implemented using an Integrated Circuit (IC), for example, the NXP NxH2180 telemetry IC 503 (FXI-EC-0303-01). The telemetry IC 503 is programmed with firmware which controls the operation of the eLabel 202. The steps performed by the firmware are discussed in detail with respect to Fig 6.

In embodiments of the invention, the skin sensing subsystem 504 is configured to prevent activation of the eLabel 202 when the SmartPatch 201 is not in use. In this manner,
accidental triggering of the activation switch 410 before the SmartPatch 201 is affixed to a user's skin does not result in discharge of the battery 408. Any suitable means for sensing or detecting that the SmartPatch 201 is in contact with the user's skin may be used.

In certain embodiments of the invention, the skin sensing subsystem 504 detects whether the SmartPatch 201 is in contact with a user's skin and, if so, the activation subsystem 501 continues to cause the battery 408 to power the telemetry subsystem 503.

On the other hand, if the skin sensing subsystem 504 detects that the SmartPatch 201 is not in contact with a user's skin, the activation subsystem enters a 'storage' or 'sleep' state, in which the battery 408 does not power the telemetry subsystem 503. Hence, in this state the antenna 404 does not transmit an identifier.

Fig 6 is a flow diagram depicting a method 600 of operation of the firmware of the telemetry IC 503 in accordance with embodiments of the invention.

At block 602, the telemetry IC 503 is initiated or activated. This step incorporates lower-level power-on reset (POR), ROM bootloader and is performed on first application of power from the battery 408 to the inputs of the telemetry IC 503. As discussed previously, the power from the battery 408 may be applied to the telemetry subsystem 503 when the activation switch 410 is activated.

At block 604, the firmware causes the telemetry IC 503 to enter a low power sleep mode (or an ultra-low power mode) for a given period of time \( t \). After expiration of the period \( t \), the firmware causes the telemetry IC 503 to 'wake up' or re-enter an active state in which operation of the telemetry IC 503 continues.

At block 606, the firmware enables, or activates, the skin sensing subsystem 504. The firmware then monitors the skin sensing subsystem 504 over a period of time, for example, 5ms. Based on outputs from the skin sensing subsystem 504 during this period of time, the firmware produces a skin sensing measurement.

Based on the skin sensing measurement, the firmware determines whether the eLabel 202 is either not attached to a user's skin or attached to a user's skin. Furthermore, if the firmware determines that the eLabel 202 is not attached to a user's skin, the firmware may determine whether the eLabel 202 is operating in free space (i.e., the SmartPatch 201 has been removed from packaging) or whether the eLabel 202 is operating within the
Following performance of the measurement, the firmware may cause the telemetry IC 503 to 'sleep' for a period up to 50ms to recover before continuing operation at block 608.

At block 608, the firmware causes the antenna coil 404 to transmit the data comprising the identifier. In embodiments of the invention, the data comprising the identifier is transmitted using magnetic induction. In further embodiments of the invention, the data may be transmitted via any wireless mode and/or standard and/or protocol of data communication, such as RF transmission, employing any known frequency band and modulation scheme. Exemplary standards include Bluetooth, Zigbee, WiFi or any other suitable transmission means.

In embodiments of the invention, the firmware causes the antenna 404 to transmit the data comprising the identifier in a burst so that \( N_{b_{s}} \) packets are transmitted interspersed with randomised delays during which the telemetry IC 503 sleeps to conserve power. In alternative embodiments, the identifier may be transmitted by any other means, for example, at regular intervals or continuously over a predefined period.

As discussed with respect to Fig 2, the packet data may be formed from a unique or quasi-unique identifier of the eLabel 202. In embodiments of the invention, the identifier is based on an identifier assigned to the telemetry IC 503 during manufacture. The packet data may also comprise a sequence number or counter that increments or decrements after transmission, and/or results from the skin sensing.

At block 610, the firmware determines an elapsed period of time since initiation, \( T_{elapse_{a}} \), of the telemetry circuitry at block 602. The elapsed period, \( T_{elapse_{a}} \), is then compared to a predefined period. For example, the predefined period may be defined in configuration settings for the telemetry IC 503. If the elapsed period, \( T_{elapse_{a}} \), is determined to be greater than the predefined period, the firmware proceeds to time-out at block 610a and operation of the telemetry IC 503 ceases.

After time-out at block 610a, the eLabel 202 returns to 'sleep' or 'storage' mode. Reactivation of the eLabel 202 using the activation switch 410 is then required to return the eLabel 202 to an operational state.
If the elapsed period, $T_{\text{elapsed}}$, is determined to be less than or equal to the predefined period, operation of the telemetry IC 503 continues at block 612, at which an activation decision is made.

At block 612, the telemetry IC 503 makes the activation decision by determining whether the skin sensing measurement (obtained at block 606) indicates that the SmartPatch 201 is attached.

If the skin sensing measurement obtained at block 606 indicates that the SmartPatch 201 is attached, operation of the telemetry IC 503 returns to block 606 at which a further measurement is obtained.

On the other hand, if the skin sensing measurement obtained at block 606 indicates that the SmartPatch 201 is not attached, operation of the telemetry IC 503 continues at block 614 at which the firmware waits for a predefined period $T_{\text{time-out}}$ before returning to block 606.

In this manner, if a skin sensing measurement obtained at block 606 indicates that the SmartPatch 201 is not attached, operation of the telemetry IC 503 returns to block 606 a finite number of times before the time elapsed since initiation, $T_{\text{elapsed}}$, is greater than the predefined period causing operation of the telemetry IC 503 to time-out at block 610a.

Additionally or alternatively, a counter may be incremented/decremented each time the skin sensing measurement indicates that the patch is not attached. In this case, operation of the telemetry IC 503 may time-out after the transmission or skin sensing has been performed a predefined number of times for example, 5, 10, 15 or 20 times. It will be appreciated that the predefined number of times after which the telemetry IC 503 times out may be selected in accordance with the size of battery or the amount of power available for performing these steps before the battery power is discharged.

It will be appreciated that the blocks 602 to 614 represent functional steps performed by the firmware. These blocks may be implemented in sequence or may be combined to increase operational efficiency or reduce power consumption. For example, blocks 606, and 610 may be implemented as a compound block.

In alternative embodiments of the invention, the method 600 may be performed without the above-described skin-sensing steps. In this case, steps 606, 610, 610a and 612 are omitted. Additionally, or alternatively, steps 604 and 614 may also be omitted.
Accordingly, after activation, the firmware may cause the antenna coil 404 to transmit the data including the identifier continuously over a predefined period, or whilst the battery 408 can provide sufficient power to the antenna coil 404 for transmission of the data. Additionally, or alternatively, the firmware may cause the antenna coil 404 to transmit the data periodically, randomly, or at any other suitable intervals.

Fig 7 is a schematic of a user-wearable device in accordance with embodiments of the invention. As discussed with respect to Fig 2, the receiver 204 may be comprised within a hub 701. The user-wearable hub 701 may additionally comprise a processor 705.

In some embodiments, the user-wearable hub 701 may include a sensor or sensors and logic circuitry/algorithms for determining one or more of user gait, user movement, user proprioception and kinesthetic events. The user-wearable hub 701 may additionally or alternatively comprise any other sensors for detecting or measuring characteristics of the user or the drug delivered by the SmartPatch 201. Additionally or alternatively, a cellular telephone, a smart telephone or any other mobile communication device may be comprised within the user-wearable hub 701.

In embodiments of the invention, the hub 701 comprises a rechargeable battery 702, which provides power to the receiver 204. The battery 702 may be removable from the hub 701 for recharging. Alternatively, the battery 702 may be fixed to the hub 701 so that the hub 710 cannot be worn whilst recharging the battery 702.

In embodiments of the invention, the hub 701 is configured to be worn about a body appendage (for example, the arm or leg), or about the head, neck or waist of the patient or user. In embodiments of the invention, the hub 701 is configured to be worn in or attached to articles of the patient's or user's clothing. In the exemplary embodiment of Fig 8, the hub is a wrist-wearable hub 800 configured to be worn around a user's wrist and comprising additional functionality for telling the time.

As discussed in relation to Fig 2, in embodiments of the invention, the receiver 204 is configured to receive transmissions of the identifier of the eLabel 202 from the antenna 404. In embodiments of the invention, the receiver 204 may receive the data in response to transmission of an interrogation signal via an antenna comprised within the receiver 204.
The processor 705 may store the data received by the receiver 204 in the memory 203. In embodiments of the invention, the data received comprises an identifier and the processor 705 may compare the identifier received by the receiver 204 to identifiers previously received within a predefined duration. Based on this comparison, the processor 705 may then determine whether a given identifier has been received for a period longer than an expected life-time of the SmartPatch 201. In this case, the processor 705 may determine that the SmartPatch 201 has not been replaced as required and the processor 705 may output an alert to the user, care-giver or remote data processing unit indicating that a replacement SmartPatch 201 is required.

Additionally or alternatively, based on the comparison, the processor 705 may determine that multiple identifiers have been received indicating that more than one SmartPatch 201 is attached to the user. In this case, the processor 705 may output a warning or indication that a possible over-dose has been administered. For example, the processor 705 may communicate with the remote data processing unit 206, which may in turn alert the user, a health professional or a care giver.

In embodiments of the invention, the hub 701 comprises a transmitter 704 that is communicably coupled to the receiver 204 and/or the memory 203. In certain embodiments of the invention, the transmitter 704 may be the antenna used to transmit the interrogation signal. Alternatively, the hub 701 may comprise the transmitter 704 in addition to the antenna used to transmit the interrogation signal.

The transmitter 704 may transmit data to the remote processing unit 206 in accordance with the identifiers received from the eLabel 202. The data transmitted by the transmitter 704 may also be indicative of a user identification. Whilst in Fig 7, the transmitter 704 is depicted as a separate element to the receiver 204, it will be appreciated that, in certain embodiments of the invention, the transmitter 704 and the receiver 204 will be a single unit.

Additionally or alternatively, the transmitter 704 may transmit the received identifier to the remote data processing unit 206 without performing any further analysis of the received identifiers. In this case, any processing of the data received from the antenna 404, for example the above-described steps, may be performed by the unit 206. Any alert to be issued to the user may be transmitted to the user-wearable hub 701 by the remote unit 206.
In embodiments of the invention, the processor 705 may be further configured to monitor location, movement and other user data such as temperature, and to transmit this data to the remote data processing unit 206.

Based on the data received from the transmitter 704, the remote processing unit 206 may determine that an alert or warning needs to be output. For example, if it is determined that no eLabel identifiers have been received for a given user (indicating that the user is not wearing a SmartPatch 201); or that multiple eLabel identifiers have been received for a given user (indicating that multiple SmartPatches 201 have been applied to a user giving rise to a risk of over-medication), the remote processing unit 206 may output a warning, message or alert to the patient or user, and/or to a caregiver or a medical practitioner. Such warning message or alert may be supplied directly to the patient or user, and/or to a caregiver or a medical practitioner, or through an intermediary, such as a call or monitoring center.

In embodiments of the invention, the user-wearable hub 701 comprises position sensing electronic or electromechanical devices. In some embodiments, the position sensing electronic device comprises a Global Satellite Navigation (GSN) receiver and a wireless chip set to enable data communications with the wireless phone network. The hub 701 may further comprise an inertial sensor or sensors for user motion and/or state detection and/or analysis, which motion and/or state may comprise one or more of gait, balance, sleep, falls, location, proprioception and kinesthetics. Exemplary motion and/or state detection devices comprise inertial sensors such as accelerometers and gyroscopes, and physical sensors such as pressure and temperature.

In embodiments of the invention, the GSN receiver receives a Global Positioning System (GPS) signal. In some embodiments, the GSN receiver receives a Global Orbiting Navigation Satellite System (GLONASS) signal. In some embodiments, the GPS receiver receives both GPS and GLONASS signals. Down conversion, code-processing and navigation-processing routine/code can be constructed from conventional designs as known to the art.

In embodiments of the invention, the positional sensing is implemented via inertial sensors, such as accelerometers, such as Microelectrochemical (MEMS) implemented accelerometers. The positional sensing may be relative, i.e., from a user starting point, such as within the user's home, and motion is detected, analyzed and uplinked as motion relative to the starting point.
In some embodiments, cell phone triangulation may additionally be used with inertial sensors, and/or the GSN receiver, or alternatively used independently or with one or more of the other position, state or motion sensors. As is known in the art, cell phone triangulation comprises determining three or more cell phone or radio towers (or base stations) that receive a signal from the cell phone. Based on knowledge of the coverage radius of the cell phone towers, and the strength of the signal received from the cell phone at each of the cell phone towers, the position of the cell phone can be determined.

In embodiments of the invention, medication compliance data, or any one or all of the user location, position, gait, proprioception, kinesthetic or movement data are collected over time, and may be analyzed. Such analysis may be performed by the processor 705. Additionally or alternatively, the processor 705 may cause the antenna 704 to transmit the data to the remote processing unit 206 for analysis.

In embodiments of the invention, the user-wearable hub 701 may further include a user-activatable alert button or interface, so that the user can summon help independently of the data output by the transmitter 704.

In embodiments of the invention, analysis of the data may include processing, for example, by computer, and further by specific algorithms developed for such data, and/or may be reviewed by a clinician, caregiver or family member. The data may be stored, in raw and/or processed form, for later use. The data may be used by the clinician, caregiver or family member to diagnose, or assist in the diagnosis, of a nascent disease or condition, or in following the progress of an existing, or known diagnosis, such as Alzheimer's. The data may be used to adjust the therapy, such as by increasing or decreasing dose amount, timing, frequency or combinations thereof. The data may be used iteratively or singularly. Analysis and presentation of data may be implemented as described in co-pending PCT application PCT/EP2012/050160, filed 5 January 2012.

In embodiments of the invention, the patch adherence and/or medication compliance aspects (for example whether the SmartPatch 201 has been operating for an allowable period of time; whether the SmartPatch 201 is 'in date'; and/or whether the time since manufacture of the SmartPatch is greater than the shelf-life of the battery 408), or any one or all of the user location, position, gait, proprioception, kinesthetics or movement, are detected by the compliance monitoring and/or user care monitoring elements, and the result is uplinked to clinician, caregiver and/or family member by any one of a variety of wireless or wired communications means, such as cell or wired phone voice, cell or wired
phone data, SMS, VoiP, fax, world wide web or the like. This information may further comprise a variety of formats, such as graphic display, oral or verbal (written) messages, audio or visual warnings or status indicators (for example, red, yellow or green light displays), or any other human perceptible message.

In embodiments of the invention, the data received from the antenna 404, position data and accelerometer data (if present) may be uploaded to a remote processing unit 206, for example a server, and can be analysed. Based on the data, alerts may be provided to the caregiver and/or physician if the user strays away from a defined area, and/or falls. Alerts are preferably provided in real time, but some or all of the data (including compliance data) may be aggregated, summarized and reported periodically, such as daily, weekly or monthly. The system can also be configured to supply alerts to the user, emergency responders, medical professionals, and/or caregivers.

In embodiments of the invention, the present invention comprises a patient or user care method, which comprises: (A) the steps of: (i) providing an adherent transdermal therapeutic patch 100 comprising a backing layer 101, medication reservoir 102, adhesive layer 103, electronics components 402 and an antenna 404; (ii) providing a user-wearable receiver 204 operable to receive data transmitted by the antenna 404; (iii) causing the antenna 404 to transmit, in any of the ways contemplated in this disclosure, data comprising an identifier, wherein the identifier is a unique or quasi-unique identifier of the patch 100; and (iv) causing the receiver 204 to output data in accordance with the data received from the antenna 404; and (B) (i) providing a user-wearable hub 701 comprising a receiver 204 having a power source, logic circuits, processor, global navigation sensing receiver, and/or one or more inertial sensors and a wireless uplink (such as analog or digital telephony) chipset, and (ii) monitoring remotely, via the wireless uplink, one or more of the user’s absolute position on the earth, relative position with respect to a predefined starting point, user gait, user fall alert or status and user proprioception and/or kinesthetic events.

In embodiments of the invention, the system operates as follows. The SmartPatch 201 is applied to the user by a caregiver or family member, and the user-wearable receiver 204 is secured appropriately to the user, and switched on. Once the eLabel 202 is adhered to the user’s skin, the antenna 404 transmits data including a unique or quasi-unique ID code to the receiver 204. As discussed previously, the ID code may be transmitted using magnetic induction. Alternatively, the ID code may be transmitted using RF transmission.
As discussed previously, the antenna 404 may transmit the ID code continuously, periodically, at random intervals or in any other suitable manner.

The receiver 204 may be comprised within a user-wearable hub 701 which additionally comprises a processor 705. On receipt of data from the antenna 404, the processor 705 may process the received data. For example, the processor 705 may store a time stamp indicative of time at which an identifier is received from the antenna 404. Based on this time stamp, the receiver may then determine an elapsed time since an identifier was received. If this elapsed time is greater than a predefined period, the processor 705 may output data indicating that the user appears to not be wearing a SmartPatch 201.

Additionally or alternatively, the processor 705 may look up time stamps of the previous occasions on which a given identifier was received. In this manner, the processor 705 can determine whether a given SmartPatch 201 is operating for an allowable period of time, i.e., that a single SmartPatch 201 is not left adhered to the user for more than the specified period. Additionally or alternatively, the processor 705 may process the data to determine whether more than one SmartPatch 201 is applied at any given time.

In embodiments of the invention, the data transmitted by the antenna 404 may comprise data indicative of an expiry date of the drug supplied in the reservoir layer of the SmartPatch 201. In this case, the processor 705 may compare the received data to data stored in the memory 203 to determine that the drug has not passed its expiry date.

In embodiments of the invention, the data are appropriately converted for data transmission, and uplinked via the wired or wireless connection, to either a local hub or base station, or directly via the public wireless network to a server for further processing.

It will be appreciated that in some exemplary embodiments, the above processing may be performed at the remote data processing unit 206 instead of, or in addition to, at the user-wearable hub 701.

In embodiments of the invention, the remote data processing unit 206 may further process the data, and provide a compliance signal to the one or more of the user, caregiver and clinician, and/or may store the data for later use. If the drug product comprised in the SmartPatch 201 is found to have expired, or if no data is received from the antenna 404, the server may send an alert signal to one or more of the user, the remote clinician, caregiver and family member advising that no therapy is occurring.
In some embodiments of the present invention, the system operates as follows. The user-worn hub 701 is secured to the user by the caregiver, and switched on. User motion and/or location is monitored and detected, and predefined events set off one or more data outputs or alerts. Such events may be fall detection, a specific user motion (or absence thereof) and a user location outside of a predetermined location of range of locations. Alerts may be provided remotely to clinician, caregiver, family member or emergency responder.

In embodiments of the invention, the system operates as follows. A SmartPatch 201 is applied to the user by the caregiver or family member, and the user-wearable hub 701 comprising the receiver 204 is also secured appropriately to the user, and switched on. The antenna 404 on the SmartPatch 201 transmits data including a unique (or quasi-unique) identifier such as an ID code and the receiver 204 receives the transmitted data. As discussed previously, the identifier may be transmitted using magnetic induction. Alternatively, the identifier may be transmitted using RF transmission.

The processor 705 comprised within the user-wearable hub 701 processes the received data. In certain embodiments, the receiver 204 looks up a time stamp of the unique code to assess whether the SmartPatch 201 meets specified requirements, for example whether the SmartPatch 201 has been operating for an allowable period of time and/or whether the SmartPatch 201 is 'in date'. The processor 705 may determine whether the SmartPatch 201 is 'in date' by accessing stored values associated with the drug product comprised within the SmartPatch 201. Additionally or alternatively, the processor 705 may determine whether the SmartPatch 201 is 'in date' by comparing a battery shelf-life associated with the SmartPatch to the date of manufacture of the SmartPatch 201.

In certain embodiments, the data may be appropriately converted for data transmission, and uplinked via the wired or wireless connection, to either a local hub or base station, or directly via the public wireless network to the remote data processing unit 206.

The server may then further process the data, and provide a compliance signal to the user, caregiver or clinician, or may store the data for later use. If the SmartPatch is found to have expired, or an identifier transmission is not received by the receiver 204, the processor 705 may send an immediate alert signal to the user, remote clinician, caregiver or family member advising that no therapy is occurring. User motion and/or location may additionally be monitored and detected, and predefined events set off one or more alerts.
Such events may be fall detection, a specific user motion (or absence thereof) and a user location outside of a predetermined location of range of locations.

In some embodiments of the invention, the SmartPatch 201 may comprise a single, contiguous or non-contiguous but co-applied, user-wearable substrate with a power source, logic circuits, processor, a wireless uplink (such as analog or digital telephony) and one or both of a global position sensing receiver, and/or an inertial sensor and chipset.

In some embodiments, the SmartPatch 201 may comprise one or more of additional sensors for determining or obtaining data relating to the user (such as impedance, temperature, oximetry, and cardiac data). In such embodiments, data such as hydration status, temperature, oxygen level and/or heart data may be supplied by the SmartPatch 201, and monitored remotely via the wireless uplink. In some embodiments, the uplink may comprise a short range protocol such as ZigBee, Bluetooth, WiFi etc., and may communicate to a user belt-worn device or desktop device in the user's home. These devices, in turn may be configured to communicate over the wireless or wired (POTS) telephone system to a server for processing and analysis, and results delivered to one or more of the user, a clinician, caregiver, relative and emergency responder.

In embodiments of the invention, the SmartPatch 201 may signal its operational status by periodic uplink (wireless telephony, WiFi, via world wide web and/or short range wireless protocol) to hub or desktop computing device. Optional physiological sensors, such as body temperature sensor, medication delivery sensor, mechanical contact sensor or inertial sensor may additionally or alternatively be used to signal compliance and operation. Optional physiological sensors may also supply physiological data for processing, analysis and recording.

In embodiments of the invention, the SmartPatch 201 comprises a single or contiguous user-wearable substrate, and provides for controlled delivery of a therapeutic agent, for example rivastigmine, over a period of greater than one day, such as 2, 3, 4, 5, 6 or 7 days. In such embodiments, the transdermal therapeutic system could additionally comprise any or all of the functionalities as described herein.

Embodiments of the present invention may comprise a patient/user management system comprising a user-adherent SmartPatch 201 comprising one or more of: control electronics 402; an antenna 404 configured to transmit data using magnetic induction or RF transmission; and a user-wearable hub 701 comprising a receiver 204 configured to
receive the data transmitted by the antenna 404. The system may further comprise an active, such as a medication. The system may further comprise a GPS receiver, and data uplink means to uplink data from the antenna 404 and said GPS receiver to a remote data link. The remote data link comprises a computing device.

Embodiments of the invention may comprise a method for monitoring compliance with a medication regimen. The method comprises the steps of: (i) providing an adherent SmartPatch 201 comprising: (ii) a medication; control electronics 402; an antenna 404 configured to transmit data; (iii) causing the antenna 404 to transmit, in any of the ways contemplated in this disclosure, data comprising a unique identifier determinative of a specific medication and dose; and (iv) causing the receiver 204 to receive the transmitted data; and (v) based on the data received from the antenna 404, outputting display data from the user-wearable hub 701. The display data may be provided directly via the user-wearable hub 701, or indirectly to a caregiver, clinician or relative via a data link/remote computer or server arrangement.

Embodiments of the invention may comprise a user location method, the method comprising: (i) providing a user-wearable hub 701 comprising a receiver 204 having a power source, logic circuits, processor, global navigation sensing receiver, and/or one or more inertial sensors and a wireless uplink (such as analog or digital telephony) chipset, and (ii) monitoring remotely, via the wireless uplink, one or more of the user's absolute position on the earth, relative position with respect to a predefined starting point, user gait, user fall alert or status and user proprioception and/or kinesthetic events.

Fig 9 is a block diagram illustrating an exemplary computing system 840 that may be employed to implement processing functionality for various aspects of the current technology such as the user-wearable hub 701 or the remote data processing unit 206 (for example, as one or more of a user/client device, media server, media capture server, media rules server, rules store, media asset library, activity data logic/database, gaming console, combinations thereof, and the like). Those skilled in the relevant art will also recognize how to implement the current technology using other computer systems or architectures.

Computing system 840 may comprise, for example, a user device such as a desktop, mobile phone, tablet device, personal entertainment device, cameras, microphones, DVR, medicament dispensing device, and so on, a mainframe, server, or any other type of special or general purpose computing device as may be desirable or appropriate for a
given application or environment. In some embodiments herein, computing system 840 comprises gaming functionalities. Computing system 840 may include one or more processors, such as a processor 804. Processor 804 can be implemented using a general or special purpose processing engine such as, for example, a microprocessor, microcontroller or other control logic. In this example, processor 804 is connected to a bus 806 or other communication medium.

Computing system 840 may also include a main memory 808, such as random access memory (RAM) or other dynamic memory, for storing information and instructions to be executed by processor 804. It will be appreciated that the main memory 808 may be the same as memory 203. Alternatively, the main memory 808 may be distinct from memory 203.

The main memory 808 may be used for storing temporary variables and/or other intermediate information during execution of instructions to be executed by processor 804. The computing system 840 may include a read only memory ("ROM") or other static storage device (not shown) coupled to bus 806 for storing static information and instructions for processor 804.

The computing system 840 may also include information storage mechanism 810, which may include, for example, one or more of a media drive 812 and a removable storage media 818. The media drive 812 may include a drive or other mechanism to support fixed or removable storage media, such as a hard disk drive, a floppy disk drive, a magnetic tape drive, an optical disk drive, a CD or DVD drive (R or RW), or other removable or fixed media drive. The storage media 818 may include, for example, a hard disk, floppy disk, magnetic tape, optical disk, CD or DVD, or other fixed or removable medium that is read by and written to by media drive 812. As these examples illustrate, the storage media 818 may include a computer-readable storage medium having stored therein particular computer software or data.

The computing system 840 may also include a communications interface 826. The communications interface 826 can be used to allow software and data to be transferred between computing system 840 and external devices. Examples of communications interface 826 can include a modem, a network interface (such as an Ethernet or other NIC card), a communications port (such as, for example, a USB port), a PCMCIA slot and card, etc. Software and data transferred via communications interface 826 are in the form of
signals which can be electronic, electromagnetic, optical, or other signals capable of being received by communications interface 826.

These signals may be provided to communications interface 826 via a channel 828. This channel 828 may carry signals and may be implemented using one or more of a wireless medium, wire or cable, fiber optics, or other communications medium. Some examples of a channel include a phone line, a cellular phone link, an RF link, a network interface, a local or wide area network, and other communications channels. Essentially any physical layer connectivity and communications protocol may be employed. In some embodiments, signals are conducted wirelessly, and may employ any suitable carrier frequency, modulation scheme and protocol, such as BlueTooth, ZigBee, CDMA, GSM and the like. Data may be stored and accessed in any manner known to the art, including local storage, remote servers and cloud computing.

In this document, the terms "computer program product" and "computer-readable storage medium" may be used generally to refer to media such as, for example, the main memory 808, the storage device 818, or the storage unit 822. These and other forms of computer-readable storage media may be involved in providing one or more sequences of one or more instructions to processor 804 for execution. Such instructions, generally referred to as "computer program code" (which may be grouped in the form of computer programs or other groupings), when executed, enable the computing system 840 to perform features or functions of embodiments of the current technology.

In an embodiment where the elements are implemented using software, the software may be stored in a computer-readable storage medium and loaded into the computing system 840 using, for example, the removable storage drive 810, the drive 812 or the communications interface 826. The control logic (in this example, software instructions or computer program code), when executed by the processor 804, causes the processor 804 to perform the functions of the technology as described herein.

In some embodiments, the computing system 840 is configured to comply with applicable regulatory requirements of health authorities. For example, in the US, the computer system 840 can implement appropriate encryption technology to comply with the Food and Drug Administration’s regulations on electronic records as set forth in FDA 21 CFR Part 11.
It will be appreciated that, for clarity purposes, the above description has described embodiments of the technology with reference to different functional units and processors. However, it will be apparent that any suitable distribution of functionality between different functional units, processors or domains may be used without detracting from the technology. For example, functionality illustrated to be performed by separate processors or controllers may be performed by the same processor or controller. Hence, references to specific functional units are only to be seen as references to suitable means for providing the described functionality, rather than indicative of a strict logical or physical structure or organization.

Although a feature may appear to be described in connection with a particular embodiment, one skilled in the art would recognize that various features of the described embodiments may be combined. Moreover, aspects described in connection with an embodiment may stand alone, or may be combined with aspects or elements of other embodiments.
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Claims:

1. A transdermal therapeutic patch comprising:
   an antenna; and
   control electronics configured to cause the antenna to transmit an identifier
   using magnetic induction;
   wherein the antenna and the control electronics are affixed to the patch,
   and the patch is configured to be removably attachable to a user.

2. The patch of claim 1, wherein the antenna is configured to transmit the identifier
   over a maximum range of 1.1 to 1.25 metres.

3. The patch of claim 1, wherein the antenna is configured to operate at a frequency
   in the range of 12.8 to 13.2 MHz.

4. The patch of claim 1, wherein the antenna is a double-sided coil antenna.

5. The patch of claim 1, wherein the control electronics are configured to cause the
   antenna to transmit the identifier periodically.

6. The patch of claim 1, further comprising:
   a power supply configured to power the antenna transmission for a period
   in the range of 24 to 72 hours.

7. The patch of claim 6, wherein the power supply is a 1.5V printed battery.

8. The patch of claim 6, further comprising:
   an activation switch configured so that triggering the switch activates the
   control electronics to cause the antenna to transmit the identifier.

9. The patch of claim 8, wherein the control electronics are further configured to:
   determine whether the patch is attached to a user; and
   if the control electronics determine that the patch is not attached to a user,
   to cause the antenna to cease transmission of the patch identifier.

10. The patch of claim 1 wherein the transdermal therapeutic patch comprises
    rivastigmine medication.
A system for monitoring drug administration, the system comprising:

- a transdermal therapeutic patch comprising an antenna and control electronics configured to cause the antenna to transmit an identifier using magnetic induction; and
- a user-wearable receiver configured to receive the patch identifier transmitted by the patch antenna.

12. The system of claim 11, wherein the user-wearable receiver comprises a rechargeable power supply.

13. The system of claim 11, wherein the user-wearable receiver comprises a transmitter, and the user-wearable receiver is configured to:

- determine whether an identifier has been received from the patch antenna; and
- responsive to the determination, to cause the transmitter to transmit data to a remote data processing unit.

14. The system of claim 11, wherein the user-wearable receiver further comprises one or more of:

- a motion sensor;
- a fall detection sensor;
- a temperature sensor;
- a location sensor; and
- a user-activatable alert.

15. The system of claim 11, further comprising a memory in communication with the user-wearable receiver.

16. A method of transmitting data from a transdermal therapeutic patch, the method comprising:

(a) detecting activation of the patch;
(b) determining whether the transdermal therapeutic patch is affixed to a user, and if so:
(c) causing an antenna coil to transmit an identifier associated with the patch using magnetic induction.
17. The method of claim 16, wherein if the transdermal therapeutic patch is determined not to be affixed to a user, the method comprises:
   (a) determining an elapsed period since the activation of the patch was detected;
   (b) if the elapsed period is less than or equal to a predefined threshold, repeating step (b); and
   (c) if the elapsed period is greater than the predefined threshold, deactivating the patch.

18. A system for monitoring compliance with a medication regimen, the system comprising:
   a transdermal therapeutic patch for administering a medication to a user, the transdermal therapeutic patch comprising:
   an antenna; and
   control electronics configured to cause the antenna to transmit an identifier.

19. The system of claim 18, wherein the control electronics are configured to cause the antenna to transmit the identifier using magnetic induction.

20. The system of claim 18, wherein the control electronics are configured to cause the antenna to transmit the identifier using radio frequency transmission.

21. The system of claim 20, wherein the control electronics are configured to cause the antenna to transmit the identifier using either active or passive RFID transmission.

22. The system of claim 18, further comprising a user-wearable receiver configured to receive transmissions from the antenna.

23. A kit for medication delivery, the kit comprising:
   a plurality of patches according to claim 1 and/or a plurality of systems according to claim 18; and
   a user-wearable receiver configured to receive transmissions from the antenna.

24. A patient management system comprising:
   a transdermal therapeutic patch according to claim 1; and
a user-wearable receiver configured to receive transmissions from the antenna.

25. A method for monitoring compliance with a medication regimen, the method comprising:
    providing a patient management system according to claim 24;
    receiving, at the user-wearable receiver, data transmissions from the patch antenna; and
    outputting data in accordance with the received transmissions.

26. The method of claim 25, wherein outputting data in accordance with the received transmissions comprises outputting, at the receiver, audio and/or visual data.

27. The method of claim 25, wherein outputting data in accordance with the received transmissions comprises transmitting data to a remote processing unit.

28. The method of claim 27, further comprising operating the remote processing unit to output an alert based on the data received from the receiver.
FIG. 3

2/6

300

Activate eLabel

302

Transmit identifier

304

Receive identifier

306

Transmit data to remote unit

308

FIG. 4a

FIG. 4b
FIG. 6

600

Activation

602

Delay

604

Skin sensing

606

Transmit

608

Elapsed time $T_{\text{elapsed}} >$ predefined value

610

YES

Time out

610a

NO

Activation decision

612

NO

Delay for $T_{\text{retry}}$

614
FIG. 9

- Processor 804
- Memory 808
- Storage devices 812
  - Media drive
  - Storage unit I/F 820
- Removable storage media 818
- Storage unit 822
- Communications I/F 826
- Channel 828
- Bus 806

Arrows indicating connections and data flow.
**INTERNATIONAL SEARCH REPORT**

**PCT/US2013/032170**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61M35/00 A61K9/70 A61M37/00

**ADD.**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
A61M A61K G06F

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

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

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</thead>
</table>

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

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

Date of the actual completion of the international search: 16 May 2013

Date of mailing of the international search report: 24/05/2013

Name and mailing address of the ISA:
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NL-2280 HV Rijswijk
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Fax. (+31-70) 340-3016

Authorized officer:
Przykutta, Andreas
<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
**INTERNATIONAL SEARCH REPORT**

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

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

1. **X** Claims Nos.: 16, 17

   because they relate to subject matter not required to be searched by this Authority, namely:

   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. **□** Claims Nos.: 

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

3. **□** Claims Nos.: 

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

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

This International Searching Authority found multiple inventions in this international application, as follows:

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

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

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

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

**Remark on Protest**

- **□** The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

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

- **■** No protest accompanied the payment of additional search fees.
<table>
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<th>Publication date</th>
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<tr>
<td>US 2002072733 A1</td>
<td>18-11-2004</td>
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<td>WO 2009126653 A1</td>
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