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DESIGN AND MANUFACTURE OF NONELECTRONIC, ACTIVE-INFUSION PATCH AND DEVICE FOR TRANSDERMAL DELIVERY ACROSS SKIN

CROSS-REFERENCE TO RELATED APPLICATION

5 The present application claims the benefit of U.S. Provisional Application Serial No. 61/744,636, filed October 1, 2012, which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

10 The present invention pertains to embodiments for the design and manufacture of active-infusion patch devices. Embodiments of the invention can include an actuating device and a volume of therapeutic drug and/or cosmetic formulation disposed within separate compartments that are connected through a membrane. One embodiment of the actuating device includes an expanding hydrogel that can expand at a constant or a fixed rate to deliver a constant dosing rate of the therapeutic drug and/or cosmetic formulation. In a further embodiment, the patch device can be operatively connected to at least one microneedle or a microneedle plate for skin poration to enhance delivery across skin.

BACKGROUND OF THE INVENTION

20 The most common routes for drug delivery are by oral administration, hypodermic injection, and transdermal delivery. Transdermal delivery is usually painless when compared to hypodermic injection and does not generate dangerous medical waste or pose a risk of disease transmission from needle reuse, which is common in developing countries (Prausnitz *et al.*, 2004). Transdermal delivery also has some advantages over oral routes, which often have poor drug absorption or results in enzymatic degradation in the gastrointestinal tract or liver (Plapied *et al.*, 2011). Transdermal drug delivery devices are typically noninvasive/minimally invasive, can be self-administered, and often result in a high degree of patient compliance. They can also provide an inexpensive drug delivery system with capacity for long-term controlled release.

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The United States Food and Drug Administration (USFDA) approved the first transdermal patch in 1981 for scopolamine, a drug that suppresses nausea and vomiting from motion sickness (Gorden *et al.*, 2003). In the United States market, more than 35 transdermal products were introduced during the last two decades, generating total sales of USD 5.7 billion in 2006 (Srodin, 2007). The market is expected to continue to increase as the use transdermal delivery devices are utilized with more substances.

Recently, the advantage of continuous drug delivery has drawn considerable attention over conventional short-term single dose delivery devices, such as those described in U.S. Published application nos. 2007/0225676, 2009/0099502, 2009/0030365, and 2011/0288485. In fact, much research has been done indicating that there are some advantages to continuous drug delivery. For example, research has shown that dyskinesia levels, a motor complication of Parkinson's disease patients, when treated with continuous subcutaneous delivery of ropinrole was lower than that of patients having twice daily oral administration (Stockwell *et al.*, 2008). Clinical studies have also shown that 63% of cancer patients preferred the use of transdermal delivery of fentanyl administrated every 3 days over chronic oral morphine analgesia in pain killing (Sloan *et al.*, 1998). For patients suffering from diabetes mellitus, continuous delivery of human insulin (short acting/regular) could be better than single dose delivery of insulin analogues (long acting), as studies have revealed that the injection of insulin analogues may lead to unexpected outcome (Hemkens *et al.*, 2009). In short, continuous drug delivery has offered some advantages over single dose/bolus therapy in different biomedical applications. Designing a continuous delivery patch that can be loaded with one or more of a variety of drugs and/or analgesics gives rise to a large market potential and greater patient convenience.

Conventional transdermal patches consist of three main components: a backing membrane preventing the drug from dehydration and contamination; a drug reservoir for drug storage therein; and a permeable membrane, directed towards and/or in contact with the skin, that controls the drug diffusion rate across skin. The permeable membrane of the patch can usually be adhered to the skin. The effectiveness of transdermal delivery is usually limited by drug permeability across

the lipoidal barrier of the stratum corneum. Drugs that are presently administered across the skin often share three constraining characteristics: low molecular mass (< 500 Da), high lipophilicity (oil soluble), and small required dosage (*i.e.*, usually only up to milligram amounts). Opening the transdermal delivery route for large hydrophilic drugs and vaccines is a major challenge, but one that, if overcome, will revolutionize healthcare and medicinal practices. The transdermal delivery of vaccines can avoid not only the use of hypodermic needles (Clenn *et al.*, 2006), but has the potential to improve immune response by targeting the delivery to immunogenic Langerhans cells in skin (Prausnitz *et al.*, 2008).

Most of the transdermal systems currently used are coupled with passive infusion (*i.e.*, drug delivery through a barrier by diffusion), which may not be applicable when significant and precise amounts of drug release are required. Active infusion, a method of drug delivery by forcing a drug-containing liquid into tissues by mechanical means, is thereby a preferred solution. Indeed, studies have shown active infusion with micro-needles is a feasible method for drug delivery (Sivamani *et al.*, 2005). McAllister *et al.* has demonstrated the use of micro-needles and pressure force (10 psi) to lower 70% of the normalized blood glucose level by insulin delivered *in vivo* (McAllister *et al.*, 2003). Regulated drug delivery devices were employed by Roxhed *et al.* with the device having a printed circuit board and Richter *et al.* used an autonomous pump (Roxhed *et al.*, 2008 and Richter *et al.*, 2004). However, the involvement of the use of battery power hampers the portable usage of the device of Roxhed's design and the pump of Richter's device is probably too bulky to be portable for daily use. The ability to easily sterilize the drug ampoule or other reservoir in patch devices is yet another concern.

The development of a small, disposable, and safe transdermal patch with long-term and consistent or steady drug delivery is therefore highly desirable. The embodiments of the subject invention address these issues in an advantageous design that can be easily manufactured and employed with a variety of substances.

BRIEF SUMMARY OF THE INVENTION

The present invention describes transdermal patches and related devices for delivery of therapeutic drugs and/or cosmetic formulations across a skin barrier at a controlled rate by a nonelectronic means. The patch device can utilize a non-electronic actuating device and a volume of therapeutic drug and/or cosmetic formulation, which can be disposed in separate compartments that are connected by a membrane. In a specific embodiment, the actuating device utilizes an expanding hydrogel that expands at a constant rate to deliver a constant rate and/or fixed amount of a therapeutic drug and/or cosmetic formulation. The patch device can be further attached to at least one microneedle or microneedle plate for skin poration to enhance delivery across skin.

BRIEF DESCRIPTION OF DRAWINGS

In order that a more precise understanding of the above recited invention can be obtained, a more particular description of the invention briefly described above will be rendered by reference to specific embodiments thereof that are illustrated in the appended drawings. The drawings presented herein may not be drawn to scale and any reference to dimensions in the drawings or the following descriptions are specific to the embodiments disclosed. Any variations of these dimensions that will allow the subject invention to function for its intended purpose are considered to be within the scope of the subject invention. Thus, understanding that these drawings depict only typical embodiments of the invention and are not therefore to be considered as limiting in scope, the invention will be described and explained with additional specificity and detail through the use of the accompanying drawings in which:

Figures 1A, 1B, 1C, and 1D illustrate one embodiment of a patch device of the subject invention, where Figure 1A is a top plan view that illustrates one embodiment of the structures of the drug reservoir and Figure 1B is a top plan view that illustrates one embodiment of the water and hydrogel reservoirs formed as part of the body piece. Figure 1C is a cross-sectional view taken along line A-A' in Figure 1A, and Figure

1D is a cross-sectional view taken along line B-B' in Figure 1B showing details of certain features.

Figures 2A, 2B, 2C, and 2D illustrate another embodiment of a patch device of the subject invention, wherein Figure 2A is a top plan view showing the water and hydrogel reservoirs of the device and Figure 2B is a top plan view showing a turnable break gate cover. Figure 1C is a cross-sectional view taken along line C-C' in Figure 2A, and Figure 2D is a cross-sectional view taken along line D-D' in Figure 2B.

Figures 3A, 3B, 3C, and 3D illustrate yet another embodiment of a patch device of the subject invention, wherein Figure 3A is a top plan view showing the structures of the water and hydrogel reservoirs of the device and Figure 3B is a top plan view showing the switch cover. Figure 3C is a cross-sectional view taken along line E-E' in Figure 3A, and Figure 3D is a cross-sectional view taken along line F-F' in Figure 3D.

Figures 4A and 4B are photographs of a polydimethyl siloxane elastic membrane, according to embodiments of the subject invention.

Figure 5 is a table demonstrating the swelling characteristics for an uncoated hydrogel, according to embodiments of the subject invention, over a time period of 4 hours.

Figure 6 is an SEM image of a cross-sectional view of a polydimethyl siloxane-coated hydrogel.

Figure 7 is a table demonstrating the swelling characteristics of uncoated and spray-coated hydrogels over a time period of 5 hours.

Figures 8A, 8B, and 8C are photographs showing a zeolite, plastic, and commercial microneedle plates, respectively.

Figure 9 is an exploded view of one embodiment of an active infusion transdermal microneedle patch, according to the subject invention. In this embodiment, part of the activator compartment and actuator compartment are formed directly into the body piece.

Figure 10 is an exploded view of another embodiment of an active infusion transdermal microneedle patch, according to the subject invention. In this

embodiment, the actuator compartment and activator compartment are formed as part of an insert that can be operably connected to the body piece.

Figures 11A and 11B are front and rear plan views, respectively, of certain components used in an embodiment of the active infusion transdermal microneedle patch, shown in Figure 10.

Figure 12 is an exploded view of yet another embodiment of an active infusion transdermal microneedle patch, according to the subject invention. This embodiment utilizes an insert placed against the body piece to form part of the actuator and activator compartments that are in operable communication.

Figures 13A, 13B, and 13C illustrate the operation of certain interior components of the embodiment in Figure 12. Figure 13A shows the device when gates are closed and Figure 13B shows the device with the gates opened. Figure 13C shows the embodiment assembled with the key unattached.

Figure 14 illustrates alternative boss shape embodiments that can be used for the lock and key components of an embodiment of an active infusion transdermal microneedle patch, according to the subject invention.

Figure 15 shows *in-vitro* study results of the effect of a number of hydrogel PDMS coatings on drug delivery efficiency.

Figure 16 shows *in-vitro* study results of DFS delivery with a patch, according to the subject invention, bonded with different types of microneedle plates, active infusion featured.

Figure 17 shows results of an *in-vitro* study of insulin delivery by an active infusion transdermal microneedle patch, according to the subject invention.

Figure 18 shows results of an *in-vivo* study for DFS delivery across skin by zeolite and a commercial microneedle plate.

Figure 19 shows the *in-vivo* study results of the pharmaceutical effect for the administration of an insulin solution by zeolite and a commercial microneedle plate.

Figure 20 shows the *in-vivo* study results of the blood insulin level for rats that were administered an insulin solution by zeolite and a commercial microneedle plate.

Figures 21A and 21B illustrate an embodiment of a wearable patch, according to embodiments of the subject invention. Figure 21A illustrates an embodiment of a

wearable patch housing and Figure 21B is a photograph showing an embodiment of a complete wearable transdermal device prototype.

DETAILED DISCLOSURE

5 The subject invention pertains, in general, to patches with transmission-capable barriers. More specifically, the subject invention provides embodiments of transdermal patches, or similar devices, capable of providing long-term sustained release of a substance. Particular embodiments of the invention provide a mechanism by which the device can be activated and allows control of the amount of substance
10 released.

 The following description will disclose that the subject invention is particularly useful in the field of drug delivery, in particular devices used for the transdermal delivery of substances. However, a person with skill in the art will be able to recognize numerous other uses that would be applicable to the devices and
15 methods of the subject invention. While the subject application describes, and many of the terms herein relate to, a use for transdermal delivery of a sustained release substance, other modifications and uses that are apparent to a person with skill in the art having benefit of the subject disclosure are contemplated to be within the scope of the present invention.

20 In the description that follows, a number of terms used in relation to methods and devices for substance release and transmission are utilized. In order to provide a clear and consistent understanding of the specification and claims, including the scope to be given such terms, the following definitions are provided.

 The term “patient” as used herein, describes an invertebrate or vertebrate
25 animal, including mammals to which the systems and methods of the present invention are applied. Mammalian species that can benefit from the disclosed systems and methods include, but are not limited to, apes, chimpanzees, orangutans, humans, monkeys, whales, dolphins; domesticated animals (*e.g.*, pets) such as dogs, cats, guinea pigs, hamsters, rabbits; veterinary uses for large animals such as cattle,
30 horses, goats, sheep; and any wild animal for veterinary or tracking purposes. Human or non-human animal patients can range in age from neonates to elderly.

Also, as used herein, and unless otherwise specifically stated, the terms “operably communicate,” “operable connection,” “operably connected,” and literary variations thereof mean that the particular elements are connected in such a way that they cooperate to achieve their intended function or functions. The “communication” or “connection” may be direct, or indirect, physical, or remote.

The term “drug” as used herein refers to any substance that can be administered transdermally by the devices of the subject invention. This can include, but is not limited to, chemicals, pharmaceuticals, supplements, vitamins, hormones, lipids, polypeptides, vaccines, anti-inflammatories, opiates, serums, or any substance used for diagnostic, therapeutic, prophylactic, or cosmetic purposes, *etc.*

Finally, reference is made throughout the application to the “proximal side” and “distal side.” As used herein, the proximal side is that side that is closest to the skin when the device is attached to a patient. Conversely, the distal side of the device is that side located furthest from the skin when the device is attached to a patient.

The present invention is more particularly described in the following examples that are intended to be illustrative only since numerous modifications and variations therein will be apparent to those skilled in the art. As used in the specification and in the claims, the singular for “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise.

Reference will be made to the attached figures on which the same reference numerals are used throughout to indicate the same or similar components. With reference to the attached figures, which show certain embodiments, it can be seen that the subject invention comprises a compartmentalized container in the form of a wearable patch that can be temporarily attached to or at least against the skin. In general, embodiments of a patch 10 include an actuator compartment 50 and an activator compartment 60 with a body piece overlay 80 having a drug reservoir therein that can be separated from at least the actuator compartment by a membrane 90. The actuator and activator compartments can be at least partially formed within or as part of a body piece 150 of the patch. Alternatively, the compartments can be partially configured with an insert 20 that fits into and/or against a body piece 150 to create the compartments. The activator compartment and actuator compartments can

have an operable communication therebetween. In a further embodiment, the patch can optionally include one or more microneedles **100** for skin poration. In particular embodiments, the patch can be disposed within a housing **200** that can further include attachment devices **220** that make the patch wearable.

5 Transdermal Patches and Related Devices

Embodiments of the transdermal patches and devices of the subject invention can be manufactured by any of a variety of techniques known to those with skill in the art. By way of non-limiting examples, the patches and devices of the subject invention can be manufactured by injection moulding, hot embossing, rapid
10 prototyping, 3-D printing, and other methods. In addition, the patches and devices of the subject invention can be manufactured using any of a variety of materials known to those with skill in the art, such as, but not limited to, acrylonitrile butadiene styrene, poly(methyl methacrylate), poly (vinyl chloride), polycarbonate, polyphenylsulfone polymer or similar polymer materials. Substitution of other manufacturing methods or
15 materials, which achieve the same purpose, in substantially the same way, with substantially the same result are within the scope of this invention.

In one embodiment, a disposable transdermal patch is between 5 mm and approximately 30 mm in diameter. In more specific embodiment, a disposable transdermal patch of the subject invention is between approximately 5 mm and
20 approximately 10 mm in diameter. In a further embodiment, a transdermal patch of the subject invention has a thickness, from the proximal side **5** to the distal side **15**, of between approximately 1 mm and approximately 10 mm. In a more specific embodiment, a transdermal patch of the subject invention has a thickness, from the proximal side **5** to the distal side **15**, of between approximately 1 mm and
25 approximately 5 mm.

A. General Description of a Transdermal Patch:

In general, a patch design can have one or more reservoirs or compartments for storing therapeutic drug and/or cosmetic formulations. In one embodiment, a
30 body piece overlay **80**, an example of which is shown in Figure 1A, can be configured with at least one drug reservoir **82**. In one embodiment, the drug reservoir is open to

both the proximal and distal sides of the body piece overlay. The drug reservoir can become sealed during assembly of the patch. In a further embodiment, the body piece overlay **80** can have at least one drug port **84** for injecting one or more drugs into the drug reservoir, usually after the patch is fully or partially assembled. In a further
5 embodiment, the drug port **84** is a channel that extends from the peripheral edge **8** of the body piece overlay to the drug reservoir in the body piece overlay. Figures 9, 10, and 12 illustrate examples of body piece overlays **80** with a drug port **84** therein.

A patch can further have one or more actuator compartments **50** for containing at least one actuator, such as, for example, an expandable hydrogel, and an activator
10 compartment **60**, in operable communication with the actuator compartment, which contains an activator, such as, for example water, which is used to trigger hydrogel swelling. Figures 1B and 1D illustrate an example of a patch body piece **150** configured with an actuator compartment **50** and an activator compartment **60**. In one embodiment, shown in Figures 1A and 1B, the storage compartment is approximately
15 25 mm in diameter and approximately 1 mm thick. In a further embodiment, the actuator compartment, which can contain hydrogel, and the activator compartment, which can contain water, are each approximately 25 mm in diameter and approximately 2.8 mm thick.

In a further embodiment, the compartments for activator and actuator
20 materials, e.g., hydrogel/water compartments, are separated from the drug reservoir **82** by a membrane **90**. The membrane can comprise any of a variety of materials, such as those having an elastic and inert nature. Some non-limiting examples of such material are the Dow membrane (Corning SYLGARD 184), 3M polymer film (COTRAN™ 9722 Polyolefin film or COTRAN™ 9716 EVA film), TEFLON film,
25 polydimethyl siloxane, polyvinyl alcohol or similar materials, or combinations thereof. Figures 4A and 4B show an example of a polydimethyl siloxane membrane that has the required thermal and chemical stability and low elastic modulus.

In one embodiment, a polydimethyl siloxane pre-cured mixture was outgassed under vacuum for 30 min. The mixture was spin-coated on a flat glass at ca. 660 rpm
30 for 1 min, and cured at 80 °C for 30 min. Round polydimethyl siloxane membranes of 16 mm diameter were cut from the spin-coated film, as shown in Figures 4A and 4B.

Attachment of the membrane to the patch can be achieved by various methods. In one embodiment, an adhesive substance or material was utilized to affix the membrane. For example, a double-sided adhesive tape can be used to affix the membrane to the drug overlay or other patch component. This attachment can also be achieved by using cyanoacrylate with polyolefin primer or by heat sealing. Variations in the materials or methods utilized for attachment of a membrane, such that they do not interfere with or inhibit operation of the patch as described, are within the scope of this invention.

(B) Mechanical Mechanisms for Activating an Actuator:

Typically, the actuator, such as a hydrogel, can be stored within the actuator compartment and can be activated when contacted by or otherwise interacted with the activator, such as water. Figures 1A-1D and 9 show an embodiment in which the compartments are formed as part of the body piece **150**. In this embodiment, an actuator is stored within an actuator compartment in the body piece. In a further embodiment, the activator can be injected through injector ports **152** within the body piece **150**, as shown, for example, in Figure 9. In one embodiment, the ports are self-sealing, wherein a flexible or elastic material is deposited into the ports. A syringe or needle can be injected through the flexible material to deposit the activator within the actuator compartment. When the needle or syringe is removed, the elastic or flexible material of the injector port automatically closes around the opening made by the needle or syringe, to inhibit or prevent the activator from leaking out. Other sealing methods are known in the art and could also be utilized with embodiments of the subject invention, including but not limited to the insertion of a plug or sealant into the port. Agitation of the patch **10** will ensure that the injected activator migrates into the actuator compartment and contacts the actuator to initiate expansion. In a still further embodiment, the actuator compartment has at least one slot **154** therein that allows the activator to migrate, usually uninhibitedly into the actuator compartment.

In an alternative embodiment, the activator compartment **60** and actuator compartment **50** are partially formed as an insert **20** that is disposed within the patch **10** and is operably connecting or abutting the body piece **150**. In one embodiment,

the actuator compartment is connected to the insert by one or more connector arms **22**. When assembled within the patch **10**, the actuator compartment formed by the insert can be sealed, so any activator within the operably connected activator compartment is inhibited from contacting the actuator. In a further embodiment, a trigger mechanism is utilized to open the actuator compartment so as to allow contact between the activator and the actuator.

Two exemplary trigger mechanisms, that can be used in various embodiments are shown, for example, in Figures 10-14. The trigger mechanisms can be attached to a turnable cover that can be rotated or turned. The trigger mechanisms can disrupt the sealed actuator compartment, so that the activator, such as, for example, water, is released from its compartment to contact the actuator, such as, for example, the hydrogel, which can initiate hydrogel swelling.

One embodiment, an example of which is shown in Figures 2A-2D and Figure 10, utilizes a break gate mechanism **30**, having a turnable break gate cover **32** with one or more breaktriggers **34** thereon, and at least one breakable gate **54** as part of the actuator compartment, where the breakable gate can have an arm **55** that forms a seal on the actuator compartment. The break gate cover can be moveably or rotatably adjacent to the body piece, such that it can be turned or rotated relative to the body piece. In a further embodiment, the body piece has an opening **210** that provides access to the break gate cover, so that it can be turned. In operation, when the break gate cover is turned, the break trigger is forced against the arm, it causes the arm to move away from the actuator compartment, opening the actuator compartment to inflow of activator from within the activator compartment.

In one embodiment, the arm applies sufficient force against the actuator compartment to form a sufficient seal. In a further embodiment, the arm and the actuator compartment can have some part thereof formed as an interdigitated profile, which forms a sufficient seal. In an alternative embodiment, the arm and actuator compartment have a frangible attachment **57** therebetween that forms the seal, such that the seal can be broken, cracked, or otherwise disrupted by the break trigger. The break gate cover **32** can also have one or more knobs **35** on the distal side **200** that can be accessed through the opening **210** and used to turn or rotate the break gate cover

relative to the body piece **150**, forcing the break triggers against the break gates, so as to break, crack, or otherwise separate the breakable gate **54**. Figure 11A shows a non-limiting example of an insert **20** with two breakable gates **54** forming part of the actuator compartment **50**, the dashed lines represent the break triggers **34** positioned
5 next to the breakable gates, such that when turned, the break triggers will exert force against the arms, forcing them away from the actuator compartment and permitting activator to flow into the actuator compartment.

An alternative trigger mechanism, shown, for example, in Figures 3A-D and 12, utilizes an insert **20**, where the actuator compartment has one or more slots **154**,
10 similar to those mentioned above. A blocking gate mechanism **40** having a switch cover **42** with at least one switchable gate **44** extending proximally **5** blocks, covers, or otherwise closes the slot, inhibiting activator in the adjacent activator compartment from contacting the actuator. In a particular embodiment, shown in Figures 12 and 13, a switchable gate and the actuator compartment are substantially circular, where the
15 switchable gate has a diameter that is slightly larger than the diameter of the actuator compartment, such that a friction fit sufficient to inhibit migration of the activator into the actuator compartment is formed between the switchable gate and the actuator compartment. In an alternative embodiment, the switchable gate can be positioned within the actuator compartment. Activation of the actuator occurs when the
20 switchable gate is rotated, away from the slot **154** in the actuator compartment, as shown, for example in Figure 13B. To further ensure that the contents of the two compartments remain separated until such time that the switchable gate is moved, a sealant can be used where the switchable gate meets the actuator compartment. In one embodiment, the sealant is a glue that prevents ingress of the activator into the
25 actuator compartment, but which is frangible enough to be broken when the switchable gate is turned or otherwise moved.

It is possible for the switchable gate and actuator compartment to have different shapes, thus, embodiments are not limited to circular or semi-circular configurations. It would be within the skill of a person trained the art to devise
30 alternative shapes and methods by which a switchable gate can be moved away from a slot or some other opening with an actuator compartment. Such variations which

provide the same function, in substantially the same way, with substantially the same result are within the scope of this invention.

In a further embodiment, lock and key mechanism 46 can be used with the switch cover to move the switchable gate 44. In one embodiment, shown, for example, in Figures 12 and 13C, the distal side 15 of the switch cover has a lock 47 in the form of a depression having a defined shape. In a further embodiment, a key 48 having a complementary shaped boss 49 that operably connects to the lock. The boss on the key can be fitted into the lock and used to turn the lock 47 in a direction that causes the switch cover to rotate, further causing a switchable gate on the proximal side 5 to rotate as well, opening the actuator compartment within the patch. The key and boss configuration can comprise any of a variety of shapes and sizes. Figure 14 illustrates some non-limiting examples of alternative shapes that can be used for a lock, in which a complementary boss can be fitted. In another embodiment, there can be multiple locks on the switch cover and a key can be required to be aligned in a specific orientation in order to operably connect with one or more of the multiple locks. In a further embodiment, the key can have one or more knobs 35, mentioned above, to assist in turning the key and boss against the lock. In a further embodiment, the key is removable from the lock, which can reduce the thickness of the patch. This embodiment is advantageous because it allows the key to be removable, reducing the height of the patch, making it more comfortable and less conspicuous to wear. In certain embodiments it also allows more control over the amount of activator that can be released into the actuator compartment. For example, the key can be turned slightly or temporarily to allow some activator to reach the actuator, causing a regulated amount of swelling. If additional swelling is desired, the key can be turned again or for a longer period to allow more, or a greater amount, of the activator to reach the actuator. One or more regulator mechanisms, known to those with skill in the art, can be incorporated into the lock and key mechanism to help control the swelling process. Thus, the rate of swelling can be controlled in certain embodiments.

To ensure that the trigger mechanisms can apply sufficient force against the insert to operably engage with the actuator compartment, it can be beneficial if the actuator compartment is secured in place. This can ensure that the actuator

compartment does not rotate and that all of the torque generated by turning of the break gate cover 32 or the switch cover 42 is directed to opening the actuator compartment. To facilitate this, the connector arms 22 can be operably engaged with one or more blocks 85 on the body piece overlay 80. The one or more blocks can abut at least one connector arm 22 preventing the entire insert from being turned. Figures 10, 11A, and 12 illustrate embodiments where the body piece overlay 80 has at least one block 85 on the distal side 15 that can be engaged with at least one connecting arm on an insert.

(C) Non-electric Actuator:

In one embodiment, the non-electronic actuation employed for delivery of stored drug in the patch 10 relies on pH- or solvent-sensitive hydrogels. The hydrogels are usually a network of a hydrophilic polymer that has a large capacity for expansion by absorbing a large amount of liquid, such as water (up to 99.9 % of dry weight). The swelling performance and characteristics of a hydrogel are controlled by various parameters, which include, but are not limited to, monomer type, initialization system of polymerization, crosslinker, conjugate, and polymerization method (Deligkais *et al.*, 2010). Zhang *et al.* modified the microstructure of hydrogel to improve drug release performance by the formation of microgels as primary structure and cross-linking of the microgels into bulk network as secondary structure (Zhang *et al.*, 2010). The release yield of drugs from the modified hydrogel was 4 times higher than that of the conventional one. Due to the high biocompatibility and diverse characteristics of hydrogel, it has been extensively studied for various uses. Kumar *et al.* reported the use of a pH-responsive hydrogel for oral insulin administration (Kumar *et al.*, 2006).

Hydrogels are well-known in the art for a multitude of uses. Embodiments of the subject invention can employ any of a variety of known hydrogels. Some non-limited examples of solvent-sensitive hydrogels that can be used with embodiments of the subject invention, include poly acrylamide-polyethylene glycol-maleic acid, poly (acrylamide-co-butyl methacrylate), poly acrylamide-polyethylene glycol-maleic acid, poly acrylamide-polyethylene glycol-bovine serum albumin, and others. Other non-

limiting examples of pH-sensitive hydrogels that could be employed with embodiments of the subject invention are polyvinyl alcohol-polyacrylic acid, poly(n-isopropylacrylamide-co-acrylamide), poly (methacrylic acid-co-ethylene glycol), and others. Gu *et al.* (Gu *et al.*, 2007) demonstrated that the incorporation of carboxyl groups into poly(N-isopropylacrylamide) matrix led to response to pH. A person with skill in the art will be able to determine an appropriate hydrogel, or similarly characteristic substance, from those known in the art. Such variations which perform substantially the same function, in substantially the same way, with substantially the same result are within the scope of this invention.

(D) Microneedles:

Microneedles have been developed for drug delivery application (see, for example, U.S. patents 8,162,901; 8,197,435; 8,062,835; 8,043,250; 8,150,505; and 7,798,987). Any of the materials known for microneedle fabrication, such as, but not limited to, silicon (see, for example, U.S. patents 3,964,482; 7,332,339; 6,844,213; 5,312,456; and 7,588,552), metals (see, for example, U.S. patents 8,137,736; 7,097,776; and 7,497,980, as well as U.S. Published application no. 2011/0237925), polymers (see, for example, U.S. patent. 6,334,856; 6,924,087; and 6,451,240; and U.S. Published Application no. 2006/0055090, as well as Yung *et al.*, 2012) and ceramics (see, for example, U.S. patent no. 7,699,819), and other materials or combinations thereof, are compatible for use in the present invention.

The manufacture of microneedles is well-known in the art, with several techniques being documented. Silicon is widely used as a material in the microelectronics industry, where the processes for using silicon, particularly for microneedle production, are well-known and quite mature. Metal is another common material used for microneedle production, that advantageously provides good mechanical strength. Polymers are also employed as a material for microneedles, usually because of good biocompatibility characteristics. Figures 8A, 8B, and 8C are photographs of examples of zeolite, plastic, and commercial microneedles that can be used with embodiments of the subject invention. The heights of zeolite, plastic, and commercial microneedles are about 150 μm , 500 μm and 600 μm , respectively. A

zeolite microneedle plate can be fabricated from a backside UV exposure with a non-transparent pre-coated substrate, while a plastic microneedle plate can be fabricated by micro-injection moulding, such as taught by Yung *et al.* (Yung *et al.*, 2012). Thus, various methods of manufacturing microneedles having various characteristics are well-known in the art.

Typically, in use, microneedles are utilized to puncture or penetrate the skin, so as to reach at least the dermis layer of the skin. A single microneedle can be utilized or a plurality of microneedles can be utilized. The embodiments of the subject invention can also utilize either a single microneedle or a plurality of microneedles. The material used, the size, and the numbers of microneedles utilized with the different embodiments of a patch of the subject invention are factors that can be determined by a person with skill in the art. Such variations which provide the same function, in substantially the same way, with substantially the same result are within the scope of this invention.

The attachment of a microneedle or microneedle plate to a patch can be accomplished by a variety of devices and techniques. Usually, the microneedle support or microneedle plate is affixed to the proximal side of the body piece overlay and over the drug reservoir therein. In one embodiment, a microneedle plate is attached using silicone adhesive or cyanoacrylate bonding. Variations in the method or devices utilized for attachment of a microneedle to a patch are within the scope of this invention.

(E) Wearable Patch Housing:

A transdermal patch of the subject invention can transmit one or more drugs through the skin. Typically, transdermal delivery results in a drug ultimately being delivered into the bloodstream, though this is not always necessary, or it may not be a direct transmission. To effect transdermal delivery of a drug, the embodiments of the patch of the subject invention are usually placed into contact with the skin. One method is to use techniques or devices that attach a patch directly to the skin, such as, by way of non-limiting examples, adhesives or sutures. Alternative embodiments employ devices that hold or press a patch into close proximity to the skin.

In one embodiment, a patch is incorporated into a wearable housing **200** that could be worn on the body and/or limbs. A housing can comprise a manufactured cavity for containing the patch and one or more attachment devices for securing it in close contact with the skin. Figures 21A and 21B illustrate one embodiment of a housing in which a patch embodiment can be secured and placed against the skin. In one embodiment, the wearable housing is made of any suitably rigid or semi-rigid material, including, but not limited to, metals, plastics, or ceramics, glass, rubber, wood products, and combinations thereof, *etc.* In a further embodiment, the housing has an opening **210** in the distal side that operably communicates the proximal side **5** with the distal side **15**, so that a lock **47** is accessible through the body piece **150** with a key **48**.

In a further embodiment, one or more attachment devices **220** can be utilized to secure the housing next to the skin. Such attachments devices can be removable and, in a further embodiment, are adjustable.

(F) Alignment Features:

The trigger mechanisms employed with certain embodiments of the subject invention can require that certain components of the patch be properly aligned to function within the device. Depending upon the method of manufacture and/or assembly of the patch components, alignment may be automatic or may require visual or tactile cues on the various components indicating their proper alignment in the overall assembly.

Embodiments of the subject invention use alignment structures to ensure that the components of the patch are properly aligned. In one embodiment, components are aligned by means of a fixed fastener mounting method. With this embodiment, one component is configured with a groove or bore **96** and another component is configured with a compatible tab **97**. To assemble the components the tab and bore can simply be aligned and the two components pushed together, so that the tab inserts into the bore. In a specific example, shown in Figures 10 and 12, the insert **20** is configured on one side, nearest the body piece **150** with tabs **97** and with bores **96** on the opposite side, nearest the body piece overlay **80**. When the tabs and bores on the

insert are aligned with their respective components on the patch, so that the tabs can be inserted into the bores, the internal components will also be aligned so they can operate as described above.

It is within the skill of a person trained in the art to devise numerous methods by which the components of a patch embodiment can be properly configured and aligned. Any such variations are within the scope of this invention.

(G) Leak-prevention Coatings:

The embodiments of the subject invention require that the activator and actuator devices and/or substances remain separated until such time that the patch device is ready to be utilized for drug delivery. While the components of the embodiments are designed to operably connect to achieve this function, it can be helpful if the points of juxtaposition of certain components include additional materials to prevent leakage.

In one embodiment, components of the patch embodiments are at least partially covered with a coating 260 of one or more materials that can form a seal or barrier between the components when a patch is assembled. In one embodiment, the components, *i.e.*, the insert and the body piece are coated with a silicon-based substance that can be compressed between the two components during assembly to form an impervious seal. Other substances that can be utilized include, but are not limited to, rubber, soft metals, plastics, ceramics, wood products, nylon, and other partially deformable materials, or combinations thereof. Alternatively, certain components can be secured with adhesives, heat sealing, cold sealing, friction fit, or other sealing methods. It is within the skill of person trained in the art to determine any of a multitude of materials and methods that can be utilized to form a sufficient seal between components of the embodiments of the subject invention. It will be understood that such variations are within the scope of this invention.

Following are examples that illustrate procedures for practicing the subject invention. These examples are provided for the purpose of illustration only and should not be construed as limiting. Thus, any and all variations that become evident

as a result of the teachings herein or from the following examples are contemplated to be within the scope of the present invention.

EXAMPLES

5 Example 1: Manually Activated Nonelectronic Active-infusion Transdermal Patch.

An active-infusion transdermal patch for drug delivery was tested, where the patch included a hydrogel compartment, water compartment, plastic membrane, drug reservoir and microneedle plate. Figures 1A-1D and 9 illustrate components utilized with the patch for this test. The hydrogel compartment and activator compartment
10 were formed as part of a backing component. In this test, a dried hydrogel was placed into the hydrogel compartment, with slots that open into the activator compartment. A chemically-inert plastic membrane was adhered between the hydrogel compartment and a body piece overlay with a drug reservoir therein. The membrane separated the compartment and reservoir to prevent contact of the drug with the hydrogel. The
15 activator compartment surrounded the actuator compartment with the hydrogel to contain sufficient activating agent (*i.e.*, water) to swell the hydrogel. The activating agent was injected into the activator compartment through two resealable injector ports within the body piece. The body piece, which caps the distal end 15 of the compartments containing hydrogel and water, acts to withstand the swelling force of
20 the hydrogel, causing the hydrogel to swell in a proximal direction towards the drug reservoir. A plate grown with microneedles was sealed over the the drug reservoir, on the opposite, proximal, side 5 from the membrane, in order to facilitate transdermal delivery.

A pre-determined amount of a drug solution was loaded into the drug reservoir
25 by syringe needle through the drug ports in the body piece overlay. To initiate drug delivery, activator, (in this case, water) was injected into the activator reservoir through the injector ports. The device was then shaken gently to allow proper contact between the swelling agent and dried hydrogel actuator. The dried hydrogel then swelled in a time-controlled manner. Volume expansion of the hydrogel caused the
30 elastic membrane to be pushed towards the drug reservoir and forced the drug out of the reservoir through the hollow microneedles. It is expected that installation of the

patch onto a patient would cause the expelled drug to be deposited to deep skin layers. The overall dimensions of the patch were 25 mm in diameter and 4 mm in height.

Example 2: Nonelectronic Active-infusion Transdermal Patch Utilizing Breakable Gate Compartment.

An active-infusion transdermal patch for drug delivery was tested, where the patch included a design that was similar to that utilized in Example 1, but which allows for storage of all necessary activators, actuators, and drugs within the patch device. Figures 2A-2D and 10 illustrate patch components utilized with this test, wherein *Figure 10 is an expanded view of a modified active infusion transdermal microneedle patch*. Note that the microneedle plate is not shown in these figures, but was attached to the body piece overlay as shown in Figure 9.

With this patch design the actuator and activator compartments are formed by a divided insert that is positioned between the body piece overlay the body piece. The actuator compartment is formed with two moveable arms. The drug delivery mechanism was the same as that utilized with the mechanical patch, described in Example 1, wherein the drug was then loaded into the drug reservoir by syringe needle through the two resealable injector ports. Hydrogel actuator and water swelling agent were loaded into their respective reservoirs, after the plastic membrane and the insert were mounted on the drug reservoir in the body piece overlay, as shown in Figure 10. A turnable break gate cover having two break triggers was then placed over the insert, and the body piece was placed over that, with the knob on the break gate cover accessible through the body piece. Alignment structures were used to correctly position the body piece with the insert, such that the break triggers were correctly aligned with the arms of the actuator compartment. Figures 11A and 11B show plan views of the active infusion transdermal microneedle patch utilized with this test. The water blocking gate in the hydrogel reservoir included two moveable arms. The turnable break gate cover included two break triggers. Blocks on the distal side of the body piece overlay, facing the insert, fit on either side of the connector arms to hold the insert in place, ensuring all torque generated by turning of the break gate was transmitted to the frangible attachment forming the seal. The seal was

broken via turning the knob on the break gate cover. By properly shaking the patch, swelling agent in actuator compartment made contact with the dried hydrogel at the center to trigger hydrogel swelling, causing the membrane to push into the drug reservoir, which in turn forced the drug out of the microneedles, and hence drug delivery. The overall dimensions of the patch in this test were 25 mm in diameter and 6.9 mm in height.

Example 3: Nonelectronic Active-infusion Transdermal Patch Utilizing a Blocking Gate Mechanism.

An active-infusion transdermal patch for drug delivery was tested, where the patch included a design that was similar to that of Example 2, but which utilized a switch cover with at least one switchable gate that opens the actuating compartment. Figures 3A-3D and 12 illustrate patch components utilized with this test, wherein Figure 12 is an expanded view. Note that the microneedle plate is not shown in Figure 12, but was positioned in the same location as shown in Figure 9, *i.e.*, proximal to the body piece overlay, over the drug reservoir.

For this test, the insert was configured with a blocking gate mechanism that included a switch cover with switchable gates extending from the proximal side, as shown, for example, in Figure 12. The switchable gates were used to close two slots within the actuator compartment. The actuator compartment was attached to the insert by connector arms.

The switchable gates were positioned over the slots in the actuator compartment, to prevent the contents of the activator compartment from making undesirable contact with the contents of the actuator compartment. To further ensure that the contents of the compartments remained initially separated, the junctions between switchable gates and the actuator compartment were sealed with epoxy resin to ensure complete isolation of swelling agent in the activator compartment, inhibiting it from reaching the hydrogel in the actuator compartment.

The proximal components of the patch were assembled similar to those in Example 1 and Example 2. However, this embodiment was employed with a housing having alignment points complementary to or that correspond to alignment points on

the back cover. The housing provided proper positioning and holding of the patch in axial and tangential directions. The alignment points were used to ensure that the switchable gates were positioned and secured over the slots in the actuator compartment during assembly of the patch.

5 The housing had an opening that allowed the lock of the switch cover to be exposed to the distal side of the housing. The switch cover was configured to operate as part of a lock and key mechanism. The lock, which was a shaped depression in the distal side of the body piece, was compatibly shaped with a boss on the proximal side of a key, shown for example in Figures 12, 13C, and 14.

10 To activate drug delivery, the key was pressed into the lock and turned counter clockwise, which simultaneously rotated the switchable gates away from the slots in the actuator compartment. Note, the key and switchable gates could have been configured to be turned clockwise as well. Activator was then able to flow into the actuator compartment, initiating swelling of the hydrogel therein. The switch cover
15 acted to resist the swelling hydrogel, forcing all of the swelling motion to be directed towards the drug reservoir and the microneedle plate.

The key utilized in this test had a diameter of 25 mm and a height, from the proximal to the distal side of 5 mm. The patch utilized in this test, without the key in place, had a diameter of 25 mm and 4.8 mm in height.

20 Example 4: Water-proofing, Leak-proofing and Assembly.

For the purposes of testing, to ensure that the activator did not prematurely contact the actuator, the components of the patch were formed with one or more seals. The patch compartments, trigger mechanisms, and optionally, the microneedle plate
25 were coated with a biocompatible water-proofing layer to provide leak-free seals. For testing the patch, a silicone coating was made from a mixture of silicone and a curing agent (50:1 w/w ratio), cured at 60 °C for 4 h.

Further, a double-coated adhesive tape, that is, one with adhesive on two sides, was cut in a circular shape and attached distal to the drug reservoir, between the body
30 piece overlay and the actuator or hydrogel compartment. The area of the adhesive tape exposed to the drug reservoir was trimmed out and a plastic membrane was then

attached to the remaining adhesive tape. Next, a prepared hydrogel was fitted into the hydrogel compartment. The drug reservoir was aligned with the hydrogel compartment by means of alignment structures and bonded in place with an adhesive to ensure a leak-free seal. A microneedle array plate was attached by direct bonding to the proximal side of the body piece overlay to form a drug reservoir between the membrane and the microneedle plate. The microneedle plate can be attached by any of various means, for example, by using silicone adhesive or cyanoacrylate bonding

Example 5: Preparation of Hydrogel.

Solvent-sensitive hydrogel, PAAm-PEG4000, was synthesized by free radical polymerisation and used in the patch embodiments of the current invention. 15 wt% acrylamide (AAm), 2 mL of 0.014 M ammonium persulfate (APS), 2.4 mol% N,N'-methylenebis(acrylamide) (MBAAm), and 9 wt% polyethylene glycol with molecular mass of 4,000 g/mol (PEG4000) was gently mixed in 7 mL deionized water (DI) water (Caykara *et al.*, 2006). The mixture was degassed with nitrogen for 10 min. Then, 1 mL of 0.08 M tetramethylethylenediamine (TEMED) was added to the mixture with stirring. The mixture was quickly poured into a plastic cylinder with inner diameter of 11 mm and was allowed to settle for polymerization. The open end of the cylinder was covered with parafilm 5 min after the start of reaction. The cylinder was allowed to stay overnight for complete reaction. After that, the hydrogel was cut into smaller pieces, with the help of a spacer. The width of the spacer was set to 3.6 mm, for which the accuracy was measured by an electronic calliper. The hydrogel was then washed with DI water for a week to remove unreacted substances. The hydrogel pieces were dried under vacuum for 2 days. The dried hydrogel had dimensions of 6.47 ± 0.03 mm in diameter and $1.7 \text{ mm} \pm 0.1$ mm in height.

Example 6: Hydrogel Surface Coating.

A dried hydrogel from Example 5 was spray coated. Polydimethyl siloxane was weighed and mixed with 10% w/w curing agent to form a pre-cured mixture. Equal weight of hexane was added to the mixture to lower the viscosity. The mixture was then poured into a sprayer with a spraying pressure 0.2 kgf/cm^2 , placing 0.3 m

above the hydrogel. The dried hydrogel was sprayed with the mixture for 10 sec. After 2 min of settling, the hydrogel was heated in an oven at 80 °C for 30 min. The hydrogel was then turned over and the entire process repeated on the uncoated side of the hydrogel. The spray-coated hydrogel was stored in a desiccator. Figure 6 is a SEM photograph of a cross-section taken from a spray-coated hydrogel.

Example 7: Hydrogel Swelling, Performance, and Behaviour.

The uncoated hydrogel swelling properties were observed with a mock setup. For the mock set-up, a transparent activator compartment for water and an actuator compartment for hydrogel were created and placed on a hard surface, and a transparent drug reservoir was placed at the top, as illustrated in Figure 5. A polydimethyl siloxane membrane was placed between the hydrogel and the drug reservoir. A dried hydrogel was put inside the hydrogel compartment. Weight was applied on top of the drug reservoir to hold the assembled substrates in place. DI water was added to the water reservoir to initiate hydrogel swelling. Photos were taken hourly for 8 hr after water addition (Canon 40D with EF-S 60/ F2.8 macro lens, Sea & Sea YS-110 strobes * 2, TTL controlled). Figure 5 illustrates a photographic progression of the uncoated hydrogel swelling property over time. Hydrogel started swelling, after the addition of water, reached about half the height of the drug reservoir in 2 hr, and then swelled very slowly afterward. The result clearly indicates that the swelling force from the hydrogel is sufficient to expand and force the polydimethyl siloxane membrane toward the drug reservoir. However, the swelling process of the uncoated hydrogel is considered too fast for long-term drug delivery (e.g. 8 hr). To achieve a slower, more controlled hydrogel swelling, a spray coating step was carried out, as described in Example 6. To verify the coating of polydimethyl siloxane onto the hydrogel, a spray coated sample was examined under scanning electron microscope (SEM). The SEM photograph in Figure 6 shows that polydimethyl siloxane of a thickness of 51.7 μm was coated onto the hydrogel by the method described above.

Figure 14 is a series of photographs showing the swelling property of a spray-coated hydrogel compared with an uncoated hydrogel. Despite the difficulty in

quantifying the volume expansion of the hydrogel by camera, the prolonged swelling process after coating was clearly observable. It is believed that the polydimethyl siloxane coating constrains water contact of the dried hydrogel, but the water contact triggers the hydrogel to swell eventually. Volume expansion of the hydrogel breaks the coating layer, allowing more water to diffuse and interact with the hydrogel.

Example 8: *In-vitro* Study.

Porcine ear skin was used as the delivery barrier in an *in vitro* experiment, because of the similar histological and physiological properties to human skin (Ah *et al.*, 2010 and Yan *et al.*, 2010). Porcine ears were freshly obtained from a local slaughter facility, gently washed with running tap water, and chopped into pieces of 50 mm in width. Visual observation was done to check if the skins were free from lesions and infections. Hairs at the back of the ear were carefully removed by clipper. Full thickness skins were obtained using manual-operated dermatome with uniform insertion force and angle. The split skins were cut into discs with 40 mm diameter. The skins were then sprayed and rubbed with 75% ethanol for 1 min to remove fatty tissues and dirt, followed by DI water washing. Thereafter the skins were blotted with Kimwipes, wrapped with aluminum foil, and stored in a -20 °C refrigerator until further use. All prepared porcine skin was used within 2 weeks.

Vertical diffusion cell was filled with 7 mL phosphate buffered saline (PBS) (137 mM sodium chloride (NaCl), 2.7 mM potassium chloride (KCl), 4.3 mM sodium phosphate dibasic heptahydrate ($\text{NaH}_2\text{PO}_4 \cdot 7\text{H}_2\text{O}$), and 1.6 mM potassium phosphate monobasic (KH_2PO_4), pH 7.4) and pre-run at 300 rpm with bath circulator for 1 hr to achieve 37 °C. Porcine skin was thawed by soaking in PBS at room temperature for 1 hr. After that, the porcine skin was mounted between the receptor and the donor cell of the diffusion system. The stratum corneum of the skin faced the donor cell while the dermis side faced the receptor cell. The skin was handled with care to avoid bubble accumulation on the receptor side of the skin. Diclofenac sodium (DFS) or insulin (70 µL) and DI water (500 µL) were loaded into the drug and water reservoirs, respectively, through the resealable injector ports. A patch, such as those described in previous examples, was gently shaken to ensure water could make contact with the

dried hydrogel inside. The patch was applied on the donor side of the skin by finger force, with the help of adhesive tapes to keep the patch in position. Samples (1 mL) were withdrawn from the receptor cell every hour with immediate replenishment of the same volume of fresh PBS. The tests were done with patches bonded with commercial (ME-C-600), zeolite (SSM-O-150), or plastic (P-O-500) microneedles.

Example 9: *In-vitro* Study Using NSAID Drug Diclofenac Sodium (DFS).

The validation of diverse drug delivery by a patch of the subject invention was tested by choosing an alternative drug. DFS, a common analgesic, was chosen as a model drug. Quantification of DFS in samples was done by analysis under ultra-performance liquid chromatography (UPLC). With a gradient method A:B = 70%:30% to 10%: 90% in 4 min (A = 0.02% trifluoroacetic acid (TFA) in H₂O; B = 0.02% TFA in acetonitrile (ACN)), flow rate = 0.45 mL/min with detection wavelength = 210 nm. All the data presented was collected from a patch having a 2-layer coated hydrogel, as described in Example 6. Figure 16 presents a graph of DFS delivery by active infusion transdermal microneedle patch with different types of microneedle plates. DFS exerts low bioavailability in transdermal application because of the presence of stratum corneum in the outermost skin. Negative control is achieved by direct pipetting of a known amount of drug on skin for diffusion. As expected, the amount of DFS transferred is relatively low. Percentage of DFS delivered ($17.6 \pm 3.2\%$) after 8 hour testing is also comparable with the result provided by Varghese's group, in which during a 6 hour test, the cumulative dose of DFS by sole diffusion was from 11.1 % to 17.9 % depending on concentration. (Varghese *et al.*, 1996). The delivery of DFS by zeolite microneedle plate adhered to the patch improves delivery rates, due to the modified dimensions and geometry of the microneedles. Plastic microneedles adhered to the patch yield the highest DFS delivery with about $73.8 \pm 4.9\%$ of drug delivered in 8 hour test. The delivery is linear with 97% confidence level ($R^2 = 0.9704$).

Example 10: *In-vitro* Study Using NSAID Drug Diclofenac Sodium (DFS) Using Coated Hydrogels.

Figure 15 presents a graph showing the effects of a number of spray-coatings on hydrogel towards the drug (*i.e.*, DFS) delivery efficiency *in-vitro*. A plastic microneedle plate was used in this experiment. As shown in Figure 15, the delivery by an adhered plastic microneedle plate with uncoated hydrogel rises exponentially at the initial stage, and starts to level off after 4 hour of testing. In contrast, the DFS delivery with a hydrogel having 2 layers of sprayed-coating hydrogel is impeded initially, but swelled up later. After 8 hours of testing, the amount of drug delivered by a patch with a 2layer spray-coated hydrogel is higher. The presence of water resistance coating provides a crucial factor for zero order hydrogel swelling in a relatively small swelling ratio condition. Total amount of drug is $60.9 \pm 6.1\%$ for uncoated hydrogel and $73.8 \pm 4.9\%$ for 2 layered coated hydrogel.

Example 11: *In-vitro* Study Using Insulin Drug.

Figure 17 presents the results of an *in-vitro* study of insulin delivery by active infusion transdermal microneedle patches using zeolite and commercial microneedles. 70 μL of 4.5 mg/ mL insulin stock was stored in the active infusion transdermal microneedle patches. The figure shows that less than 5% of insulin permeated across the non-porated pig skin in the skin patch test (negative control), understood to be due to insulin being a too bulky molecule for passive transdermal delivery. Figure 17 shows that a linear insulin delivery rate is obtained from both active infusion transdermal microneedle patch with zeolite and commercial microneedles. The longer commercial microneedles had a faster delivery rate than the shorter zeolite microneedle.

Example 12: *In-vivo* Study Using NSAID Drug Diclofenac Sodium (DFS).

A *in-vivo* test was conducted on Sprague Dawley rates between approximately 230g - 250g to analyze DFS delivery. The rats were anesthetized by a ketamine/xylazine cocktail, and then the abdominal hairs were completely removed by a hair clipper following by chemical depilatory creams. 200 μL of 5 mg/ml DFS in phosphate buffered saline (PBS) was injected through rats' naked skin with either zeolite microneedles or commercial microneedles in bolus. A negative control

consisted of placing excess DFS solution on rats' naked skin. After 5 min, the skins were washed by iced DI water. About 1 mm diameter of skin samples at the injection sites were carefully cut and then weighed in 2 ml centrifuge tubes. Then the skin samples were homogenized in 5 fold PBS buffer by sonication. DFS was extracted from the homogenate by liquid-phase extraction using 500 μ l ethyl-acetate for twice. The ethyl-acetate was collected into 1.5 ml centrifuge tubes and then removed under vacuum. The residues were reconstituted by 500 μ l ACN:H₂O (50:50 w/w ratio) and 200 μ l of the reconstituted solution was send for UPLC analysis. Figure 18 shows a graph of the results of in-vivo DFS delivery across the skin by the different microneedles plates. The transdermal DFS delivery by the commercial microneedle patches showed a nearly 5 times increase when compared with the negative control. While the zeolite microneedle could further have more than 3-fold increase in term of the delivery amount than the commercial microneedle, indicating that although the commercial microneedles were longer, the zeolite microneedles demonstrated better effectiveness for delivery of the DFS across the outermost layer of the skin.

Example 13: *In-vivo* Study Using Insulin Drug.

An *in vivo* test of insulin delivery was conducted on Sprague Dawley rats weighing between approximately 230g - 250g, which were fasting overnight, but free to access water one day before the test. The rats were anesthetized by a ketamine/xylazine cocktail, and the abdominal hairs were completely removed by a hair clipper followed by chemical depilatory creams. About 80 μ l of 100 IU/ml human insulin solution was transdermal administrated to individual rats by either zeolite microneedles or the same type of commercial microneedles used in Example 12. Fixed dosed 0.1 IU insulin solution or saline was also subcutaneously injected by syringes to simulate the positive and negative control respectively. The rats' blood glucose levels were recorded by a portable glucose meter (Roche, Accu-Chek Performa Nano) for 6 hours at different time intervals. For the first 4 hours 200 μ l of blood samples were also collected by squeezing the rats' tails. The blood samples were centrifuge at 13000G for 3 min and then the blood plasma was pipetted into 1.5 ml centrifuge tubes and stored under -80 °C for blood insulin test. The blood insulin

levels were tested by an ELISA kit (Mercodia, Human Insulin ELISA). Some samples were followed with a 5 fold dilution using the blank calibrator provided by the kit in order to prevent exceeding the calibration limit.

Figure 19 shows a graph of the pharmaceutical effect of the administration of the insulin solution by different microneedle patches. For all zeolite microneedle, commercial microneedle, and the positive control, a significant pharmaceutical effect could be observed after 1 hour, when the blood glucose level of the rats dropped by about 4-fold from the original level and was subsequently maintained for some hours.

Figure 20 shows a graph of the blood insulin level of the rats used for this *in-vivo* test. The result was consistent with the observed pharmaceutical effect, as indicated by the $C_{\max}$ being the highest and $T_{\max}$ being the fastest for the rat that received insulin administration by the transdermal patch. In pharmacokinetics, the administration efficiency of a certain drug is commonly evaluated by its $C_{\max}$ and $T_{\max}$. $C_{\max}$ represents the maximum plasma concentration of the drug and $T_{\max}$ represents the time after administration of a drug when the maximum plasma concentration is reached which the rate of absorption equals the rate of elimination.

Example 14: Wearable Transdermal Device.

Figures 21A and 21B a wearable patch housing design drawing (Figure 21A) and a prototype of a wearable transdermal patch with belt (Figure 21B). Figure 21A show this embodiment with dimensions of the housing to be 31 mm in diameter and 4.87 mm in height. The photograph of the prototype shows the transdermal patch housed within the cavity so that could be worn on the body and the limbs for securing the patch in close contact with the skin.

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CLAIMS

What is claimed is:

1. A transdermal patch device comprising:

a body piece having a proximal side and a distal side;

an activator access in the body piece;

5 an actuator compartment within the body piece and operably connected with the activator access;

a drug reservoir at a proximal side of the body piece, a distal side of the drug reservoir adjacent a proximal side of the actuator compartment; and

a transdermal drug delivery zone at a proximal side of the drug reservoir;

10 wherein in an initial, pre-activated state, actuator within the actuator compartment is isolated from an activator;

wherein, upon initiation by a user, an activator transits through the activator access into the actuator compartment and contacts the actuator, causing the actuator to swell, whereby the actuator expands in a proximal direction and thereby transmits
15 force to the distal side of the drug reservoir, whereby a drug in the drug reservoir is forced through the transdermal drug delivery zone and out of the device.

2. A transdermal patch according to claim 1, wherein the activator access comprises an activator compartment within the body piece.

20

3. A transdermal patch according to claim 1, wherein the activator access comprises an injector port.

4. A transdermal patch according to claim 2, further comprising:

25

an opening in the body piece;

a turnable cover within the body piece and having a distal side accessible through the opening in the body piece;

an insert in operable communication with the proximal side of the turnable cover, where the activator compartment and the actuator compartment are formed of
30 the insert; and

at least one trigger mechanism on the turnable cover by which a user can initiate open connection between the actuator compartment and the activator compartment.

5 5. A transdermal patch according to claim 4, further comprising at least one breakable gate on the insert.

10 6. A transdermal patch according to claim 5, wherein the trigger mechanism is a break trigger that opens the at least one breakable gate when the turnable cover is rotated, whereby open connection is initiated between the actuator compartment and the activator compartment.

15 7. A transdermal patch according to claim 4, further comprising at least one slot within the actuator compartment.

20 8. A transdermal patch according to claim 7, wherein the trigger mechanism is a switchable gate on the turnable cover that opens and closes the slot when the turnable cover is rotated, whereby open connection is initiated between the actuator compartment and the activator compartment.

 9. A transdermal patch according to claim 4, wherein the turnable cover further comprises a lock accessible through the opening in the body piece.

25 10. A transdermal patch according to claim 9, further comprising a key for removably engaging with the lock to rotate the turnable cover.

 11. A transdermal patch according to claim 2, further comprising a body piece overlay in which the drug reservoir is disposed.

30 12. A transdermal patch according to claim 11, further comprising a drug port operably connected to the drug reservoir in the body piece overlay.

13. A transdermal patch according to claim 12, wherein the drug port is sealable.

5 14. A transdermal patch according to claim 11, further comprising at least one arm on the insert and at least one block on the body piece overlay, wherein the block engages with the arm to inhibit the insert from being rotated.

10 15. A transdermal patch according to claim 11, further comprising a membrane between the actuator compartment and the drug reservoir.

16. A transdermal patch, according to claim 11, further comprising a microneedle plate adjacent to the drug delivery zone.

15 17. A transdermal patch according to claim 16, wherein the microneedle plate comprises plastic, metal, ceramic, silicon, glass, or zeolite.

20 18. A transdermal patch device according to claim 14, further comprising one or more alignment structures on at least one of the body piece, the body piece overlay, or the insert.

25 19. A transdermal patch according to claim 4, further comprising a coating that forms a seal between two or more adjacent components within the transdermal patch.

20. A transdermal patch according to claim 19, wherein the coating comprises a silicon-based material.

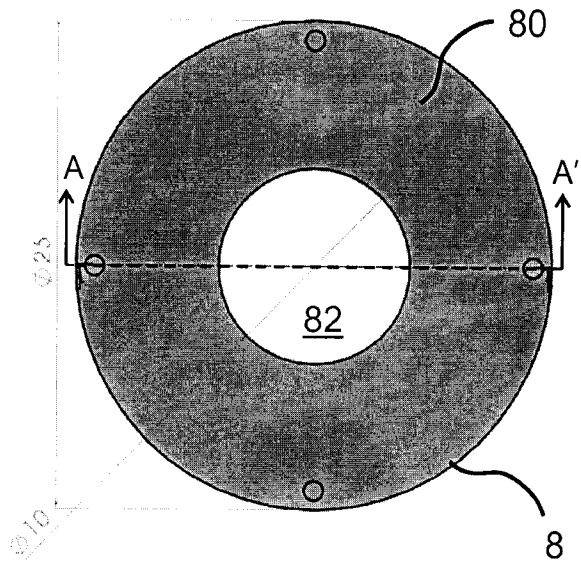


FIG. 1A

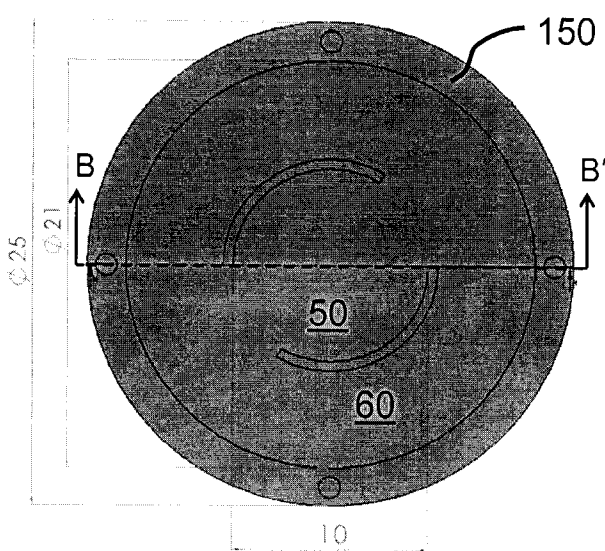


FIG. 1B

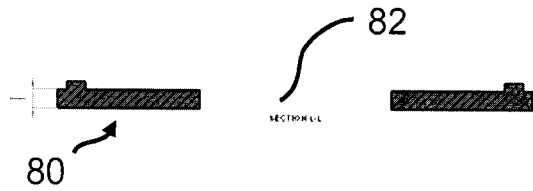


FIG. 1C

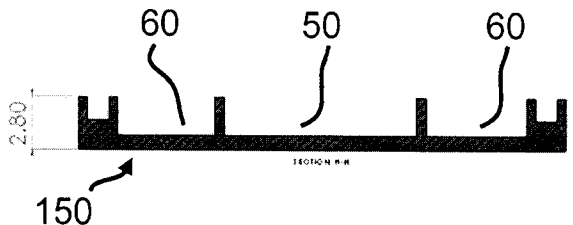
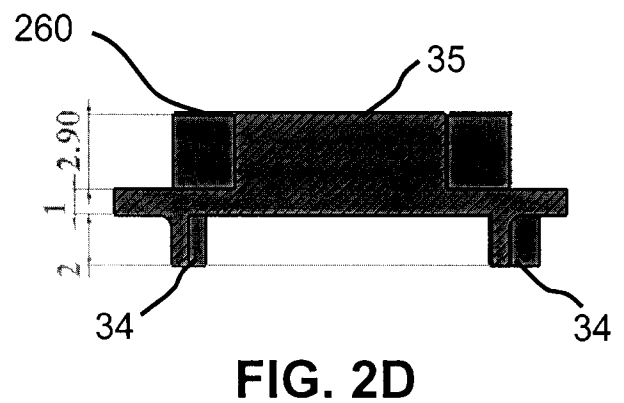
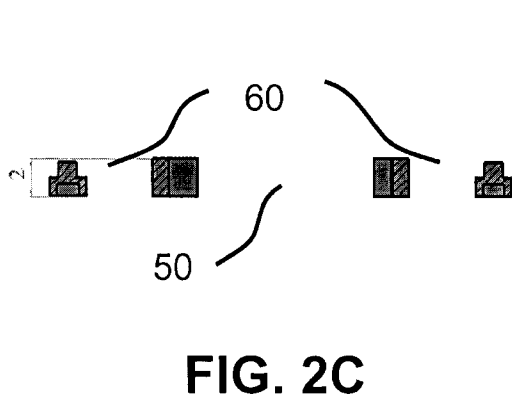
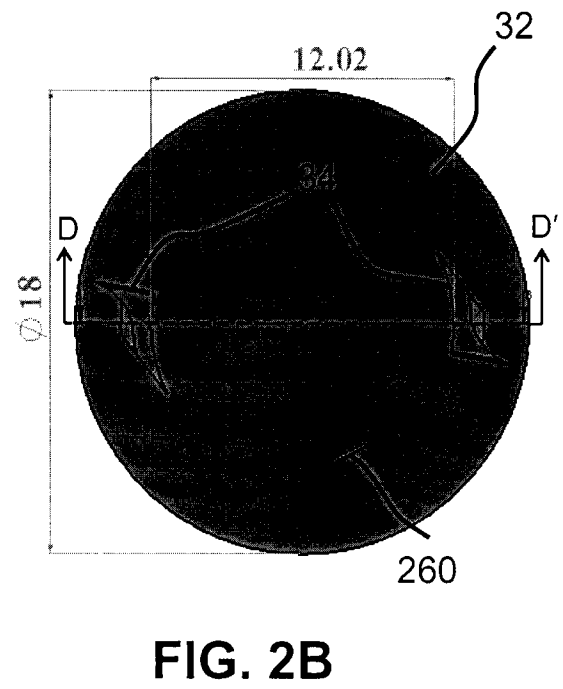
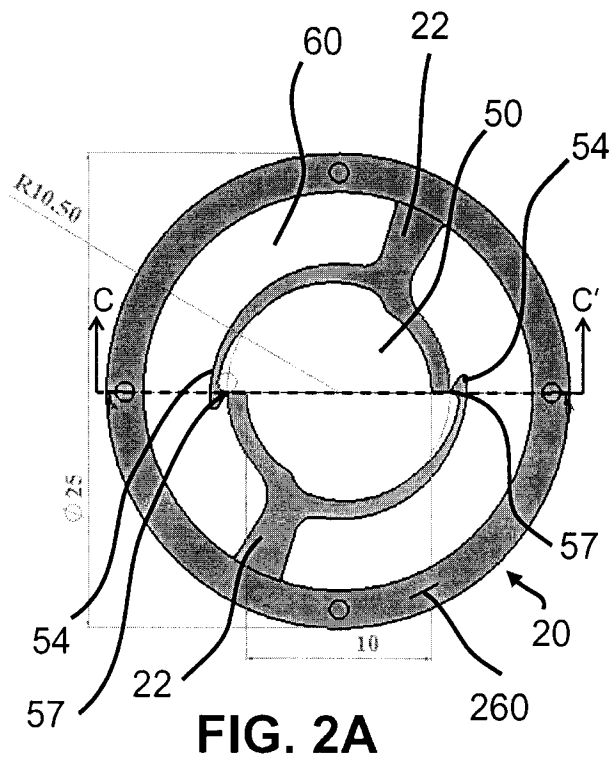


FIG. 1D



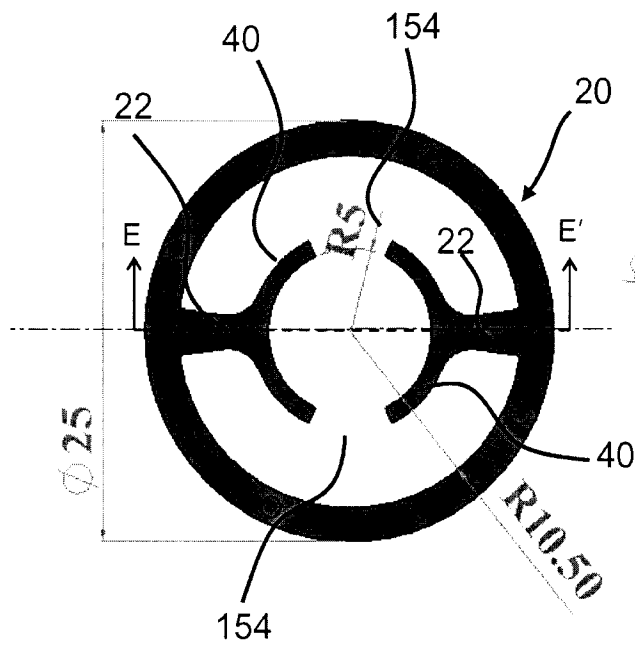


FIG. 3A

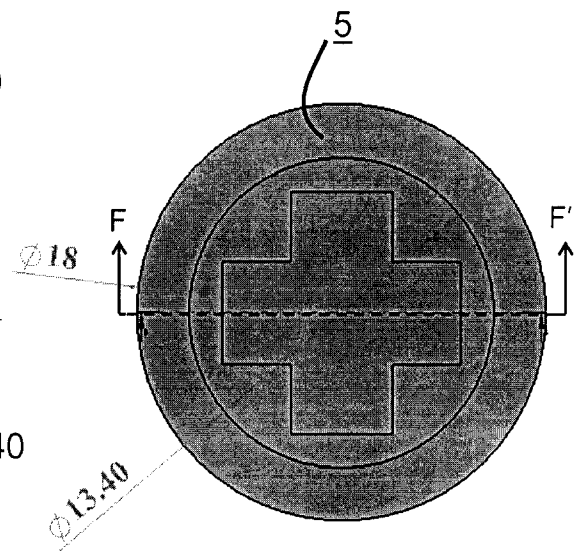


FIG. 3B

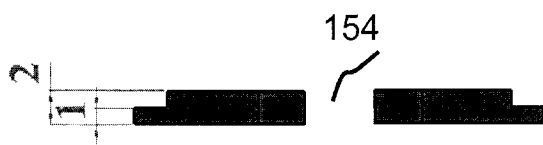


FIG. 3C

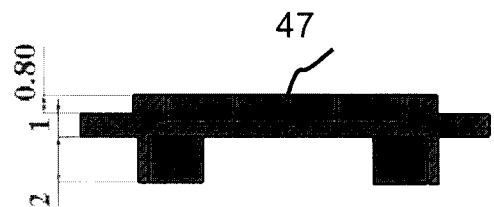


FIG. 3D

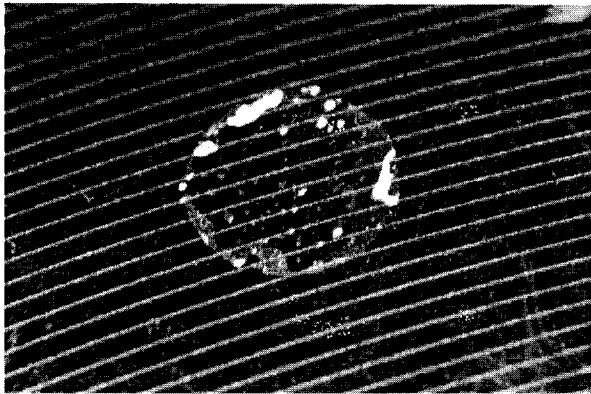


FIG. 4A

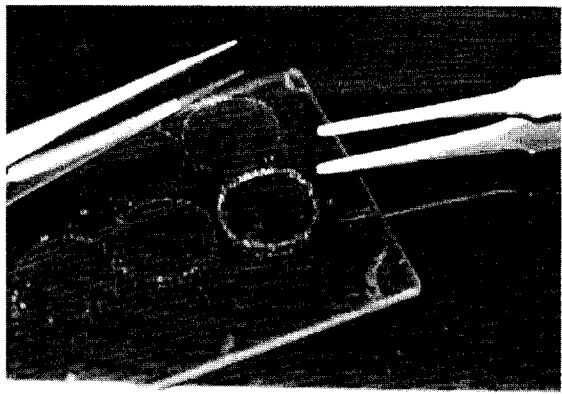


FIG. 4B

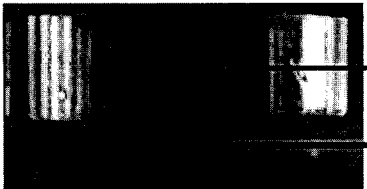
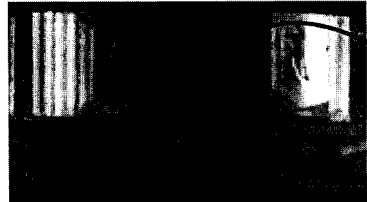
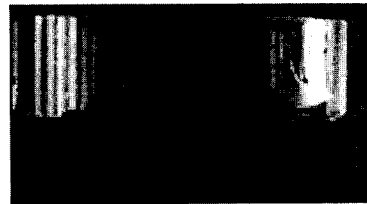
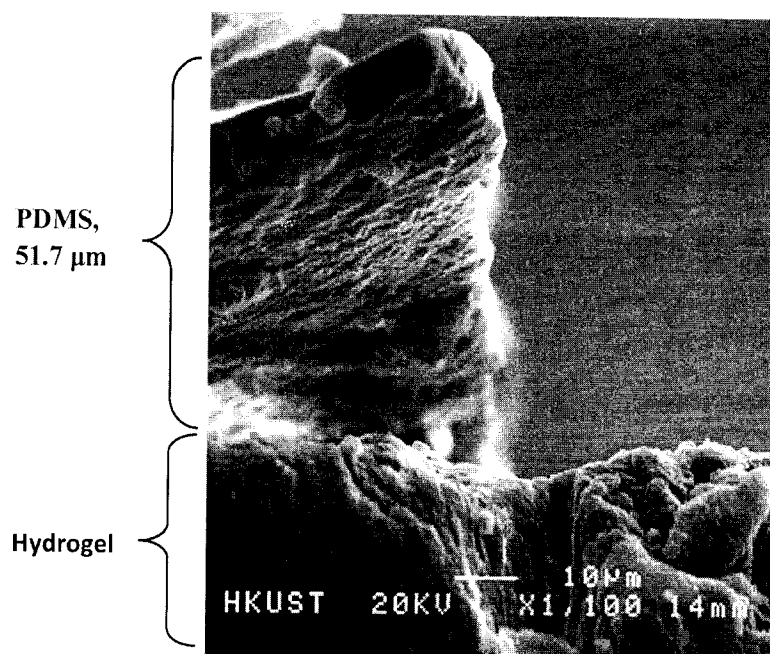
Time (hr)	Image of uncoated hydrogel swelling
0	2.46 mm {  85 50
1	
2	 90
3	
4	

FIG. 5

**FIG. 6**

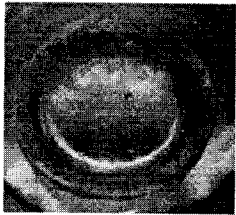
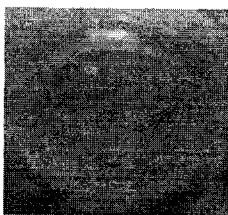
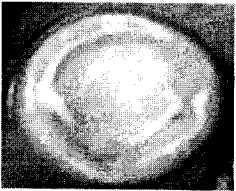
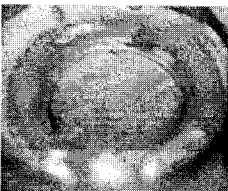
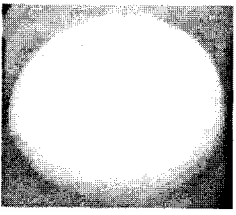
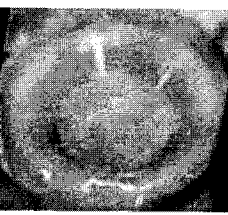
Time (hr)	Image of uncoated hydrogel swelling	Image of spray-coated hydrogel swelling
0		
1		
3		
5		

FIG. 7

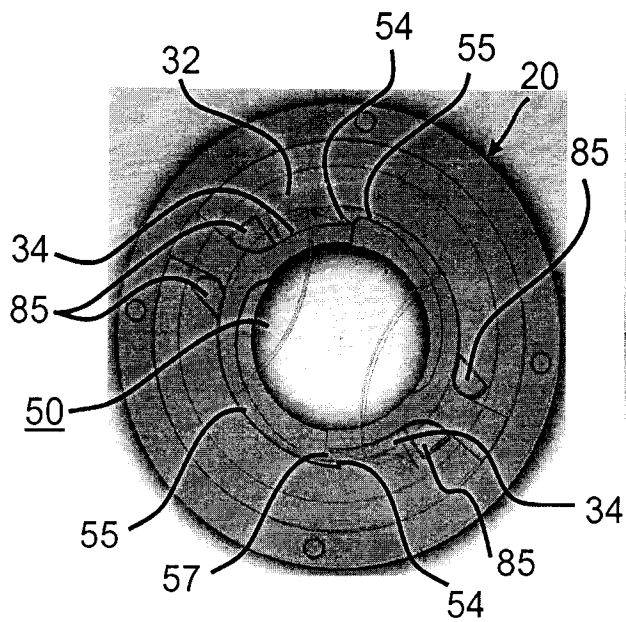


FIG. 11A

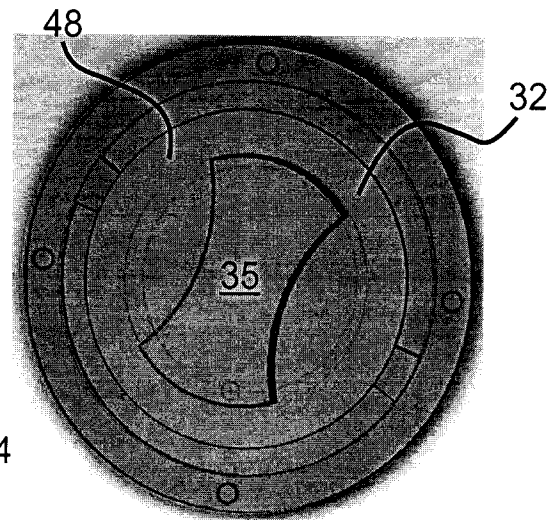


FIG. 11B

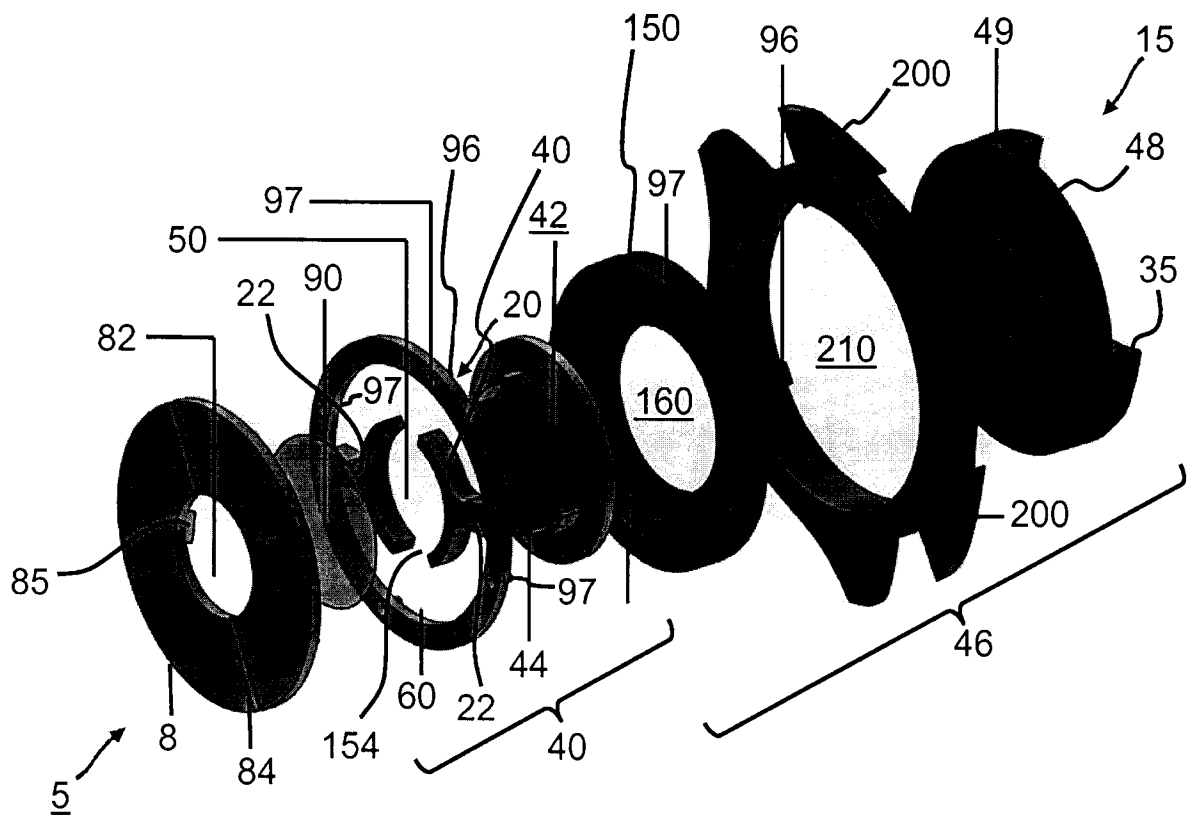


FIG. 12

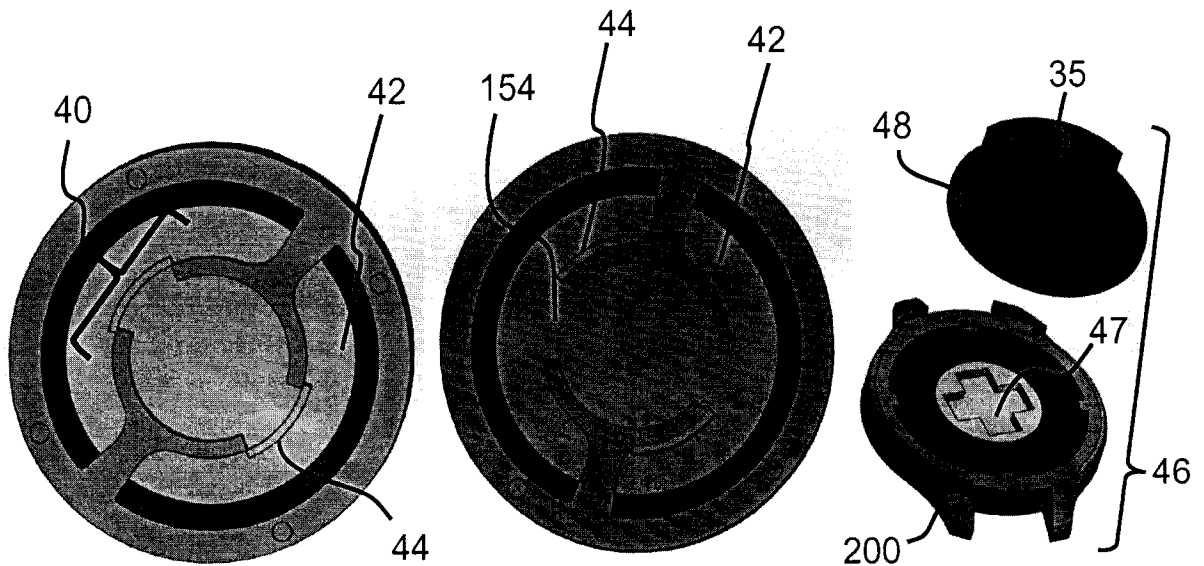


FIG. 13A

FIG. 13B

FIG. 13C

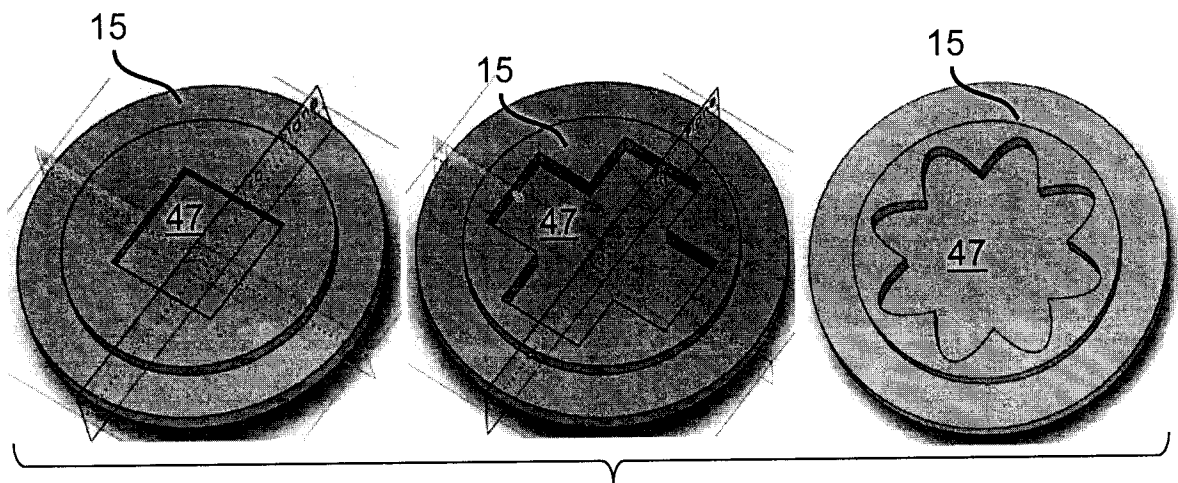
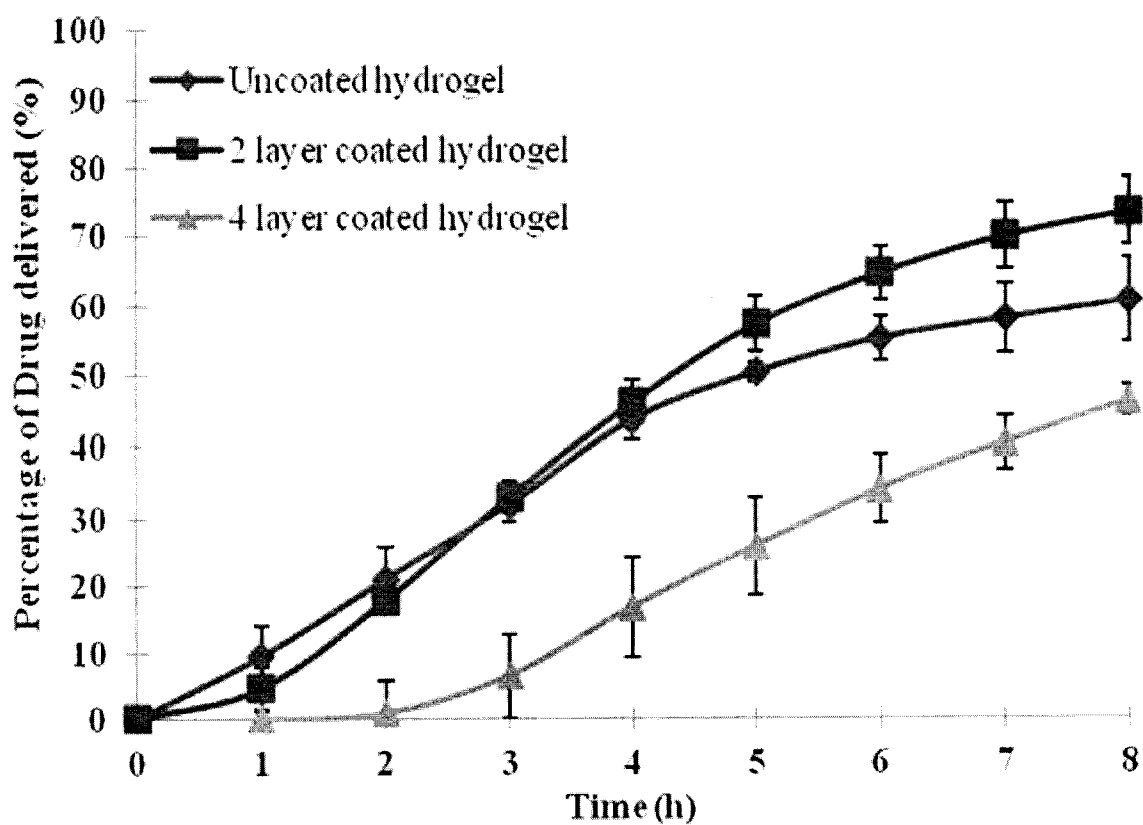
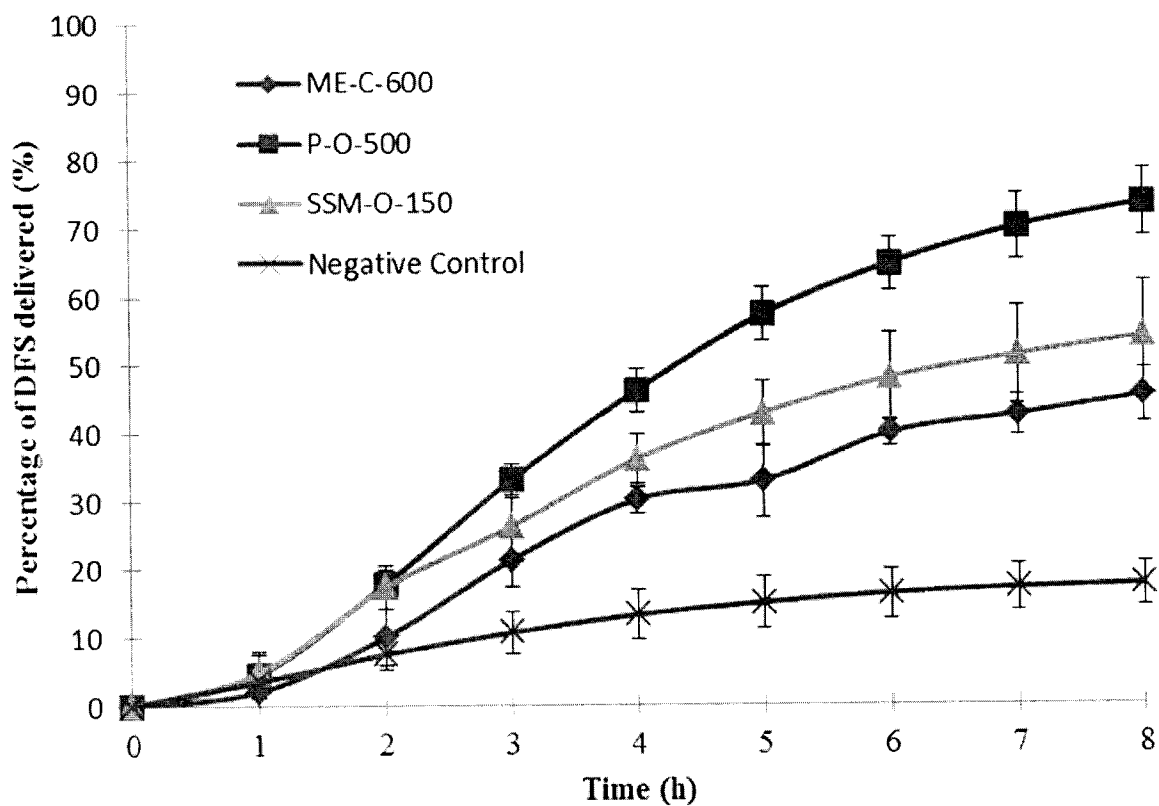


FIG. 14

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**FIG. 15****FIG. 16**

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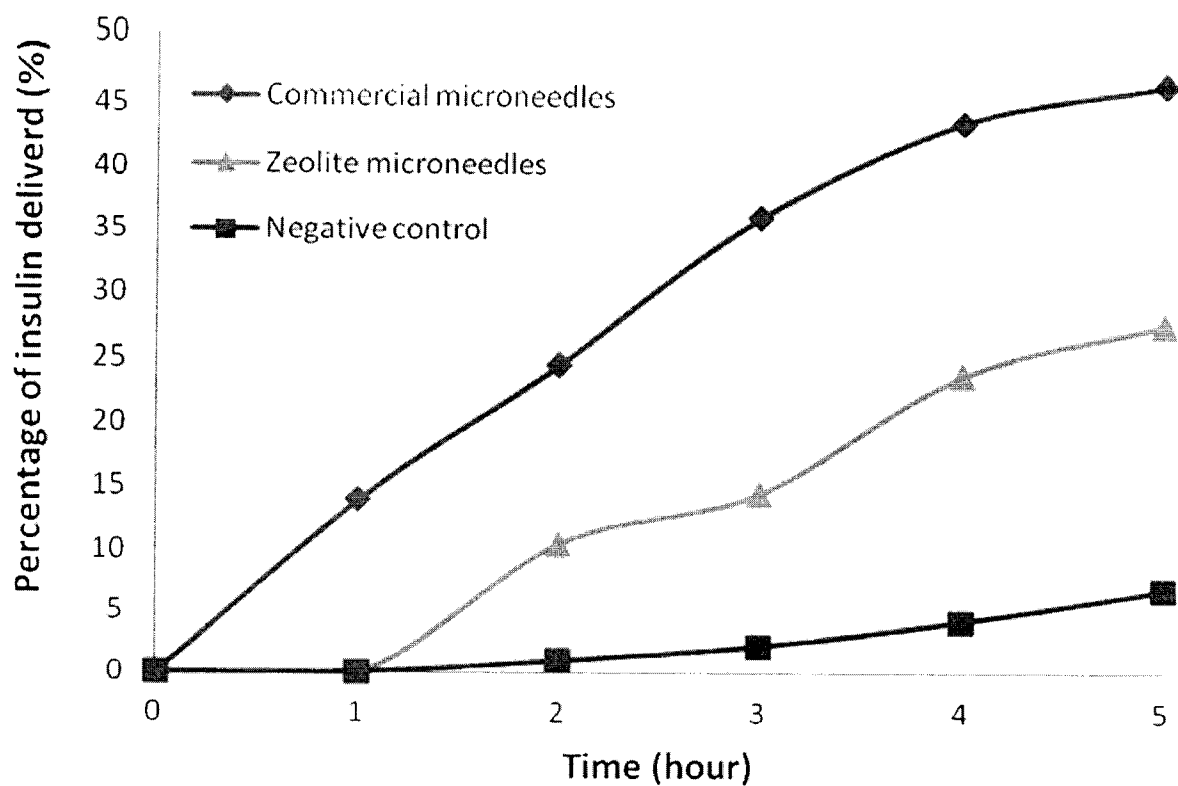


FIG. 17

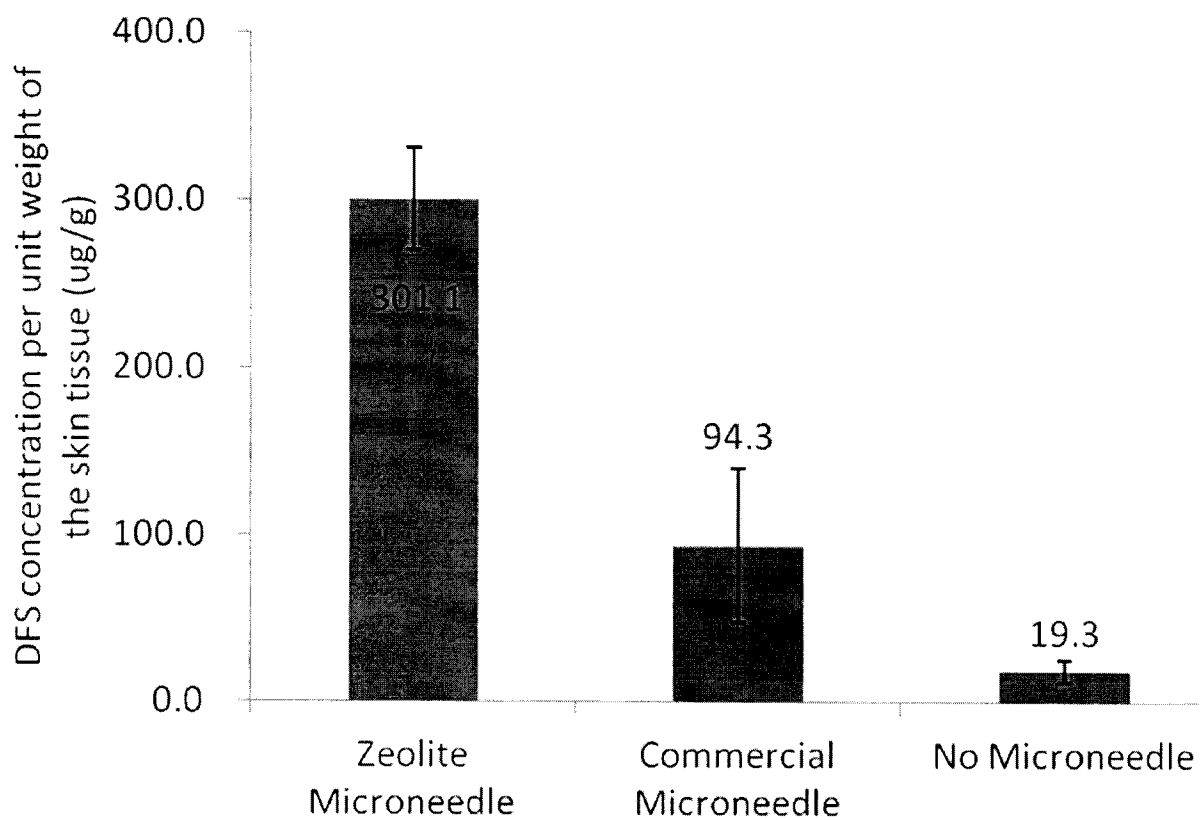
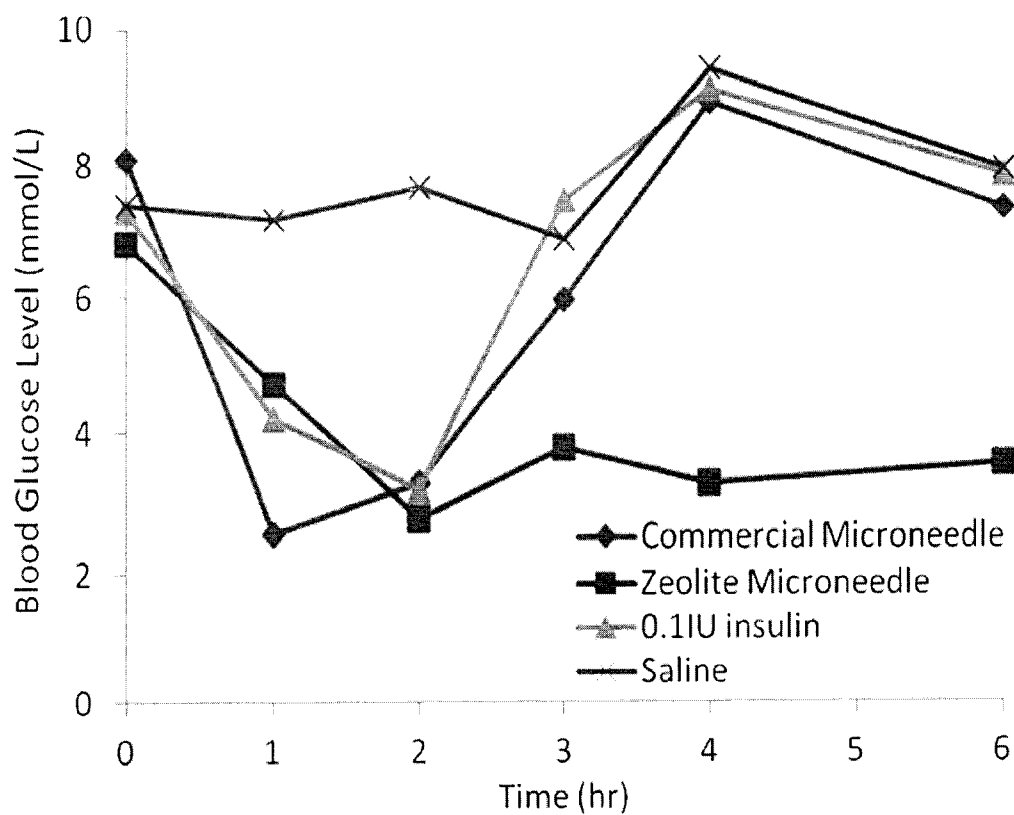
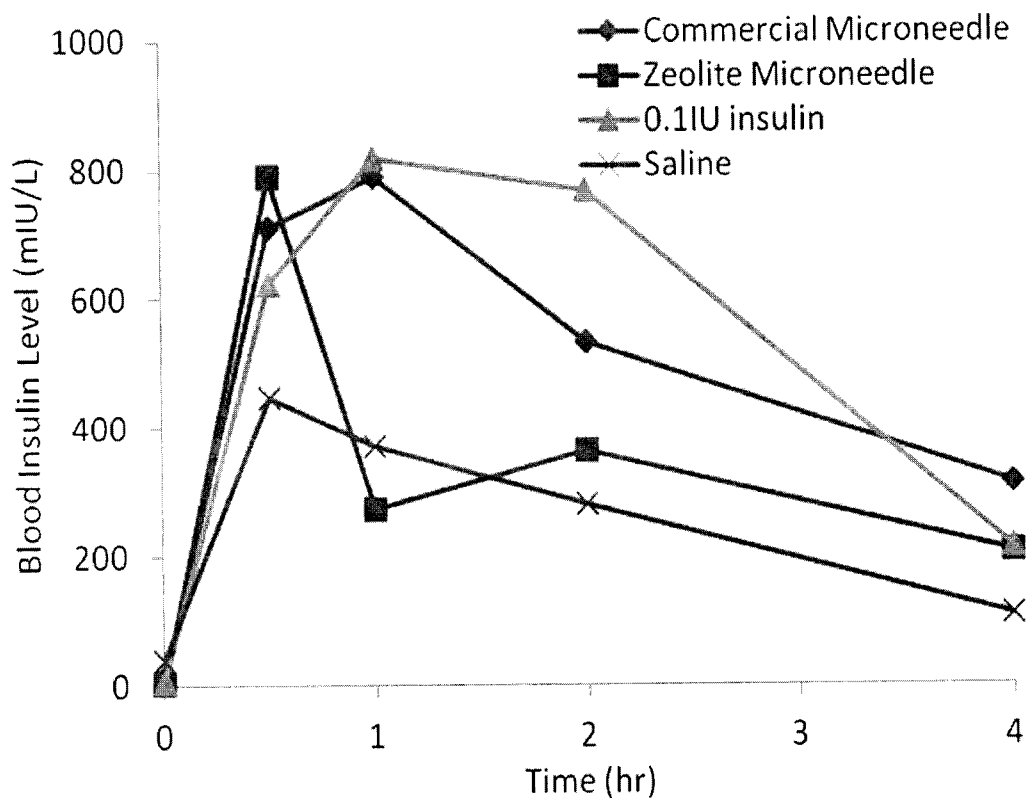


FIG. 18

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**FIG. 19****FIG. 20**

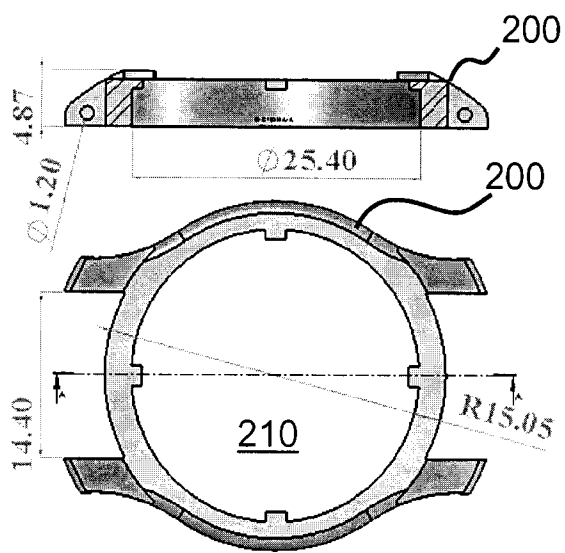


FIG. 21A

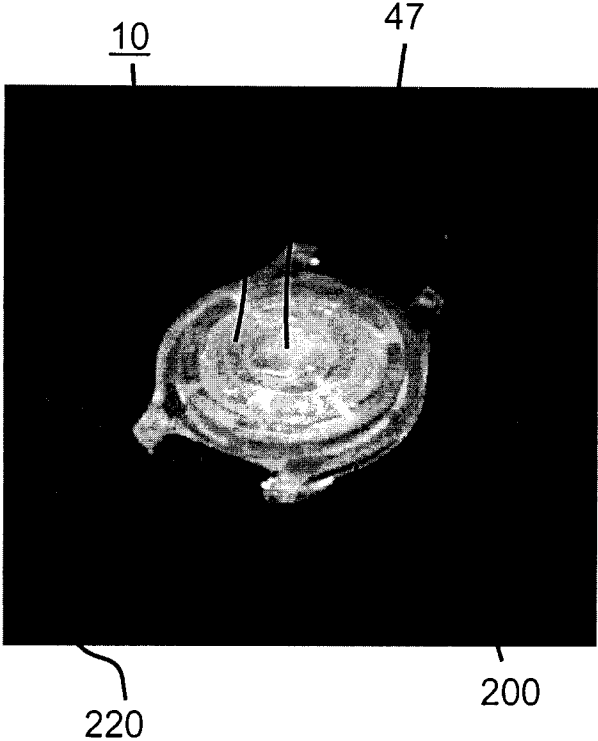


FIG. 21B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/001123

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/70 (2006.01) i

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)

IPC: A61K9/-; A61M37/-; A61M39/-; A61D7/-

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)

WPI,EPODOC,CNPAT,CNKI: Hong Kong University of Science and Technology, Yeung K, patch??. trans 1w dermal, TTS, TDDS, skin, drug?, transfer+, infus+, deliver+, release+, control+, long 1w term, activate+, water, actuat+, hydrogel, swell+, expand+, expans+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5800420 A (ELAN MEDICAL TECHNOLOGIES LIMITED) 01 Sept. 1998 (01.09.1998) abstract, column 14-15, Fig. 1	1-3, 11-13, 15-17
A	CN 101002756 A (TAO, Ran) 25 Jul. 2007 (25.07.2007) the whole document	1-20
A	CN 1186659 A (CHONGQING MEDICAL UNIVERSITY) 08 Jul. 1998 (08.07.1998) the whole document	1-20
A	US 4879119 A (YAMANOUCHI PHARMACEUTICAL CO., LTD.) 07 Nov. 1989 (07.11.1989) the whole document	1-20
A	US 4908213 (SCHERING CORPORATION) 13 Mar. 1990 (13.03.1990) the whole document	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:	“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
“A” document defining the general state of the art which is not considered to be of particular relevance	“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
“E” earlier application or patent but published on or after the international filing date	“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
“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)	“&” document member of the same patent family
“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	

Date of the actual completion of the international search 04 Nov. 2013 (04.11.2013)	Date of mailing of the international search report 21 Nov. 2013 (21.11.2013)
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer JIANG Bizhu Telephone No. (86-10)62413605

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2013/001123

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
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		AU 6370298 A	12.11.1998
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		AU 713246 B2	25.11.1999
		EP 0789540 A1	20.08.1997
		US 5807375 A	15.09.1998
CN 101002756 A	25.07.2007	None	
CN 1186659 A	08.07.1998	None	
US4879119 A	07.11.1989	None	
US 4908213	13.03.1990	AU 5106890 A	26.09.1990
		JP H04503357 A	18.06.1992
		EP 0384386 A1	29.08.1990
		EP 0471668 A1	26.02.1992
		WO 9009808 A1	07.09.1990