Title: TOPICAL OR TRANSDERMAL DELIVERY KIT

Abstract: The invention relates to delivery devices and methods using the dermal/topical and transcutaneous/transdermal route being applicable in the fields of therapy, cosmetics, and esthetics, and uses thereof for topical or transdermal delivery of a wide variety of effective agents like preventive and therapeutic vaccines, nanoparticle based medicines, drugs and cosmetic substances. More particularly, the invention provides specially designed, empty patch based delivery kits suitable for non-invasive transdermal delivery of active substances being in liquid or gel like form, said kits being especially useful for targeting epidermal Langerhans cells and, thereby, draining lymph nodes.
TOPICAL OR TRANSDERMAL DELIVERY KIT

Field of the invention:
The invention relates to delivery devices and methods using the dermal/topical and transcutaneous/transdermal route being applicable in the fields of therapy, cosmetics and esthetics, and uses thereof for topical or transdermal delivery of a wide variety of effective agents like preventive and therapeutic vaccines, nanoparticle based medicines, drugs and cosmetic substances. More particularly, the invention provides specially designed, empty patch based delivery kits suitable for non-invasive transdermal delivery of active substances being in liquid or gel like form, said kits being especially useful for targeting epidermal Langerhans cells and, thereby, draining lymph nodes.

Background of the invention:
One of the main problems in transcutaneous drugs/biologies delivery is to find a means to successfully transport a substance across the skin barrier layer, i.e. the stratum corneum. The stratum corneum is made up of keratinized cells, with the intercellular region composed of lipids and desmosomes. The stratum corneum plays a crucial role in barrier function and impacts on the occurrence of irritant reactions and absorption. The stratum corneum is hygroscopic, but impermeable to water, and behaves like a tough, but flexible membrane. Some chemicals are able to penetrate it and reach the underlying tissues and blood vessels without any assistance. These substances are characterized by a low molecular weight, lipophilicity and effectiveness at low dose levels.

The largest dose of drug in a patch form is that of nicotine at 21 mg.
Even though such molecules are absorbed through the skin it is a very slow process that is driven by passive diffusion. Hence, the delivery system must be kept in continuous contact with the skin for a considerable time (hours to days).
The major products currently marketed are the Transdermal Therapy Systems (TTS). Transdermal therapeutic systems (TTSs), commonly called "patches," generally consist of three parts: an adhesive, an active pharmaceutical drug, and enhancing agents. A number of types of TTS are currently available; these include reservoir, matrix, and local-action transcutaneous patches. Reservoir TTSs have a depot where liquid containing the active ingredient is stored for release through a rate-controlling membrane. The depot may be filled in advance (see e.g. WO2008145119) or upon use by syringe (US 5,827,530) or by other means (WO2008116925). In a matrix TTS, a mixture of the active ingredient, an adhesive, and other components is contained in a single layer that is directly adjacent to the skin; a rate-controlling membrane is not necessary (see e.g. WO99/07349). The matrix TTS film backing is a plastic derivative; the local-action transcutaneous TTS film backing is a nonwoven polyester. A local-action transcutaneous (LAT) patch is used to deliver nonsteroidal antiinflammatory drugs (NSAIDs) through the skin. It is similar to a matrix TTS, except that it includes a nonwoven polyester backing that supports an NSAID formulation.

Developing a TTS is, however, a complex and lengthy process, which is influenced for example by the stability (shelf life), the concentration and formulation of the active pharmaceutical ingredients (API) within the reservoir, the strict quality guidelines imposed on its production by current good manufacturing practices (cGMP) and the limited number of specialized companies than have sufficient knowledge for manufacturing them.

Furthermore, the rate and amount of absorption from a TTS can be influenced by many factors, including of course the nature of the drug (permeability and effective dose), the drug's concentration in the TTS reservoir, the
area of skin covered by the TTS, the inclusion of penetration enhancers and the type of penetration enhancer and
or the use of active transfer of drugs through the skin by means of iontophoresis, sonophoresis and electropora-
tion.

In practice, for each API, a completely new TTS has to be developed.

In WO-99/13915 applicants first experiences with transcutaneous application of substances is disclosed.

BALB/c mice were anaesthetized, and the backs of the mice were shaved. 0.1 ml of a liquid preparation was ap-
plied on the skin for one hour. The experiments demonstrated that

1) transcutaneous delivery of a substance to Langerhans cells was possible and

2) that the transduced Langerhans Cells migrated to the lymph nodes and therefore it was concluded that in

vitro isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the

lymphoid organs.

Although this did prove the assumption that transcutaneous delivery is possible, the method used could not be
transferred to human patients. As, in these experiments, no means of confining the applied preparations within a
particular space were used. Therefore, the mice had to be separated and anaesthetized to keep them from spilling
the contents, to prevent oral ingestion of the preparations and to prevent contamination.

In WO/2004/065575, the following improved procedure is disclosed:

1. Identify the sites for administration. For example, the left and right upper back (trapezius/suprascapular
region) and the ventral aspect of the proximal left and right thigh. Any other sites covered by skin or mu-
cosa can be also used.

2. Gently shave the administration sites using a disposable razor.

3. Disinfect the administration sites using 70% isopropyl alcohol swabs.

4. Gently abrade the surface at the sites. This can be done by rubbing an exfoliating sponge repeatedly (50
times back and forth) over the area, applying light pressure but taking care not to break the skin.

Use a new side of sponge for each site. Other exfoliation methods can be applied here as well, for example
using a special device.

5. Apply an adhesive to each site and immediately strip off in one quick movement to remove residual cell
matter on the skin surface. Repeat taping and stripping procedure at a 90 degree angle to the first taping
and stripping procedure with the same adhesive.

6. Using the 1 ml-syringe and needle draw the composition. Using the 1 ml-syringe (without needle !), apply
the composition to one site.

7. Distribute the liquid composition evenly over the administration site using the tip of the syringe, taking
care to avoid spillage beyond the administration site to ensure optimal dosing.

8. Cover the area with the non-absorbent wound dressing.

Although this procedure is already much improved compared to the procedure as used with the mice, it still
proved problematic during the subsequent clinical trial. The main problem being the lack of a means of contain-
ment from the time point at which the liquid formulation is applied, until the time point at which the wound
dressing is applied that covers and confines the administration area.

Even with the utmost care of the medical personnel and the best co-operation of the test subjects, always part of
the liquid preparation was lost by leaking and spillage. This resulted in dose inequality amongst patients and un-
wanted exposure of the medical personnel towards the applied treatment.
Object of the invention

We wanted, therefore, to find a practical and versatile method for transcutaneously delivery of substances, including preventive and therapeutic vaccines and small particles. The main object of the present invention is to provide methods and devices for safe, easy an needle-free delivery of different amounts of any (gel, fluid, unstable, sensitive etc.) substances directly to the surface of the skin, wherein the substances can be targeted to lymphoid tissues, blood or dermis, and the dose of the substances can be adjusted by volume, concentration, patch size or number of patches.

Our initial focus was on finding a practical method for transcutaneous delivery of preventive and therapeutic vaccines to epidermal Langerhans cells. The preferred route of administration for administering substances that should be taken up by Langerhans cells and subsequently delivered to the lymph node system is transcutaneous, because

1. The highest density of Langerhans cells is found in the epidermis, the area just below the stratum corneum, therefore a needle injection would miss these cells.

2. Langerhans cells are the precursor of dendritic cells. Langerhans cells are specialized to pick up pathogens, migrate to the lymph nodes and mature to antigen-presenting dendritic cells. Antigen presentation by dendritic cells is important for the induction of effective immune responses.

3. Transcutaneous administration of substances has been shown to be safe, convenient, non-toxic and not invasive, in the sense that no needles are used.

The transcutaneous delivery kit includes a skin preparation method that improves the penetration of substances across the skin and a special patch that serves to contain pharmaceutically acceptable formulations. The patch should be applied on a prepared skin characterized by an interrupted and cleaned stratum corneum. The cleaning and interruption also allows the incorporated substances to better access the layers of epidermal Langerhans cells. Only in a later stage, we understood that we developed a device and a procedure applicable for transcutaneous delivery of substances that do not have to be picked up by the Langerhans cells at all to be effective, like pharmaceutically acceptable formulations of small molecules.

Summary of the invention:

The transdermal delivery kit according to the invention (an advantageous embodiment of which is termed "DermaPrep" hereinafter) contains at least a patch, which comprises a liner and a film provided with an adhesive layer wherein said adhesive layer is arranged around at least one inner surface not covered with adhesive.

The adhesive layer is preferably arranged in a continuous line around the inner surface not covered with adhesive and there are means for opening and/or closing the space between the skin and said inner surface not covered with adhesive, said space having been created upon applying said patch to the surface of the skin.

According to a preferred embodiment, said means for opening and/or closing the space between the skin and said inner surface not covered with adhesive is said liner, which is divided by at least one cutting line providing at least one part covering at least one section of the adhesive and providing at least one lead in opening to the space between the skin and said inner surface not covered with adhesive, after removing the other part(s) of the liner and applying the patch to the skin.

According to another preferred embodiment, the patch is rectangular and said cutting line is arranged askew at one corner thereof and there is a printed casting sheet on back side of the film.
According to another preferred embodiment, the film is a 1.0 mm polyurethane film and the adhesive layer is a double coated Acrylate layer.

The delivery kit may contain a razor with at least two blades, for shaving the skin site to be covered by the patch, a body sponge, for exfoliating the skin site to be covered by the patch and medical tapes, for removal of the residual cells from the surface of the skin site to be covered by the patch.

The delivery kit preferably contains an applicator of liquid formulations, for feeding a predetermined dose of the substance(s) into the space between the skin and the inner surface not covered with adhesive.

The method according to the invention comprises the steps of identifying and preparing the appropriate administration skin site and applying the patch and the substance on the skin site.

The appropriate administration skin site comprises one or more steps of marking the site, shaving the site, disinfecting and cleaning the site, exfoliation of the site and removing of residual cells from the surface of the skin site.

The substance may be applied first on the skin site, and then the patch may be applied, after removing the whole liner (preferably when applying cosmetics or esthetics), or the patch may be applied first on the skin site, after removing the first part of the liner and the substance is applied through the lead in opening to the space between the skin and the inner surface not covered with adhesive, using a syringe (without needle) or any other applicator and the inner surface not covered with adhesive and provided with the substance is closed by removing the remaining part(s) of the liner.

The film may be removed after 1 - 24, preferably after 3 hours.

The invention further provides for the use of the kit of the invention for the topical or transdermal delivery of medical or cosmetic substances. The substances delivered by the kits and methods of the invention are advantageously immunomodulatory substances, like antigenic substances, immunosuppressive substances, immunostimulators and the like; nanoparticle based therapeutics comprising e.g. nucleic acid molecules capable of expressing at least one immunomodulatory substance; cosmetic substances like skin re-juvenilating materials such as hyaluronic acid, Restylane, collagen, botox, alpha-hydroxy-acids, estrogens, vitamin C and retinoids and the like.

In the uses according to the invention, the substances to be delivered are advantageously stored separately from the kit of the invention used.

The uses according to the invention advantageously comprise the pre-treatment of the skin at the administration site, advantageously by exfoliating the upper layer of the skin.

The features and advantages of the invention will be more apparent from the following detailed description of the device and method according to the invention given hereafter by way of illustration and in reference to the accompanying drawing.

**Brief description of the drawings**

**Figure 1:** Anatomical representation of the target Langerhans cells located under the stratum corneum in the epidermis. Comparison between horizontal administration using our transcutaneous delivery device with the vertical administration (e.g. needle injection and gene gun).

**Figure 2:** Transcutaneous delivery kit, patch components and the substance administration procedure.

**Figure 3:** Transcutaneous administration patch components and application procedure.

**Figure 4:** Administration of liquid formulations.
**Figure 5:** Description of the use of DermaPrep kit for administration of DermaVir Nanoparticles comprised of pDNA and PEIm.

**Figure 6:** The experiment represented in this figure demonstrated that the herein provided transcutaneous delivery kit successfully delivers liquid formulation into the body.

**Figure 7:** Tissue distribution of DermaVir vaccine administered with DermaPrep: (a) % tissue distribution of penetrated pDNA copies (1% of the detected pDNA) in 10 rabbits per test days (● - test day 7 or ○ - day 30). pDNA-based DermaVir vaccine was administered with the prototype device DermaPrep according to Instruction of Use. (b) Average copy numbers of pDNA detected in the lymph nodes on days 7, 30 and 60.

**Detailed description of the invention:**

The invention provides practical and versatile device and procedure for transcutaneous/transdermal delivery of diverse substances, including small molecules, drug products, cosmetics, esthetics, preventive and therapeutic vaccines, nanomedicines, nanoparticles and small particles.

One of the main problems in transcutaneous drugs/biologicals delivery is to find a means to facilitate transport of substances across the skin's barrier layer. Therefore, a first part of our transcutaneous delivery kit is a skin pretreatment procedure for reproducibly interrupting and cleansing this barrier layer. The second part of our transcutaneous delivery kit, the patch that is fillable with substances, should be applied over this pretreated skin area. In fact, during application of the patch, the pre-treated skin becomes an integral part of the patch assembly.

In earlier patent applications, i.e. WO-99/13915 and WO-2004/065575, we have described various procedures and the initial transcutaneous delivery method that we used to deliver DermaVir formulation (pDNA+PEIm complexes) across the skin and into the Langerhans cells. However, the described methods and the kit were not very practical in use and therefore to facilitate wide spread use once in commercial use, we were forced to find much improved ways for both the procedure as well as the patch component of the kit.

This forced us to rethink our transcutaneous administration procedure and device. Up until that point we had been using commercially available materials and components and we realized that these did not provide us with a decent solution, so we had to come up with our own designs for making the transcutaneous delivery kit and the procedure work properly.

After due experimentation we have developed the following transcutaneous delivery procedure and kit. The procedure consists of two distinct steps, (a) preparation of the skin and (b) the application of the patch and (c) administration the active substance under the patch.

We now present a device that enables reproducible transport of molecules across the stratum corneum and that is very flexible as the API is only incorporated within the system during application.

A schematic presentation of the whole procedure is presented in Figure 2. What happens during the actual administration (points 7 and 8) is presented in Figure 3.

1. **Identify the appropriate administration sites:**
   - Each administration skin-site corresponds to the size of one skin-patch. Recommended administration skin-sites are on the upper back and/or ventral upper thigh.
   - Note: The same administration sites can be used for subsequent administrations.

2. **Mark the administration sites (helpful but not required):**
   - Hold the skin patch to the administration skin-site and use a surgical marker to demarcate the outer corners of the patch. This mark serves as a guide for preparing the skin-site for administration.
3. **Shave** the entire marked skin site using a disposable razor with at least two blades.

4. **Disinfection and cleaning**: Disinfect the entire shaved skin-site using an alcohol swab. Wait for the skin-site to dry. Repeat this procedure three times using a fresh alcohol swab.

   Note: It is important that this procedure is performed thoroughly as it is the first step in removing the oily layer from the surface of the skin. In addition, it improves adherence of the patch to the skin and thereby reduces the risk of leakage after liquid administration.

5. **Exfoliation**: Exfoliate the marked skin-site by rubbing a body sponge back and forth over the demarcated area, applying pressure, but taking care not to break the skin. This should result in visible erythema (redness) at the skin-site. Rubbing of the body sponge might be performed up to 2-100 times, preferable 50 times back and 50 times forth, depending on the API properties.

6. **Removal of the residual cells from the skin surface**: Apply the first medical tape to the skin-site and immediately strip off in one quick movement. Repeat this process using same piece of medical tape, in order to cover whole area of the skin-site. Then apply second medical tape at 90 degree angle, and repeat process to cover whole area.

7. **Apply the transparent film dressing (patch) on the treated skin site**: Apply the patch so that the opened at the corner positioned to the top. Once the patch is adhered to the skin a container pocket is created between the patch and the skin.

8. **Administration**: 
   a) API formulations are applied under the patch using a syringe (without needle) or other applicators of liquid formulations (Figure 4: Administration of liquid formulations) via the open corner formed by (A), into the pocket formed by the transparent film dressing.
   b) Make sure that there are no bubbles left under the transparent film dressing and the whole surface is covered by a fluid layer.
   c) Remove the backing from (A) and seal the pocket completely.

9. **Removal of transparent film dressing**: The transparent film dressing should be removed after 1-24 hours, preferable after 3 hours. All treated sites can be washed with clean water.

**Development history of skin preparation procedure**:

As presented above the skin preparation procedure consists of the following steps: shaving, disinfecting, exfoliation, and stripping. The procedure has to ensure the cleansing and that the stratum corneum is adequately interrupted or removed, to no longer pose a barrier for entry of the applied substances into the deeper layers of the skin and more particularly into the epidermis where the Langerhans cells are located (Figure 1).

This skin preparation procedure induces mild and transient erythema that is essential to activate the Langerhans cells to pick up preventive and therapeutic vaccines, nanoparticles, small particles. These cells then migrate to the draining lymph nodes and mature to dendritic cells. Skin preparation does not cause bleeding or scar formation as it disrupts only layers of the stratum corneum and does not penetrate the dermis.

Dermabrasion resulting a scar formation would remove the epidermis together with the Langerhans cells and therefore would defeat the purpose of targeting the vaccines, nanomedicines and nanoparticles to Langerhans
cells. Transient mild erythema is an important indicator, because it represents the danger signal induced by the sponge exfoliation triggering cytokine production by keratinocytes and Langerhans cell migration to the lymphoid organs.

There are many alternative ways of reaching the same required result and therefore we do not want to limit ourselves in any ways to the exact steps used in this procedure.

Different means and methods of shaving and disinfecting the site may be used, different exfoliation procedures may be followed as well as different taping and stripping procedures.

It is only our preference to follow the procedure as outlined above and by using the materials described below.

Material specifications for skin preparation:

Any kind of electric and disposable razor blades can be used, but most preferably a double bladed one is applied. The desinfecting step is preferably performed by swabbing with 70 % isopropyl alcohol or ethanol. The body sponge surface should be sufficiently rough to disrupt the skin. Our preference is for a body sponge, that is similar to 3M™ Buf-puf; is a non sterile, flexible sponge for external use; the intended use is to cleanse and exfoliate skin. Most preferably we use a stronger sponge made of polyurethane pre-polymer foam, supplied to us by Illbruck (Washington, MN, USA) (now name Pinta FoamTech).

The Medical Tape is used to make sure that the loose skin material is removed. Any kind of tape may be used but we prefer to use a tape equivalent to 3M™ plastic medical tape 1526, with an intended use is to cleanse the skin. Our preferred material is 3M™ 1526 non-latex hypoallergenic single coated acrylate adhesive with printed paper liner

This skin preparation method has been shown to effectively remove the stratum corneum barrier layer at the site of application for the patch. This really is a major advantage, as this facilitates the transcutaneous absorption of any compound (API) administered under the patch.

Development history of the patch:

As described above, before arriving at our final presentation, the kit assembly was not really practical as it caused much leakage of material from the application area, leading to loss of material and unwanted exposure.

After careful deliberation we came to the conclusion that we needed to find a way to make a confinement area that was accessible for some time to enable the application of the compositions and that could be sealed of afterwards to avoid spillage and exposure.

The built up of the patch is illustrated in Figure 3. A is liner part A, B is liner part B, C is double coated adhesive + 1 mil polyurethane film and D is the casting sheet.

Surprisingly, we could create such a confinement area by divisioning the patch liner in two distinct parts, called A and B. After removal of the liner part B, the patch is applied to the exfoliated skin of a patient. The patch will stick to the skin by means of the double adhesive layer attached to the film C. The casting sheet D is removed at this point.

The confinement area needed for safely and effectively administering the liquid substances is created in this way. The skin forms one side of the area, the backing is provided by film C and the borders are sealed off by the adhesive layer B.

At the same time, the adhesive layer, cannot adhere to the skin in the place where liner A is still present and this creates the possibility for loading substances into the confinement area.
Only, after administration of the liquid substances into the confinement area, liner A is removed and the confinement area is completely sealed off by pressing the remaining and now exposed adhesive layer on the skin.

The whole produce ensures that the possibilities of leakage is enormously reduced, that a well-defined area is created that can be used to apply the compositions in a reproducible manner and that the risk of accidental exposure is greatly reduced.

Furthermore, it gives the now disclosed transcutaneous delivery kit and procedure an unexpected versatility. The versatility lies in the fact that by using this kit and procedure, that we are now capable of delivering any compound via the transcutaneous route, and especially substances that are not stable in ordinary patches. Any substance can be taken directly from the freezer, dissolved and applied to a patient without the need for elaborate stability studies.

The size of the application area has no real limitations and this gives the product a great dosing flexibility. In some applications, it may be only be necessary to use 0.1 ml of fluid, in other it may be 5 or 10 ml. In all cases, in principle the same delivery system can be used, either by using smaller patches or in contrast by enlarging the patch and/or by applying one or more patches to one and the same subject simultaneously.

The material to be filled into the patch upon assembly could be liquids, syrups, creams, paste or gels. The patch could also be filled with powders. Those powders could be dissolved or suspended by adding a solvent, preferably aqueous, before closing off the confinement area.

The combined features of a guaranteed passage across the stratum corneum, no need for stability studies and no limitations for size make the developed transcutaneous delivery kit ideal for use in research and for general delivery of a wide variety of substances.

Substances that can be delivered transcutaneously with this procedure could be preventive and therapeutic vaccines, nanomedicines, nanoparticles, peptides, proteins, DNA, RNA, RNAi, oligonucleotides, small organic and inorganic molecules, sugars, natural extracts, cosmetics, esthetics etc.

**Examples:**

**Example 1: Instructions for use on DermaPrep patches:**

**DermaPrep for Administration of liquid formulations**

**Procedure**

1. Identify the appropriate administration sites;

Each administration skin-site corresponds to the size of one skin-patch. Recommended administration skin-sites are on the upper back and/or ventral upper thigh. One skin-patch holds 0.6-1.2 mL of liquid.

Note: The same administration sites can be used for subsequent administrations.

2. Mark the administration sites:

Hold the skin patch to the administration skin-site and use a surgical marker to demarcate approximately 3 cm from the outer corners of the patch. This mark serves as a guide for preparing the skin-site for administration.

3. Shave the entire marked skin site using a disposable razor with at least two blades.

4. Disinfection:

Disinfect the entire shaved skin-site using an alcohol swab. Wait for the skin-site to dry. Repeat this procedure three times using a fresh alcohol swab.
Note: It is important that this procedure is performed thoroughly as it is the first step in removing the oily layer from the surface of the skin. In addition, it improves adherence of the patch to the skin and thereby reduces the risk of leakage after liquid application.

5. Exfoliation:
Exfoliate the marked skin-site by rubbing the yellow body sponge 50 times back and 50 times forth over the demarcated area, applying pressure, but taking care not to break the skin. This should result in visible erythema at the skin-site.

6. Removal of the residual cells from the skin surface:
Apply the first medical tape to the skin-site and immediately strip off in one quick movement. Repeat this process using same piece of medical tape, in order to cover whole area of the skin-site. Then apply second medical tape at 90 degree angle, and repeat process to cover whole area.

7. Apply the transparent film dressing (patch) on the treated skin site:
Ask the patient to bend down slightly and apply the patch according to the patch label.

8. Administration:
Ask the patient to sit straight to facilitate the application of at least half of the syringe under the transparent film. 0.8 mL liquid is applied under one transparent film using a 1-mL syringe (without needle) via the open corner formed by (A), into the pocket formed by the transparent film dressing.
Make sure that there are no bubbles left under the transparent film dressing and the whole surface is covered by a fluid layer.

Remove the backing from (A) and seal the pocket completely.

9. Removal of transparent film dressing:
The transparent film dressing should be removed after 3 hours. All treated sites can be washed with clean water.
Note: Transparent films must be double-bagged and may be discarded with general waste but must be kept safely out of reach of children or animals.

Example 2: DermaVir Biodistribution Study in Rabbits
The purpose of this study was to provide data on the distribution of the nanomedicine DermaVir developed for the treatment of HIV/AIDS. DNA plasmid encoding HIV genes was complexed with PEIm and dextrose to form a nanoparticle. The objective of the transdermal kit administrator was to deliver the nanoparticle to the lymph node dendritic cells.

Transcutaneous administration procedure and device was used as invented here.
On Day 1, the skin on both the left and right dorsal side of 62 New Zealand White rabbits was pre-treated as described in example 1. 40 animals received one administration with 0.8 ml of the aqueous test article (DermaVir), containing 0.1 mg DNA complexed with PEIm and dextrose, and 22 received 0.8 ml of the control article (aqueous dextrose solution), in both cases administered underneath two skin patches.

Animals were sacrificed on days 7, 30 or 60 for detection of plasmid distributed in organs and tissues (23 tissue samples per rabbit, including skin and muscle at treatment sites, untreated skin, whole blood, plasma, kidneys, lungs, heart, brain, thymus, spleen, liver, axillary, popliteal, inguinal, iliac and mesenteric lymph nodes, bone marrow, ovary or testes) via real-time quantitative PCR with a lower level of quantitation of < 10 copies/100 ng genomic DNA.
Tissue distribution by PCR of plasmid DNA in DermaVir (pLWXul) on Days 7, 30 and 60 showed that control animals were all negative for plasmid.

In DermaVir- treated animals at Day 7, each tissue was positive in at least one rabbit, with the exception of bone marrow, which was negative in all 10 rabbits. Skin from the scalp, treatment-site muscle, and axillary, inguinal, iliac and mesenteric lymph nodes were plasmid positive in at least 6 out of 10 rabbits. Treatment site skin samples were positive in all 10 animals.

By Day 30, plasmid levels had decreased in all DermaVir-treated animals. Whole blood, plasma, heart, lung, liver, bone marrow and testes were plasmid negative in all 10 animals. Kidney, brain, thymus, spleen and popliteal lymph nodes were plasmid positive in only one animal each and at or below the level of quantitation. Other lymph nodes, ovaries, untreated skin and treatment site muscle remained positive in a number of rabbits, and treatment-site skin remained positive in all 10 rabbits.

Only tissues that were positive at Day 30 were examined at Day 60, with the exception of testes. Ovary, brain, kidney and axillary, popliteal, inguinal and iliac lymph nodes remained sporadically plasmid positive in 1 of 3 rabbits; untreated skin was positive in 6 of 10 rabbits; treatment site muscle in 4 rabbits. Treatment site skin remained positive in all ten rabbits (see next Figure), at levels approximately tenfold lower compared to Day 7.

### Example 3: Example of successful transdermal application of standard drugs like fentanyl and nicotine with the invented procedure and patch

The ease with which drugs can be delivered through the skin has made the use of transdermal drug delivery patches popular for certain drugs. A number of patched are available for delivering a variety of drugs. Androderm patches manufactured by TheraTech (now Watson Pharmaceutical), Testosterone and analoges patches as manufactured by Alza, and nicotine scopolamine patches are also available. Other types of transdermal drug delivery patches are also known in the art.

Typically when a drug patch is applied to a patient's skin, the drug in the drug formulation is absorbed into the patient's skin. The absorption rate at which the drug leaves the drug formulation and penetrates across the patient's skin is dependent upon the skin barrier function, including the oily layer, stratum corneum, etc. Therefore, the length and efficacy of the transcutaneous patch treatment depend not only of the drug formulation but also on the skin barrier function.

Once past the patient's skin, some of the drug is absorbed into the patient's systemic circulation and carried throughout the body to a desired target tissue. The concentration of the drug in the patient's systemic circulation (the blood drug concentration) will be dependent upon the transdermal permeation rate of the drug. Transdermal drug delivery is a very slow process. For example, the 25µg/hr Duragesic fentanyl transdermal patch contains 2.5 mg of fentanyl and is intended to deliver 25 µg of it into the body per hour. That is a rate of 1% per...
hour. In one embodiment of our invention, our transdermal delivery kit and procedures is used to improve the delivery rate of the drugs by decreasing the skin barrier function. The increased drug delivery rate allows a shorter patch administration time to reach the appropriate blood drug concentration.

Another embodiment of the invention our transdermal patch supports the administration of substances, which are not co-formulated within the patch. This embodiment allows the administration of high concentration of drugs (API) in pharmaceutically accepted liquid formulation. Also, since the drug and the transdermal administration device are stored separately, our invention supports the administration of drug formulations, which are stored in frozen or powdered form and reconstituted to liquid formulation prior to administration.

In one embodiment, a liquid formulation containing for example high concentration of fentanyl or nicotine (API) is stored at appropriate temperature in a pharmaceutically suitable container (e.g. frozen temperature to improve the stability of the API and in plastic container with applicator as depicted in Figure 4 for simple administration of an appropriate dose under the patch).

Skin preparation procedure and patch application is performed as described in this patent application and the liquid API formulation is administered under the patch.

The skin barrier function is significantly decreased under the patch since the oily layer is cleansed and the stratum corneum is interrupted. Therefore, using the device described in this application the API will penetrate through the pre-treated skin faster than through the untreated skin. In addition, the desired plasma concentration of the API can be adjusted by the concentration of the API in the liquid formulation.

Advantages of this invention for transdermal drug administration:

- improved skin penetration of API
- shortening of the time wearing the patch to reach appropriate plasma API concentration
- no need for API and patch co-formulation
- API can be dosed in high concentration in liquid formulation
- API can be stored in low temperature that generally improve shelf-life
- Versatile use with many different substances (similar to syringe)

Example 4: Example of microdermabrasion for skin re-juvenilation using the skin pre-treatment procedure

One of the manifestation of aging skin is decreased ability to shed dead cells, resulting in various unsightly skin conditions. The mainstay of topical therapy of photo-aging skin is the chemical peel. A chemical peel is a procedure in which a topically applied wounding agent creates smooth, rejuvenated skin by way of an organized repair process. Complications of chemical resurfacing, including permanent sequelae, such as pigmentary dyschromias, infection, or scarring, may occur even though a controlled chemical wound induced.

Dermabrasion helps to "refinish" the skin's top layers through a method of controlled surgical scraping. The treatments soften the sharp edges of surface irregularities, giving the skin a smoother appearance. Dermabrasion is most often used to improve the look of facial skin left scarred by accidents or previous surgery, or to smooth out fine facial wrinkles, such as those around the mouth. It's also sometimes used to remove the pre-cancerous growths called keratoses. Dermabrasion can be performed on any areas of skin including the face. It can be used alone, or in conjunction with other procedures such as facelift, scar removal or revision, or chemical peels. Typi-
cally dermabrasion is conducted under anesthetic. Microdermabrasion is a cosmetic procedure in which the stratum corneum is partially or completely removed by light abrasion. Different methods include mechanical abrasion from jets of zinc oxide or aluminum oxide crystals, fine organic particles, or a roughened surface. Microdermabrasion is used to remove sun-damaged skin and to remove or lessen scars and dark spots on the skin. The procedure is not very painful and requires no anesthetic. Microdermabrasion can be used medically for scar removal when the scar is raised above the surrounding skin, but is less effective with sunken scars.

One embodiment of the present invention relates to dermabrasive skin care using the pre-treatment procedure with the administration of cosmetics or esthetics. It is expected that the pretreatment improves the penetration of cosmetics or esthetics to the epidermis and the dermis and the healing responses stimulate new cell growth, elastin and collagen production and improve skin tone and texture.

1. **Disinfection:**
   Disinfect the skin-site using an alcohol swab. Wait for the skin-site to dry. Repeat this procedure three times using a fresh alcohol swab.

2. **Exfoliation:**
   Exfoliate the skin-site by rubbing the body sponge back and forth over the target area, applying pressure, but taking care not to break the skin. This should be repeated until the exfoliation results in visible erythema at the skin-site. Preferred 50 time back and 50 time forth.

3. **Removal of the residual cells from the skin surface:**
   Apply the first medical tape to the skin-site and immediately strip off in one quick movement. In certain skin area (e.g. face) this process might be avoided. Repeat this process using same piece of medical tape, in order to cover whole area of the skin-site. Then apply second medical tape at 90 degree angle, and repeat process to cover whole area.

4. **Administer substances that enhance skin structure:**
   Pre-treatment of the skin decrease the barrier function of the skin and improves penetration of substances. For cosmetic re-juvenation, Hyaluronic acid (also called Hyaluronan) in an suitable formulation can be used. Hyaluronic acid is present in both the dermis and the epidermis. 50% of the body’s naturally produced hyaluronic acid that is found in the epidermis is metabolized and excreted in less than 24 hours. Like hyaluronic acid produced in the body, hyaluronan acid taken as a nutritional supplement moisturizes from the dermis to the epidermis - from deeper layers of the skin to the outer layer.

The extracellular matrix fills up the space between the skin cells. This makes the skin soft, smooth and elastic. But as we age, hyaluronic content in the skin changes due to two separate clinically proven factors.

   (a) There is a decrease in synthesis of hyaluronic acid.

   (b) Recompartmentalization - from the epidermis to the dermis.

Both changes leave the epidermis depleted in hyaluronic acid resulting in thinning, aging, and decreased moisture in the skin.

Therefore, for skin re-juvenilation the following embodiment present a clear advantage:

1. Microdermabrasion using the skin-pretreatment procedure removes the damaged skin
2. Administration of substances following pre-treatment that needs to penetrate the epidermis and the dermis, like Hyaluronic acid, will penetrate to the dermis and epidermis resulting in younger-looking and moisturized skin.

3. Healing responses stimulate new cell growth, elastin and collagen production and improve skin tone and texture.

On the basis of the description and examples, the main advantages of the invention are:
The skin does become an integral part of the patch and the patch needs not to be filled with a syringe and needle. Painless, needle free administration and effective transport of substances. The substances can be stored frozen or lyophilized and reconstituted prior to administration.

The dose can be selected by the volume and concentration of the substance or by the size and number of patches. Leaking of the substance is avoided.

There is no need for API and patch co-formulation and API can be dosed in high concentration.

In view of the many possible embodiments to which the principles of our invention may be applied, it should be recognized that the illustrated embodiments are preferred examples only of the invention, and should not be taken as a limitation on the scope of the invention. Among others, means for opening and/or closing the space between the skin and the inner surface not covered with adhesive may be any known elements as valves, seals, flaps etc., though the divided liner seems to be the simplest and easiest way to keep open and then close said space. The scope of the invention is defined by the following claims. We, therefore, claim as our invention all that comes within the scope and spirit of these claims.

**Example 5: Use of DermaPrep for vaccine delivery to the lymphoid organs**

During the discovery phase of DermaPrep development, we have demonstrated in mice and monkeys that after topical administration of a vaccine onto the prepared skin surface the antigen reached the draining lymph nodes and induced potent immune responses. We have shown that activated epidermal LCs picked up and transported the antigen from the skin to the local lymphoid tissues. To evaluate the potency of vaccine delivery to the lymphoid organs we performed a biodistribution study using DermaVir as model vaccine in combination with the prototype DermaPrep device. 30 rabbits received a single dose vaccine in glucose solution and 12 rabbits received glucose solution as negative control. The tissue distribution of the vaccine was examined by qPCR on days 7, 30 and 60 on 10 rabbits sacrificed every test days.

The vaccine distribution pattern demonstrated that DermaPrep effectively targets the vaccine to the lymphoid organs (Fig. 7). At day seven 99% of the vaccine remained on the treated skin sites and 1% penetrated into the tissues. This result was expected based on the suggested mechanism of action, because the LCs sampling the skin surface can pick up only a portion from the vaccine. However, 56% of the penetrated vaccine (average copy number 421 pDNA copies/100 ng chromosomal DNA; SD%=127) was detected in the lymph nodes and 32% (average copy number: 158 copies/100 ng DNA; SD%=222) in the treatment-site muscles. The distribution of the penetrated vaccine in tissues from plasma, whole blood, kidney, heart, brain, thymus, spleen, lung, liver and genitalia was ranged from 0.3 to 6% while the bone marrow was undetectable.

Thirty days after vaccination we found the same distribution pattern despite the antigen levels decreased in all tissues (Fig. 7A). The vaccine was still in the lymph nodes (47%; average copy number: 36 pDNA copies/100 ng DNA; SD%=105). This was a confirmation of the biodistribution results obtained seven days after vaccination, since it was obtained from different groups of animals sacrificed on a different day. Sixty days after vaccination
the amount of the vaccine decreased further. We sporadically detected weak positive signals in the lymph nodes (average copy number: 17 pDNA copies / 100 ng DNA; SD% = 200) (Fig. 7B). On days 7, 30 and 60 no vaccine was detected in any control animals.

5 Example 6: Clinical safety study with DermaPrep

We investigated the local reactions associated to the use of DermaPrep in 36 subjects during a placebo controlled, double blinded clinical study conducted with DermaVir and Placebo vaccines. DermaPrep administration was completed when the patch was removed, three hours after skin preparation. Similarly to the rabbit studies we found no differences between the Vaccine and the Placebo groups regarding adverse reactions, therefore the data presented here describes the effects of the DermaPrep medical device.

According to the protocol the treating physician team recorded whether local reactions occurred due to the adhesive used to secure the patch to the skin or to the Vaccine/Placebo administration. Local reactions were graded after every vaccine administration using the Local Reaction Immunization Site Assessment Scale (Table 1). Out of 672 DermaPrep vaccinations we found three times more adverse reactions, mainly erythema, caused by the adhesive (390) compared to the skin preparations and vaccinations (127), despite the acrylate adhesive used for manufacturing the patch is a frequently used medical grade adhesive (3M 1509). At the time of the removal of the patch we found 12% of subjects with mild and 1% with moderate skin reactions. Grade 1 side effects including macular eruption, papular eruption, erythema and pruritus and ulceration occurred in 88, 97, 296, 2 and 3 cases, respectively. The most severe adverse reactions were grade 2 (4 macular eruptions, 8 papular eruptions and 19 erythema cases). There were no Grade 3 or Grade 4 reactions and all skin reactions were reversible. Based on these results we concluded that DermaPrep is a safe and well tolerated vaccine administration device.

Table 1. Skin reactions associated with subsequent DermaPrep vaccine administrations in human subjects

<table>
<thead>
<tr>
<th>Number of events after 672 DermaPrep applications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Vaccination Site</td>
</tr>
<tr>
<td>Adhesive Tape</td>
</tr>
<tr>
<td>Grade 1 (&lt;%)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Macular Eruption</td>
</tr>
<tr>
<td>61 (9.1)</td>
</tr>
<tr>
<td>Papular Eruption</td>
</tr>
<tr>
<td>75 (11.2)</td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>79 (11.8)</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>0 (0)</td>
</tr>
<tr>
<td>Ulceration</td>
</tr>
<tr>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Grade 1 (mild): Macular or papular eruption, erythema, or induration that is asymptomatic or mildly symptomatic

Grade 2 (moderate): Macular or papular eruption, erythema or induration with pruritus, mild blistering or other associated moderate symptoms.
What we claim is:

1. A topical or transdermal delivery kit containing at least a patch, which comprises
- a liner (1 and 2) and
- a film (3) provided with an adhesive layer (4)

wherein
- said adhesive layer (4) is arranged around at least one inner surface not covered with adhesive, providing a space (5) between the skin and said inner surface not covered with adhesive upon applying the patch to the skin.

2. The delivery kit as claimed in claim 1, wherein
- said adhesive layer (4) is arranged in a continuous line around the inner surface not covered with adhesive, providing a closed space (5) between the skin and said inner surface not covered with adhesive upon applying the patch to the skin.

3. The delivery kit as claimed in claim 2, wherein
- there are means for opening and/or closing the space (5) between the skin and said inner surface not covered with adhesive.

4. The delivery kit as claimed in claim 3, wherein said means for opening and/or closing said space (4) between the skin and said inner surface not covered with adhesive is said liner (1 and 2), which is divided by at least one cutting line (6) providing at least one first part (1) covering at least one section of the adhesive layer (4) and providing thereby at least one lead in opening (7) to the space between the skin and said inner surface not covered with adhesive after removing the other part(s) (2) of the liner and applying the patch to the skin.

5. The delivery kit as claimed in claim 4, wherein said patch is rectangular and said cutting line (6) is arranged askew at one corner thereof.

6. The delivery kit as claimed in any of claims 1 to 5, wherein there is a printed casting sheet (8) on the back side of the film (3).

7. The delivery kit as claimed in any of claims 1 to 6, wherein said film (3) is a 1.0 mm polyurethane film.

8. The delivery kit as claimed in any of claims 1 to 7, wherein said adhesive layer (4) is a double coated Acrylate layer.

9. The delivery kit as claimed in any of claims 1 to 8, containing a razor with at least two blades, for shaving the skin site to be covered by the patch.

10. The delivery kit as claimed in any of claims 1 to 9, containing a body sponge, for exfoliating the skin site to be covered by the patch.

11. The delivery kit as claimed in any of claims 1 to 10, containing medical tapes, for removal of the residual cells from the surface of the skin site to be covered by the patch.

12. The delivery kit as claimed in any of claims 1 to 11, containing an applicator (9) of liquid formulations, said applicator being advantageously useful for measuring the volume of the liquid formulation to be applied.

13. A method for targeted transdermal delivery of medical, cosmetic or esthetic substances by using a kit as claimed in any of claims 1 to 12, comprising the steps of
- identifying and preparing the appropriate administration skin site and
- applying the patch and the substance on the skin site.
14. The method as claimed in claim 13, wherein preparing the appropriate administration site comprises one or more steps of marking the site, shaving the site, disinfecting and cleaning the site, exfoliating the site and removing residual cells from the surface of the site.

15. The method as claimed in claim 13, comprising the use of a kit as claimed in claim 2, wherein the substance is applied first on the skin site, and then the patch is applied after removing the whole liner.

16. The method as claimed in claim 13, comprising the use of a kit as claimed in any of claims 3-5, wherein:
   - the patch is applied first on the skin, after removing the first part of the liner,
   - the substance is applied through the lead in opening into said space between the skin and the inner surface not covered with adhesive, using a syringe (without needle) or any other applicator and, optionally,
   - the inner surface not covered with adhesive and provided with the substance is closed by removing the remaining part(s) of the liner and attaching the thereby provided adhesive surface to the skin.

17. The method as claimed in any of claims 13 to 16, wherein the film is removed after 1 - 24, preferably after 3 hours.

18. Use of a kit as claimed in any of claims 1 to 12 for the topical or transdermal delivery of medical, cosmetic or esthetic substances.

19. The use as claimed in claim 18 for the delivery of an active substance to the draining lymph nodes.

20. The use as claimed in claim 18 or 19 wherein a kit as claimed in claim 2 is used and wherein the substance is applied first on the skin site, and then the patch is applied after removing the whole liner.

21. The use as claimed in claim 18 or 19 wherein a kit as claimed in any of claims 3 to 5 is used and wherein:
   - the patch is applied first on the skin, after removing the first part of the liner
   - the substance is applied through the lead in opening into said space between the skin and the inner surface not covered with adhesive, using a syringe (without needle) or any other applicator and, optionally, the inner surface not covered with adhesive and provided with the substance is closed by removing the remaining part(s) of the liner and attaching the thereby provided adhesive surface to the skin.

22. The use as claimed in any of claims 18 to 21 for the delivery of an immunomodulatory substance.

23. The use as claimed in any of claims 18 to 22 for the delivery of an antigenic substance.

24. The use as claimed in any of claims 18 to 22 for the delivery of an immunosuppressive substance.

25. The use as claimed in any of claims 18 to 24 for the delivery of a nucleic acid capable of expressing at least one immunomodulatory substance.

26. The use as claimed in any of claims 18, 20 or 21 for the topical or transdermal delivery of a skin rejuvenating material.

27. The use as claimed in claim 26 for the delivery of a substance selected from the group consisting of hyaluronic acid, Restylane, collagen, botox, alpha-hydroxy-acids, estrogens, vitamin C and retinoids.

28. The use as claimed in any of claims 18 to 27 wherein said substance is stored separately from said kit.

29. The use as claimed in any of claims 18 to 28, wherein said use comprises the pretreatment of the skin at the administration site, advantageously by exfoliating the upper layer of the skin.

30. The use as claimed in any of claims 18 to 29 for the delivery of nanoparticles.

31. The use as claimed in any of claims 18 to 30 for the delivery of active substances being present in a composition applied in gel condition.
Figure 3

1. Step one - peel off liner 1 using liner 2 to hold the patch

2. Step two - apply the patch firmly to the skin with 2 at the top right corner

3. Step three - remove the printed casting sheet 8

4. Step four - introduce the substance into the area between the patch and the skin via the corner tab

5. Step five - remove liner part 2 and seal off 3

Legend:
- 1 = Liner
- 2 = a 1.0 mil polyurethane film with double coated Acrylate adhesive around the edges
- 3 = Casting sheet
- 4 = 6 = 7 = 8
Figure 4
Ingredients

- One yellow Body Sponge
- Four Medical Tapes
- Two Transparent Film Dressings (Patch)

In addition, the following materials are required:
- Liquid
- Gloves
- Marker
- Razor
- Cotton Pad
- Alcohol
- Syringe

Mark The Treatment Sites

Without removing the backing, hold the patch to the treatment site and use a surgical marker to demarcate approximately 3 cm from the outer corners of the patch. This will serve as a guide for preparing the skin for application.

Shaving

Shave the entire marked skin site using a disposable razor.
Apply The Skin Patch ll.
- Apply patch to the skin so that the triangle corner is positioned at the top right hand corner of the site.
- Once the patch is adhered to the skin, a pocket is created between the patch and the skin surface.
- Firmly press and smooth the entire perimeter of patch to ensure complete contact with the skin and prevent leaking.
- Once liquid formulation is applied to the pocket.

Apply The Patch lll.
- Remove the first stabilizing printed layer and firmly press again along edges of adhesive patch to ensure complete contact with the skin.

Application Of Liquid Formulation
- Carefully insert e.g., the 1-ml syringe (without needle), via the open right top corner formed by the triangle backing, into the pocket formed by the patch, so that the tip reaches the lower third of the pocket.
- Slowly expel the liquid formulation into the pocket, and withdraw the syringe.

Bubbling
- Make sure that there are no bubbles left under the patch and the whole surface is covered by a fluid layer.
Figure 5 continued

Remove The Triangle Backing
- Remove the triangle backing and seal the pocket.

Sealing
- Seal the pocket completely.
- Note: Check that all edges of the transparent film dressing adhere well and are sealed. If NOT, or in case of leakage, reinforce transparent film dressing borders with surgical tape.

Removal And Disposal Of Skin Patch
- Keep the patch on the skin as required.
- Note: Patches must be double-bagged and may be discarded with general waste but must be kept safely out of reach of children or animals.
### A. CLASSIFICATION OF SUBJECT MATTER

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

#### INV.

A61K 9/70

ADD.

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, MEDLINE, 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>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>examples 21-22, claims 1-47, figures 1-3</td>
<td>1-31</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C

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 document 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
- "S" document member of the same patent family

Date of the actual completion of the international search

20 May 2010

Date of mailing of the international search report

14/06/2010

Name and mailing address of the ISA/

European Patent Office, P B 5818 Patentlaan 2

NL-2280 HV RIJSWIJK

Tel (+31-70) 340-2040, Fax (+31-70) 340-3016

Authorized officer

Sindel, Ulrike
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2587613 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1811934 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20070085773 A</td>
</tr>
</tbody>
</table>