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(57) Abrégé/Abstract:
A transdermal medicament delivery device in the form of a printed temporary tattoo (2) which conceals the fact that the wearer is taking a drug. The ornamental appearance actually provides an incentive for wear. The medicated tattoo (2) includes a section of cardstock base paper (70), a clear base (50) bearing an ink design on one side, the clear base being attached to the cardstock base paper (70) on the other side by a release base (60) that dissolves when wet to allow detachment of the base paper, and an adhesive layer (20) coated over the ink design on the clear base for adhesion to the skin. A medicament or drug (30) is incorporated into the adhesive layer for diffusion therefrom into the skin of the wearer, and the adhesive layer (20) has predetermined permeability characteristics to ensure effective transdermal delivery of the medicament (30). The process for making the transdermal tattoos includes lithographic printing and silk screen coating to create the necessary layers, inclusive of drug deposition on the control membrane. Th net result is less susceptible to being dislodged, thereby allowing more conventional low-strength skin adhesives to make intentional removal easy and painless. Moreover, the tattoo can provide an outward visual indication of the progress of delivery.

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MEDICATED TATTOOS

Technical Field

The present invention relates to transdermal drug and nutraceutical delivery and, more particularly, to a transdermal medicament delivery device in the form of a printed temporary tattoo.

Background Art

Topical drug delivery is well-known for the treatment of local skin disorders, but the use of the skin as a route for systemic drug delivery is a more recent development. Very few transdermal products have been approved to date, largely because of the complexities involved in achieving a consistent delivery rate. There are many variables that influence the absorption of drugs across the skin and into the general circulation, including the biological properties of the skin, chemical properties of the drug, and the interactions between skin and drug delivery system. Systematic studies have led to compilations of permeability data for a range of drugs through skin, both stratum corneum and dermis. These studies reflect the large variability and slowness of the process for most drugs. Consequently, only a few drug candidates are currently available in dosage forms for transdermal drug delivery. There are efforts to improve the process which involve conditioning the skin. For example, U.S. Patent No. 5,455,611 to Eppstein et al. teaches the need to condition the skin by chemical enhancers and ultrasound in order to promote the effectiveness of transdermal drug delivery.

On the other hand, there are a number of formulation approaches to the drug delivery device itself. For example, the structure of existing transdermal devices may be simple two-layer designs. For example, US Patent No. 4,598,004 to Heinecke shows a drug delivery bandage including a pressure sensitive adhesive on a liner, the liner in turn being securely adhered to a drug delivery strip.

Alternatively, transdermal designs may include more complex materials and

structures to accomplish drug delivery, depending on the particular application.

For example, U.S. Patent No. 4,666,441 to Andriola et al. shows an original transdermal patch construction with multiple pockets.

U.S. Patent No. 5,788,983 to Chien et al. shows a controlled-delivery transdermal patch in which medicaments are held in micro-reservoirs and diffuse through a permeable membrane to the skin.

Microencapsulation of substances is another recognized transdermal delivery approach. For example, U.S. Patent No. 4,597,960 to Cohen teaches microencapsulated astringents for transdermal delivery.

All of the foregoing and other known transdermal devices are formed as multi-layer laminated "patches" that contain a drug reservoir. For example, more than 75 percent of the patches in the world contain 3M components which include a protective backing, an underlying drug reservoir, a controlled release membrane for leaching the drug, and an underlying skin adhesive. A wide variety of skin contact adhesives may be used including silicone, acrylate, polyisobutylene (PIB) and rubber based adhesives. 3M employs a proprietary lamination process to bond the foregoing, and the net result presents a number of significant problems. First of all, the intricate lamination process is not well-suited for mass production as the drug must be injected into the reservoir, and such patches are quite expensive to manufacture. In addition, the patches do not maintain a low profile on the skin and are susceptible to being dislodged. The cloth generally absorbs moisture and this detracts from the efficacy and facilitates dislodgement. The current way of preventing premature dislodgment is to increase the strength of the adhesive, but those who have used nicotine patches will agree that this makes intentional removal difficult and painful, and often leaves irritable skin marking. Aside from cost, there are serious practical disadvantages. The patches are unsightly and advertise the fact that the wearer is taking a drug, thereby providing a disincentive to wear them. Moreover, aside from blood tests, there is absolutely no way to monitor whether the drug is being absorbed or not.

There is an another consumer oriented technology that is also developing

rapidly, and this offers as-yet untapped benefits to the transdermal industry. Temporary tattoos possess many qualities that could make transdermals more practical, such as economy of manufacture (using standard lithographic and silk screen printing processes), ease of application, temporary effect, and motivation to wear them for their aesthetic appeal. United States Patent No. 5,776,586 is one example of a tattoo process involving standard lithographic and silk screen procedures. The process simply involves coating pre-laminated cardstock with a water-soluble release agent, applying a transparent membrane, printing a tattoo design on the membrane, and applying a protective coating.

Since tattoos are printed they can easily be made to display simulative child appealing characters or other indicia, thereby providing a great incentive for children to take their medicine. Moreover, by this process the printed tattoo can be made with ink that disappears or changes color as the medicine is absorbed, for the first time giving a positive indication of the rate and efficacy of transdermal delivery.

Consequently, it would be greatly advantageous to adapt temporary tattoos and their lithographic/silk screen production processes to transdermal medicament delivery, and to thereby introduce all of the potential aesthetic and display advantages of temporary tattoos in the transdermal field.

Disclosure of Invention

It is, therefore, an object of the present invention to provide a transdermal medicament delivery device in the form of a printed temporary tattoo.

It is another object to simplify manufacturing by eliminating lamination and instead relying on lithographic printing and silk screen coating to create the necessary layers, inclusive of drug deposition on the control membrane.

It is another object to provide a low profile transdermal that does not absorb moisture and is less susceptible to being dislodged, thereby allowing more conventional low-strength skin adhesives to make intentional removal easy and painless.

It is another object to provide a transdermal medicament delivery device that provides an outward visual indication of the progress of delivery.

It is still another object to provide a transdermal medicament delivery device that looks like a tattoo so as not to advertise the fact that the wearer is taking a drug, the ornamental appearance actually providing an incentive for wear.

It is another object to provide a transdermal device that displays ornamental simulative child appealing characters (fixed, appearing over time, or disappearing) or other indicia in order to give children an incentive to take their medicine without a fight.

According to the present invention, the above-described and other objects are accomplished by providing a transdermal medicament delivery device in the form of a printed temporary tattoo, and a process for making the same. The medicate tattoo includes a section of cardstock base paper, a clear base bearing an ink design on one side, the clear base being attached to the cardstock base paper on the other side by a release base that dissolves when wet to allow detachment of the base paper, and an adhesive layer coated over the ink design on the clear base for adhesion to the skin. A medicament or drug is incorporated into the adhesive layer for diffusion therefrom into the skin of the wearer, and the adhesive layer has pre-determined permeability characteristics to ensure effective transdermal delivery of the medicament.

The process for making the transdermal tattoos includes the steps of lithographic printing of the ink design on top of a clear base, silk screening a drug substance layer onto said the clear base opposite said ink design, and adhering a cardstock base to the drug substance layer.

Brief Description of Drawings

Other objects, features, and advantages of the present invention will become more apparent from the following detailed description of the preferred embodiment and certain modifications thereof when taken together with the accompanying

drawings in which:

FIG. 1 is an exploded diagram of the transdermal tattoo 2 according to the present invention.

FIG. 2 illustrates an embodiment in which the underlying adhesive layer 20 is specially-formed with microscopic pores to control the leaching out of the active medicament from the drug substance layer 30.

FIGs. 3 and 4 illustrates two steps in a process for applying a paste/solution form of the medicament and adhesive by silk screening to leave pattern deposits 120 of medicament on the transdermal tattoo 2.

FIG. 5 illustrates a transdermal tattoo 2 incorporating a color-scale 23 for visual comparison to give the user an indication of absorption progress.

FIG. 6 illustrates a transdermal tattoo 2 with thermometer-like gradient scale indicator 43 to give the user an indication of absorption progress.

FIG. 7 illustrates a transdermal tattoo 2 with disappearing character spots 33 to reinforcing useage by children.

Best Mode(s) for Carrying Out the Invention

The structure of the transdermal tattoo according to various embodiments of the present invention is herein described, along with preferred production methods, and various candidate drug substances that can be delivered. In addition, the description includes the manner of applying the medicated tattoo 2, and optional absorption progress indicators and child reinforcement features that can be incorporated to increase the utility of the invention.

1. Structure of the Transdermal Tattoo 2.

FIG. 1 is an exploded diagram of the transdermal tattoo 2 according to the present invention. The transdermal tattoo 2 generally comprises the following seven layers:

20. Adhesive layer

30. Drug substance layer

40. Colored layer

50. Clear base

60. Release base

70. Base Paper.

The base paper 70 is conventional cardstock. A 10 point thickness is preferred, although anywhere from 6 to 15 point thicknesses are acceptable. Specifically, a 10 point recycled content base paper 70 with excellent water absorption, and no lamination, is best suited. A matte-finish holds the inked design very well.

Base paper 70 is coated with a release base 60 that dissolves when wet to allow detachment of the base paper 70 from the functional (skin-attached) portion of the transdermal tattoo 2. The release base 60 preferably comprises nonyl phenol polyoxyethylene sulfate and/or ammonium polyoxyethylene alkylphenylether sulfate. As will be described, the release base 60 is preferably screen-printed onto the base paper 70 before the colored layer 40 is printed thereon, as this helps to prevent the colored ink from absorbing into the paper 70.

A clear base 50 is adhered by the release base 60 to the base paper 70 to provide a flexible skin-attachable substrate that preserves the quality of the ink colored layer 40.

The colored design layer 40 is an inked design that is printed atop the clear base 50 (opposite base paper 70) in mirror-image fashion. This way, when the clear base 50 is applied to the skin of the wearer, the colored design layer 40 shows upward there through and appears as a tattoo design. Thus, the device 2 does not advertise the fact that the wearer is taking a drug, and the ornamental appearance provides an incentive for wear. The colored design layer 40 preferably comprises non-toxic printing inks, and preferably any standard Food & Drug approved dyes such as FD&C yellow #5 aluminum lake, FD&C yellow #6 aluminum lake, FD&C blue #1 aluminum lake, FD&C red #7 aluminum lake, synthetic iron oxide pigment(black), and/or other inks of vegetable origin. For example, Colorcon® produces acceptable regulated printing inks for the medical industry, and specifically for narrow-web pouch and label

applications.

The drug substance layer 30 comprises an active medicament to be delivered transdermally. The drug substance may be incorporated as a separate layer 30 as shown in FIG. 1, or alternatively may be mixed in with an adhesive layer 20 as will be described. Any number of drug substances may be delivered transdermally by use of the present device 2, inclusive of over-the counter drugs such as acetominaphen, prescription drugs such as insulin, and vitamins and dietary supplements such as vitamin C.

The drug substance layer 30 is coated with an adhesive layer 20 for bonding with the skin. The adhesive layer 20 is preferably an acrylic resin adhesive such as Tegaderm (3M)®, Bioclosure (Johnson & Johnson)®, Op-site (Smith & Nephew - England)®, or Unifex (Howmedica)®. Alternatively, the drug substance may be incorporated directly into the adhesive layer 20. Both embodiments are described more fully below.

In either case, in order to ensure efficacy of skin-absorption for each of these substances it is necessary to control the desorption properties of the drug substance layer 30 and the adhesive layer 20.

FIG. 2 illustrates one embodiment for accomplishing the above, the underlying adhesive layer 20 being specially-formed with microscopic pores 22 to control the leaching out of the active medicament from the drug substance layer 30. It should be understood that the single-ply micro-porous adhesive layer can be replaced with a porous membrane coated with adhesive. There are a variety of suitable porous skin-contacting absorption papers including a skin interface called Macroflux® by Etrans that will serve this purpose. It should also be noted that microscopic channels or other designs may be used rather than pores to likewise control the leaching out of the active medicament from the drug substance layer 30. In these embodiments, the size and number of the pores 22 and/or channels will largely determine the permeation rate of active medicament from the drug substance layer 30 through the underlying adhesive layer 20.

As yet another alternative, the drug substance is incorporated directly into the adhesive layer 20 for time-release therefrom. In this case, the medicament can be added into the adhesive layer 20 in a controlled or sustained release form in a number of different ways described below.

2. Production Method

The medicated tattoos are printed in the same manner as conventional temporary tattoos, using offset lithography and silk screen techniques. The specific stages of the present production process are as follows:

Step 1: Original artwork such as photographs, illustrations and text, are entered and/or scanned into a conventional computer, and the elements are combined into a singular tattoo design using existing design layout software.

Step 2: Full size films are output using a high-resolution imagesetter. These can either positives or negatives.

Step 3: Printing plates are made from the films using a known photochemical process. The plates are designed to cause ink to adhere only to the image or artwork on the plate, and this is accomplished by exposing them to high-intensity light through the films, and then chemically treating the plates so that non-image areas are water absorbent.

Step 4: The flexible plates are attached to the plate cylinders of a conventional lithographic press and the colored layer 40 is printed onto clear base 50. Lithography is a method of printing by which the ink adheres only to the image or artwork on the printing plate. Water is used to wash the ink away from all areas except the image area and that is where the ink adheres. The inked image is then transferred or offset to a rotating blanket cylinder which in turn transfers the image directly onto the clear base 50.

In the foregoing manner, the colored layer 40 is printed atop the base-paper 70 backed clear base 50 during a first run, and then the drug substance layer 60 is coated or silk-screened onto the opposing side of the clear base 50 (over the colored layer 40)

during a second run. A higher degree of uniformity can be achieved by use of a conventional reverse roll coater such as is available from Kroenert and Egan machinery. The silk-screen printing is more time consuming but can be accomplished in a known manner by forcing the drug substance layer 60 through a photographically treated screen.

Solvents are commonly used as needed during the above-described manufacturing process as drying retarders, and these may include butyl cellosolve, ethyl acetate, hexane, toluene, etc.

As stated above, the drug substance layer 30 may be incorporated as a separate layer as shown in Fig. 1 for permeation through the microscopic pores of FIG. 2 or the microscopic channels. In both of these cases the drug substance layer 30 is prepared by mixing the medicament in a water based paste followed by drying.

Alternatively, the drug substance may be incorporated directly into the adhesive layer 20 in a variety of time-release forms.

Examples are given for both of the above-described production methods in the context of preparing a medicated tattoo of approximately 3.0" x 2.5" dimensions, containing 80mg of acetaminophen (N-4-hydroxyphenyl acetamide), which is the proper dosage for a child (under 12) for 4 hours.

METHOD 1. Discrete drug substance layer 30 (for controlled desorption through adhesive layer 20).

The medicament is mixed in a water based paste, followed by drying, then applying adhesive layer 20 to produce an approximately 3.0 ml dry film layer. Since acetaminophen is not water soluble, a water emulsion can be made, then thickened to produce a runnable paste. To disperse the acetaminophen in water a surface active agent compatible with the drug substance(lauryl sulfate, for example) is needed. The dispersion can be made by use of a high speed dispersator which will provide a stable dispersion of micron sized micelles (structures made up of long polymeric molecules whose two ends have differing polarity, a polar or "hydrophilic" end and a nonpolar or

"hydrophobic" end). The hydrophobic ends come together to form a central, nonpolar core or chamber. The central core can accept a wide variety of organic molecules and carry them into solution in polar solvents. A thickening agent (e.g., pectin, agar, gelatin, hydroxypropyl cellulose to name a few) can be added to obtain the desired viscosity and flow properties for application. The drug substance layer 30 is then partially dried and can be applied by a conventional reverse roll coater or silk screen process. Using this method, the adhesive layer 20 serves directly as a permeable membrane for release of the drug substance layer 30. The size of the microscopic pores (Fig. 2) or channels may be varied to control the release rate of the medicament.

METHOD 2. Medicament in the adhesive layer 20.

In this case, the medicament diffuses out of the adhesive layer 20 directly into the skin. To produce a 3.0 mil dry adhesive layer containing 80mg of drug substance, 11.5 lbs of acetaminophen per 100 lbs of adhesive is required. For a 2.0 ml dry adhesive layer, 17.1 lbs of drug substance per 100lbs of adhesive is required. The estimated weight of adhesive is 0.260 g for the 2.0 mil dry layer and 0.380 g for the 3.0 mil dry layer, so the drug substance makes up about 30.25% of the former and 20.5% of the latter. Acetaminophen is not soluble in water, but is soluble in ethyl acetate and butyl cellosolve. A solution of acetaminophen in ethyl acetate and/or butyl cellosolve can be made, then thoroughly mixed into the adhesive (e.g., planetary mixer or similar mixer). Ethyl acetate is more desirable since it also acts as a skin-penetration enhancer and is safe. After partial drying to a paste/solution form, the medicament will desorb directly out of the adhesive layer 20, thereby eliminating the need for a separate drug substance layer 30.

To gain more control over the desorption rate compared to the paste/solution form described above, the medicament can be infused or mixed into the adhesive layer 20 in a number of ways. For one, using an adhesive layer 20 as in FIG. 2 that is specially-formed with microscopic pores 22, the medicament can be infused into the

pores 22. This is best accomplished by a silk-screening process depicted in FIGs. 3 and 4.

As shown in FIG. 3, the transdermal tattoo 2 inclusive of clear base 50 with colored design layer 40 is overlayed by a silk screen 56 selectively coated with an emulsion 54. The paste/solution form of the medicament 30 is squeegeed onto the silk screen 56 and penetrates the screen 56 in patterns defined by the emulsion 54.

As seen in FIG. 4, the silk screen 56 and emulsion 54 are removed and the product is dried to leave pattern deposits 30 of medicament on the transdermal tattoo 2. In this embodiment, the size and number of the pattern deposits 30 will largely determine the permeation rate of active medicament into the skin. The adhesive layer 20 is then applied around the pattern deposits 30, filling in the open space, by squeegee or by reverse roll coating.

As an alternative to the above, the active medicament can be incorporated in the adhesive layers in a number of known controlled or sustained release forms, inclusive of i) microcapsules; ii) microemulsion (containing droplets in the size range of approximately 100-1000 angstroms; iii) liposomes; iv) niosomes; v) hydrogel. A more detailed description these alternate forms is given below.

i. Microencapsulation

Microencapsulation is a process by which tiny parcels of the medicament are enclosed in capsules which range in size from one micron (one-thousandth of a millimeter) to seven millimeters. The capsules are dispersed throughout the adhesive layer 20 and release their contents over time. Of the four typical mechanisms by which core material is released from a microcapsule (mechanical rupture of the capsule wall, dissolution of the wall, melting of the wall, and diffusion through the wall), the present invention requires a time-release effect that is best achieved by the latter three. The capsule wall material is preferably an organic polymer. Specifically, when delivering acetominaphen according to the present invention, the drug may be encapsulated in ethyl cellulose or hydroxypropyl methylcellulose and starch. Rather

than being released all at once, the acetominaphen diffuses through the shell in a slow, sustained dose. Other pharmaceuticals, vitamins, and minerals can be encapsulated, and their delivery can be controlled and targeted in this manner. There are a number of established processes for microencapsulating drug substances.

ii. Microemulsion

It has been shown that a small amount of monomer can be added to vesicles formed from ionic surfactants without disrupting the structure of the vesicles. John D. Morgan, Christopher A. Johnson, Eric W. Kaler, "Polymerization of Equilibrium Vesicles", Langmuir, 1997, v. 13, pp. 6447-6451. Once polymerized these solutions yield a suspension of semi-rigid hollow polymer spheres. These spheres can be used as nanoencapsulation devices for transdermal delivery, their polymeric nature allowing the desired controlled and sustained drug release. Drugs or any biologically active compound can be dissolved, entrapped or encapsulated into the nanoparticle, or simply adsorbed onto its surface.

iii. Liposomes

Liposomes are lyotropic liquid crystals composed mainly of amphiphillic bilayers that have dispersing capabilities. Research into the use of acetominaphensomes for topical skin application was pioneered in the early 1980's. Mezei M. and Gulusekharam V., Liposomes, a selective drug delivery system for the topical route of administration, Life Sci. 26: 1473-1477 (1980), Mezei M. and Gulusekharam V., Liposomes, a selective drug delivery system for the topical route of administration: Gel dosage form, J. Pharm. Pharmacol. 34: 473-474 (1982). Subsequent research has indicated that liposomal encapsulation could be beneficial for treating disorders such as acne, alopecias and various cancers, as well mediating accelerated systemic delivery via transport through the shunt pathway. Lauer A. C., Lieb L. M., Ramachandran C., Flynn G. L., and Weiner N. D., Transfollicular Drug Delivery, Pharm. Res. 12: 179-186 (1995). Liposomal carriers have been successful in

enhancing the clinical efficacy of a number of drugs. These have included tretinoin for the treatment of acne, glucocorticoids for the treatment of atopic eczema, lignocaine and tetracaine as anesthetics. The first marketed topical liposomal drug, Pevaryl Lipogel, is produced by Cilag AG. This product contains 1% econazole in a liposomal gel form. This liposomal gel form is suitable for use directly as the drug substance layer 30 of the medicated tattoo of the present invention.

There are two types of liposome-skin interactions: 1) adsorption and fusion of loaded vesicles on the surface of the skin leading to increased thermodynamic activity and enhanced penetration of lipophilic drugs; and 2) interaction of the vesicles within the deeper layers of the stratum corneum promoting impaired barrier function of these strata for the drug. The most suitable liposome for the present application will depend on the desired liposome-skin interaction, which in turn will depend on the desired pharmacological effect.

iv. Niosomes

Niosomes or non-ionic surfactant vesicles are now widely studied as an alternative to liposomes. An increasing number of non-ionic surfactants have been found to form vesicles capable of entrapping hydrophobic and hydrophilic solutes. These non-ionic surfactant vesicles appear to be similar in terms of their physical properties to liposomes, being prepared in the same way and under a variety of conditions, forming unilamellar or multilamellar structures. They are an inexpensive alternative, of non-biological origin, to liposomes.

v. Hydrogels

Hydrogel polymers have the ability to absorb fluid and swell, and as it swells an incorporated drug is released in a controlled manner. By varying the physical and chemical properties of the polymer, as well as the shape, drug release can be controlled over a range of time periods, from a few hours to several days. A precise amount of medicament is incorporated into the polymer by immersing the hydrogel in

a solution of the drug for a predetermined time. The hydrogel is then dried with the drug in place. The drug-loaded hydrogel polymer is used directly as drug substance layer 30. When the tattoo is wetted and inserted onto the skin drug release begins immediately. This release is sustained as the hydrogel swells in the water from application, and the clear base 50 seals the hydrated hydrogel drug substance layer 30 against the skin. At the end of the dosing period, the spent hydrogel polymer is expelled along with the colored layer 40. There are already a number of commercially available transdermal hydrogel pads that offer topical pain relief treatment with methyl salicylate, hydrocortisone, and lidocaine. However, these depend on renal or vaginal body fluids for hydration of the hydrogel. The present medicated tattoo is well-suited for delivery via a hydrogel inasmuch as application of the tattoo already requires a wetting process.

In all of the foregoing cases, skin penetration enhancers can also be added to control the rate of absorption. See, for instance, US Patents Nos. 4,537,776, 4,973,468, 4,820,720, 5,006,342, and 4,863,970 disclose known penetration enhancers.

3. Candidate Drug Substances

In addition to acetaminophen, a wide variety of drug substances may be delivered by use

of the transdermal tattoo 2. For example, the transdermal tattoo 2 can be used for delivery of nutraceuticals, and even cosmetic compounds for skin care and rejuvenation. More specifically, there is an ongoing evaluation of the topical delivery of vitamin C to prevent or reverse skin damage due to sun exposure or aging. Vitamin C stimulates the production of collagen in the skin. The transdermal tattoo 2 is capable of effectively delivering concentrations of Vitamin C into the skin. It is also possible to deliver natural progesterone to designated receptor sites throughout the body, thereby affording long-term relief for pre-menstrual symptoms.

Likewise, there is an established need for transdermal delivery of certain FDA regulated drugs (inclusive of many different organic chemical compounds), proteins,

peptides and macro-molecules, DNA and oligonucleotides for gene therapy-related treatments, vaccines, and prescription narcotic analgesics including Anileridine, Butorphanol, Codeine, Damorphine, Fentanyl , Hydrocodone, Hydromorphone, Levorphanol, Morphine, Nalbuphine, Oxycodone, Oymorphone Pentazocine, Pethidine (meperidine), Propoxyphene, as well as other drugs such as insulin, etc.

In all of the above cases, the 1) viscosity of paste solution form; 2) size of micropores/microchannels; and/or 3) control over time-release vehicle, or combination thereof will determine the rate of diffusion of medicament out of the adhesive layer to the skin. The rate of absorption into the skin will depend on the concentration gradient existing between the saturated solution of drug reaching the skin and the lower concentration in the skin, as this gradient drives absorption. It should be apparent that diffusion experiments must be conducted to determine each drug's permeability coefficient (Papp) from which the diffusion coefficient(D) may be determined since Papp=D*K/h (K is the partition coefficient and h is the skin thickness). There is an inevitable variation in dose delivered among patients, but the nominal delivery rates (25, 50, 75, and 100 μg of acetominaphen per hour) are sufficiently accurate.

4. Medicated Tattoo Application

To apply the finished transdermal tattoo 2, the medicated tattoo 2 is held against the skin at the desired location and water is applied to the base paper 70 to wet it and to soften or dissolve the release layer 60. The base paper 70 and any residue is removed, leaving the functional portion (layers 20-40) in place. Once dried, the clear layer 50 with underlying colored design layer 30 and underlying drug substance layer 30 bonds to the skin, and the medicament in the drug substance layer 30 begins to gradually diffuse (directly or through discrete adhesive layer 30) into the skin. To obtain optimum effect, the transdermal tattoo 2 should be applied to dry, hairless skin (such as on the forearm) approximately 8-12 hours before the effect is required.

5. Absorption Progress Indicator

In use, the transdermal tattoo 2 appears to be an ordinary tattoo and the colored layer 30 may take the form of any of various designs. Contrary to conventional transdermals, the present device 2 conceals the fact that the wearer is taking a drug. In fact, the ornamental appearance provides an incentive for wear. Moreover, the utility can be increased further by the addition of a progress indicator that provides an outward visual indication of the progress of delivery. Using any of the above-described construction alternative it becomes possible to incorporate an indicator dye system that will produce a color change. The color change can be effected by the passage of time, or by the absorption of drug substance. Either case provides tremendous utility because the transdermal tattoo 2 can give a self-monitoring feature to indicate dosage progress.

In an absorption-dependent embodiment the indicator dye is incorporated into the drug substance layer 30 and migrates toward the skin along with the medicament. As the indicator dye moves toward the skin and away from the colored design layer 40, the outward appearance of the colored design layer 40 lightens, thereby indicating absorption progress. FIG. 5 illustrates a transdermal tattoo 2 incorporating this feature wherein the base paper 70 is printed and labeled with a color-scale 23 for visual comparison to give the user a reference. As the medicine is absorbed the color fades, and the percent absorption is readily apparent by a simple comparison with color-scale 23. The effect is accentuated by the use of complementary colors for the indicator dye and the translucent colored design layer 40, e.g., yellow and green show a distinct tonal change.

Alternatively, the color change feature can be implemented in the drug substance layer 30 by use of photochromic or luminescent liquid dyes or crystals. When sunlight is applied, photochromic dyes becomes excited and the molecular structure is changed, allowing a color to appear (or disappear). A variety of colors and effects can be achieved depending on the desired effect. For example, PPG® produces Photosol® photochromic dyes crystalline organic dyes four base colors:

blue, yellow, purple and orange/red. When combined, additional colors such as green, brown and gray can be produced. Alternatively, luminescent organic fluorophers can be used to yield a luminescent effect. These properties can be controlled such that an image will fade or diminish over time, thereby indicating a measure of the effective lifetime of the transdermal tattoo 2.

Alternatively, FIG. 6 illustrates a transdermal tattoo 2 gradient index feature wherein drug substance layer 30 is dye-encoded and contained within a reservoir adjoining a thermometer-like gradient scale indicator 43 labeled with a gradient scale 43 for visual comparison to give the user a reference. As the medicine is absorbed, the level of medicine in the channel 43 is lowered by capillary action, and the percent absorption is readily apparent by a simple comparison with the gradient scale.

It is a further object to provide a transdermal device 2 that displays ornamental simulative child appealing characters (fixed, appearing over time, or disappearing) or other indicia in order to give children an incentive to take their medicine without a fight.

6. Child Reinforcement

The above-described color-change feature can also be employed to provide a significant incentive to children to wear the transdermal tattoo 2. For example, as shown in FIG. 7, indicator dye combinations as described above can be used that cause a character to appear, or the spots 33 of a character to disappear over time, thereby reinforcing useage.

In all of the above-described color indicator embodiments, the color producing ingredient used in the drug substance layer 30 may comprise any from among the following list:

1. liquid crystals
2. thermochromic substances
3. photochromic substances
4. phosphorescent substances

5. radiation cured inks

6. adhesive component

Obviously, many modifications may be made without departing from the spirit of the present invention. Accordingly, it will be appreciated by those skilled in the art that within the scope of the appended claims, the invention may be practiced other than has been specifically described herein.

Industrial Applicability

Topical drug and vitamin delivery is a well-known approach to the treatment of local skin disorders, and as the technology advances it is becoming more feasible as a route for systemic drug delivery. However, very few transdermal products have been approved to date, largely because of the complexities involved in achieving a consistent delivery rate. There are many variables that influence the absorption of drugs across the skin, and presently there is no known mechanism for monitoring the rate of absorption. However, there is another consumer oriented technology, vastly different in context yet relevant in substance, that offers untapped benefits to the transdermal industry. Temporary tattoos are popular due to the variety of aesthetic and visual effects that they create. The melding of temporary tattoo technology with transdermal drug delivery promises an array of advantages, including economy of manufacture (using standard lithographic and silk screen printing processes), ease of application, temporary effect, and motivation to wear the transdermals for their aesthetic appeal. Since tattoos are printed they can easily be made to display simulative child appealing characters or other indicia, thereby providing a great incentive for children to take their medicine. Moreover, by this process the printed tattoo can be made with ink that disappears or changes color as the medicine is absorbed, for the first time giving a positive indication of the rate and efficacy of transdermal delivery. There is a great industrial need to adapt temporary tattoos and

their lithographic/silk screen production processes to transdermal medicament delivery, and to thereby introduce all of the potential aesthetic and display advantages of temporary tattoos in the transdermal field.

Claims

1. A method of producing a transdermal medicament delivery device, comprising the steps of:

lithographic printing of an ink design on top a clear base;

adhering a cardstock base via a water-soluble release layer to one side of said clear base;

coating a drug substance and skin-adhesive onto the other side of said clear base over said ink design.

2. The method according to claim 1, wherein said step of coating a drug substance layer further comprises roll-coating said drug substance in paste suspension onto said clear base opposite said ink design.

3. The method according to claim 2, wherein said drug substance and skin-adhesive are mixed in said paste suspension.

4. The method according to claim 3, wherein said drug substance is incorporated in said paste suspension in controlled-release form.

5. The method according to claim 4, wherein said drug substance is incorporated in said paste suspension as any one from among the group of controlled release microemulsions, liposomes, niosomes, and hydrogels.

6. The method according to claim 1, wherein said step of coating a drug substance and skin-adhesive further comprises a first step of coating a drug substance onto the other side of said clear base over said ink design, and a second step of coating an adhesive layer onto said drug substance.

7. The method according to claim 6, wherein said adhesive layer is formed with one from among the group of micropores and microchannels to control the leaching out of the drug substance.

8. The method according to claim 1, wherein said step of coating a drug substance and skin-adhesive further comprises a first step of coating a drug substance onto the other side of said clear base over said ink design, a second step of applying a microporous membrane onto said drug substance, and a third step of coating an adhesive layer onto said microporous membrane.

9. A transdermal medicated tattoo, comprising:

a clear base bearing an ink design on one side, said clear base being attached to said cardstock base paper on the other side by a release base that dissolves when wet to allow detachment of the base paper;

an adhesive layer coated over the ink design on said clear base for adhesion to the skin, said adhesive layer having pre-determined permeability characteristics;

a medicament incorporated in the adhesive layer for diffusion therefrom into the skin of the wearer.

10. A transdermal medicated tattoo according to claim 9, wherein said drug substance and skin-adhesive are formed from a mixed paste suspension.

11. A transdermal medicated tattoo according to claim 10, wherein said drug substance is incorporated in said paste suspension in controlled-release form.

12. A transdermal medicated tattoo according to claim 11, wherein said drug substance is incorporated in said paste suspension as any one from among the group comprising controlled release microcapsules, microemulsions, liposomes, niosomes, and hydrogels.

13. A transdermal medicated tattoo, comprising:

a section of cardstock base paper;

a clear base bearing an ink design on one side, said clear base being attached to said cardstock base paper on the other side by a release base that dissolves when wet to allow detachment of the base paper;

an adhesive layer coated over the ink design on said clear base for adhesion to the skin, said adhesive layer being formed with one from among the group of micropores and microchannels having pre-determined permeability characteristics;

a medicament incorporated in the adhesive layer for diffusion therefrom into the skin of the wearer.

14. A transdermal medicated tattoo, comprising:

a section of cardstock base paper;

a clear base bearing an ink design on one side, said clear base being attached to said cardstock base paper on the other side by a release base that dissolves when wet to allow detachment of the base paper;

a drug substance layer having a medicament incorporated therein for diffusion into the skin of the wearer.;

an adhesive layer coated over the drug substance layer for adhesion to the skin, said adhesive layer having pre-determined permeability characteristics.

15. The transdermal medicated tattoo according to claim 14, further comprising a permeable membrane between said drug substance layer and adhesive layer for controlling desorption of said medicament through said adhesive layer.

16. The transdermal medicated tattoo according to claim 14, further comprising an indicator dye incorporated into the drug substance layer that migrates with said medicament to indicate absorption progress.

17. The transdermal medicated tattoo according to claim 14, further comprising an indicator dye incorporated into the drug substance layer that changes over time to indicate useful life.

18. The transdermal medicated tattoo according to claim 14, further comprising a dye incorporated into the drug substance layer and visible in conjunction with said colored design layer to provide a color-changing design as a child incentive to wear.

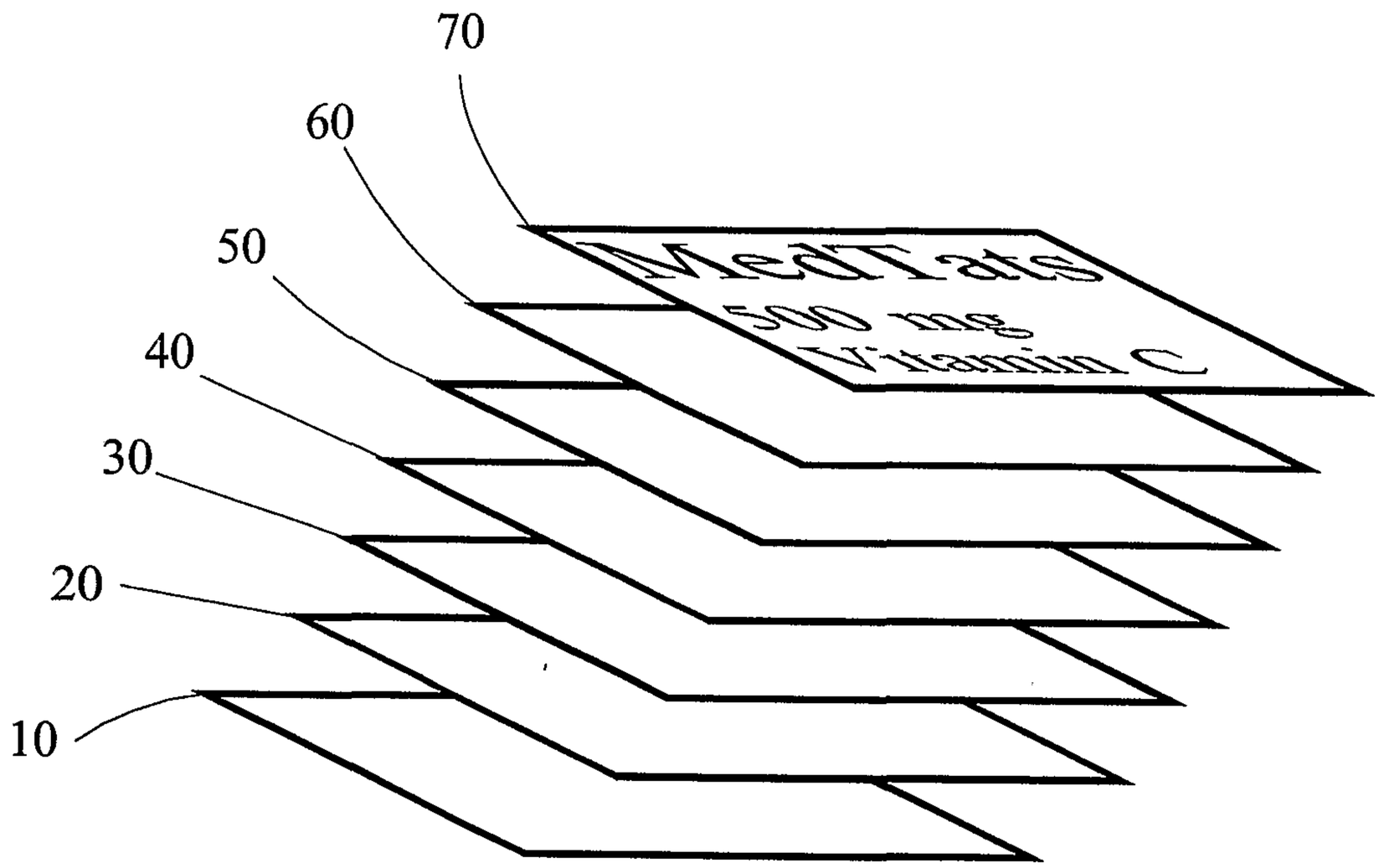

FIG. 1

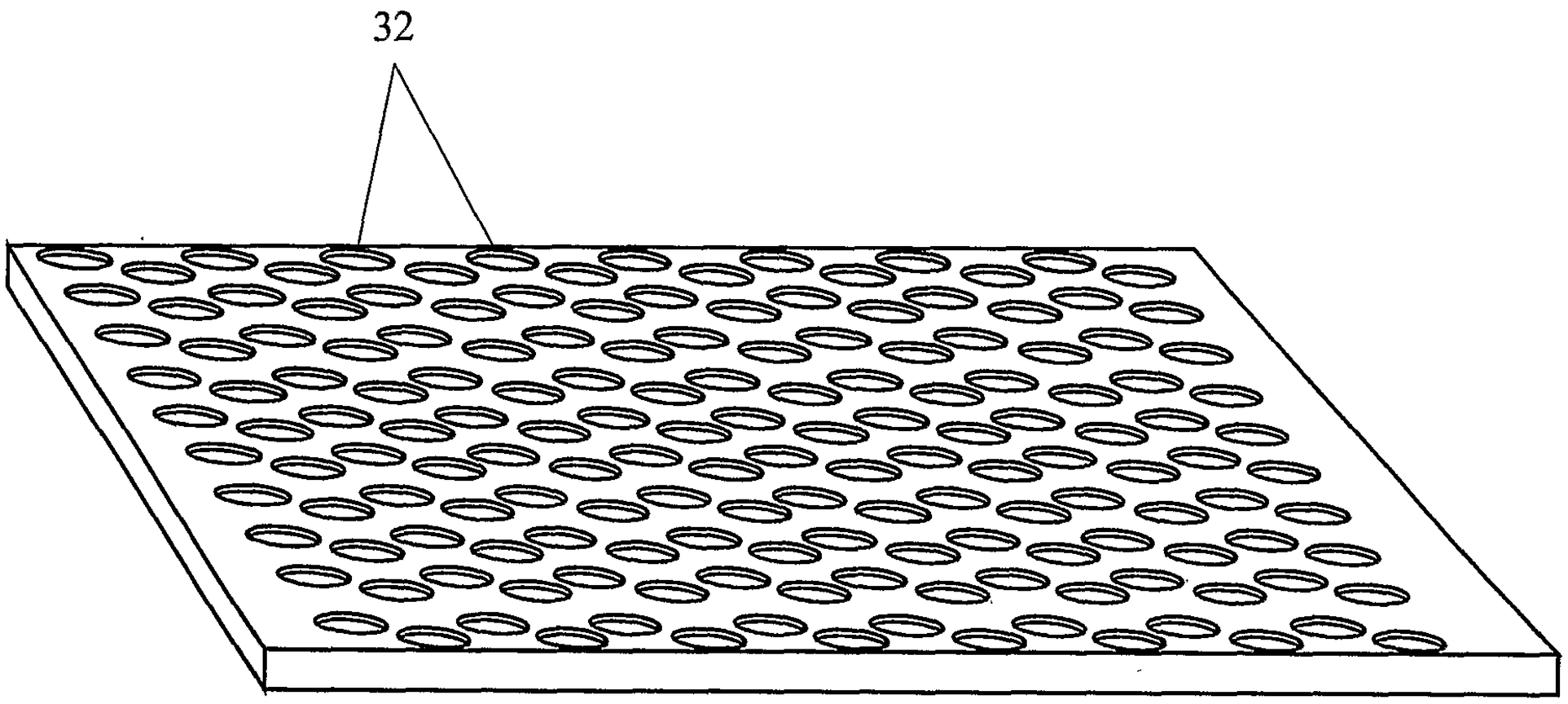

FIG. 2

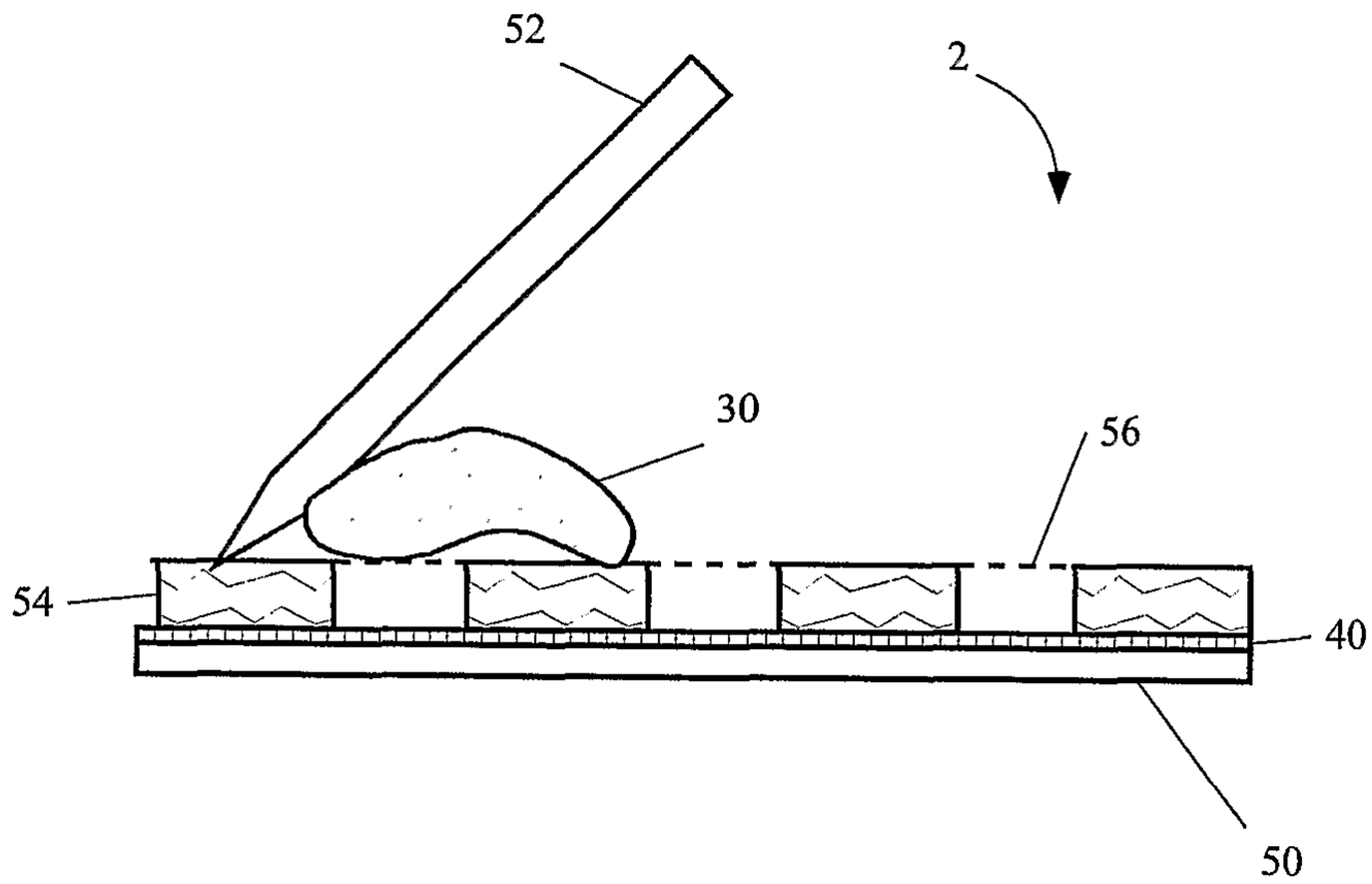

FIG. 3

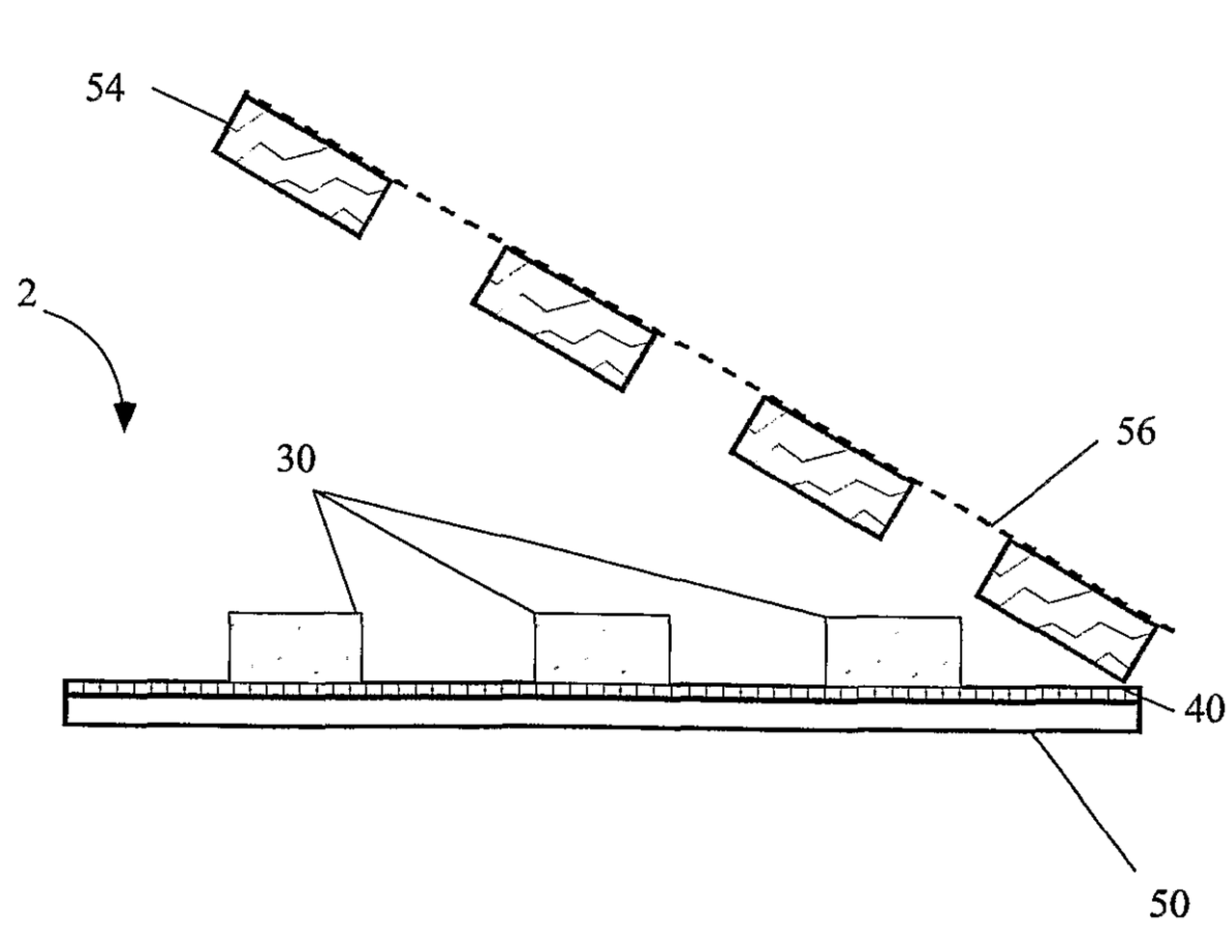

FIG. 4

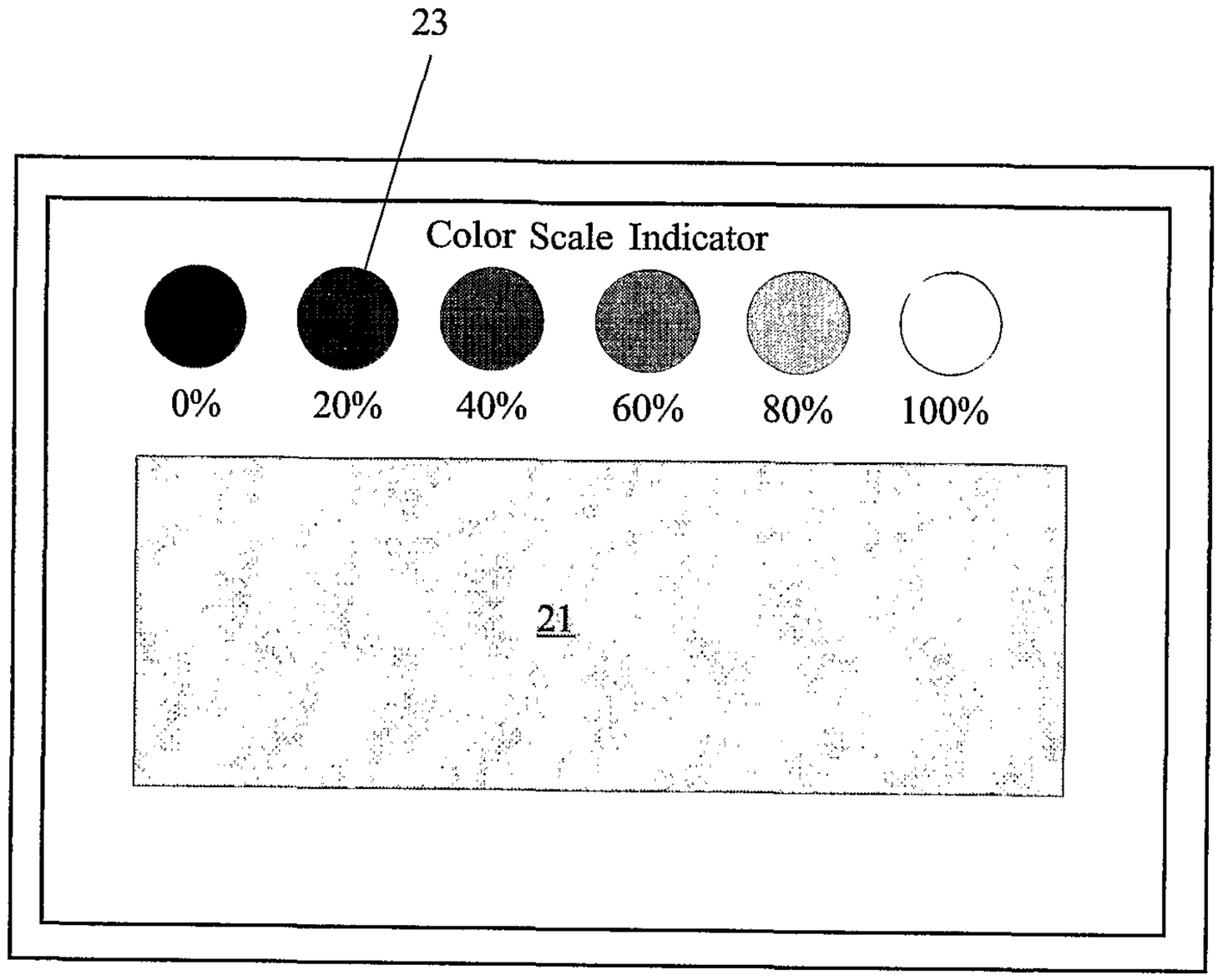

FIG. 5

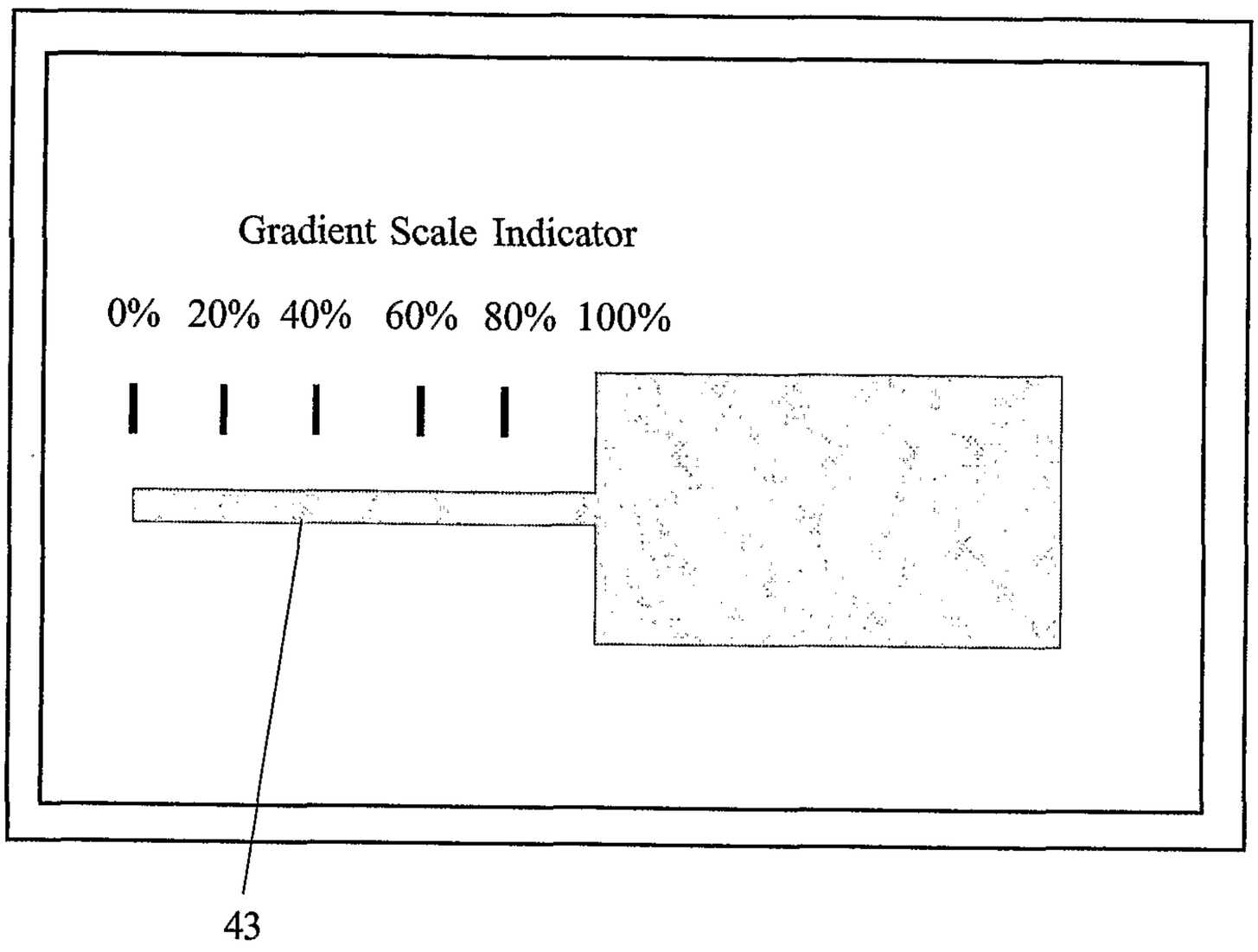

FIG. 6

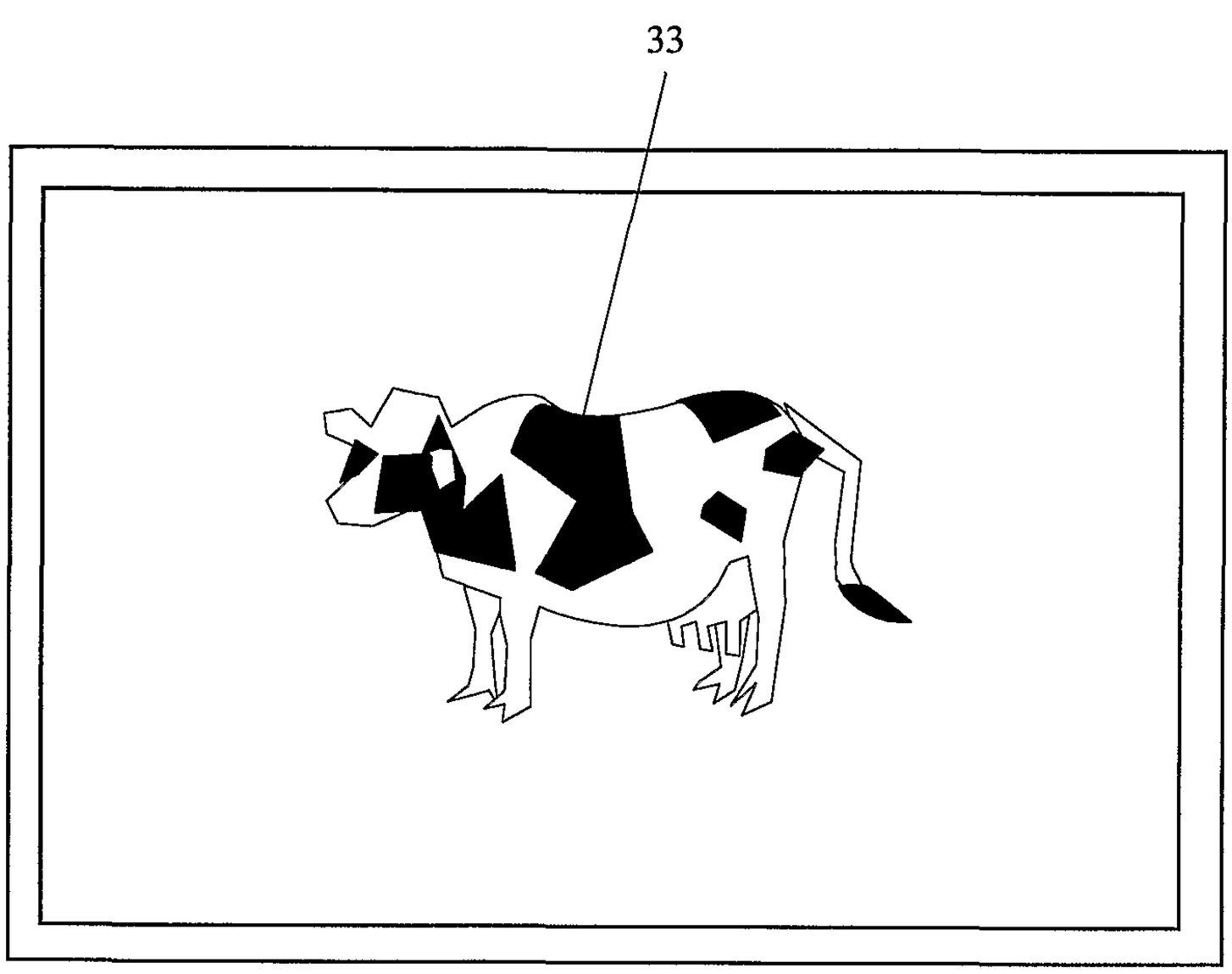

FIG. 7