Sept. 11, 1962  F. MEYER  3,053,255
PROCESS OF PERCUTANEOUSLY ADMINISTERING EXACT
DOSES OF PHYSIOLOGICALLY ACTIVE AGENTS
AND COMPOSITE UNIT THEREFOR
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The present invention relates to an article of manufacture and a process for dispensing dosed quantities of physiologically active material for percutaneous absorption.

The application of salves, ointments, liniments, powders, which may contain pastes, cerates, or other externally applicable preparations of physiologically active agents to the outer skin surface has been employed by the medical profession and in the cosmetic arts for a long time. This mode of application may have for its purpose to bring about a topical effect, for instance, it may cause local disinfection or it may be intended for a far-reaching absorption effect extending through other parts of the body than those where the preparation has been applied topically, such as, for instance, the long known treatment with a mercurial ointment, i.e., with ammonium hydrargyri, used in the treatment of syphilis.

There are numerous other examples of the topical application of medication for local effect but only comparatively few examples for systemic action. The reason for this is that it is quite easy to topically apply to the skin in this manner a definite quantity of a liquid, a powder, an ointment, a jelly, or the like preparation. Yet in most cases it is not possible to determine how much of the medication has been taken up by the organism through absorption or whether it only superficially penetrated the skin. Furthermore, it is also usually not possible to determine how much of the preparation has evaporated or how much of it remains on the skin as non-penetrating residue.

Up to the present time it was not possible to regulate and control the percutaneous absorption of a specific material, i.e., to cause a definite quantity of material (an exact dose) to be absorbed. Examples of uncontrolled percutaneous absorption have occurred with ointments containing salicylic acid, which ointments may cause serious toxic effects and even death through poisoning. However, in a few cases, percutaneous dispensing of toxicologically relatively harmless active agents have proven to be more or less effective, for instance, in the treatment with hormone preparations.

In general it can be stated that the lack of a method of percutaneously administering a precise dose of a therapeutically active agent to be absorbed by the skin had the result that percutaneous administration of such physiologically active agents was found only limited use in medical practice. This is so, notwithstanding the pressing need for a method of administration of this type and for means for carrying out such a method. This need is evidenced by numerous publications concerning skin permeability. See, for instance, "Die Durchlassigkeit der Haut fuer Arzneien und Gifte" (in translation: The permeability of the skin for drugs and poisons), Berlin, 1942, by E. Buergi, who is one of the foremost toxicologists. Similarly, from more recent publications, for instance, of G. Hadgraft and F. Somers in "J. Pharm. Pharmacol." vol. 6, page 944 (1954) and G. Hadgraft, F. Somers and H. S. Williams in "J. Pharm. Pharmacol." vol. 8, page 1027 (1956); as well as of Gemmell and Morrison in "J. Pharm. Pharmacol." vol. 9, page 641 (1957), two things clearly emerge:

1. The extensive protective and defense function of human skin toward outside chemical influences.

2. The extensive and practical interest in the percutaneous dispensing of therapeutically active agents (compare, for instance, Czetsch-Lindenwald and Schmidt-La Baume, 1950, Heidelberg: "Salben, Puder, Externa, die neueren Heilmittel der Medizin" (in translation: Ointments, powders, external agents, the external remedies in medicine), 3rd edition, Berlin—Göttingen—Heidelberg, 1950. One condition of such percutaneous administration is, that a definite and as complete an absorption as possible as well as administration of the required dosage can be achieved.

It is one object of the present invention to provide a new and highly advantageous method of percutaneously administering definite doses of physiologically active agents.

It is a further object of this invention to provide a device or assembly for effecting this purpose.

Other objects of the present invention and advantageous features thereof will become apparent as the description proceeds.

The new process according to the present invention, which will be described more in detail hereinafter and which permits the administration of physiologically and cosmetically active agents through the skin, has made possible a number of substantial advantages:

1. Active agents, which normally are not absorbed by the skin or are only taken up sparingly, are now rendered readily absorbable.

2. The percutaneous absorption of active agents, which normally penetrate the skin only in small quantities, or only slowly from conventional preparations such as ointments, jellies, or solutions (for instance, containing salicylic acid, iodine, or hormones), is definitely promoted or accelerated.

3. Percutaneous absorption becomes readily controllable and can be adjusted so that it is practically complete.

4. Percutaneous absorption of the active agent can be exactly dosed.

These advantages permit in many cases percutaneous administration of active agents, which heretofore could be administered only parenterally. Both methods of administration can now be used equally well. It is, of course, understood that percutaneous application according to the present invention cannot replace all forms of parenteral administration. For instance, it cannot replace administration by intravenous injection when the introduction of the active agent by this route is necessary in order to cause rapid action of the active drug. Likewise it cannot replace administration by injection into the cerebrospinal fluid in the spinal canal.

The process according to the present invention shows the following advantages over the usual forms of injection, i.e., over subcutaneous, intracutaneous, intramuscular, and even over intravenous injections:

(a) Less annoyance for the patient since the pain of injection is absent;

(b) Less danger of infection;

(c) More convenient handling for the physician, since sterilization of syringes and needles is dispensed with.

The new process according to the present invention has the further particular advantage that it permits non-disturbing, convenient, and at the same time safe administration of such active agents which on oral administration are partially or totally destroyed in the gastro-intestinal tract, which for other reasons are not absorbed quickly enough or completely enough. Such agents are, for instance, curare, strophanthin, convallatoxin, adrenalin, acetyl choline, or agents which are badly tolerated on oral administration, such as saponin containing drug extracts.

The process according to the present invention makes it further possible to vary within wide limits the rate of absorption of active agents. Herefore such variation in
the rate of absorption could be achieved only by enteral administration through the gastro-intestinal tract or parenterally by way of injection.

In principle the process according to the present invention consists in first applying to an absorptive carrier material a measured quantity (dose) of the active agent to be absorbed by the skin. This absorptive carrier material is covered with a non-absorbive, non-permeable separator material. A second layer of absorptive material serving as the reservoir for the active agent is placed on top of said separator layer. This reservoir layer is somewhat thicker than the carrier layer. One or several wicks of absorptive material are provided to make a connection between the reservoir layer and the carrier layer. In use a liquid vehicle supplied to the reservoir layer is carried through the wicks to the carrier layer wherein it picks up the active agent and causes it to be absorbed by and through the skin in a definite predetermined dose.

The manner in which the process according to the present invention is carried out and the means used thereby will become apparent from the following description and the annexed drawings.

In said drawings:

FIG. 1 is a top plan view of a plaster-like preparation embodied in the present invention;

FIG. 2 is a cross-sectional view taken along line 2-2' of FIG. 1;

FIG. 3 is a cross-sectional view taken along line 3-3' of FIG. 2;

FIG. 4 is a cross-sectional view of another embodiment of the present invention; and

FIG. 5 illustrates curves showing the anesthetizing effect of a preparation according to the present invention.

In accordance with the present invention an active agent, which is to be absorbed by the skin, is measured out (by volume or by weight) in solid form, for instance, 0.1 mg. of g- or k-strophanthin, or in liquid form, for instance, 0.04 cc. of an 0.25% alcoholic solution of g-strophanthin, and is applied to an absorptive carrier for the active agent, for instance, paper, cellulose, silk, linen, nylon, and other artificial fiber tissue, and the like material. The carrier material impregnated with a measured predetermined amount of active agent may then be applied to the skin before or after completing the assembly of the parts of the preparation used in the present invention. This carrier material impregnated with active agent is then covered with a non-absorbent, non-permeable separator material having about the same surface area as the carrier material. The separator material may consist, for instance, of a film or foil of 0.1 mm. to 0.5 mm. thickness and made from rubber, wax paper, a subordinately liquid impermeable synthetic resin, such as polyvinyl chloride, and the like. This separator material is preferably provided with one or more openings which have as their purpose to receive the wicks described more in detail hereinafter. Upon the non-permeable separator material there is placed the reservoir material. This reservoir material consists of a layer of absorbent fibrous material, such as cotton, paper, cellulose, linen, silk, nylon, or other natural or synthetic fiber material, and serves to take up the solvent, the function of which is also described hereinafter. This reservoir has also about the same surface area as the carrier layer. However, it is thicker than the latter and has a thickness, for instance, of several mm. The reservoir has sufficient capacity to take up, for instance, from 0.5 cc. to 1 cc. of a suitable solvent or solvent mixture which is free of active agent. This solvent functions as a "guide rail," i.e., it causes the active agent to be absorbed by the skin by dissolving it out of the active agent carrier. The solvent and the active agent dissolved therein together penetrate the skin. Therefore, the solvents are called "transporting substances" or "vehicles." The vehicle flows out of the reservoir carrier to the active agent carrier by means of one or more wicks which are made from absorbent mate-
the "transport substance" or vehicle to the reservoir carrier 6, for instance, by a pipette, either before or after the assembly is secured to the skin. The assembly can also be provided with means secured to it for fastening it to the skin, such as with an adhesive strip. In this case the carrier 4 with active agent and the adhesive layer 5 are protected from becoming dirty by a common protective layer 7 which is separated before use.

In the modification of this invention as shown in FIG. 4 an arrangement is provided whereby a complete unit is supplied containing both the active agent carrier 4 impregnated with active agent and vehicle contained in the reservoir carrier 6. This arrangement is made possible through the use of a non-permeable confining or blocking layer 8 consisting, for instance, of a film of polyvinyl chloride or the like liquid impermeable plastic material which serves to prevent putting into operation diffusion of the "transport substance" or vehicle through the wicks 5 into the active agent carrier 4 and dissolution of the active agent present in carrier 4. In use of this modification of the invention the assembled unit is placed on the skin and then blocking layer 8 is removed or torn, for instance, by pulling it out sideward. By this operation wick 5 is brought into communication with reservoir 6 whereby the carrier contained in the reservoir is conveyed to the carrier 4 and functions as described above.

The "transport substances" or vehicles that may be used in accordance with the present invention are liquids which must meet the following requirements:

1. They must be sufficiently absorbable through the unbroken skin.
2. They must have sufficient dissolving power for the active agent which is to be brought in contact with the skin for absorption.
3. They must be toxicologically unobjectionable for the skin or the whole organism.

The following "transport substances" or vehicles are particularly suitable for the purpose of the present invention:

(a) Mono- or polyvalent primary, secondary, or tertiary aliphatic, cycloaliphatic, or aromatic alcohols containing 2 to 10 carbon atoms, such as hexanol, cyclohexanol, benzyl alcohol, butanediol-(1,2), glycerol; secondary or tertiary amyl alcohol, 3-hexanol-1;
(b) Aliphatic, cycloaliphatic, or aromatic hydrocarbons, such as n-hexane, n-hexane-(1), cyclohexane, ethyl benzene;
(c) Aliphatic, cycloaliphatic, or aromatic aldehydes, or ketones having 4 to 10 carbon atoms, such as heptyl aldehyde, cyclohexanone, benzaldehyde;
(d) Aliphatic, cycloaliphatic, or aromatic esters having 4 to 10 carbon atoms, such as amyl acetate, benzyl propionate;
(e) Ethereal oils or their aromatic constituents, such as oil of eucalyptus, oil of rue, cumin oil, linoleum, thymol, 1-pinene, carvone, fenchone;
(f) Halogenated aliphatic or cycloaliphatic hydrocarbons having 2-8 carbon atoms, such as n-hexyl chloride, n-hexyl bromide, cyclohexyl chloride.

The low molecular compounds of this group, such as dibromo ethane, trichloroethylene, are less suitable because of their low compatibility; however, they may be used in mixtures with other vehicles.

(g) Mixtures of substances under (a) to (f) given above.

The following examples are further illustrative of the present invention. However, it is to be understood that this invention is not restricted thereto.

Example 1

To an active agent carrier 4 of the unit illustrated in FIG. 3, which consists of silk strips having a surface area of 2 sq. cm., there are applied 0.02 mg. of eserine base dissolved in 10.02 cc. of ethyl alcohol. The alcohol is then evaporated leaving carrier 4 uniformly impregnated with said eserine base. The active agent carrier is then covered with separator strip 3, consisting of a polyvinyl chloride film of 0.2 mm. thickness and having three perforations, one of them indicated at 9. On said separator strip 3 there is placed a reservoir 6 consisting of a thick layer 3 mm. thick which is covered with carrier layer 4 by three wicks 5 (silk filaments 0.3 mm. thick) which pass through the perforations 9 in separator layer 3. The reservoir layer 6 is provided with 0.3 cc. of a vehicle mixture of amyl alcohol, n-hexanol, and cyclohexane in the proportion of 10:25:65.

The following pharmacological tests were carried out to show the advantageous effect of such a unit preparation in comparison with a conventional 1% eserine ointment.

Three of these assembled units are secured to shaved abdominal skin of 3 male mice having a body weight of from 18 g. to 20 g. with the aid of cover 2 and conventional adhesive tape strips 1. Within 30 minutes after application the known eserine effect on the striated muscles due to absorption of eserine is detected. This results in an increase in chewing movement on periodic stimulation of the chewing muscles (masseter muscle) by constant, rectangular electric current impulses of 1/2 cy per second, 2.5 m/sec. and 8 ma. (For the method compare F. Eicholtz, R. Hotovy, and H. Erdniss; "Arch. int. pharmacodyn." vol. 80 (1949), page 62.) Thirty minutes after the onset of the eserine effect, the assembly is taken off and the non-absorbed residue on carrier 4 is determined according to the method described by F. Meyer in "Arzneimittelforshung" vol. 1, page 165 (1951). Despite the sensitivity of this chemical analytical method, eserine is no longer detectable.

0.5 g. each of conventional eserine ointments containing 1% of eserine are applied to 4 sq. cm. of shaved abdominal skin of two groups of 3 mice each. Unguentum mollis (German Pharmacopoeia, 6th edition, 1947 printing of the Arbeitsgemeinschaft Medizinischer Verlage G.m.b.H. of Berlin), i.e. an ointment consisting of one part of yellow petrolatum and one part of lanoline is used as ointment base for the first group of mice, while unguentum cereum (German Pharmacopoeia 6th edition etc.) consisting of 7 parts of peanut oil and 3 parts of yellow wax is used as ointment for the second group of mice. No eserine effect could be recorded with all six experimental animals on observation for 2 hours, although an amount of eserine is applied to the skin which is about 250 times as large as that applied by means of the assembled unit according to the present invention.

Example 2

Three guinea pigs having a body weight of from 350 g. to 400 g. receive 1 mg. of g-strophanthin dissolved in 0.04 cc. of ethanol with the aid of a 4 sq. cm. carrier 4 made of filter paper which was affixed to their shaved abdominal skin, whereby the procedure is the same as described in Example 1. The separator layer made of a film of polyvinyl chloride having an area of 4 sq. cm. and being 0.1 mm. thick was perforated in eight places 9 (FIG. 3). Through these openings (0.3 mm. in diameter) 8 silk filaments 5 of 0.3 mm. thickness were pulled. Said filaments 5 serve to form the wicks connecting reservoir 6 and carrier 4. A cellulose layer 0.5 cm. thick and having an area of 4 sq. cm. serves as reservoir 6. It is supplied and impregnated with 1 cc. of a vehicle liquid consisting of cyclohexanone, ethylene glycol, hexanol, and cyclohexane in the proportion of 10:10:50:30. The outside covering 2 is provided by a flexible polyvinyl chloride film having an area of 9 sq. cm. which is secured to the abdominal skin by means of a muslin bandage. All three animals show 30 to 45 minutes after application the typical, reversible poisoning effects of strophanthin, such as muscular tremor, convulsions, and respiratory impairment. The assembly is removed after 50 minutes. The
non-absorbed residue on carrier 4 is determined with the aid of the color reaction agent described by Kedde as cited by J. E. Bush and D. A. H. Taylor in “Biochem. J.”, vol. 52 page 643 (1952). This reagent consists of 3,5-dinitrobenzoic acid in alcoholic potassium hydroxide.

The test results were only weakly positive as indicated by a slight rose coloration indicating the presence of traces of strophanthine, i.e. less than 0.005 mg. to 0.015 mg. approximately uniformly distributed over carrier 4. The same dose of 0.1 mg. of g-strophanthine, and even a dose of 11 mg. of strophanthine administrated orally or, respectively, cutaneously in the form of an ointment has no noticeable effect.

Example 3

Three guinea pigs having a body weight between 380 g. and 400 g. receive 0.1 mg. of g-strophanthine by the aid of a unit preparation ready for use according to the invention. The unit is applied to the shaved abdominal skin of the animals. The active agent carrier, and the two wicks (FIG. 4) consist of filter paper strips 2 cm. wide and 6 cm. long (Schleicher & Schuell filter paper No. 20436). An area of 2 cm. by 2 cm. (4 sq. cm.) in the middle of these strips serves as active agent carrier, 0.1 mg. of strophanthine dissolved in 0.04 cc. of ethanol are applied to the carrier. Both ends of the strips (length wise 2 cm. x 2 cm.) serve as band forming wicks 5. They are passed around separator strip 3 having an area of 4 sq. cm. and consisting of a non-perforated film of polyvinyl chloride having a thickness of 0.1 mm. as shown in FIG. 4. A layer of pressed cotton 3 mm. thick and having an area of 4 sq. cm. serves as reservoir carrier 6. Said layer is impregnated with 1 cc. of the “transporting liquid” or vehicle mentioned in Example 2, i.e. with a mixture of cyclohexanone, ethylene glycol, hexanol, and cyclohexane in the proportion 10:10:50:30. The outside covering 2 consists of a flexible polyvinyl chloride film showing an area of 9 sq. cm. The edges 1 of said cover 2 are provided on their underside with an adhesive so that they form an adhesive tape which serves to secure the assembly to the skin. A blocking layer 8 is arranged between the reservoir 6 and the wick and carrier zone. Said blocking layer 8 consists of polyvinyl chloride. It is secured at its margins to the outer covering 2 and is removed before using the unit so that reservoir 6 communicates with wicks 5.

Within 45 minutes after the application of such a unit to the skin of the three experimental animals there was observed in all the animals the reversible poisoning effects described in Example 2. Analysis of the residue in the carrier in accordance with the Kedde method described hereinabove shows a difference from the results obtained in Example 2. Non-absorbed residue is found only in the middle of the carrier in an ill defined band of about 2 mm. to 3 mm. width. This finding clearly demonstrates the functioning of the wicks, which are passed around the separator layer 3. They permit the vehicle liquid to flow into the carrier from the two sides, i.e. from the outer portion toward the center.

Example 4

Two groups each of three guinea pigs receive 0.1 mg. of g-strophanthine using a unit ready for use and applying said unit to the shaved abdominal skin of the animals. The same conditions as used in Example 3 are employed. The only difference is that the vehicle liquid of Examples 2 and 3 is replaced by the same volume of two different mixtures.

With the first group of three animals there is employed a mixture of cyclohexanone, ethylene glycol, n-hexanol, and cyclohexane as used in Examples 2 and 3, but in other proportions, namely in the proportion of 5:15:70:10. With the second group of three animals a mixture of ethylene glycol and n-hexanol in the proportion of 70:30 is employed.

In contrast to the results achieved with the vehicles of Examples 2 and 3, wherein within 45 minutes after application of the unit according to the present invention the characteristic poisoning effects of strophanthine are observed, the results in these experiments are different. With the first group of animals (transporting liquid: cyclohexanone, ethylene glycol, n-hexanol) in the proportion 5:15:70:10) the above described toxic effects are observed only 3 hours after administration. With the second group of animals (transporting liquid: ethylene glycol and n-hexanol in the proportion of 70:30) the assembly is left on the skin for 20 hours without the slightest toxic effects being observed. After the expiration of such a period of observation of almost one day, the three units are removed and the amount of non-absorbed residue on the carrier is determined. Chemical analysis according to Kedde's method was negative. All of the active agent was absorbed (very slowly).

It is evident from these observations that the speed of percutaneous absorption of an active agent from an assembly according to the present invention can be varied within wide limits by varying the composition of the transporting liquid or vehicle.

Example 5

For many purposes it is important to determine whether the quantity of therapeutically active agent applied has been completely taken up by the blood stream, i.e. to find out whether part of the active agent has been retained by the superficial skin layers. If this were the case, the active agent, for instance, the strophanthine, would also have been deposited in the residue on the carrier. The following experiments show that a measured quantity of g-strophanthine, administered according to the present invention, is quantitatively absorbed in the blood stream. As the small therapeutic doses of 0.1 mg. of strophanthine, as hereinafter administered, cannot be detected with certainty by chemical analysis in the blood, faeces, or the organs, biological methods must be used to find out how much of the strophanthine has entered the blood stream. In these experiments a predetermined quantity of g-strophanthine, such as one half of the lethal dose of intravenous infusion is applied to the skin. That this amount is quantitatively absorbed and has entered the blood stream can readily be ascertained by subsequently injecting intravenously the other half of the lethal dose. If all the animals are killed, it is obvious that all the strophanthine administered precutaneously must have been absorbed through the skin into the blood stream.

For this purpose fifteen guinea pigs (under urethane anaesthesia 2 g./kg. of body weight) are given by intravenous infusion lethal doses of g-strophanthine used in the further experiments. The lethal dose amounts to 0.31 mg./kg. ± 0.048 mg./kg. at a speed of infusion of 0.0047 mg./min. To ten other animals similarly anaesthetized with urethane, there was administered half the lethal dose, i.e. 0.15 mg. of g-strophanthine per kg. body weight by means of a 4 sq. cm. carrier applied to the skin in accordance with the procedure of Example 3. The assembly is allowed to remain on the skin for 90 minutes under the conditions of Example 3, to cause absorption of the active agent. Thereafter it was determined which amount of strophanthine intravenously injected, causes death of the thus pretreated animals. It was found that 0.18 mg./kg. ± 0.08 mg./kg. are required to kill the animals. Thus the sum of the amount of active agent absorbed precutaneously (0.15 mg./kg.) and that required to kill the animals on intravenous administration (0.18 mg./kg. ± 0.08 mg./kg.) corresponds approximately to the previously determined lethal dose of 0.31 mg./kg. Since the test with the residue on the 10 carriers according to Kedde's reaction was negative, it has been proved that the quantity of active agent applied to the skin practically completely entered the blood stream.

The present process not only permits absorption of toxic
doses but also permits precutaneous absorption of exact, small, therapeutically effective doses.

In the same manner as described above in connection with p-strophantin, other cardio-active glycoicides, such as k-strophantin and convallatoxine, various alkaloids such as morphine and strychnine as well as barbiturates, such as phenyl ethyl barbituric acid, can be administered precutaneously in therapeutic as well as toxic doses.

**Example 6**

Five guinea pigs receive 0.04 cc. of a 10% solution of procaine in base form in b-hexanol with the aid of a 4 sq. cm. carrier made of linen tissue. These carriers are applied to the shaved abdominal skin in the same manner as described in Example 1. Separation layer 3 is placed over the carrier 4 also measuring 2 cm. x 2 cm. It consists of a flexible polyvinyl chloride film which is provided with 25 round openings of 0.2 mm. diameter. Silk filament wicks 5 are passed through each of these openings. The wicks communicate with the superposed reservoir 6. Said reservoir is made of a 3 mm. thick layer of cotton having a surface area of 4 sq. cm. The reservoir 6 contains 1 cc. of a transporting liquid for vehicle consisting of hexanol and cyclohexamone in the proportion of 1:4.

After allowing the unit to remain on the skin for 45 minutes, precutaneous absorption of the procaine is determined by its pain killing effect. Whether anesthesia is achieved, is determined by exposing the animals to mechanical irritation or, respectively, to electrical irritation by means of rectangular electrical impulses of 30 cycles per sec. and a duration of 1 m sec. with variations in current intensity of from 0.2 ma. to 2.5 ma. and determining the dose required to suppress pain reaction of the animals.

**Example 7**

Two volunteers are used in the following experiment. 1 mg. of procaine per sq. cm. of skin surface is applied to the untreated skin of the back of the left hand of each of the persons, whereby the conditions of Example 6 are observed. After 40 minutes a very definite anesthetic effect sets in. The intensity of electrical stimulation can be raised many times until pain reaction sets in. While the normal stimulus threshold is attained by the application of impulses of 0.2 ma. to 0.5 ma., precutaneous treatment with procaine according to the present invention raises said threshold to about 2 ma. before pain sets in. The unbroken curve illustrated in FIG. 5 shows said anesthetizing effect which subsisted only very slowly, i.e. within 60 minutes.

**Example 8**

The volunteers used in the experiment of Example 7 receive, by application to the back of the hand, under the conditions described in Examples 6 and 7, 1 mg. of procaine per sq. cm. of skin surface and, in addition thereto, 1 mg. of 2-(a-naphthyl methyl) imidazoline nitrate sold under the trademark "Primin" by Ciba A. G. of Basel, Switzerland. Said imidazoline compound was also present in the active agent carrier 4 containing the procaine base.

As shown in FIG. 5, the anesthetizing effect produced by said mixture of procaine and imidazoline compound after an exposure for 40 minutes is somewhat greater (broken curve) and of more prolonged duration than when procaine alone (unbroken curve) is applied. It follows that absorption of procaine by the deep layers of skin which are supplied with blood vessels can be retarded somewhat. Thus, it is possible to retain an active agent like procaine in the skin for a prolonged period of time or to attain a higher concentration of the active agent in the skin by the addition of a vasoconstrictor drug.

If, on the other hand, nicotinic acid amide or nicotinic acid methyl ester, each of which is a vasodilator, are added to the same dose of procaine, i.e. 1 mg. per sq. cm. of skin, the duration of action is shortened, as is evident from the dotted curve in FIG. 5.

The results described hereinabove in the examples have been confirmed in actual clinical use, for instance, with cardiac patients to whom strophanthin was administered, with patients suffering, for instance, from intestinal distension or puritus to whose paracentesis was administered, with patients to be exposed to the action of local anesthetics such as procaine, with patients under morphine, for producing sedative and hypnotic effects, for instance, by administration of barbiturates, and others.

Of course, many changes and variations in the composition and size of the active agent carrier, the separator layer, the reservoir carrier, the blocking layer, the covering layer, the protective layer, and the adhesive, in the composition of the transporting liquid or vehicle, in the physiologically active agents, in the mode of impregnating the active agent carrier with the physiologically active agent and the reservoir carrier with the transporting liquid or vehicle, in the mode of applying and securing the assembled unit to the skin, and the like may be made by those skilled in the art in accordance with the principles set forth herein and the claims annexed thereto.

I claim:

1. A composite unit useful for the administration of measured doses of physiologically active agents by precutaneous absorption, said unit comprising a carrier layer of absorbent material impregnated with said active agent, a separator layer of non-absorbent, non-permeable material superposed over said carrier layer, a reservoir layer of absorbent material disposed above said separator layer, a non-permeable, non-absorbent blocking layer between said reservoir layer and said separator layer to separate said layers from each other, said blocking layer being adapted to prevent liquid from flowing from said reservoir layer to said carrier layer when intact and adapted to be moved when the unit is to be used so as to bring said reservoir layer into contact with said underlying separator layer, wick means in contact to said carrier layer, said wick means being adapted to be brought into communication with said reservoir layer when said blocking layer is moved, said reservoir layer being charged with a transporting fluid for said active agent, said transporting fluid being superposed over said reservoir layer and adapted to prevent evaporation of said transporting fluid.

2. The composite package according to claim 1, wherein the cover layer is provided at its borders with an adhesive layer adapted to secure the unit preparation to the skin when in use.

3. The composite package according to claim 1, wherein pipette means are provided for applying said transporting liquid to said reservoir layer.

4. The composite package according to claim 1, wherein said composite package is provided with a protective layer adjacent to the carrier layer, said protective layer being adapted to be removed before use and application of said composite package to the skin.

5. The composite unit according to claim 1, wherein the separator layer, the blocking layer, and the cover layer consist of non-absorbent non-permeable plastic material.

6. A composite unit for the administration of a measured dose of a physiologically active agent by precutaneous absorption, which unit comprises a carrier layer of absorbent material capable of retaining a measured dose of said active agent and carrying said measured dose, a separator layer of non-absorbent, non-permeable material superposed over said carrier layer, a reservoir layer composed of absorbent material disposed above said separator layer, a liquid vehicle for said active agent, the absorbent material of the reservoir layer being impregnated with said liquid vehicle, and wick means between the reservoir layer and the carrier layer and bypassing the separator layer to place the reservoir layer in communication with the carrier layer, the cross-sectional area of the wick
means being such that an amount of the vehicle equal to that absorbed by the skin from the active agent carrier may flow therethrough.

7. The composite unit of claim 6, wherein said liquid vehicle is absorbable through the unbroken skin, has sufficient dissolving power for the active agent to make the same absorbable through the unbroken skin and is toxicologically unobjectionable to the human organism.

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