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(56) Documents Cited

GB 2086224 A	**EP 0450986 A2**	**EP 0360516 A2**
EP 0279977 A2	**EP 0275716 A1**	**EP 0275550 A1**
EP 0272918 A2	**EP 0224981 A2**	**EP 0181970 A1**
WO 86/06281 A1		

(58) Field of Search
UK CL (Edition L) **A5B BLG**
INT CL[5] **A61L 15/44**

(54) Medicinal patches for percutaneous administration

(57) A controlled-releasing medicinal patch for percutaneous administration, which delivers a certain amount of physiologically active agent (drug) through the skin or mucous membranes which is prepared by a lamination techinque and comprises percutaneous penetration enhancer (fatty acid ester, polyoxyethylene derivative,glycerin fatty acid ester, propylene glycol fatty acid ester, pyrrolidone derivative), adhesive resin (silicone polymer, natural or synthetic gums, acrylic resin), drug or its precursor and any other additives.

The medicinal patch diffuses and delivers the physiologically active agent efficiently to the desired locus through the skin and minimizes the skin-irritation due to its preparation method employing lamination technique and controlling the water retain percentage in the adhesive vehicle.

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FIG. 1

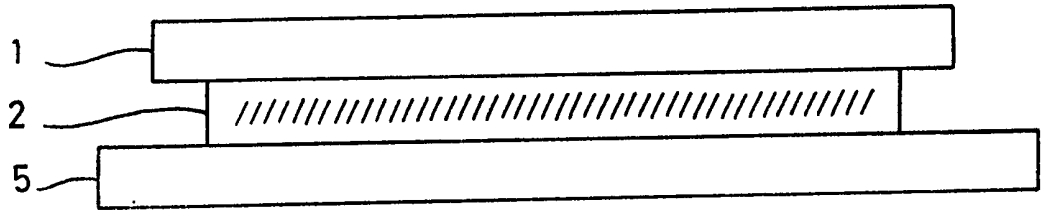


FIG. 2

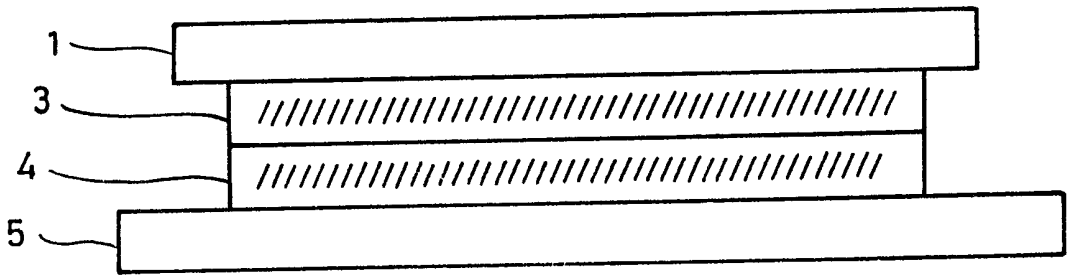
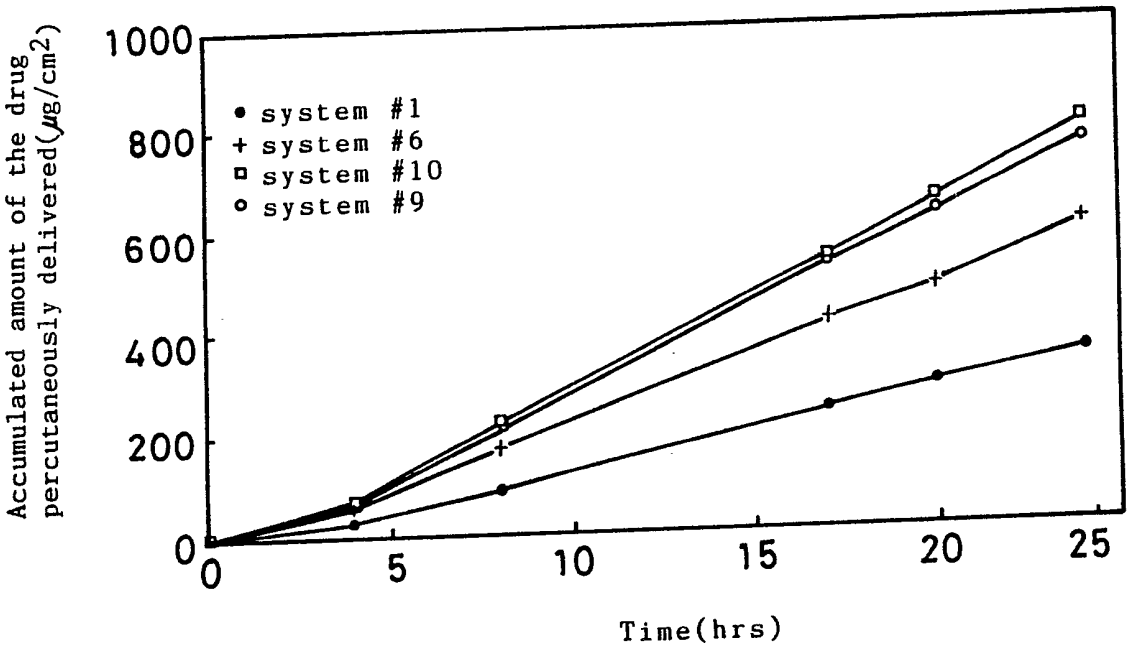


FIG. 3


Accumulated amount of the drug percutaneously delivered(μg/cm²)
1000
800
600
400
200
0
0
5
10
15
20
25
Time(hrs)
• system #1
+ system #6
□ system #10
○ system #9

MEDICINAL PATCHES FOR PERCUTANEOUS ADMINISTRATION

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The present invention relates to a controlled-release medicinal patch which continuously delivers a certain amount of drugs such as physiologically active agents through the skin or mucous membranes. More specifically, the present invention relates to a medicinal patch which, when applied on the skin, dissolves the maximum level of drug in the adhesive layer contacting with the skin, delivers percutaneously the necessary amount of drug and enhances the percutaneous penetration of drug.

2. DESCRIPTION OF THE PRIOR ART

It has been widely used to deliver drugs(physiologically active agents) through the skin by employing a patch, a sort of percutaneous administrating preparations, for the purpose of the systemic or topical penetrating of drugs. These methods of percutaneous administration offers many advantages over the traditional oral administration of drugs. For example, in the method of oral administration, a great level of drug is degraded by the metabolism in the liver prior to being absorbed into the intestine and exhibiting its efficacy at the desired locus. However, in the method of percutaneous administration, the efficacy of absorbed drug is not seriously decreased by the metabolism in the liver because the absorbed drug does not pass

through the liver first during the body circulation. Particularly in the case of non-steroidal anti-inflammatory agents, their percutaneous administration gives an advantage of decreasing the gastrointestinal damage which is apt to be caused in the oral administration.

Based on the above-mentioned advantages, recently, studies on the transdermal drug delivery system which overcomes the first-past effect or gastrointestinal damage induced in the oral administration and enhances the effectiveness and safety of drugs have been widely proceeded and, as a result, penetrating topical pharmaceutical compositions containing nitroglycerin, scopolamine and the like became commercially available. The above delivery system offers its own inherent advantages associated with the continuous and constant releasing characteristics of the drug and eliminates the problem of rapid metabolism induced in the oral administration. Moreover, this system improves the compliance of a patient while exhibiting the same therapeutic effect as in the oral administration of large amounts, and consequently provides markedly increased conveniences for a patient in the treatment of disease.

In the meanwhile, many drawbacks of the above transdermal drug delivery system have also been indicated in connection with the difficulty in applying it to various drugs. Because the skin surrounding a living body surface must serve as a barrier to the invasion of pathogens and toxic materials, it is highly impermeable. Accordingly, extensive attempts have been made for the purpose of enlarging the utility of transdermal delivery system and eliminating the barrier properties of the skin and

membranes.

Many studies which were intended to use a system having the least contacting area with the skin, have been focused on enhancing the diffusion of drugs through and across the above mentioned barrier. Particularly, a great deal of attempt has been made to enhance the percutaneous penetration for the skin barrier itself. According to the investigations reported up to now, though somewhat progress has been achieved as a result of the above-mentioned trials, in case of using the system frequently or in large amounts, the damage and irritation of the skin tissue on which the system was applied were still induced and in the worse case, the systemic side-effect might be caused. It is also known that conventional non-steroidal anti-inflammatory and analgesic agents exhibit poor anti-inflammatory and analgesic effects when administered percutaneously.

However, all of the non-steroidal anti-inflammatory and analgesic agents for oral administration generally cause several side-effects including gastrointestinal damage. Therefore, a great deal of attempts has been continued for the purpose of administrating the non-steroidal anti-inflammatory and analgesic agents via various pathway and large numbers of patches containing percutaneous penetration enhancers employed to facilitate the absorption of the drug have already been formulated. In general, as the penetration enhancer, the following compounds have been used: for example, salicylic acid, urea, dimethyl sulfoxide, propylene glycol, glycerin, azon and many other compounds. However, in some cases, even these enhancers can not raise the percutaneous absorption of drug to

a level above the necessary amount.

The following compounds have been reported to serve as a penetration enhancer for percutaneous delivery of drugs: for example, dimethyl sulfoxide (U.S. Pat. No. 3,551,554), ethanol (U.S. Pat. Nos. 4,615,699, 4,698,062 and 4,262,539), cyclourea (U.S. Pat. No. 4,667,131) and substituted-aza cycloalkane-2-one (U.S. Pat. Nos. 3,989,816, 4,316,893 and 4,405,616).

U.S. Pat. Nos. 4,557,934 and 4,537,776 disclose topical compositions of non-steroidal anti-inflammatory and analgesic agents, anti-viral agent and any other active agents, which contain ethanol, a specific glycol, pyrrolidone, 1-(2-hydroxyethyl)-aza-cyclopentane-2-one and 1-35% 1-dodecyl azacycloheptane-2-one(azon).

A method of using oleic acid, a sort of fatty acid, as an useful penetration enhancer [See. Cooper, E.R., J. Pharm. Sci., Vol.73 No.8 pp1153-1156(1984)] has been also disclosed. Cooper describes a method of enhancing the percutaneous penetration of active agent(salicylic acid) by using oleic acid of solid phase in various concentrations in the presence of solvent(propylene glycol), and also a method of using the oleic acid together with other polyhydric alcohols. Cooper asserts that his methods are useful in promoting the percutaneous penetration of non-polar molecules and show different effects depending on the chain-length of fatty acid. In addition, cooper points out the fact that the percutaneous penetration of polar molecules may be significantly effected and enhanced by detergents. However, the detergents are generally reported not to enhance the percutaneous penetration of nonpolar molecules. Therefore, cooper's methods

teach that the percutaneous penetration of nonpolar molecules can be enhanced by adding small amounts of fatty acid, polyhydric alcohols or alcohols to the formulations.

Patel, et al., J. Soc. Cosmetic Chem., 36, 303-311 (1985) describe that propylene glycol, a polyhydric alcohol which has been widely used as a solvent in the preparation of conventional percutaneous delivering system may cause the skin-irritation and/or sensitization when the concentration exceeds 10 percent. Therefore, it has been demanded that the percutaneous penetration enhancer must primarily show no or the least side effect for the skin and at the same time, be compatible with the percutaneous delivering system.

U.S. Pat. No. 4,490,206 relating to the use of medicinal patches discloses the use of a percutaneous delivering system of different type which comprises physiologically active agent uniformly dispersed in the adhesive layer. According to this system, the physiologically active agent is dispersed in the pressure-sensitive, adhesive layer which is to be applied on the skin. And, when the system is applied on the skin of a patient, the active agent is diffused across the skin from the adhesive layer and delivered to the desired locus of the patient. Many other percutaneous delivering systems of various types are known and all of them have their own merits and demerits depending on the system by which the physiologically active agent is delivered percutaneously.

U.S. Pat. No. 4,738,670 discloses a medicinal plaster which comprises anti-inflammatory and analgesic agents mixed in polyisobutylene adhesive layer together with a carrier such as

triglyceride. The disclosure of this patent, however, mainly deals with the supporting material of the plaster and does not state whether the carrier employed can serve as the percutaneous penetration enhancer or not.

It is possible to reduce the side effect induced by an absorption of large amount of drug in a short time by regulating the absorption of the drug. It is also possible to maintain the level in blood to a constant concentration over a prolonged period by decreasing the frequency of administration.

However, it is frequently occurred that the drug administration using a patch shows poor bioavailability due to the difficulty of penetration of the corresponding drug across the skin. To solve this problem, attempts to increase the absolute amount of drug in a patch to a level of ensuring the percutaneous absorption of necessary amounts have been made. For example, Japanese Unexamined Pat. Pub. No. 60-185713 and U.S. Pat. No. 4,031,894 disclose preparations for percutaneous absorption which comprise drug dissolved in bases for patch, ointment, cream and the like to a level exceeding the saturating concentration and dispersed in the form of recrystallized minute particles. If the patch of this type is applied on the skin surface, the drug dissolved in base is absorbed percutaneously and then, the drug existing in the form of minute particles is gradually dissolved and supplemented. Accordingly, it is thought that it is possible to deliver larger amounts of drug across the skin than in the conventional preparations which contain the corresponding drug to a level below the saturating solubility. However, in practical, the drug existing in the

form of minute particles is hard to redissolve in base and the absorption rate of the drug across the skin is not relatively high.

Alternatively methods of enhancing the percutaneous absorption of drug by sealing the sweat have been also attempted. For example, Japanese Examined Pat. Pub. No. 60-51478 and Japanese Unexamined Pat. Pub. No. 62-153215 disclose methods for enhancing the percutaneous absorption of active agent by selecting substantially water-impermeable film as a upper film of a patch. However, these methods also have defects, that is, the skin-irritation may be induced by the sweat and excretions and the patch is readily peeled off from the skin by the sweat. In order to eliminate the above problems, Japanese Examined Pat. Pub. No. 53-33984, Japanese Unexamined Pat. Pub. No. 56-20514 and Japanese Unexamined Pat. Pub. No. 56-51412 propose that highly supporting materials such as non-woven fabric or hygroscopic urethane be employed. However, these trials have also failed in delivering ultimately the necessary amount of drug across the skin.

To reduce the skin-irritation and improve the feeling of adhesiveness, methods of employing water-soluble vehicle such as gelatin, polyvinylalcohol, dextrin, arabic gum, carboxymethyl cellulose, methylcellulose, hydroxy ethyl cellulose, polyvinylpyrrolidone, sodium alginate, sodium polyacrylate and the like have been also proposed. For example, Japanese Unexamined Pat. Pub. No. 58-167510 and Japanese Unexamined Pat. Pub. No. 64-16718 disclose methods for preparing a patch by coating the water-soluble vehicle containing drug and penetration

enhancer on a non-woven fabric. However, since the patches prepared by the above methods show weak skin-adhesiveness, they can not be applied independently on the skin and must be used together with a sticking fabric and moreover, the effect of delivering drug across the skin is not sufficient.

SUMMARY OF THE INVENTION

The primary object of the present invention is to provide a percutaneous delivering system which serves useful and appropriate functions for percutaneous administration. This primary object of the invention can be accomplished by attaining the following detailed objects according to the present invention.

An object of the present invention is to provide a medicinal patch for percutaneous administration, which employs the pressure-sensitive adhesives compatible with the percutaneous delivering system and contains useful percutaneous penetration enhancer and skin-irritation inhibitor, whereby

(a) being in the type of the tape which can deliver efficiently anti-inflammatory and analgesic agents and any other drugs across the skin,

(b) showing significantly reduced skin-irritation,

(c) exhibiting rapid efficacy for diseases such as arthritis due to an excellent releasing and transferring property of the physiologically active agent through the skin, and

(d) reducing an unpleasant feeling of adhesiveness via to an excellent efficacy obtained in the least applied area of

the skin.

Another object of the present invention is to provide a medicinal patch for percutaneous administration, in which the concentration of drug in vehicle is adjusted to a level of the maximum value by selecting, as an adhesive vehicle, acrylic adhesive and rubbery adhesive having similar solubility parameter with the drug, whereby the drug can be absorbed more efficiently through the skin due to the increased solubility of the drug in vehicle, and the adhesion property and skin-irritation can be reduced.

Still another object of the present invention is to provide a controlled-releasing medicinal patch for percutaneous administration, in which the water-retention in the adhesive vehicle is controlled by employing lamination techniques, whereby the drug can be delivered to the concentration desired through the skin or mucous membranes more effectively.

DETAILED EXPLANATION OF THE INVENTION

The transdermal absorption of a drug by the use of a patch is carried out based on the difference of the drug concentrations between in a vehicle and in skin of a living body. In practice, the drug is absorbed through the stratum corneum by way of the following steps:

(1) Diffusion in a vehicle;

(2) Integration from the vehicle to the surface of stratum corneum;

(3) Diffusion in the stratum corneum;

(4) Integration from the stratum corneum to the lower epidermal tissue;

(5) Diffusion in the epidermic and dermic layers; and

(6) Transfer from the derma to the blood vessel.

It is generally considered that the process of the transdermal absorption of drug is divided into the diffusion process and the integration process. However, in practical, the coupling with the tissue and the metabolic reaction are proceeded simultaneously with the diffusion of the drug. The diffusion can be described and calculated by Fick's the first law which shows the relationship between the density gradient and the migrating speed of drug and Fick's the second law which shows the change of drug concentration at a certain locus as a function of time.

$J/A = -D \ C/x$ ..... Fick's the first law

$C/t = D \ ^2C/x^2$ ..... Fick's the second law

where A = drug-diffused area

C = drug concentration

D = diffusion coefficient

J = speed of penetration

t = time(hr)

x = location

The skin penetrating effect of a drug is determined, in many cases, by the speed of penetration at the normal state and the speed of penetration at the normal state(J) can be described by:

$J = ACvKDL$

where Cv = drug concentration in the vehicle,

K = partition coefficient of the drug between the skin and the vehicle,

L = effective skin thickness

A & D = the same as defined above

In addition, the penetration coefficient(Kp) can be described by:

$Kp = KD/L$

where K, D and L represent the same as defined above.

As can be seen in the above, it is advantageous to increase the drug concentration in vehicle to deliver large amounts of the drug through the skin, however there is a limit in the methods presently used.

According to the present invention, as one of the means to increase the drug solubility in the adhesive vehicle and reduce the adhesion property and skin irritation, the drug concentration in the vehicle is adjusted to a level of the maximum value by selecting and preparing the adhesive having similar solubility parameter with the drug. As the most suitable adhesive for the above-mentioned purpose, acrylic adhesives are included. The acrylic adhesives provide advantages in controlling the water retention and the drug solubility in the adhesive vehicle since they are easy to regulate the incorporation ratio of the monomers to be polymerized. However, when a patch comprising the above adhesives is applied on the

skin, the solubility parameter in the adhesive vehicle is changed as the water content in the vehicle is increased due to the water exhalation from the skin as compared with that of immediately after the patch was prepared, and the saturation solubility of the drug is also changed. Consequently, the solubility of the drug shows significant difference with the practical value and at the same time, the delivering amount of the drug through the skin and the adhesion property are seriously decreased.

To overcome the above-mentioned problems of the prior arts, the lamination technique is employed in the present invention. And as the support(1) in Fig. 1 and Fig. 2, monolayered film or laminated film of polyethylene, polypropylene, polyethylene terephthalate and the like; non-woven fabric ; or cotton fabric is used and if necessary non-woven fabric or cotton fabric in the form of a laminate with the water-impermeable plastic film may be used. As an adhesive, the laminated adhesives which can build the adhesive layer of the adhesive vehicle(2) in Fig. 1 or of the adhesive vehicles(3,4) in Fig. 2 and form the multilayer of the adhesive vehicle(3) and the adhesive vehicle(4) as depicted in Fig. 2 can be used.

The adhesive vehicle(3) in Fig. 2 laminates an adhesive composition having higher water retention than that of the lower layer, and contains the drug incorporated in an amount above the saturation value, if necessary, together with the additives such as skin penetration enhancer and the like. The adhesive vehicle(4) in Fig. 2

has lower water retention than that of the upper layer, employs an adhesive having high drug solubility, and contains the drug incorporated in an amount above the saturation value as is in the upper-layered adhesive vehicle(3) together with the skin penetration enhancer and any other additives.

In addition, the drug can be continuously delivered in a constant amount transdermally through the skin or mucous membranes by laminating appropriately the plural numbers of the adhesive vehicle(2) in Fig. 1 as is in the laminated layer of the adhesive vehicle(3) and the adhesive vehicle(4) in Fig. 2. At this case, the adhesive vehicle(2) should be selected from those which can form the multilayer to serve the same function as the adhesive vehicles(3,4) in Fig. 2.

The releasing film(5) in Fig. 1 and Fig. (2) is consisted of a releasing paper and a releasing film incorporated with silicone- or fluoro- releasing agent. To describe in detail, in case of intending to deliver the drug in large amounts through the skin, the adhesive vehicle having low water retention is introduced in the lowest layer contacting with the skin to prevent the decrease of the drug solubility and the adhesion property due to the water exhalation from the skin, and the adhesive vehicle having high water retention is introduced as the layer goes up upper one. Accordingly, when the patch is applied on the skin, as the water exhales from the skin surface, the water is transmitted to the upper layer

through the adhesive layer, and the lower adhesive layer contacting with the skin contains only a fixed amount(small amount) of water, thereby the saturating concentration of overall drug and the physical properties of the adhesive are maintained constantly and the side effects for the skin due to an accumulation of the sweat or excretion can be reduced. By this way, the delivery of the drug through the skin is effectively proceeded. If the support is a non-woven fabric, cotton fabric or any other air-permeable plastic film, the delivering efficiency of the drug can be regulated to the maximum level by laminating the support or controlling its own water-permeability. By employing the above-regulated support for the preparation of a medicinal patch to deliver a large amount of the drug percutaneously, a favorable result can be obtained.

Alternatively, in case of intending to obtain a burst effect by delivering large doses of drug through the skin just after application, the adhesive vehicle having the desired level of water retention is selected as the adhesive layer and the drug is saturated therein. When applying the above preparation on the skin, a large amount of the drug is delivered through the skin just after application due to the high concentration of the drug. However, as the adhesive vehicle adsorbs the water of the skin, the solubility of the drug is gradually lowered and thereby the delivery of the drug through the skin is also decreased. Thereafter, when the absorption of the water reach the normal state, only a constant amount of the drug

is appropriately delivered through the skin and the release of the drug is controlled.

The laminating number of the above adhesive vehicle is typically 1 to 10 layer(s), preferably 1 to 5 layer(s). The thickness of each layer is typically 5 to 150μm, preferably 10 to 100μm. And the thickness of the overall adhesive vehicle is typically 3 to 200μm, preferably 50 to 500μm.

The adhesive resins such as silicone polymer, natural or synthetic gums, acrylic resin and the like may be used as the adhesives; rosin resin, polyterpene resin, petroleum resin, terpene phenol resin and the like may be used as the adhesiveness-conferring agent; and the plasticizer, filler, antioxidant and the like may be optionally employed for the preparation of a medicinal patch according to the present invention. Particularly as the acrylic resin, an adhesive resin such as co(polymer) of C_4-C_{18} aliphatic alcohol with (meth)acrylic alkyl ester having alkyl group and/or the polymer of (meth)acrylic alkyl ester having C_4-C_{18} alkyl group with different functional monomer such as vinyl acetate may be used. Examples of the (meth)acrylic acid copolymer include butyl acrylate, isobutyl acrylate, hexyl acrylate, octyl acrylate, 2-ethylhexyl acrylate, iso-octyl acrylate, decyl acrylate, isodecyl acrylate, lauryl acrylate, stearyl acrylate, methyl methacrylate, ethyl methacrylate, butyl methacrylate, isobutyl methacrylate, 2-ethylhexyl methacrylate, iso-octyl methacrylate, decyl methacrylate, etc. and examples of the functional monomers

include monomer containing hydroxy group, monomer containing carboxyl group, monomer containing amide group, monomer containing amino group, etc.. Examples of the monomer containing hydroxy group include hydroxy alkyl(meth) acrylate such as 2-hydroxyethyl (meth)acrylate, hydroxypropyl (meth)acrylate, etc.. Examples of the monomer containing carboxyl group include α-ß unsaturated carboxyl acid such as acrylic acid, methacrylic acid and the like ; maleic mono alkyl ester such as butyl malate and the like; maleic acid; fumaric acid; crotonic acid, etc., and anhydrous maleic acid can also form the same type of co(polymer) as the maleic acid. Examples of the monomer containing amide group include alkyl (meth)acrylamide such as acrylamide, dimethyl acrylamide, diethyl acrylamide and the like; alkylethylmethylol (meth) acrylamide such as butoxymethyl acrylamide, ethoxymethyl acrylamide and the like; diacetone acrylamide; vinyl pyrrolidone; dimethyl aminoacrylate, etc.

In addition to the above exemplified monomers for copolymerization, vinyl acetate, styrene, α-methylstyrene, vinyl chloride, acrylonitrile, ethylene, propylene, butadiene and the like may be employed, and the copolymers with these compounds also exhibit good properties. The (meth)acrylic alkyl ester as a (co)polymeric component is preferably incorporated in the adhesive in an amount above 50% by weight.

For the purpose of increasing or decreasing the water retention of the adhesive vehicle, in case of employing

acrylic resin, the water retention can be regulated by copolymerizing hydrophilic monomer, monomer containing carboxyl group, monomer containing amide group, monomer containing amino group and the like, and in case of employing rubbery and silicone resins, the water retention can be regulated by incorporating the vehicle with an adhesiveness-conferring agent or other additives. As an alternative mean, the water retention of the adhesive vehicle can be also regulated by employing highly water-absorptive resin, polyhydric alcohols and water-absorptive inorganic substances. Examples of the highly water-absorptive polymer include mucopolysaccharides such as hyaluronic acid, chondroitin sulfate, dermatan sulfate and the like; highly water-absorptive polymer having a large number of hydrophilic groups in molecules such as chitin, chitin derivatives, starch and carboxy-methylcellulose; and semi-synthetic and synthetic highly water-absorptive resin of polyacrylic, polyoxyethylene, polyvinyl alcohol, and polyacrylonitrile homo- or copolymer. Examples of the water-absorptive inorganic substances useful in the present invention include powdered silica, zeolite, powdered ceramic and the like. Examples of the polyhydric alcohols include propylene glycol, glycerin, sorbitol and the like. The water-absorptive substances such as highly water-absorptive polymers, water-absorptive inorganic substances and polyhydric alcohols can be incorporated in the adhesive vehicle in an amount of 0.1-40% by weight, preferably 1-20% by weight. Examples of the rubbery adhesives which can be

used in the present invention include natural gum, polyisoprene, polyisobutylene, styrene-butadiene-styrene copolymer, styrene-isoprene-styrene copolymer, styrene-ethylene/propylene-styrene copolymer, styrene-ethylene/butylene-styrene copolymer, polyvinyl ether, polyurethane, polybutadiene, styrene-butadiene copolymer, styrene-isoprene copolymer, styrene-isoprene-butylene block copolymer and the like. As the silicone resin adhesives, silicone gum such as polyorgano siloxane can be used.

If necessary, various additives, for example an adhesiveness-conferring agent such as rosin resin, polyterpene resin, coumarone-indene resin, petroleum resin, terpene phenol resin, etc.; an adhesiveness auxiliary agent such as liquid polybutene resin, petroleum resin, terpene phenol resin, etc.; plasticizer such as liquid polybutene resin, mineral oil, lanolin, liquid polyisoprene, liquid polyacrylate etc.; softeners; fillers; and antioxidants may be added to the adhesive vehicle.

The present invention provides a pharmaceutical preparation in the form of a transdermal delivery system which contains physiologically active agents dispersed or dissolved in a certain pressure-sensitive, adhesive layer. The pressure-sensitive, adhesive layer is characterized in containing a specific percutaneous penetration enhancer and this enhancer is characterized in not decreasing the original adhesion power of the pressure-sensitive, adhesive layer. Any other additives may be optionally incorporated in the adhesive layer to obtain an improved adhesion

property.

Examples of the percutaneous penetration enhancer typically used for increasing the transdermal delivery of the drug include dodecyl sulfoxide mono- or dimethyl acetamide, N-hydroxy ethyl lactide, higher fatty acid ester, salicylic acid, sorbitol, urea, glycerin, squalene, squalane, acetylated lanolin, cetyl laurate, olive oil, castor oil, lauric acid, oleic acid, lauryl alcohol, oleyl alcohol, ethoxystearyl alcohol, derivatized paraffin, vaseline, camphor, glycerin fatty acid ester, fatty acid mono- (or di-) ethanolamide, ethylene glycol mono ethyl ether, polyoxyethylene alkyl ether, polyoxyethylene alkyl ester, polyoxypropylene alkyl ether, propylene glycol mono(di)alkyl ester, propylene glycol monolaurate, polyoxyethylene lauryl ether, pyrrolidone derivative and the like.

The inventors have found that the percutaneous penetration efficiency of the drug can be markedly increased by employing the percutaneous penetration enhancer such as polyoxyethylene derivative, pyrrolidone derivative and the like. It has been also found that the above increased penetration efficiency by employing the enhancer is effectively exhibited particularly in relation to the non-steroidal anti-inflammatory and analgesic agent such as ketoprofen. Thus, in one aspect of the present invention, a medicinal patch composition for percutaneous administration which comprises the vehicle containing one or more compound(s) selected from the group consisting of

fatty acid ester(for example, methyl laurate, isopropyl myristate), polyoxyethylene derivative, glycerin fatty acid ester, propylene glycol fatty acid derivative, pyrrolidone derivative and the like as the percutaneous penetration enhancer in the proportion of 1 to 39% by weight of the overall vehicle, and physiologically active agent is provided.

To be recognized as an useful percutaneous penetration enhancer, several requirements are demanded. Particularly important requirements are as follows:

first, it should be a dermatologically acceptable compound which does not induce the primary irritation or sensitization when applied on the skin;

second, it should miscible with the vehicle and active agent in the percutaneous delivery system. If the enhancer is immiscible with those substances, the phase-separation and/or reactions destroying or arresting the physiological activities of the active agent may be occurred;

third, it should not possess its own pharmacological activity, is predictable and considerable influence on enhancing the percutaneous delivery of the active agent, and is preferably approved by FDA(Food and Drug Administration, USA).

The inventors have tested numerous compounds to seek one or more useful compound(s) satisfying the above requirements as the percutaneous penetration enhancer and found that propylene glycol monolaurate can be used as the representative one. Another compounds found to be useful

as the enhancer is polyoxyethylene lauryl ether. The inventors have also found that alpha-bisabolol among bisabolol, camomile oil, allantoin and di-pantenol is the most effective agent as a lenitive agent for decreasing the skin primary irritation.

The safe and effective amount of physiologically active agent employed in a medicinal patch composition according to the present invention means an amount to provide therapeutically effective level in blood and/or therapeutically effective topical concentration by the transdermal delivering method.

The incorporating amount of these percutaneous penetration enhancer is 0.1 to 40% by weight, preferably 1 to 20% by weight.

In addition to the components described above, tocopherol, tocopheryl acetate, BHA, BHT and the like may be optionally employed as an antioxidant of drug, penetration enhancer and any other additives and the preservatives such as ethyl paraben, methyl paraben and butyl paraben may be also added.

The selection of the vehicle(adhesives) for a tape or a patch preparation is not specifically limited if the adhesives can maintain the adhesiveness for a long period of time at the normal temperature when the preparation is applied on the skin surface. Examples of such vehicle include adhesives such as rubbery and silicone resins. Typically, acrylic and rubbery resins are employed.

The selection of the drug (physiologically active

agents) incorporated in the vehicle is not specifically limited if the drug can exhibit the percutaneous absorption property by the method of transdermal administration and also its solubility can be changed as the water retention percentage in the vehicle is changed. As non-steroidal drugs, the pharmacologically effective compound selected from the group consisting of methyl salicylate, salicylic acid, ibuprofen, ketoprofen, flurbiprofen, indomethacin, diclofenac sodium, flufenamic acid, naproxen, mefenamic acid, fenoprofen, fenclofenax, piroxicam and the precursors thereof can be used in a safe and effective amount.

Examples of other drugs include an antipyretic and anti-inflammatory agent, a steroidal anti-inflammatory agent, a vasodilator, a hypertension and arrhythmia treating agent, an anti-hypertensive agent, an anti-cough and expectorant agent, an anti-tumor agent, hormone preparations, an anti-asthmatic and anti-nasal allergic agent, anti-histamine preparations, an anti-coagulant, antispasmodic, cerebral circulation or metabolism improving agent, an anti-depressant, an anti-anxiety agent, an anti-hyperglycemia, local anesthetic or anti-ulcer agent, an antirheumatic and antiarthritic agent and the like.

As the support of a tape and a patch preparations, any supporting material typically used in conventional preparations can be employed. Examples of such supporting materials include cellulose acetate, ethyl cellulose, polyethylene terephthalate, plasticized vinyl acetate-

vinylchloride copolymer, nylon, ethylene-vinyl acetate copolymer, plasticized polyvinylchloride, polyurethane, polyethylene, polyvinylidene chloride, aluminum and the like. These materials are typically used, for example, in the form of a mono-layered sheet(film) or two or more layered laminate. In addition to aluminum, cotton fabric or non-woven fabric can be also used as the support.

The medicinal patch composition according to the present invention may additionally contain other components such as a lenitive agent for alleviating the skin irritation and organic and inorganic fillers for the purpose of reducing and preventing the skin-irritation and the deterioration of adhesion property which are frequently occurred due to incorporating drugs and percutaneous penetration enhancers in a patch or a tape preparation. Examples of the lenitive agent for alleviating the skin-irritation include bisabolol, camomile oil, alantoin, glycerol, di-pantenol and the like. These agents may be present in an amount of 0.01-10% by weight, preferably 0.1-5% by weight.

Examples of the organic and inorganic substances which may be employed to improve the adhesion property include organic high-molecular particles such as cellulose, polyethylene, nylon 6, nylon 12, polypropylene, polyethylene terephthalate, etc. and inorganic substances such as zinc oxide, calcium oxide, silica, kaolin, talc, titanium oxide, etc.. These organic and inorganic substances may be present in an amount of 0.1-30% by

weight, preferably 0-10% by weight.

The concentration of the physiologically active agent incorporated in the adhesive layer may from 1 to 40% by weight, preferably from 5 to 35% by weight, more preferably from 7 to 30% by weight of the sum obtained by adding the weight of the active agent to the weight of the adhesive vehicle.

As can be seen from the above description, though the saturating concentration of the physiologically active agent varies depending on the composition of the adhesive layer, it is desirable to incorporate the physiologically active agent to a level of approximate saturating solubility in each adhesive layer consisting of various compositions.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1 is the cross sectional view of a release-controlled, mono-layered patch for percutaneous administration.

Fig 2 is the cross sectional view of a multi-layered patch for percutaneous administration according to the present invention.

Fig 3 shows graphs representing the change of the percutaneous delivering amount of drug as a function of time when the percutaneous delivery system according to the present invention was applied on the skin of a guinea pig.

PREFERRED EMBODIMENT OF THE INVENTION

The present invention will be embodied by way of the following examples. However, these examples are provided for the illustration purpose only and should not be construed as limiting the scope of the invention, which is properly delineated in the accompanying claims.

Example 1

An anti-inflammatory/analgesic composition for transdermal administration in the form of a patch was prepared by mixing homogeneously the following components.

Ketoprofen	10
Propylene glycol monolaurate	10
Tocopheryl acetate	1
Zinc oxide	5
Acrylic resin A[1]	74
total	100

note) [1] fluid of butyl acrylate-octyl acrylate-vinyl acetate copolymer resin (solid content 48.0%)

The mixture was coated on to the silicone treated PET stripping liner, left stand for 20 minutes or more at ambient temperature and dried for 10 minutes or more at 90°C.

The resulting material having 80μm thickness based on the dried condition is then combined together with an elastic non-woven fabric to produce the final patch in the form of a tape.

Example 2

An anti-inflammatory/analgesic composition for percutaneous administration in the form of a patch was prepared by mixing homogeneously the following components

according to the ratio(% by weight) indicated below.

Indocin	10
Glycerol monooleate	10
Tocopheryl acetate	1
Zinc oxide	5
Acrylic resin B[1]	75
total	100

note) [1] fluid of vinyl acetate-resin polymer (solid content 31.0%)

The resulting mixture was coated on to the silicone treated releasing paper, dried and combined together with an elastic non-woven fabric to produce the final patch.

Example 3

An anti-inflammatory/analgesic composition for percutaneous administration in the form of a patch was prepared by mixing the following components homogeneously according to the ratio(% by weight) indicated below.

Diclofenac sodium	10
Polyoxyethylene (3) lauryl ether	10
Tocopheryl acetate	1
Bisabolol	2
Zinc oxide	5
Acrylic resin A[1]	75
total	100

note) [1] fluid of butyl acrylate-octyl acrylate-acetate copolymer resin (solid content 48.0%)

The mixture was coated on to the silicone treated PET stripping liner and dried. Thereafter, the resulting material was combined together with an elastic non-woven fabric to produce the final patch in the form of a tape.

Example 4

* Adhesive 1

To a reaction vessel equipped with a reflux condenser and a stirrer, 97.4 parts of 2-ethylhexyl acrylate, 2.5 parts of methacrylic acid, 0.1 parts of polyethylene glycol di-acrylate, 1.0 parts of benzoyl peroxide and 100 parts of ethyl acetate were added and, under nitrogen atmosphere, the polymerization reaction was proceeded slowly with stirring.

To regulate the polymerization degree, 100 parts of ethyl acetate was added to the reaction mixture slowly during the polymerization reaction, and the reaction was conducted for 9 hours. The polymerization degree was 99.9%. To the resulting polymer solution, an appropriate amount of ethyl acetate was added to adjust the solid content to about 40% by weight.

* Adhesive 2

Under the same conditions as described above, the copolymerization reaction was carried out by employing 70 parts of 2-ethylhexylacrylate, 10 parts of acrylic acid, 1.0 parts of benzoyl peroxide (BPO) and 20 parts of vinyl acetate and adding ethyl acetate thereto.

The polymerization degree was above 99.9%. Aluminum acetate(200rpm) was also added to obtain self-curable product.

To the resulting polymer solution, ethyl acetate was added in an appropriate amount in order to adjust the solid content to about 40% by weight.

* Preparation of an "Adhesive vehicle(3)" :

To the "Adhesive 1" obtained in the above, ketoprofen was added in an amount of 20% by weight based on the solid content and dissolved therein to a concentration exceeding the saturating solubility.

The resulting mixture was coated on to the silicone treated releasing paper. At this time, the coating amount was adjusted that coating thickness of 50μm based on the dried condition was obtained.

* Preparation of an "Adhesive vehicle(4)" :

To the "Adhesive 2" obtained in the above, drug was added in an amount of 20% by weight and dissolved therein to a concentration exceeding the saturating solubility. The resulting mixture was coated on to the silicone treated releasing paper to a thickness of 30μm based on the dried condition.

The "Adhesive vehicle(4)" was first transferred to the polyethylene film and then, the "Adhesive vehicle(3)" was laminated therewith to produce a patch comprising two layers of adhesive vehicles 3 and 4 as depicted in Fig. 2. Thereafter, the patch was dried by leaving stand at the normal temperature for 15 minutes and then at 90°C for 10 minutes.

Example 5

* Preparation of the "Adhesive vehicle(4)" :

To the "Adhesive(1)" obtained in Example 4, ketoprofen was added in an amount of 20% by weight based on the solid content and dissolved therein to a concentration exceeding the saturating solubility.

After hyaluronic acid powder of 5% by weight was added to the resulting mixture and dispersed uniformly therein, this mixture was coated on to the silicone treated releasing paper to a thickness of 40μm based on the dried condition and dried.

Then, the "Adhesive vehicle(4)" obtained as above was transferred to a polyester film and the "Adhesive vehicle(3)" obtained in Example 4 was laminated therewith to produce a patch comprising two-layered adhesive vehicles.

Example 6

* Preparation of an "Adhesive vehicle(3)" :

To the "Adhesive(1)" obtained in Example 4, ketoprofen was added in an amount of 20% by weight based on the solid content and dissolved therein to a concentration exceeding saturating solubility. To the resulting mixture, polyoxyethylene(3) lauryl ether of 30% by weight as a percutaneous penetration enhancer and tocopherol acetate of 0.5% by weight as an antioxidant were added and dissolved. Then, colloidal silica of 3% by weight was incorporated to improve the decrease of adhesion property due to the addition of the percutaneous penetration enhancer.

The adhesive vehicle obtained in this manner was coated on to a releasing paper to a thickness of 60μm based on the dried condition and dried.

* Preparation of an "Adhesive vehicle(4)" :

To the "Adhesive(2)" obtained in Example 4, ketoprofen was added in an amount of 20% by weight based on the solid

content and dissolved to a concentration exceeding the saturating solubility. After polyoxyethylene(3) lauryl ether of 10% by weight was added to the mixture as a percutaneous penetration enhancer, tocopherol acetate of 0.5% by weight was also added and dissolved as an antioxidant. The resulting mixture was coated on to a releasing paper to a thickness of 40μm. Then, the "Adhesive vehicle(3)" was transferred to a polyester film and the "Adhesive vehicle(4)" was laminated therewith to produce a patch comprising two-layered adhesive vehicles.

Example 7

To the "Adhesive 2" obtained in Example 4, ketoprofen was added in an amount of 20% by weight based on the solid content and dissolved therein to a concentration exceeding saturating solubility.

After propylene glycol monooleate of 10% by weight was added to the mixture as a percutaneous penetration enhancer, tocopherol of 0.5% by weight and bisabolol of 2% by weight were also added and dissolved as an antioxidant and a lenitive agent of the skin-irritation, respectively.

Thereafter, cellulose powder(diameter of particles 5-15μm) of 3% by weight was uniformly dispersed therein as a regulating agent of the water retention and the resulting mixture was coated on to a releasing paper to a thickness of 70μm and dried.

Example 8

An anti-inflammatory/analgesic composition for transdermal administration in the form of a patch can be

prepared by mixing homogeneously the following components according to the ratio(% by weight) indicated below.

Ketoprofen	10
Propylene glycol monolaurate	5
Tocopheryl acetate	2
Zinc oxide	10
Rubbery resin C[1]	73
total	100

[1]styrene-butadiene-styrene block copolymer	100
terpene resin	75
polybutene	20
liquid paraffin	20
BHA	

2

The mixture obtained in this manner was coated on to a stripping paper and dried. The resulting material was combined together with an elastic non-woven fabric to produce the final patch.

Example 9

An anti-inflammatory/analgesic composition for transdermal administration in the form of a patch can be prepared by mixing homogeneously the following components according to the ratio(% by weight) indicated below..

Piroxicam	10
Glycerin monooleate	5
Tocopheryl acetate	2
Zinc oxide	10
Rubbery resin C[1]	73
total	100

[1]styrene-butadiene-styrene block copolymer	100
terpen resin	75
polybutene	20
liquid paraffin	20
BHA	2

The mixture obtained in this manner was coated on a stripping paper and dried. The resulting material was combined together with an elastic non-woven fabric to produce the final patch in the form of a tape.

Example 10

An anti-inflammatory/analgesic composition for transdermal administration in the form of a patch can be prepared by mixing homogeneously the following components according to the ratio(% by weight) indicated below.

Ketoprofen	15
Polyoxyethylene sorbitan monolaurate	5
L-menthol	3
DL-camphor	2
Tocopherol acetate	2
Zinc oxide	10
Rubbery resin C[2]	73
total	100

[2]styrene-isoprene-styrene block copolymer	100
hydrogenated rosin	80
polybutene	20
lanolin	20
BHA	2

The mixture obtained in this manner was coated on a stripping paper and dried. The resulting material was combined together with an elastic non-woven fabric to produce the final patch in the form of a tape.

PERCUTANEOUS PENETRATION TEST

Using a male-guinea pig weighing about 350g, the abdominal hair was removed by hair clipper Then, a certain section of the abdominal skin was excised, stored

in a refrigerator(below -20°C) and used by thawing at need.

The excised skin was placed in the middle of the Franz-type diffusion cell with its corneous side looking upward and the space below the cell was charged with 0.05M phosphate buffered saline solution of pH 7.4. The patch obtained in Example 1 was applied on the skin while the receiver solution (buffer solution) was stirred at a constant speed (600rpm).

After a given period of time passed, a portion of the receiver solution was taken for test and a fresh buffer solution was supplemented in the same amount as taken therefrom. From the test solution, the concentration of ketoprofen was determined by High Pressure Liquid Chromatography(HPLC).

* Analysis condition for HPLC

. column : $C_{18}\mu$ Bondapak [Waters Chromatography, Inc., milton Massachusetts 01757 USA]

. mobile phase : 55:45 V/V

nol : 0.02M phosphate buffered solution(pH 4.0)

. flow rate : 1 ml/min.

. detector : 254nm wave length ultraviolet

With the same method as described above, the percutaneous penetrating effect of ketoprofen for patches prepared according to various recipes (see Table 1 below) including the patch of Example 1 was determined and the results are summarized in Table 2 below.

Table 1 : Patches used for the percutaneous penetration test

Patch No.	concentration of ketoprofen (%)	penetration enhancer[1] (%)	penetration enhancer[2] (%)	penetration enhancer[3] (%)	zinc oxide (%)	tocopherol acetate (%)
1	10				5	1
2	20				5	1
3	25				5	1
4	30				5	1
5	40				5	1
6	10	10			5	1
7	10	20			5	1
8	30	10			5	1
9	10		10		5	1
10	10			10	5	1
11	20		5		5	1
12	20			5	5	1
13	10				10	2
14	10		5		10	2
15	15			5	10	2

note) 1. The contents(%) of all components are by weight.
2. The remaining contents of the patches numbering 1 to 12 correspond to those of acrylic resin (solid) and the remaining contents of the patches numbering 13 to 15 correspond to those of rubbery resin (solid).
3. [1]propylene glycol monolaurate
4. [2]polyoxyethylene(3) lauryl ether
5. [3]glyceryl monooleate

Table 2 : Comparison of the percutaneous penetrating effect of ketoprofen for the patches given in Table 1

Patch No.	Speed of percutaneous penetration (μm/cm^2/hr)	Retention time (hrs)	Ratio of the percutaneous penetration speed*
1	15.5(2.62)	2.19(0.31)	1.00
2	20.7(3.01)	1.96(0.41)	1.34
3	24.5(2.87)	1.93(0.45)	1.58
4	31.7(1.71)	1.47(0.21)	2.05
5	34.6(2.30)	1.38(0.39)	2.23
6	26.8(3.68)	1.95(0.51)	1.73
7	35.7(2.96)	2.01(0.47)	2.30
8	45.3(4.17)	1.58(0.40)	2.92
9	34.2(3.91)	1.94(0.52)	2.21
10	36.2(4.25)	2.09(0.63)	2.34
11	33.2(3.75)	1.68(0.37)	2.14
12	35.2(3.75)	1.96(0.31)	2.26
13	20.5(2.15)	2.53(0.74)	1.32
14	34.4(1.78)	1.57(0.45)	2.22
15	35.1(2.35)	1.64(0.76)	2.26

note: 1. Numerals in parenthesis represent the values of standard deviation.
2. Each trial was performed at least four times.
3. * The ratio was calculated based on the speed of percutaneous penetration when the content of ketoprofen was 10% and the penetration enhancers were not employed.

[Results]

The percutaneous penetrating effect of ketoprofen was increased when the content of ketoprofen in the adhesive layer was increased to a concentration exceeding the saturating solubility for the purpose of enhancing the

transdermal delivery of ketoprofen.

As compared with the general phenomenon that when the penetration enhancer is contained in the adhesive layer by conventional techniques, the effect of transdermal delivery of drug is reduced by half due to a sharp decrease of the adhesion property, the penetration enhancer according to the present invention exhibited excellent penetration enhancing effect without a noticeable change of the adhesion property.

SKIN PRIMARY IRRITATION TEST

A patch prepared in the same manner as described in Example 1 was cut to the size of 2.5cm^2 and after the stripping liner was removed therefrom, the patch was applied on a part of a healthy adult's forearm for a period of 24 hours.

At 24 hours the patch was removed and, after 30 minutes, the level of the skin primary irritation was observed and estimated according to the following grading system.

Grade	The level of irritation
0	No irritation
1	The minimum irritation
2	A little irritation (erythema)
3	Severe irritation (erythema, edema)
4	Extremely severe irritation (erythema, edema)

By using the level of irritation observed, the

reactivity was calculated according to the following equation :

$$\text{Reactivity}(\%) = \frac{\text{the sum of } \left(\text{the number of reactor(s)} \times \text{grade}\right)}{\text{the number of subjects} \times 4} \times 100$$

The recipe of the patches used for the skin primary irritation test are listed in Table 3 and the results are summarized in Table 4.

Table 3 : Patches used for the skin primary irritation test

Patch No.	Ketoprofen (%)	acrylic resin used in Example 1 (%)	penetration enhancer[1] (%)	penetration enhancer[2] (%)	bisabolol (%)
1	10	90			
2	10	80	10		
3	10	80		10	
4	10	79.5	10		0.5
5	10	79	10		1
6	10	78	10		2
7	10	75	10		5
8	20	58	20		2
9	10	78		10	2
10	20	69		10	1

note) 1. [1]propylene glycol monolaurate
2. [2]polyoxyethylene(4) lauryl ether
3. The contents(%) of all components are by weight.

Table 4: Result of the skin primary irritation test

Patch No.	The number of subjects	Reactivity (%)	The frequency of an occurrence of the skin side effect (including the itch)
1	17	2.9	2/17
2	17	5.9	4/17
3	15	6.7	4/15
4	15	5.0	3/15
5	15	0.0	0/15
6	15	0.0	0/15
7	15	5.0	3/15
8	17	4 4	3/17
9	15	1.7	1/15
10	17	0.0	0/17

As can be seen from the above data, though the effect of reducing the skin primary irritation was not observed in every case of employing bisabolol, the bisabolol can be used as an effective lenitive of the skin irritation at the concentration of 1 to 2%. In addition, since the irritation level of the whole patches was below 10%, these patches are estimated to possess the safety for the skin irritation.

COMPARATIVE EXAMPLE 1

The "Adhesive vehicle(3)" prepared in Example 4 was singly coated on a releasing paper and the resulting material was laminated on to a polyethylene film to produce

a mono-layered patch.

COMPARATIVE EXAMPLE 2

To the "Adhesive vehicle(1)" prepared in Example 4, ketoprofen was added in an amount of 20% by weight based on the solid content and dissolved to a concentration exceeding the saturating solubility. To the resulting mixture, tocopherol of 5% by weight as an antioxidant, propylene glycol monooleate of 10% by weight as a percutaneous penetration enhancer and bisabolol of 2% by weight as a lenitive agent of the skin irritation were added and dissolved. The resulting mixture was coated on a releasing paper to a thickness of 70μm and dried.

PERCUTANEOUS PENETRATION TEST USING THE PATCHES PREPARED IN EXAMPLES 4-7 AND COMPARATIVE EXAMPLES 1-2

By the same manner as described above in relation to the percutaneous penetration test, the patches prepared in Examples 4-7 and Comparative examples 1-2 were tested and the results are listed in Table 5.

Table 5 : Comparison of the percutaneous penetration speed of ketoprofen

Patch	The speed of skin penetration ($\mu g/cm^2/hr$)	Retention time (hrs)	Relative penetration speed
Example 4	17.7(3.79)	2.78(0.74)	1.97
Example 5	15.6(2.28)	3.14(1.45)	1.73
Example 6	27.4(2.11)	1.75(1.23)	3.04
Example 7	18.8(3.18)	2.20(0.79)	2.09
Example 8	26.5(2.15)	1.86(0.71)	1.71
Example 10	21.4(1.78)	1.27(0.85)	1.38
Comparative example 1	9.0(3.45)	3.05(1.05)	1.00
Comparative example 2	22.4(2.79)	1.67(0.68)	2.49

note) Numerals in parenthesis represent the values of standard deviation.

SKIN PRIMARY IRRITATION TEST USING THE PATCHES PREPARED IN EXAMPLES 4-6 AND COMPARATIVE EXAMPLES 1-2

By the same manner as described above in relation to the skin primary irritation test, the patches prepared in Examples 4-6 and Comparative examples 1-2 were tested and the results are listed in Table 6.

Table 6 :

Patch	The number of subjects	Reactivity (%)	The Frequency of an occurrence of the skin side effect(in ding the itch)
Example 4	13	5.8	2/13
Example 5	13	5.8	3/13
Example 6	13	3.8	2/13
Example 7	13	0.0	0/13
Example 8	13	0	0/13
Example 10	13	3.8	2/13
Comparative example 1	13	3.8	2/13
Comparative example 2	13	1.9	1/13

WHAT IS CLAIMED IS :

1. A medicinal patch for percutaneous administration, which comprises

adhesives applied on one surface of the support, as a pressure-sensitive, adhesive layer in the form of monolayered or multi-layered laminate and a releasing film formed on the adhesive layer,

said adhesives being composed of 0.1-40% by weight one or more percutaneous penetrating enhancer(s) selected from the group consisting of fatty acid ester, polyoxyethylene derivatives, glycerin fatty acid ether, propylene glycol fatty acid ester and pyrrolidone derivative; one or more adhesive resin(s) selected from the group consisting of silicone polymer, natural or synthetic gums and acrylic resin; and 0.1-50% by weight drug or its precursor of which solubility changes as the water retain in the adhesive layer changes; and one or more additive(s) selected from the group consisting of adhesiveness-conferring agent, plasticizer, filler, lenitive agent for decreasing the skin-irritation and antioxidant.

2. A medicinal patch of Claim 1, in which the acrylic resin is the copolymer of C_4 - C_{18} aliphatic alcohol with acrylic alkyl ester having alkyl group or the polymer of ()acrylic alkyl ester having C_4 - C_{18} alkyl group with different functional monomer such as vinyl acetate.

3. A medicinal patch of Claim 2, in which the ()acrylic alkyl ester copolymer is incorporated in an amount above 50% by weight.

4. A medicinal patch of Claim 1, in which the synthetic rubbery resin comprises styrene-butadiene-styrene, styrene-isoprene-styrene, styrene-ethylene/propylene-styrene or styrene-ethylene/butylene-styrene block copolymer as the main component and contains one or more additive(s) selected from the group consisting of adhesiveness auxiliary agent, adhesiveness-conferring agent, inorganic fillers, softener and antioxidant.

5. A medicinal patch of Claim 1, in which the water retain of the adhesives is controlled by regulating the incorporation ratio of the monomer having hydrophilic group among the monomers in the copolymerization reaction.

6. A medicinal patch of Claim 1 or Claim 5, in which the adhesives comprise one or more compound(s) selected from the group consisting of a highly water-absorptive polymer, a water-absorptive inorganic substance and a polyhydric alcohol in an amount of 0.01-40% by weight.

7. A medicinal patch of Claim 1, in which the adhesiveness-conferring agent is rosin resin, polyterpene resin, petroleum resin or olefin resin.

8. A medicinal patch of Claim 1, in which the lenitive agent for decreasing the skin irritation comprises one or more compound(s) selected from the group consisting of bisabolol, camomile oil, allantoin, glycerol and di-pantenol and presents in an amount of 0.01-10% by weight.

9. A medicinal patch of Claim 1, in which the drug is the one selected from the group consisting of an antipyretic and anti-inflammatory agent, a steroidal anti-inflammatory

agent, a vasodilator, a hypertension and arrhythmia treating agent, an anti-hypertensive agent, an anti-cough and expectorant agent, anti-tumeric agent, local anesthetic, hormone preparations, an anti-asthmatic and anti-nasal allergic agent, anti-histamine preparations, an anti-coagulant, anti-spasmodic, cerebral circulation or metabolism improving agent, an anti-depressant, an anti-anxiety agent, an anti-hyperglycemia, local anesthetic, or anti-ulcer agent, an antirheumatic and antiarthritic agent and the precursor thereof.

10. A medicinal patch of Claim 1, in which an nonsteroidal anti-inflammatory and analgesic agent is present in an amount of 1-40% by weight as the drug.

11. A medicinal patch of Claim 10, in which the nonsteroidal anti-inflammatory and analgesic agent is ketoprofen, dichlophenaxsodium, indocin, flurbiprofen or piroxicam.

12. A medicinal patch of Claim 1, in which the fatty acid ester is methyl laurate or isopropyl myristate.

13. A medicinal patch of Claim 1, in which the polyoxyethylene derivative is a polyoxyethylene ether or polyoxyethylene ester which contains 2-20 moles of polyoxyethylene group linked to oleyl or lauryl group.

14. A medicinal patch of Claim 1, in which the fatty acid of the glycerin fatty acid ether is lauryl acid or oleic acid.

15. A medicinal patch of Claim 1, in which the fatty acid of the propylene glycol fatty acid ester is lauryl acid or

oleic acid.

16. A medicinal patch of Claim 1, in which the adhesives contain one or more compound(s) selected from the group consisting of cellulose, polyethylene, nylon 6, nylon 12, polypropylene, polyethylene terephthalate, zinc oxide, calcium oxide, silica, kaolin, talc and titanium dioxide in an amount of 0.1-30% by weight as the organic polymer and inorganic substances to improve the adhesion property.

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Examiner's report to the Comptroller under Section 17 (The Search Report)

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Relevant Technical fields

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(ii) Int Cl (Edition 5) A61L 15/44

Search Examiner

J F JENKINS

Databases (see over)

(i) UK Patent Office

(ii)

Date of Search

5 MARCH 1993

Documents considered relevant following a search in respect of claims 1 TO 16

Category (see over)	Identity of document and relevant passages		Relevant to claim(s)
X	GB 2086224 A	(NITTO ELECTRIC) - see Examples 1 to 5	1-3 and 10
X	EP 0450986 A2	(SEKISUI KKKK) - see Examples 1 to 8, 10 to 13	1-3, 9 and 12
X	EP 0360516 A2	(DOW CORNING) - see Examples 8 to 14	1,9,10
X	EP 0279977 A2	(ALZA CORPN) - see Examples I to III	1-3,9
X	EP 0275716 A1	(RUTGERS) - see Examples 1 and 2, Table 1, Formulation 2 and Table 2 Formulation 2	1-3, 9 and 12
X	EP 0275550 A1	(TEIKOKU SEIYAKU KK) - see Example 2	1-3,9-11 and 16
X	EP 0272918 A2	(CYGNUS RESEARCH CORPN) - see Examples	1, 9 and 5
X	EP 0224981 A2	(PACO RESEARCH CORPN) - see Examples 1 to 10	1, 9, 12 and 16
X	EP 0181970 A1	(SEKISUI KKKK) - see Examples 1 to 4	1-3, 9

		to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family, corresponding document.

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Databases (see over)

(i) UK Patent Office

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Search Examiner

J F JENKINS

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Documents considered relevant following a search in respect of claims

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
X	WO 86/06281 A1 (RIKER LABS) - see Examples	1-3,9,14

to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

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A: Document indicating technological background and/or state of the art.

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