Title: TRANSDERMAL PREPARATIONS COMPRISING EPERISONE, TOLPERISONE OR SALTS THEREOF

Abstract: The present invention relates to transdermal preparations comprising eperisone, tolperisone or salts thereof, which is skeletal muscle relaxant, and more particularly, relates to transdermal preparations characterized in that, in delivering eperisone, tolperisone or its salts through skin, mixture of fixed ratio of acrylate adhesive having hydroxy group and acrylate adhesive without hydroxy group is used as a substrate, thereby maximizing percutaneous absorption of eperisone, tolperisone or salts thereof, raising the stability of eperisone, tolperisone or salts thereof, within substrate layer, and providing superior skin adhesion.
Transdermal preparations comprising eperisone, tolperisone or salts thereof

Technical Field

The present invention relates to transdermal preparations comprising eperisone, tolperisone or salts thereof (hereinafter, referred to as “eperisone etc.”), which are skeletal muscle relaxant.

Background Art

Spasticity is one of skeletal muscle disorders due to increase of muscle tone, and appears following lesions of the central nervous system such as ischemic stroke, trauma and several types of neuronal degeneration. Since various neurotransmitters, neuromodulators, receptors and related ion-channels are involved in the interneuronal control of muscle tone, centrally acting muscle relaxant is usually used for the treatment of spasm. Centrally acting muscle relaxant reduces the increased muscle tone and inhibits the hyperactive reflexes by antagonizing the receptor activation coupled to the excitation of motor functions or by acting on the receptors related to inhibitory functions. Problems in using such centrally acting muscle relaxant are central depression and muscle weakness.

Eperisone etc., a centrally acting muscle relaxant with a low incidence of central depression, are widely used in the treatment of muscle spasm for the relief of myotonia and spinalgia. Eperisone etc. inhibit both monosynaptic and polysynaptic reflex via acting on spinal cord and upper central level, leading to exhibition of muscle relaxation through decrease of muscle tone. However, eperisone etc. exhibit
disadvantages, i.e. very low bioavailability and variable plasma level due to first-pass effect during absorption. Further, frequent administration is needed due to very short duration of the muscle relaxation effect of absorbed eperisone etc. and all commercial products are injection or oral preparations, have a problem in patient’s compliance.

To resolve such problems, many attempts to develop transdermal preparations, by which drug can be administered into body through skin surface, have been made. U.S. Pat. No. 5,252,588 discloses the transdermal preparations comprising eperisone and water-swellable crosslinked polyvinylpyrrolidone.

The present invention provides formulations which, compared to the USP 5,252,588, exhibit superior skin permeation and have adequate adhesive property upon attachment on the skin, thereby achieving good adhesion through application period and providing less pain and less skin abrasion at the time of removal, thus more convenience for patients.

Disclosure of the Invention

The present invention is to provide transdermal preparations that guarantee stability of eperisone etc. within adhesives, and have skin adhesion adequate for application while maximizing skin permeation of the drug.

The present invention relates to transdermal preparations having adhesive layer comprising drug selected from eperisone, tolperisone and salts thereof, and, as an adhesive, mixture of acrylic adhesive having hydroxy group and acrylic adhesive without hydroxy group.

Drug used in the present invention is selected among eperisone, tolperisone and their salts, and as a salt, hydrochloride or phosphate is preferred.
Eperisone, tolperisone or salts thereof can exist within adhesives as dissolved or crystal state, and preferably, the content of the drug is 5 to 20 w/w% to total weight of the adhesive layer. In general, it is known that skin permeation of drug increases in proportion to drug concentration within adhesives. Therefore, in case drug concentration within adhesives is too low, it is unable to deliver sufficient amount of drug for pharmacological effect through the skin. However, on the contrary, in case drug concentration is too high, skin permeation of the drug increases no more over certain level, and affects physical property of adhesive layer, resulting in adverse effect on skin adhesion of the preparation.

Acrylic adhesive used in the present invention consists of mixture of acrylic adhesive having hydroxy group and acrylic adhesive without hydroxy group. Mixing ratio of acrylic adhesive having hydroxy group and hydroxy-free acrylic adhesive is preferred to be in a range of 8:2 to 5:5, by weight ratio. Said adhesives are used in viscous liquid state with addition of organic solvent, and majority of the organic solvent is evaporated upon drying after coating and only acrylic adhesive is remained.

Acrylic adhesive having hydroxy group is used to maximize skin permeation of drug.

The acrylic adhesive having hydroxy group consists of copolymer of monomer with hydroxy group and monomer without hydroxy group.

As the monomer having hydroxy group, at least one selected from a group consisting of hydroxyethyl(metha)acrylate and hydroxypropyl(metha)acrylate can be used. The monomer having hydroxy group is used, preferably, 1 to 20 w/w% of total
weight of monomer used for polymerization of acrylic adhesive having hydroxy group.

As the monomer without hydroxy group, one or more monomer selected from a group consisting of general alkyl(metha)acrylate monomer such as butylacrylate, methylacrylate, methylethacrylate and 2-ethylhexylacrylate, acrylic acid and vinylacetate, can be used.

In particular, as the monomer without hydroxy group, it is preferred to use 2-ethylhexylacrylate and vinylacetate together, and 2-ethylhexylacrylate is preferred to be in a range of 49 – 80 w/w% of total weight of acrylic adhesive having hydroxy group, and vinylacetate is preferred to be in a range of 19 – 50 w/w% of total weight of acrylic adhesive having hydroxy group.

As commercial product sold as acrylic adhesive having hydroxy group, Duro-Tak 87-2287, Duro-Tak 87-2510 and Duro-Tak 87-2516 etc. (National Starch and Chemical) can be enumerated.

In addition, in case of acrylic adhesive without hydroxy group, as it contains no functional group to react with drug, eperisone etc., it raises stability of eperisone etc. within adhesives, thus used along with acrylic adhesive having hydroxy group.

Said acrylic adhesive without hydroxy group consists of copolymer between general alkyl(metha)acrylate monomer such as butylacrylate, methylacrylate, methylethacrylate and 2-ethylhexylacrylate, and vinylacetate monomer. Preferably, acrylic adhesive without hydroxy group consists of 2-ethylhexylacrylate and vinylacetate monomer, and 2-ethylhexylacrylate is preferred to be in a range of 50- 80 w/w% to total weight of hydroxy-free acrylic adhesive and vinyl acetate is preferred to be in a range of 20 –50 w/w% to total weight of hydroxy-free acrylic adhesive.
As commercial product of such hydroxy-free acrylic adhesive, Duro-Tak 87-4098 (National Starch and Chemical), Gelva® Multipolymer Solution 3067 and Gelva® Multipolymer Solution 3083 (SOLUTIA) can be enumerated.

General acrylic adhesive used in prior technology has carboxyl group. This is derived from acrylic acid, one of the monomers used for adhesives. Such general acrylic adhesive has carboxyl group alone or both carboxyl group and hydroxy group. As such acrylic adhesive, Duro-Tak 87-2074, Duro-Tak 87-2194, Duro-Tak 87-2353, Duro-Tak 87-2677 and Duro-Tak 87-2825 (National Starch and Chemical) can be enumerated, and as acrylic adhesive having amide group, Duro-Tak 87-9301 (National Starch and Chemical) can be enumerated, and there is also acrylic adhesive having vinylpyrrolidone such as TSR (Sekisui). Such acrylic adhesive is not used in the present invention but was used for a comparison.

The preparations according to the present invention can contain further solubilizer to raise the content of eperisone etc. within adhesive layer.

In the present invention, solubilizer is used to allow fixed concentration of eperisone etc. to be contained within adhesive layer whose main component is acrylic adhesive. As such solubilizer, distilled water, ethanol, isopropanol, diethyleneglycol monoethylether, polyethylene glycol, glycerin and dimethylsulfoxide can be enumerated and one or more of them can be used, and the amount thereof is preferred to be 1-20w/w% of total weight of adhesive layer.

Additionally, the preparations of the present invention can further contain skin
permeation enhancer to increase percutaneous absorption rate of eperisone etc..

As skin permeation enhancer used in the present invention, higher fatty acid such as oleic acid; higher alcohol such as lauryl alcohol; higher fatty acid ester such as isopropyl myristate; fatty acid ester of glycerin such as glyceryl monolaurate; fatty acid ether of polyethylene glycol such as polyethylene glycol lauryl ether; fatty acid ester of polyethylene glycol such as polyethylene glycol laurate; fatty acid ether of propylene glycol such as propylene glycol lauryl ether; fatty acid ester of propylene glycol such as propylene glycol laurate; sorbitan fatty acid ester such as sorbitan monolaurate; polyethylene glycol sorbitan fatty acid ester such as polyethylene glycol sorbitan monolaurate; terpenes such as menthol, menthol derivatives and limonene; sulfoxides such as dimethylsulfoxide, dodecylsulfoxide; pyrrolidones such as N-methyl-2-pyrrolidone; amides such as lauryldiethanolamide; N-hydroxy methyl lactide, sorbitol, urea, squalene, olive oil, mineral oil and their derivatives, can be enumerated and one or more of them can be used, and preferably, 1-20 w/w% of total weight of adhesive layer.

As backing material of transdermal preparations according to the present invention, such backing material as used in conventional transdermal preparations can be used. For example, material with good permeability to air and moisture, such as non-woven fabric, cotton cloth and woven fabric, or mono film or multi film laminate of polyethylene terephthalate, polyurethane, polyethylene, polypropylene, ethylene vinyl acetate and aluminum-treated polyethylene can be used, and if necessary, non-woven fabric or cotton cloth can be laminated with plastic film that is not moisture permeable, to be used.
The transdermal preparations comprising eperisone etc. according to the present invention is characterized by being matrix type or drug-in-adhesive type patch. In case of such patch, the formulation is not much different from plaster and cataplasm, thus can have the form of plaster or cataplasm.

**Best mode for carrying out the invention**

In the below, the present invention is explained through Examples and Experimental Example, yet the present invention is not limited by them.

**Comparative Example 1-1**

**Ingredient**

- Tolperisone hydrochloride 20 w/w%
- Glyceryl monolaurate 5 w/w%
- Polyethyleneglycol(400) 5 w/w%
- Acrylic adhesive (Duro-Tak 87-2194) 70 w/w%(dried weight)

Herein, dried weight means the weight resulted from evaporation of organic solvent contained in said adhesive product.

**Method**

1. Tolperisone hydrochloride, glyceryl monolaurate and polyethyleneglycol(400) were added to acrylic adhesive and completely dissolved by stirring.
2. Said mixture was coated on release liner to allow depth after drying to be 25 μm.
3. Dried in an oven at 80°C for 20min.
4. Polyethylene film was laminated.
Comparative Example 1-2

Ingredient

Tolperisone hydrochloride 20 w/w%
Glyceryl monolaurate 5 w/w%
Polyethylene glycol(400) 5 w/w%
Acrylic adhesive (Duro-Tak 87-9301) 70 w/w% (dried weight)

Method

1. Tolperisone hydrochloride, glyceryl monolaurate and polyethylene glycol(400) were added to acrylic adhesive and completely dissolved by stirring.
2. Said mixture was coated on release liner to allow depth after drying to be 25 μm.
3. Dried in an oven at 80°C for 20 min.
4. Polyethylene film was laminated.

Comparative Example 1-3

Ingredient

Tolperisone hydrochloride 20 w/w%
Glyceryl monolaurate 5 w/w%
Polyethylene glycol(400) 5 w/w%
Acrylic adhesive (Gelva® Multipolymer Solution 3083) 70 w/w% (dried weight)

Method

1. Tolperisone hydrochloride, glyceryl monolaurate and polyethylene glycol(400) were
added to acrylic adhesive and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 25 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyethylene film was laminated.

**Comparative Example 1-4**

**Ingredient**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolperisone hydrochloride</td>
<td>20 w/w%</td>
</tr>
<tr>
<td>Glyceryl monolaurate</td>
<td>5 w/w%</td>
</tr>
<tr>
<td>Polyethyleneglycol(400)</td>
<td>5 w/w%</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-2516</td>
<td>70 w/w%(dried weight)</td>
</tr>
</tbody>
</table>

**Method**

1. Tolperisone hydrochloride, glyceryl monolaurate and polyethyleneglycol(400) were added to acrylic adhesive and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 25 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyethylene film was laminated.

**Comparative Example 2-1**

**Ingredient**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eperisone hydrochloride</td>
<td>5 w/w%</td>
</tr>
<tr>
<td>Polyoxylated lauryl ether</td>
<td>3 w/w%</td>
</tr>
<tr>
<td>Propyleneglycol</td>
<td>5 w/w%</td>
</tr>
</tbody>
</table>
Acrylic adhesive (Duro-Tak 87-2074) 87 w/w%(dried weight)

Method

1. Eperisone hydrochloride, polyoxyethylene (2) lauryl ether and propyleneglycol were added to acrylic adhesive and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 100 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyethylene film was laminated.

10 Comparative Example 2-2

Ingredient

Eperisone hydrochloride 5 w/w%
Polyoxyethylene (2) lauryl ether 3 w/w%
Propyleneglycol 5 w/w%

15 Acrylic adhesive (Duro-Tak 87-2353) 87 w/w%(dried weight)

Method

1. Eperisone hydrochloride, polyoxyethylene (2) lauryl ether and propyleneglycol were added to acrylic adhesive and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 100 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyethylene film was laminated.
Comparative Example 2-3

Ingredient

Eperisone hydrochloride 5 w/w%
Polyoxyethylene (2) lauryl ether 3 w/w%
Propylenglycol 5 w/w%
Acrylic adhesive (Duro-Tak 87-4098) 87 w/w%(dried weight)

Method

1. Eperisone hydrochloride, polyoxyethylene (2) lauryl ether and propylenglycol were added to acrylic adhesive and completely dissolved by stirring.
2. Said mixture was coated on release liner to allow depth after drying to be 100 μm.
3. Dried in an oven at 80°C for 20min.
4. Polyethylene film was laminated.

Comparative Example 2-4

Ingredient

Eperisone hydrochloride 5 w/w%
Polyoxyethylene (2) lauryl ether 3 w/w%
Propylenglycol 5 w/w%
Acrylic adhesive (Duro-Tak 87-2510) 87 w/w%(dried weight)

Method

1. Eperisone hydrochloride, polyoxyethylene (2) lauryl ether and propylenglycol were added to acrylic adhesive and completely dissolved by stirring.
2. Said mixture was coated on release liner to allow depth after drying to be 100 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyethylene film was laminated.

5. **Comparative Example 3**

   **Ingredient**

   - Eperisone hydrochloride: 10 w/w%
   - Polyplasdone INF-10: 5 w/w%
   - Acrylic adhesive (TSR): 85 w/w%(dried weight)

   **Method**

   1. Eperisone hydrochloride, polyplasdone INF-10 were added to acrylic adhesive and completely dissolved by stirring.
   2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.
   3. Dried in an oven at 80°C for 20min.
   4. Polyester film was laminated.

5. **Comparative Example 4-1**

   **Ingredient**

   - Eperisone hydrochloride: 10 w/w%
   - Propyleneglycol monolaurate: 2.5 w/w%
   - Diethyleneglycol monoethylether: 2.5 w/w%
   - Acrylic adhesive (Duro-Tak 87-4098): 85 w/w%(dried weight)
Method
1. Eperisone hydrochloride, propylene glycol monolaurate and diethylene glycol monoethylether were added to acrylic adhesive and completely dissolved by stirring.
2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.
3. Dried in an oven at 80°C for 20 min.
4. Polyester film was laminated.

Comparative Example 4-2

Ingredient

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eperisone hydrochloride</td>
<td>10 w/w%</td>
</tr>
<tr>
<td>Propylene glycol monolaurate</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Diethylene glycol monoethylether</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-2287)</td>
<td>85 w/w% (dried weight)</td>
</tr>
</tbody>
</table>

Method
1. Eperisone hydrochloride, propylene glycol monolaurate and diethylene glycol monoethylether were added to acrylic adhesive and completely dissolved by stirring.
2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.
3. Dried in an oven at 80°C for 20 min.
4. Polyester film was laminated.

Comparative Example 4-3

Ingredient

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eperisone hydrochloride</td>
<td>10 w/w%</td>
</tr>
</tbody>
</table>
Propyleneglycol monolaurate 2.5 w/w%  
Diethyleneglycol monoethylene 2.5 w/w%  
Acrylic adhesive (Duro-Tak 87-2287) 25.5 w/w%(dried weight)  
Acrylic adhesive (Duro-Tak 87-4098) 59.5w/w% (dried weight)

Method

1. Eperisone hydrochloride, propyleneglycol monolaurate and diethyleneglycol monoethylene were mixed with two kinds of acrylic adhesives and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyester film was laminated.

Comparative Example 4-4

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eperisone hydrochloride</td>
<td>10 w/w%</td>
</tr>
<tr>
<td>Propyleneglycol monolaurate</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Diethyleneglycol monoethylene</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-2287)</td>
<td>34 w/w%(dried weight)</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-4098)</td>
<td>51 w/w% (dried weight)</td>
</tr>
</tbody>
</table>

Method

1. Eperisone hydrochloride, propyleneglycol monolaurate and diethyleneglycol monoethylene were mixed with two kinds of acrylic adhesives and completely
dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyester film was laminated.

Example 1

Ingredient

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eperisone hydrochloride</td>
<td>10 w/w%</td>
</tr>
<tr>
<td>Propylene glycol monolaurate</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Diethylene glycol monoethylether</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-2287)</td>
<td>42.5 w/w% (dried weight)</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-4098)</td>
<td>42.5 w/w% (dried weight)</td>
</tr>
</tbody>
</table>

Method

1. Eperisone hydrochloride, propylene glycol monolaurate and diethylene glycol monoethylether were mixed with two kinds of acrylic adhesives and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyester film was laminated.

Example 2

Ingredient

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eperisone hydrochloride</td>
<td>10 w/w%</td>
</tr>
</tbody>
</table>
Propyleneglycol monolaurate  
2.5 w/w%  

Diethyleneglycol monoethylether  
2.5 w/w%  

Acrylic adhesive (Duro-Tak 87-2287)  
51 w/w% (dried weight)  

Acrylic adhesive (Duro-Tak 87-4098)  
34 w/w% (dried weight)

Method

1. Eperisone hydrochloride, propyleneglycol monolaurate and diethyleneglycol monoethylether were mixed with two kinds of acrylic adhesives and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 50 µm.

3. Dried in an oven at 80°C for 20min.

4. Polyester film was laminated.

Example 3

Ingredient

Eperisone hydrochloride  
10 w/w%  

Propyleneglycol monolaurate  
2.5 w/w%  

Diethyleneglycol monoethylether  
2.5 w/w%  

Acrylic adhesive (Duro-Tak 87-2287)  
59.5 w/w% (dried weight)  

Acrylic adhesive (Duro-Tak 87-4098)  
25.5 w/w% (dried weight)

Method

1. Eperisone hydrochloride, propyleneglycol monolaurate and diethyleneglycol monoethylether were mixed with two kinds of acrylic adhesives and completely
dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyester film was laminated.

Example 4

Ingredient

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolperisone hydrochloride</td>
<td>10 w/w%</td>
</tr>
<tr>
<td>Propyleneglycol monolaurate</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Polyethyleneglycol 400</td>
<td>2.5 w/w%</td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-2287)</td>
<td>59.5 w/w%</td>
</tr>
<tr>
<td>(dried weight)</td>
<td></td>
</tr>
<tr>
<td>Acrylic adhesive (Duro-Tak 87-4098)</td>
<td>25.5 w/w%</td>
</tr>
<tr>
<td>(dried weight)</td>
<td></td>
</tr>
</tbody>
</table>

Method

1. Tolperisone hydrochloride, propyleneglycol monolaurate and polyethyleneglycol 400 were mixed with two kinds of acrylic adhesives and completely dissolved by stirring.

2. Said mixture was coated on release liner to allow depth after drying to be 50 μm.

3. Dried in an oven at 80°C for 20min.

4. Polyester film was laminated.

Experimental Example 1: Skin permeability test

Abdominal hair of male guinea pig (350g) was cut with hair clipper, completely removed with shaver, and full skin of desired abdominal site was taken, frozen (below -20°C) and stored for future use in experiment.
The skin was thawed and cut into 2 x 2 cm² size, and the patches prepared in Comparative Example and Example were cut into size of 1.5 x 1.5 cm² and attached on the stratum corneum.

The skin was mounted on franz-type diffusion cell in such mode that the portion to which the patch was attached faces the upside, and the lower part of the device was filled with buffer solution of desired pH and the diffusion cell was maintained at 37°C. Receptor solution (buffer solution) was stirred at 600 rpm. After fixed amount of time was passed, an aliquot of the receptor solution was taken, and the same amount of fresh buffer solution was filled. The sample was subjected to HPLC analysis and the result was represented in Table 1.

Table 1. Amount permeated of eperisone etc. in transdermal preparation through guinea pig’s skin

<table>
<thead>
<tr>
<th>Patch No.</th>
<th>Amount permeated over 24hr (µg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative Example 1-1</td>
<td>52.5</td>
</tr>
<tr>
<td>Comparative Example 1-2</td>
<td>68.3</td>
</tr>
<tr>
<td>Comparative Example 1-3</td>
<td>33.0</td>
</tr>
<tr>
<td>Comparative Example 1-4</td>
<td>107.1</td>
</tr>
<tr>
<td>Comparative Example 2-1</td>
<td>42.9</td>
</tr>
<tr>
<td>Comparative Example 2-2</td>
<td>76.7</td>
</tr>
<tr>
<td>Comparative Example 2-3</td>
<td>35.2</td>
</tr>
<tr>
<td>Comparative Example 2-4</td>
<td>118.1</td>
</tr>
<tr>
<td>Comparative Example 3</td>
<td>78.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Comparative Example 4-1</td>
<td>50.3</td>
</tr>
<tr>
<td>Comparative Example 4-2</td>
<td>122.2</td>
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<td>Comparative Example 4-3</td>
<td>62.9</td>
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<td>Example 1</td>
<td>83.6</td>
</tr>
<tr>
<td>Example 2</td>
<td>92.4</td>
</tr>
<tr>
<td>Example 3</td>
<td>102.8</td>
</tr>
<tr>
<td>Example 4</td>
<td>98.3</td>
</tr>
</tbody>
</table>

As can be confirmed from the above Table 1, flux of the patch using acrylic adhesive having hydroxy group is much higher than that using other acrylic adhesive.

In addition, among the patches containing both acrylic adhesive having hydroxy group and hydroxy-free acrylic adhesive, the patch using higher content of acrylic adhesive with hydroxy group, e.g. Examples 1 to 3, showed superior flux over the others.

**Experimental example 2: Peel adhesion test**

Peel adhesion was measured with textile analyzer (TX2, MHK Trading co.) according to PSTC-1 test method. Prepared patches were cut into size of 2.5cm x 10cm and attached to stainless steel substrate, and measured peel adhesion while detaching at constant speed and the result was represented in Table 2.
Peel adhesion

<table>
<thead>
<tr>
<th>Patch No.</th>
<th>Peel adhesion (g Force)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative Example 1-4</td>
<td>1345</td>
</tr>
<tr>
<td>Comparative Example 2-4</td>
<td>1587</td>
</tr>
<tr>
<td>Comparative Example 3</td>
<td>1261</td>
</tr>
<tr>
<td>Comparative Example 4-2</td>
<td>1337</td>
</tr>
<tr>
<td>Example 2</td>
<td>748</td>
</tr>
<tr>
<td>Example 3</td>
<td>839</td>
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As can be confirmed from the above Table 2, in case of Comparative Examples 1-4, 2-4, 3 and 4-2, too high peel adhesion is likely to cause pain to patients at the time of removal from the skin, and skin irritation can be increased due to abrasion of stratum corneum and physical stimulus. In contrast, Examples 2 and 3 exhibit adequate peel adhesion, leading to low probability of spontaneous detachment during the patch’s application and easy detachment at the time of removal.

Experimental Example 3: Stability test

Prepared patches were put in aluminum pack, filled with nitrogen gas and stored in an oven at 40°C, relative humidity 75%, and after fixed amount of time was passed, the pack was opened, drug was extracted and its residual amount was determined. The result was given in Table 3.

Table 3

Residual Amount of Eperisone etc. within Patch

<table>
<thead>
<tr>
<th>Patch No.</th>
<th>Residual amount (%)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Comparative Example 1-1</td>
<td>98.3</td>
</tr>
<tr>
<td>Comparative Example 1-2</td>
<td>99.5</td>
</tr>
<tr>
<td>Comparative Example 1-3</td>
<td>100.5</td>
</tr>
<tr>
<td>Comparative Example 1-4</td>
<td>97.2</td>
</tr>
<tr>
<td>Comparative Example 2-4</td>
<td>96.5</td>
</tr>
<tr>
<td>Comparative Example 4-2</td>
<td>98.1</td>
</tr>
<tr>
<td>Example 2</td>
<td>101.0</td>
</tr>
<tr>
<td>Example 3</td>
<td>99.3</td>
</tr>
</tbody>
</table>

As can be seen from the Table 3, eperisone etc. were the most stable in the patch of Comparative Example 1-3, which used hydroxy-free acrylic adhesive. The patches of Comparative Examples 1-4, 2-4, and 4-2, which used only acrylic adhesive with hydroxy group, showed a problem in the stability. However, as result of mixing said two types of adhesives in suitable ratio, the stability was improved so that no problem will occur in actual storage.

**Industrial applicability**

The present invention relates to transdermal preparations comprising eperisone etc, central skeletal muscle relaxant, which achieve extension of drug effect duration compared to the conventional oral preparation or injections, enabling development of once a day or once on alternate days formulation, and exhibit superior skin permeation over that introduced in the prior patent, providing transdermal preparations of smaller size.
CLAIMS

1. Transdermal preparations having adhesive layer comprising drug selected among eperisone, tolperisone and salts thereof, and as an adhesive, mixture of acrylic adhesive having hydroxy group and acrylic adhesive without hydroxy group.

2. The transdermal preparations in Claim 1, where the content of drug is 5 to 20 w/w% to total weight of adhesive layer.

3. The transdermal preparations in Claim 1, where the salt is hydrochloride or phosphate.

4. The transdermal preparations in Claim 1, where mixing ratio between acrylic adhesive having hydroxy group and acrylic adhesive without hydroxy group is 8:2 to 5:5.

5. The transdermal preparations in Claim 1, where acrylic adhesive having hydroxy group is random copolymer of hydroxy-containing monomer and hydroxy-free monomer.

6. The transdermal preparations in Claim 5, where the content of the hydroxy-containing monomer is 1 to 20 w/w% of total weight of monomer used for polymerization of acrylic adhesive having hydroxy group.
7. The transdermal preparations in Claim 5, where the hydroxy-containing monomer is at least one selected from a group consisting of hydroxyethyl(metha)acrylate and hydroxypropyl(metha)acrylate.

8. The transdermal preparations in Claim 5, where the hydroxy-free monomer is at least one monomer selected from a group consisting of alkyl(metha)acrylate monomer, acrylic acid and vinylacetate.

9. The transdermal preparations in Claim 8, where the hydroxy-free monomer is 2-ethylhexyl acrylate and vinylacetate, and the content of 2-ethylhexylacrylate is 49 to 80 w/w% to total weight of acrylic adhesive having hydroxy group and the content of vinylacetate is 19 to 50 w/w%.

10. The transdermal preparations in Claim 1, where the acrylic adhesive without hydroxy group consists of alkyl(metha)acrylate monomer and vinylacetate.

11. The transdermal preparations in Claim 10, where acrylic adhesive without hydroxy group consists of 2-ethylhexylacrylate and vinylacetate, and the content of 2-ethylhexylacrylate is 50 to 80 w/w% to total weight of acrylic adhesive without hydroxy group and the content of vinylacetate is 20 to 50 w/w%.

12. The transdermal preparations in Claim 1, characterized in further containing at least one kind of solubilizer selected from a group consisting of distilled water, ethanol, isopropanol, diethyleneglycol monoethylether, polyethyleneglycol, glycerin
and dimethylsulfoxide, in a range of 1 to 20 w/w% to total weight of adhesive layer.

13. The transdermal preparations in Claim 1, characterized in further comprising at least one kind of skin permeation enhancer selected from a group consisting of higher fatty acid such as oleic acid; higher alcohol such as lauryl alcohol; higher fatty acid ester such as isopropyl myristate; fatty acid ester of glycerin such as glycercyl monolaurate; fatty acid ether of polyethyleneglycol such as polyethyleneglycol lauryl ether; fatty acid ester of polyethyleneglycol such as polyethyleneglycol laurate; fatty acid ether of propyleneglycol such as propyleneglycol lauryl ether; fatty acid ester of propyleneglycol such as propyleneglycol laurate; sorbitan fatty acid ester such as sorbitan monolaurate; polyethyleneglycol sorbitan fatty acid ester such as polyethyleneglycol sorbitan monolaurate; terpenes such as menthol, menthol derivatives and limonene; sulfoxides such as dimethylsulfoxide and dodecylsulfoxide; pyrrolidones such as N-methyl-2-pyrrolidone; amides such as lauryldiethanolamide; N-hydroxy methyllactide, sorbitol, urea, squalene, olive oil, mineral oil and their derivatives, in a range of 1 to 20 w/w% to total weight of adhesive layer.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
CAPLUS(STN), MEDLINE(STN), WPI, USPATFULL, JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
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<td>A</td>
<td>JP 8291067 A2 (SEKISUI CHEM. CO., LTD.) 5 NOVEMBER 1996 see the whole document</td>
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<tr>
<td>A</td>
<td>EP 1163902 A2 (PACIFIC CORP.) 19 DECEMBER 2001 see the whole document</td>
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<td>A</td>
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<td>A</td>
<td>JP 6040917 A2 (NICHIBAN CO., LTD.) 15 FEBRUARY 1994 see the whole document</td>
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Date of the actual completion of the international search

Date of mailing of the international search report

Name and mailing address of the ISA/KR
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Facsimile No. 82-42-472-7140

Authorized officer
YOO, JUN SEOK
Telephone No. 82-42-481-8163

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