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(54) **Titre :** Topical pharmaceutical preparation.

(57) **Abrégé :**

The invention discloses a topical pharmaceutical preparation, which comprises, in an admixture with carriers and/or diluents conventionally applicable in topical pharmaceutical preparations, at least one peptidaceous pharmacon; one or more constituents selected from the groupo comprising capsaicine, histamine and cantharis extract; and at least one epithelizing agent.

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TOPICAL PHARMACEUTICAL PREPARATION

FIELD OF INVENTION

The invention relates to topically applicable pharmaceutical preparations which enable one to introduce peptidaceous pharmacons in living organisms by transdermal resorption. The topically applicable pharmaceutical preparations according to the invention may be e.g. ointments, creams, gels, lotions, solutions, suspensions and similar formulations routinely utilized in topical treatments, which can be applied onto the skin surface optionally in supported forms. Particularly preferred representatives of them are those wherein the topically applicable formulation is applied onto a support capable adhering to skin, i.e. plasters (patches), which enable safe dosing and easy handling.

BACKGROUND TO INVENTION

Topically applicable pharmaceutical preparations are outstandingly preferred formulations with respect to the treatment comfort of the patient. In contrast to parenteral formulations, like injections, the introduction of which is painful or at least unpleasant and requires either assistance of a doctor or of a nurse, or, when self-administered, requires practice and skill from the patient, a topical formulation can be applied to the place of treatment easily and painless even by the patient. Topical formulations are also more preferred than oral ones for patients who suffer from dysphagia or are averse to the taste of the medicine. A specific advantage of topical formulations is that the patient can, either at first sight or by touching his skin, easily ascertain whether he has applied the medicine or not, thereby the risk of inadvertent overdosing or underdosing considerably decreases.

Despite of these advantages topically applicable formulations are utilized in medical practice in a rather narrow range, generally only for the treatment of external injuries and local inflammations. The reasons of this fact lie primarily on the physiological features of active agent resorption. In order to enable a topically applied active agent to reach the target organ in an appropriate concentration the

active agent should penetrate not only through the skin but also through the walls of the subdermal blood vessels. Even skin and vessel walls are of highly restricted permeability owing to their physical structures (porosity and semipermeable membrane structure). Further significant hindrance arises from the so-called barrier function of the horny layer, which latter serves essentially to protect living organisms from foreign substances contacting the skin. There have already been elaborated some topical formulations which can successfully replace oral ones for the introduction of the active agent concerned. One of them is an antirheumatic patch marketed in Hungary since about 15 years under the name MOTTO®, which comprises formic acid (as an antirheumatic agent), salicylic acid and optionally a pain-relieving agent in an emulsion formed with Unguentum emulsificans (a cream comprising nonionic tensides, Ph.Hg.V.), which is applied on a support capable of adhering to skin. NITRODERM®, a composition sold by Ciba-Geigy Co. (German Federal Republic), comprises nitroglycerol (as a cardiac agent) in a gel formed with methyl or carboxymethyl cellulose, which is applied on small polyurethane sponges capable of adhering to skin. SALONPAS®, a composition sold by Hisamitsu Pharmaceutical Co. Inc. (Japan), comprises methyl salicylate (as an anti-inflammatory agent) and a methol in a thick mass formd with polyvinyl alcohol, which is applied on small polyurethane sponges capable of adhering to skin. The active agents in these known compositions are strongly polar substances of relatively low molecular weights, thus they have much more chance for resorption than less polar substances with higher molecular weights.

Peptidaceous compounds form an important group of pharmaceutically active substances. In the specification and claims the term "peptidaceous compound" or "peptidaceous pharmacon" refers generally to any pharmaceutically active substance the molecule of which comprises at least two amino acids bound together by a peptide bond. A narrower group of them with outstanding pharmaceutical importance is the group of polypeptides, of which natural hormones and artificial analogues and derivatives thereof are of particular interest. A member of this latter group with outstanding importance from the aspects of

public health is insuline. Hormones and hormone analogues which regulate fine balances of the organism are hazardous substances, thus with these substances it is particularly necessary to decrease the risks of inadvertent overdosing or underdosing. Some representatives of hormones and hormone analogues, in particular insuline, can be introduced only parenterally. Thus it would be highly desirable to introduce these active agents topically in the living organism. However, topical preparations applicable for introducing peptidaceous pharmacons in living organisms have not been disclosed before.

SUMMARY OF INVENTION

Based on studies, it has been found that, upon utilizing specific auxiliary agents, peptidaceous pharmacons can be brought to a form capable of transdermal resorption. This recognition enables one to produce topically applicable pharmaceutical preparaions comprising pharmacons.

Thus, the invention relates to a topically applicable preparation for introducing a peptidaceous pharmacon in a living organism. The preparation according to the invention comprises in admixture with carriers and/or diluents conventionally applied in topical pharmaceutical preparations, optionally applied onto a support capable of adhering to skin:

(i) at least one peptidaceous pharmacon;

(ii) one or more constituents selected from the groupo comprising capsaicine, histamine and cantharis extract; and

(iii) at least one epithelizing agent.

The preparations according to the invention may comprise as peptidaceous pharmacon preferably a natural hormone or a synthetic analogue or derivative thereof, particularly preferably insuline. The amounts of peptidaceous pharmacons contained in a unit dose (i.e. in a dose for a single treatment) of the preparations according to the invention (such as in a single plaster) may be about the same as

present in the conventional oral or parenteral unit dose forms. Thus, as an example, plasters according to the invention applicable in the treatment of diabetes mellitus may comprise 0.1-50 IU of insuline for one plaster or for a unit plaster fragment (e.g. for 1 cm^2 of plaster surface).

Capsaicine, histamine and cantharis extract (the active agent of Tinctura cantharidis), which form component (ii) of the preparations according to the invention, are rubefacient local vasodilators. These substances have been applied for a long time in the therapy as external rubs for stimulating subdermal circulation e.g. for the treatment of chilblains, extremital pains, rheuma and the like [Kiráy, Rácz, Török: Bor- és nemibetegségek (Skin and Venereal Diseases, in Hungarian); 1927 and subsequent pages (Medicina Könyvkiadó, Budapest, 1986)]. As epithelizing agent, which is component (iii) of the preparation according to the invention, any agent known to be applied in the therapy to loosen the upper epithelial layer of skin can be utilized. Characteristic representatives of such agents are listed e.g. in the textbook cited above. Salicylic acid, sodium chloride, urea and resorcinol are examples of epithelizing agents which can be utilized with good results in the preparations according to the invention.

Although, as it appears from the textbook cited above, components (ii) and (iii) of the preparation according to the invention have already been utilized before separately in compositions for topical treatment, no data can be found in the literature on their combined use and on their prospective combined effects. No data can be found in the literature, either, that component (ii) or component (iii) would have been utilized before in combination with a peptidaceous pharmacon for the purpose of topical treatments.

In the preparations according to the invention components (i) and (ii) interact with one another, which is verified e.g. by the observation that when capsaicine is added to an insuline suspension (such as to a preparation sold by Novo Nordisk under the name Insulin lente MC), a transparent solution forms. The accurate nature of this interaction has not yet been elucidated, however, most probably hydrogen

bonds are formed between the loose hydrogen-bearing groups and the local hydrogen acceptor centers of the two components (such as between the HO- and HOOC- groups of capsaicine and the -NH_2 groups of insuline). The transdermal resorption ability of peptidaceous pharmacons from the preparations according to the invention can be attributed basically to this interaction.

The preparations according to the invention must contain component (ii) at least in an amount enabling the above interaction to take place, it is preferred, however, when the preparations contain more component (ii) than this minimum. For any individual peptidaceous pharmacon/component (ii) pairs the minimum and suitable ratios can be determined easily by tests belonging to the routine knowledge of one skilled in pharmacotechnology. As a guidance, e.g. insuline-containing preparations according to the invention may contain 0.001-0.3 g, preferably 0.003-0.1 g, particularly preferably 0.005-0.05 g of component (ii) for 10 IU of insuline.

The preparations according to the invention may contain components (ii) and (iii) in a weight ratio of 1:(0.01-10), preferably in a weight ratio of 1:(0.03-3), particularly preferably in a weight ratio of 1:(0.05-2).

It is observed that the higher is the amount of components (ii) and (iii) in the preparation according to the invention, the faster is the resorption of the active agent.

The preparations according to the invention comprise components (i)-(iii) in admixture with conventional carriers and/or diluents for topical preparations, of which the following are listed as examples: water, alcohols (also comprising glycerol), glycols, gellifying agents (such as methyl cellulose, carboxymethyl cellulose, polyvinyl alcohol and polyvinyl acetate), ointment bases (such as lanoline), ionic and nonionic tenzides and the like.

The preparations according to the invention may also comprise the peptidaceous pharmacon in enveloped form (such as closed into a cyclic starch for microencapsulated). Use of such an envelope may be necessary from

pharmacotechnological considerations, for instance when the peptidaceous pharmacon concerned is incompatible with the selected carriers or diluents. For instance, hydrophilic pharmacons, when closed into an envelope of hydrophobic surface, can be rendered compatible with oily carriers. In such instances the interaction between components (i) and (ii) proceeds at the rate of liberation of component (i) from the envelope.

If desired, the preparations according to the invention may also comprise other pharmaceutically active or activity-increasing agents to be introduced together with the peptidaceous pharmacon. Examples of such components are zinc compounds which are sometimes added together with insuline.

If desired, the preparations according to the invention may also comprise an indicator suitable to detect the presence of the peptidaceous pharmacon. Substances which react with a visually observable change (most suitably with a colour reaction) to the presence or absence of the pharmacon concerned can be utilized as indicators. Ninhydrine, which indicates the presence of a peptidaceous substance by blue colouration, is a very suitable indicator to show the presence of peptidaceous substances. A great advantage of such indicator-containing preparations is that the patient can easily conclude from the colour change of the applied composition (e.g. from the dissapearance of the blue colour of ninhydrine) whether resorption has taken place or not, and, if necessary, can change the already exhausted plasters at due intervals. The preparations according to the invention may comprise the indicator in amounts which provide good observability. These amounts are well known to one skilled in analytics or can be determined easily by routine tests.

EXAMPLES

The following examples serve to demonstrate the composition and manufacture of the preparations according to the invention.

Example 1

0.28 ml of Tinctura capsaicini (Ph. Hg. V., capsaicine-containing 70 % alcohol solution) and 0.05g of salicylic acid were added to 10 ml of an intramuscularly administerable acqueous suspension comprising 40 IU/ml of insuline (sold by Novo Nordisk under the trade name Insulin rapitard). Upon adding the capsaicine, a transparent solution formed from the insuline suspension. 0.01 % by weight of ninhydrine were added to the solution, whereupon the colour of the solution turned blue. The resulting solution was gellified by adding 15 % by weight of methyl cellulose, and the resulting gel was applied onto a polyurethane sponge plaster with an active surface of 20 cm^2. The gel applied was covered with aluminium foil.

Example 2

10g of Unguentum nonionicum emulsificans (Ph.Hg.V., an oily gel formed nonionic tenzides) was admixed with 10 g (400 IU) of crystalline insuline, 0.05 g of crystalline salicylic acid and 0.28 ml of Tinctura capsaicini. The resulting oily ointment was applied onto a polyurethane sponge plaster with an active surface of 20 cm^2, and the ointment applied was covered with aluminium foil.

PATENT CLAIMS

1. A topical pharmaceutical preparation, which comprises, in an admixture with carriers and/or diluents conventionally applicable in topical pharmaceutical preparations,

   (a) at least one peptidaceous pharmacon;

   (b) one or more constituents selected from the groupo comprising capsaicine, histamine and cantharis extract; and

   (c) at least one epithelizing agent.

2. A preparation as claimed in claim 1, which is applied onto a suitable support capable of adhering to skin.

3. A preparation as claimed in claim 1 or claim 2, which comprises an indicator which is adapted to react to the presence or absence of the peptidaceous pharmacon by a visually observable change.

4. A preparation as claimed in claim 3, in which the indicator is ninhydrine.

5. A preparation as claimed in any of the preceding claims, which comprises salicylic acid, sodium chloride, resorcinol or urea as the epithelizing agent.

6. A preparation as claimed in any one of the preceding claims, in which the peptidaceous pharmacon is a natural hormone or a synthetic analogue or derivative thereof.

7. A preparation as claimed in any one of the preceding claims, in which the pepdaceous pharmacon is insuline.

8. A preparation as claimed in any one of the preceding claims, which comprises 0.01-0.3 g of the capsaicine, histamine and/or cantharis extract for 10 IU of pepdaceous pharmacon being insulin.

9. A preparation as claimed in any one of the preceding claims, which comprises 0.003-0.1 g of the capsaicine, histamine and/or cantharis extract for 10 IU pepdaceous pharmacon being insulin.

10. A preparation as claimed in any one of the preceding claims, which comprises 0.005-0.05 g of the capsaicine, histamine and/or cantharis extract for 10 IU of pepdaceous pharmacon being insulin.

11. A preparation as claimed in any of the preceding claims, which comprises the capsaicine, histamine and/or cantharis extract and the epithelizing agent(s) in a weight ratio of 1:(0.01-10).

12. A preparation as claimed in any one of the preceding claims, which comprises the capsaicine, histamine and/or cantharis extract and the epithelizing agent(s) in a weight ratio of 1:(0.03-3).

13. A preparation as claimed in any one of the preceding claims, which comprises the capsaicine, histamine and/or cantharis extract and the epithelizing agent(s) in a weight ratio of 1:(0.05-2).

14. A topical pharmaceutical preparation substantially as hereinbefore described.