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CHEMICAL ABSTRACTS, vol. 97, no. 19, November 8, 1982, page 52, ref. nr. 156157v; Columbus, Ohio, US W.H. AELLIG: "Clinical pharmacological experiments with bopindolol (LT 31-200): a long acting beta-adrenoceptor blocking drug with partial agonist activity."	

Description

This invention relates to pharmaceutical compositions, especially for the systemic transdermal administration of pharmacologically active agents.

Many pharmaceutical compositions have been proposed for the sustained transdermal administration of pharmacologically active agents into the systemic circulation. These generally comprise essentially a solid reservoir or matrix made of a solid polymer or gel containing the pharmacologically active agent dispersed throughout. On one side of the drug reservoir there is a backing member impermeable to the drug and on the other side a protective peel strip which is taken off before use. The backing member may be larger than the drug reservoir and may carry near its edges an adhesive layer to retain the protective peel strip and, when this is removed, to stick the unit to the skin. Additionally or alternatively a drug-permeable adhesive layer may be provided on the reservoir to retain the protective peel strip and stick the unit to the skin. In some proposals the drug reservoir has attached to it a drug-permeable control membrane or member, through which the pharmacologically active agent passes, in order to regulate the rate of passage of the active agent, e.g. to prevent dose dumping.

In use after the peel strip has been removed, the unit is stuck onto the skin and the pharmacologically active agent passes from the drug reservoir to the skin. More complicated systems have been proposed to improve the penetration rate of the pharmacologically active agent through the skin. However, most systems do not provide a sufficient penetration rate of the pharmacologically active agent or suffer from other disadvantages. Before the priority date of the present application the transdermal pharmaceutical compositions for systemic administration of drugs commercially available on a wide scale were restricted to pharmacologically active agents which exist in liquid form e.g. scopolamine or nitroglycerin, and which in any event easily penetrate the skin.

There is thus a need for new approaches to the transdermal application of solid and liquid pharmacologically active agents using controlled release systms.

We have now surprisingly found that the pharmacologically active agent bopindolol, 4-(2-benzoyloxy-3-tert-butylaminopropoxy)-2-methylindole, a beta-blocker which is known for oral administration e.g. for the treatment of hypertension, has especially interesting properties for transdermal administration. This is hereinafter referred to as the active agent of the invention.

The penetration of bopindolol through the skin may be observed in standard in vitro or in vivo tests.

One in vitro test is the well known diffusion test which may be effected according to the principles set out in GB 2098865 A and by T.J.Franz in J.Invest.Dermatol (1975) 64, 194-195. Solutions containing the active agent in unlabelled or radioactively labelled form are applied to one side of isolated pieces of intact human skin or hairless rat skin about 2 cm^2 in area.The other side of the skin is in contact with physiological saline. The amount of active agent in the saline is measured in conventional manner, e.g. by HPLC or spectrophotometric techniques, or by determining the radioactivity.

In one aspect the present invention provides the use of bopindolol as active agent in the manufacture of a medicament suitable for systemic transdermal administration. In a further aspect the present invention provides a pharmaceutical composition for the transdermal systemic administration of an active agent characterised in that the active agent is bopindolol.

In general for application e.g. behind the ear an amount of bopindolol from about 1 to 6 mg is indicated, e.g. 5 mg for a dose for 1 to 3 days.

The active agent of the invention may be administered in any conventional liquid or solid transdermal pharmaceutical composition, e.g. as described in Remington's Pharmaceutical Sciences 16th Edition Mack; Sucker, Fuchs and Spieser, Pharmaceutische Technologie 1st Edition,Springer and in GB 2098865 A or DOS 3212053. Conveniently the composition is in the form of a viscous liquid, ointment or solid matrix. The active agent may be incorporated in a plaster.

We have now found that bopindolol may be advantageously administered transdermally from a drug reservoir comprising a hydrophilic polymer having the pharmacologically active agent dispersed throughout.

In a further aspect the present invention provides a pharmaceutical composition for the transdermal systemic administration of a pharmacologically active agent characterised in that it contains bopindolol in a reservoir comprising a hydrophilic polymer. In yet a further aspect the present invention provides the use of bopindolol in a hydrophilic polymer for the manufacture of a transdermal medicament suitable for systemic administration of the active agent through intact skin.

The hydrophilic polymers take up water and are permeable to water, e.g. moisture from the skin, although the polymers may be insoluble in water. The polymers may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum corneum at a pH of from 4 to 7, preferably at skin pH,

e.g. 5.5. If desired they may be soluble in organic solvents. Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

The polymer preferably has a mean molecular weight of from 50,000 to 300,000 Daltons, such as 100,000 to 200,000 Daltons, and is preferably film forming.

Hydrophilic polyacrylates are preferred polymers. The acrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl groups such as methyl or ethyl groups. Preferably at least 2% of the alkyl groups may contain polar substituents, e.g. a hydroxy group.

It has been found that polyacrylates containing cationic functional groups are especially preferred.

Transdermal pharmaceutical compositions for the systemic administration of pharmacologically active agents through intact skin wherein the active agent is in a reservoir comprising a polyacrylate containing catonic functional groups are novel and form part of the present invention.

The present invention also provides the use of bopindolol in a polyacrylate containing cationic groups for the manufacture of a medicament suitable for transdermal systemic administration of the pharmacologically active agent through intact skin of a subject.

Examples of cationic groups include dialkylaminoalkyl groups, e.g. dimethylaminoalkyl groups.

Especially preferred cationic groups include quaternary ammonium groups, preferably a tri(alkyl)-aminoalkyl group. Examples of such groups are trimethylaminoethyl ester groups.

The polyacrylate may contain some carboxylic acid groups in free form or salt anions, e.g. chloride anions in order to balance the cationic groups.

The ratio of cationic groups to neutral groups is preferably from 1:10 to 1:50 e.g. from 1:20 to 1:40.

Preferably the polymers have an alkali count (defined in analogous manner to acid count) of from about 10 to about 200 mg KOH per gram polymer, e.g. 10 to 30 mg KOH per gram polymer.

Examples of commercially available polymers of this type include: -

1) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions are present. Mean Molecular weight 150000 Daltons. Viscosity (20 °C), maximum 15 mPas (cP). Refractive index 1.380 - 1.385. Density 0.815 - 0.835 g/cm^3. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm, Darmstadt, W.Germany) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).

2) Polymer of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C_{1-4})alkyl ester groups. Chloride ions are present. Mean molecular weight 150,000. Viscosity (20 °C) 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm).

The drug reservoir may contain plasticizers and/or softeners preferably skin compatible tensides e.g. to provide flexibility to the unit, and/or to dissolve partially or totally the pharmacologically active agent in the reservoir.

Examples of additives include: -

1) Polyoxyethylene fatty alcohol ethers. The alcohol may e.g. be a C_{12-18} alcohol. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(10) oleyl ether. A suitable ether may have a viscosity (25 °C) of about 100 cP (100 mPas), a solidification point of about 16 °C, an HLB value of 12.4 and an acid count maximum 1.0 (Brij 97 Registered Trade Mark available from Atlas Chemie W.Germany).

2) Polyoxyethylene Sorbitan fatty acid esters. The fatty acid may be e.g. a C_{12-18} fatty acid. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, W.Germany.

3) polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, W.Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF W.Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, W.Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate e.g. Product of 35 moles ethylene oxide and castor oil e.g. Brand Chremophor EL Registered Trade Mark, obtainable from BASF, W.Germany.

9) Triacetin – (1,2,3).

The amount and type of additive required will depend on a number of factors,e.g. the HLB value of the tenside and the flexibility of the unit required. Surprisingly the amount of additive does not significantly influence the capability of the polyacrylate to form films. Generally the weight ratio of tenside to the hydrophilic polymer is from about 1:10 to 5:1, e.g. 1:10 to 1:3.

The drug reservoir may contain skin penetration promoters, e.g. 1 – dodecylazacycloheptan – 2 – one – (azone) and N,N – diethyl – m – toluamide (DEET).

The amount and type of skin penetration promoter, and/or additives present will depend on a number of factors. Generally the weight ratio of skin penetration promoting agent to hydrophilic polymer will be from about 1:1 to 1:10. Preferably the amount of tenside and/or skin penetration promoter is from 3 to 50%, preferably 20 to 40% by weight of the pharmaceutical composition.

If desired the drug reservoir may contain a hydrophobic elastomer, e.g. a synthetic resin. Such resins are conventional in the plaster art. Suitable resins include non – swellable acrylate resins. These may if desired be adhesive. The weight ratio of hydrophilic polymer to resin may for example be from 1:0.5 to 1:10. The resin may contain modifiers, extenders, e.g. of softening point about 50 to 100 ° C. Such extenders may have adhesive or softening properties. Examples of such extenders include resin acids, glyceryl and phthalate esters of resin acids, hydrogenated abietyl alcohol and its phthalate esters. The extenders for example be present in an amount of from 5 to 40% of the weight of the resin.

Any pharmacologically active agent capable of penetration of the skin may be dispersed throughout the hydrophilic polymer. The indication for which the active agent is used is not critical. It is preferred that the daily transdermal dose for such agents is less than 20 mg per day, e.g. less than 10 mg per day.

The active agent for use in any of the pharmaceutical compositions mentioned above may be in free form e.g. free base form or in pharmaceutically acceptable salt form e.g. pharmaceutically acceptable acid addition salt form.

Such acid addition salt forms include the hydrogen malonate, hydrogen maleate, hydrogen fumarate, hydrochloride, tartrate etc. Preferably a solid active agent has an average particle diameter of from 30 to 50 µm. The active agent may be partly suspended and/or partly dissolved in the reservoir. It may be dispersed so finely that to the eye a smooth homogenous film results.

The pharmaceutical compositions of the invention are useful for the systemic administration of pharmacologically active agents through intact skin, as indicated in standard in vitro and in vivo tests.

The release of active agent from the pharmaceutical compositions may be followed for example by determining e.g. by ultraviolet spectroscopy, the amount of active agent released on shaking the pharmaceutical composition in 0.9% NaCl solution at 37 ° C at a paddle speed of about 120 rpm.

The penetration of the active agent through isolated rat and human skin may be followed in the well known diffusion test effected according to the principles, e.g. set out in GB 2098865 A and in T.J.Franz, J.Invest.Dermatol (1975), 64, 191 – 195. The pharmaceutical compositions of the invention are applied to the external side of isolated rat or human skin pieces about 2 cm^2 in area. The rat skin is hairless. The other side is continuously washed with physiological saline. The amount of active agent in the saline is determined in conventional manner, e.g. HPLC. The penetration flux over 24 hours may then be ascertained, and if desired the steady state flux. The penetration flux rate is in the order of 1 to 10 micrograms/cm^2/ hour.

Alternatively the penetration of the active agent may be followed in vivo by applying the pharmaceutical composition to intact skin, e.g. on the chest, back, arm or behind the ear, of a subject and measuring the amount of active agent in the blood.

The pharmaceutical compositions of the invention may be used for the same indications as known for oral or intravenous administration. The amount of pharmaceutically active agent to be administered will individually depend on the drug release characteristics of the pharmaceutical compositions, the drug penetration rate observed in in vitro and in vivo tests, the potency of active agent, the size of the skin contact area, the part of the body to which the unit is stuck, and the duration of action required. The amount of active agent and area of the pharmaceutical composition etc may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of the active agent in a pharmaceutical composition according to the invention to intact skin and blood levels of active agent observed after oral or intravenous administration of a therapeutically effective dose of the pharmacologically active agent.

Given the daily dose of a drug for oral administration, the choice of a suitable quantity of drug to be incorporated in a transdermal composition according to the invention will depend upon the pharmacokinetic properties of the active agent, including the first pass effect; the amount of drug which can be absorbed

through the skin from the matrix in question for a given area of application and in a given time; and the time for which the composition is to be applied. Thus, a drug with a high first pass effect may require a relatively low quantity in the transdermal composition when compared with the oral daily dose, since the first pass effect will be avoided. On the other hand, generally a maximum of only approx. 50% of the drug in the matrix is released through the skin in a 3 day period.

The pharmaceutical compositions of the invention in general have for example an effective contact area of drug reservoir on the skin of from about 1 to about 50 square centimetres, preferably about 2 to 20 square centimetres, and are intended to be applied for from 1 – 7 days, preferably 1 – 3 days.

Examples of representative doses of bopindolol are a dose of 1 to 10 mg in a patch of 10 cm^2 to be administered once over 3 consecutive days in each week for treatment of hypertension.

The pharmaceutical compositions of the invention may be produced in conventional manner by dispersing or dissolving the pharmacologically active agent through a hydrophilic drug reservoir.

The weight ratio of pharmacologically active agent to hydrophilic polymer may vary between wide limits. The weight ratio may be for example sufficient to produce a supersaturation of the pharmacologically active agent in the drug reservoir. In general the weight ratio is from 1:10 to 1:1.

If the drug reservoir is not itself adhesive a pressure sensitive adhesive may be used to stick the drug reservoir to intact skin. Any conventional adhesive may be used, e.g. a polyacrylate. The layer may be applied to the drug reservoir and have a thickness of from 1 to 200 µms preferably 10 to 100 µms. If the adhesive layer is thin enough then the pharmacological agent will pass through it. Alternatively the adhesive layer may be applied to the edges of an outer cover for the drug reservoir and the outer cover stuck to the intact skin holding the drug reservoir in close contact with the intact skin.

The drug reservoir may be produced in conventional manner, e.g. in an adhesive plaster or patch. If it is a polymer matrix it may be produced by dispersing or dissolving the pharmacologically active agent in a solution of the polymer and other additives in a volatile organic solvent, e.g ethanol, methylene chloride, or acetone. A film is formed by spreading the dispersion or solution over the outer protective cover. The wet film may have a thickness of about 0.05 to 0.5 millimetres, e.g. 0.1 to about 0.3 millimetres. The film is allowed to dry, e.g. at room temperature or a slightly elevated temperature below 50 ° C. The drug reservoir may be built up in a series of layers and then any adhesive layer provided in the last layer.

The pharmaceutical compositions of the invention may be produced in conventional manner for skin penetration pharmaceutical compositions. Figure 1 of the accompanying drawings gives a schematic cross – section through the layers of a representative pharmaceutical composition according to the inven – tion. Figure 2 of the accompanying drawings gives a schematic cross – section of a another embodiment, e.g. in the form of a bandage or plaster. In figures 1 and 2 there are several layers a – d and in the case of Figure 2, additionally layer e. Layer a is a medical cover made out of e.g. polyester/aluminium laminate foil. Layer b is an occulsive foil, e.g. of aluminium foil. If desired this may be omitted. Layer c may be made out of 1 to 10 layers of a drug reservoir. The drug reservoir is a homogenous dispersion of active agent particles or a solution of active agent in a polymer matrix. Layer d may be an adhesive layer. In one embodiment (not shown) the layer d may extend to between the outer edges of layer a and layer e. Alternatively the layer e may be omitted completely. Layer a may extend around layers b to d in Figure 2. Layer e is a protective peel off layer which is stuck to the adhesive layer as well as to the edges of the cover layer a.

On use any protective layer e is peeled off and the unit stuck to intact skin.

In the following examples all temperatures are in degrees Centigrade and are uncorrected. All amounts are in parts by weight unless otherwise stated.

Details of components are given in Lexicon for Pharmazie, Kosmetic and angrenzende Gebiete by H.P.Fiedler, 2 Edition, Cantor Aulendorf, W.Germany or from the relevant manufacturers.

In the following examples, the indicated terms have the meaning shown below: –

PAM Amine polymer RL: Polyacrylate/methacrylate cationic polymer as defined above under the term EUDRAGIT RL 100.

PAM Amine polymer RS: Polyacrylate/methacrylate cationic polymer as defined above under the term EUDRAGIT RS 100.

PAM Amine polymer E: Polymethacrylate cationic polymer as defined above under the term EUDRAGIT E 100.

Polyoxyethylene(10) oleyl ether: BRIJ 97 as defived above. Glycerin Polyethylene glycol(35) ricinoleate = Cremophor EL as defined above.

Polyoxyethylene(20) sorbitan monooleate = Tween 80 as defined above.

Polyethylene(7) glycol glyceryl cocoate = Cetiol HE as defined above.

Acrylate synthetic resin is self cross-linking acrylate Brand Durotack 280-2416 available from Delft National Chemie Zutphen Netherlands available as a light yellow solution containing as solvent 57% ethyl acetate, 32% ethanol, 9% hexane, 2% methanol: solids content 41%, Viscosity (Brookfield) = 2100-6000 mPas, Plasticity (Williams) ± 3 mm, Density 0.94 Flashpoint 0.94.

EXAMPLE A: Preparation of pharmaceutical composition containing a hydrophilic polymer

Composition	
Pharmacologically active agent	20%
Hydrophilic polymer	40%
Tenside	40%

1.2 g of hydrophilic polymer are dissolved in 3 g acetone or ethanol or other appropriate volatile organic solvent with stirring in 1 to 2 hours. 0.6 g pharmacologically active agent and 1.2 g of tenside softener are added. The mixture is vigorously stirred for about 5 to 20 minutes with a high speed stirrer to give a viscous mass.

The mass is spread as a film on top of an aluminised polyester foil (thickness 23 µm) using a conventional apparatus, e.g. an Erichsen film apparatus Model 411/150. The mass is spread across the foil at a speed of 18 mm/sec to produce a film of thickness 0.2 mm when wet.

The film is allowed to dry at room temperature over 4 to 6 hours. The resultant hydrophilic polymer drug matrix weighs 8.5 mg per square centimetre and contains 1.7 mg active agent per square centimetre.

A further film of an acrylate adhesive (Rohm Pharma 7708/47) is then applied onto the drug polymer matrix as a thin layer (0.1 mm thickness) in analogous manner.

The aluminium foil is then cut up into patches about 10 sq cm in area.

Unless otherwise stated the drug matrix is built up from one film layer. It may if desired be built up as more than one layer.

The release of active agent is measured in vitro in standard skin diffusion tests through freshly isolated hairless rat skin. The rat skin piece is located in a Franz diffusion chamber - see T.J.Franz, J.Invest.Dermatol 1975 (64) 191-195. The receptor phase is pumped continuously and every hour samples are taken and measured for active agent content using HPLC. The trial lasts 24 hours and the penetration flux over 24 hours (hereinafter referred to as "flux") and if desired a steady state flux after a lag time of 3 to 10 hours is measured.

EXAMPLE 1 - 4: Bopindolol pharmaceutical compositions

The following compositions are made in analogous manner to Example A.

Example	1	2	3	4
Bopindolol hydrogen malonate	1.275 g	1.275 g	-	-
Bopindolol free base	-	-	1.0 g	1.0 g
PAM Amine polymer RL	1.225 g	1.225 g	-	-
PM Amine polymer E	-	-	2.665 g	2.665 g
Polyoxyethylene-(10) oleyl ether	-	0.25 g	1.335 g	-
Polyethylene-(9) glycol glyceryl cocoate	-	-	-	1.335 g
Azone	2.5 g	2.25 g	-	-

Solvent	CH_2Cl_2	CH_2Cl_2	CH_3OH	CH_3OH
Solvent amount (g/g dry film)	1.0	1.0	4.0	4.0
Thickness of wet film (mm)	0.25	0.25	0.3	0.3
Spreading speed (mm/sec)	6	6	6	6
Acrylate adhesive film (Wet film thickness)	None	None	None	None
Active Agent Penetration through isolated rat skin. Penetration Flux (microgram/ cm^2/hr)	1.7	4.0	11.1	8.6
Steady Rate flux (microgram/cm^2/hr)	5.7	12.5	59.0	33.0

EXAMPLE C: Bopindolol penetration from solutions

Solutions of the following compositions are made up and the penetration rate observed.

Constituents	C1	C2	C3
Bopindolol hydrogen malonate	-	1.0 g	1.0 g
Bopindolol (free base)	1.0 g	-	-
Ethanol (ml)	0.049	0.049	0.048
Acetone (ml)	0.049	-	-
Polyethylene glycol (7) glyceryl cocoate	0.003	0.003	-
Water	-	-	0.048
Azone	-	-	0.048
Active agent Penetration through the rat skin (microgram/cm^2/hr)			
Flux	0.8	0.3	6.0
Steady state Flux	-	-	5.8

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition for the transdermal systemic administration of an active agent characterised in that the active agent is bopindolol.

2. A composition according to claim 1 in the form of a solid matrix.

3. A pharmaceutical composition for the transdermal systemic administration of an active agent, characterized in that the active agent is bopindolol and the skin penetration flux is at least 0.3 microgram/cm^2/hour, if measured through isolated rat skin.

4. A pharmaceutical composition according to claim 3 having a penetration flux of at least 0.8 microgram/cm^2/hour.

5. A pharmaceutical composition for the transdermal systemic administration of a pharmacologically active agent characterised in that it contains bopindolol as an active agent in a reservoir comprising a hydrophilic polymer in the form of a solid matrix.

6. A composition according to claim 5 wherein the polymer is a polyacrylate polymer.

7. A composition according to claim 5 wherein the polymer is a polyacrylate polymer containing cationic functional groups.

8. A composition according to any one of claims 5 to 7 wherein the polymer is an acrylate/methacrylate polymer.

9. A composition according to any one of claims 5 to 8 wherein the polymer contains trimethylaminoethyl ester groups.

10. A composition according to any of claims 5 to 9 in the form of an adhesive plaster or patch comprising a) a cover layer, b) a drug reservoir comprising 1 to 10 layers of a homogeneous dispersion of active agent particles or a solution of active agent in a polymer matrix, and d) an adhesive layer, reservoir c) being located between layers a) and d).

11. A composition according to any preceding claim wherein a skin compatible tenside is present.

12. A composition according to any preceding claim wherein a hydrophobic elastomer is present.

13. A process for the production of a pharmaceutical composition for transdermal administration which comprises dispersing a) bopindolol in a polyacrylate polymer containing cationic ester groups, to form a drug reservoir, b) bopindolol through a hydrophilic polymer or c) bopindolol in a suitable transdermal excipient, and optionally applying an adhesive layer.

14. Use of bopindolol as active agent in the manufacture of a medicament suitable for systemic transdermal administration.

15. Use according to claim 14 wherein the medicament is a composition as defined in any one of claims 1 to 12.

Claims for the following Contracting State : AT

1. A process for the production of a pharmaceutical composition for systemic transdermal administration which comprises formulating bopindolol in conventional manner to produce a skin penetration pharmaceutical composition, preferably in the form of a solid matrix.

2. A process for the production of a pharmaceutical composition for systemic transdermal administration which comprises dispersing or dissolving bopindolol through a hydrophilic drug reservoir in the form of a solid matrix.

3. A process for the production of a pharmaceutical composition for systemic transdermal administration which comprises dispersing or dissolving bopindolol through a polyacrylate polymer reservoir.

4. A process according to claim 3 wherein the polymer contains cationic functional groups.

5. A process for the production of a pharmaceutical composition for transdermal administration which comprises dispersing a) bopindolol in a polyacrylate polymer containing cationic ester groups, to form a drug reservoir, b) bopindolol through a hydrophilic polymer or c) bopindolol in a suitable transdermal excipient, and optionally applying an adhesive layer.

6. A process according to claim 4 or 5 wherein the polymer contains trimethylaminoethyl ester groups.

7. A process according to any one of claims 3 to 6 wherein the polyoacrylate polymer is on acrylate/methacrylate copolymer.

8. A process according to any one of claims 1 to 7 wherein a skin compatible tenside is mixed in.

9. A process according to any one of claims 1 to 8 wherein a hydrophobic elastomer is mixed in.

10. Use of bopindolol as active agent in the manufacture of a medicament suitable for systemic transdermal administration.

11. Use according to claim 10 wherein the medicament is a composition prepared as defined in any one of claims 1 to 9.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische Zusammensetzung zur transdermalen systemischen Verabreichung eines Wirkstoffes, dadurch gekennzeichnet, dass der Wirkstoff Bopindolol ist.

2. Eine Zusammensetzung gemäss Anspruch 1 in Form einer festen Matrix.

3. Pharmazeutische Zusammensetzung zur transdermalen systemischen Verabreichung eines Wirkstoffes, dadurch gekennzeichnet, dass der Wirkstoff Bopindolol ist und die Hautpenetration mindestens 0.3 Mikrogramm/cm^2/Stunde ist, gemessen an isolierter Rattenhaut.

4. Pharmazeutische Zusammensetzung gemäss Anspruch 3 mit einer Penetrationsflux von mindestens 0.8 Mikrogramm/cm^2/Stunde.

5. Pharmazeutische Zusammensetzung zur transdermalen systemischen Verabreichung eines pharmakologisch aktiven Wirkstoffes, dadurch gekennzeichnet, dass sie Bopindolol als Wirkstoff enthält, in einem Reservoir, dass ein hydrophiles Polymer in Form einer festen Matrix enthält.

6. Zusammensetzung gemäss Anspruch 5, in der das Polymer ein Polyacrylatpolymer ist.

7. Zusammensetzung gemäss Anspruch 5, in der das Polymer ein Polyacrylatpolymer mit kationischen funktionellen Gruppen ist.

8. Zusammensetzung gemäss einem der Ansprüche 5 bis 7 in der das Polymer ein Acrylat/Methacrylat-Polymer ist.

9. Zusammensetzung gemäss einem der Ansprüche 5 bis 8 in der das Polymer Trimethylaminoethylestergruppen enthält.

10. Zusammensetzung gemäss einem der Ansprüche 5 bis 9 in Form eines Heftplasters oder Lappen aus a) einer Deckschicht, b) einem Wirkstoffreservoir mit 1 bis 10 Schichten einer homogenen Dispersion von Wirkstoffteilchen oder einer Wirkstofflösung in einer polymeren Matrix enthaltend und d) eine Klebstoffschicht, mit dem Reservoir c) zwischen Schichten a) und d) angeordnet.

11. Zusammensetzung gemäss einem der vorhergehenden Ansprüche in Anwesenheit eines hautverträglichen Tensids.

12. Zusammensetzung gemäss einem vorhergehenden Anspruch, mit einem hydrophoben Elastomeren.

13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung zur transdermalen Verabreichung dadurch gekennzeichnet, das
a) Bopindolol in einem Polyacrylatpolymeren mit kationischen Estergruppen zur Bildung eines Wirkstoffreservoirs,
b) Bopindolol in einem hydrophilen Polymeren oder
c) Bopindolol in einem geeigneten transdermalen Hilfsmittel dispergiert und
gegebenenfalls eine Klebstoffschicht aufgebracht wird.

14. Verwendung von Bopindolol als Wirkstoff bei der Herstellung eines Medikamentes geeignet zur systemischen transdermalen Verabreichung.

15. Verwendung gemäss Anspruch 14, wobei das Medikament eine Zusammensetzung ist, definiert in einem der Ansprüche 1 bis 12.

Patentansprüche für folgende Vertragsstaat : AT

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung zur transdermalen Verabreichung, dadurch gekennzeichnet, dass Bopindolol in herkömmlicher Weise zu einer hautpenetrierenden pharmazeutischen Zusammensetzung, Vorzugsweise in Form einer festen Matrix, verarbeitet wird.

2. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung zur transdermalen Verabreichung, dadurch gekennzeichnet, dass Bopindolol in einem hydrophilen Wirkstoffreservoir dispergiert oder gelöst und in Form einer festen Matrix gebracht wird.

3. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung zur transdermalen Verabreichung, dadurch gekennzeichnet, dass Bopindolol in einem Polyacrylatpolymerreservoir dispergiert oder gelöst wird.

4. Verfahren gemäss Anspruch 3, in dem das Polymer kationische funtionelle Gruppen enthält.

5. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung zur transdermalen Verabreichung, dadurch gekennzeichnet, dass
a) Bopindolol in einem Polyacrylatpolymeren mit kationischen Estergruppen dispergiert und daraus ein Wirkstoffreservoir geformt wird oder
b) Bopindolol in einem hydrophilen Polymeren oder
c) Bopindolol in einem geeigneten transdermalen Hilfsmittel dispergiert wird und
eventuell eine Klebstoffschicht aufgebracht wird.

6. Verfahren gemäss Anspruch 4 oder 5 mit einem Polymeren mit Trimethylaminoethylestergruppen.

7. Verfahren gemäss einem der Ansprüche 3 bis 6 mit einem Polyacrylatpolymeren aus Acrylat/Methacrylatcopolymeren.

8. Verfahren gemäss einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, dass ein hautverträgliches Tensid mithineingemischt wird.

9. Verfahren gemäss einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, dass ein hydrophobes Elastomer mithineingemischt wird.

10. Verwendung von Bopindolol als Wirkstoff bei der Herstellung eines Medikamentes, das zur systemischen transdermalen Verabreichung geeignet ist.

11. Verwendung gemäss Anspruch 10 wobei das Medikament eine Zusammensetzung ist, hergestellt nach dem Verfahren gemäss einem der Ansprüche 1 - 9.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Une composition pharmaceutique pour l'administration systémique transdermique d'une substance active, caractérisée en ce que la substance active est le bopindolol.

2. Une composition selon la revendication 1 sous forme d'une matrice solide.

3. Une composition pharmaceutique pour l'administration systémique transdermique d'une substance active, caractérisée en ce que la substance active est le bopindolol et que le flux de pénétration dans la peau est d'au moins 0,3 microgramme/cm^2/heure, mesuré sur la peau isolée de rats.

4. Une composition pharmaceutique selon la revendication 3 ayant un flux de pénétration d'au moins 0,8 microgramme/cm^2/heure.

5. Une composition pharmaceutique pour l'administration systémique transdermique d'une substance pharmacologiquement active, caractérisée en ce qu'elle contient du bopindolol comme substance active dans un réservoir comprenant un polymère hydrophile sous forme d'une matrice solide.

6. Une composition selon la revendication 5, dans laquelle le polymère est un polyacrylate.

7. Une composition selon la revendication 5, dans laquelle le polymère est un polyacrylate contenant des groupes fonctionnels cationiques.

8. Une composition selon l'une quelconque des revendications 5 à 7, dans laquelle le polymère est un poly(acrylate/méthacrylate).

9. Une composition selon l'une quelconque des revendications 5 à 8, dans laquelle le polymère contient des groupes ester triméthylaminoéthyliques.

10. Une composition selon l'une quelconque des revendications 5 à 9 sous forme d'un pansement ou d'un timbre adhésifs, comprenant a) une couche de protection, b) un réservoir de médicament comprenant de 1 à 10 couches d'une dispersion homogène de particules de substance active ou une solution de substance active dans une matrice polymère et d) une couche adhésive, le réservoir c) étant situé entre les couches a) et d).

11. Une composition selon l'une quelconque des revendications précédentes, dans laquelle un tensio – actif compatible avec la peau est présent.

12. Une composition selon l'une quelconque des revendications précédentes, dans laquelle un élastomère hydrophobe est présent.

13. Un procédé de préparation d'une composition pharmaceutique pour l'administration transdermique, qui comprend la dispersion a) du bopindolol dans un polyacrylate contenant des groupes ester cationiques, pour former un réservoir de médicament, b) du bopindolol à travers un polymère hydrophile ou c) du bopindolol dans un excipient transdermique approprié, et éventuellement l'application d'une couche adhésive.

14. L'utilisation du bopindolol comme substance active pour la fabrication d'un médicament approprié pour l'administration sytémique transdermique.

15. L'utilisation selon la revendication 14, dans laquelle le médicament est une composition telle que définie à l'une quelconque des revendications 1 à 12.

Revendications pour l'Etat contractant suivant : AT

1. Un procédé de préparation d'une composition pharmaceutique pour l'administration systémique trans – dermique, qui comprend la formulation du bopindolol d'une manière classique pour produire une

composition pharmaceutique destinée à pénétrer la peau, de préférence sous forme d'une matrice solide.

2. Un procédé de préparation d'une composition pharmaceutique pour l'administration systémique transdermique, qui comprend la dispersion ou la dissolution du bopindolol à travers un réservoir de médicament hydrophile sous forme d'une matrice solide.

3. Un procédé de préparation d'une composition pharmaceutique pour l'administration systémique transdermique, qui comprend la dispersion ou la dissolution du bopindolol à travers un réservoir constitué de polyacrylate.

4. Un procédé selon la revendication 3, dans lequel le polymère contient des groupes fonctionnels cationiques.

5. Un procédé de préparation d'une composition pharmaceutique pour l'administration systémique transdermique, qui comprend la dispersion a) du bopindolol dans un polyacrylate contenant des groupes ester cationiques, pour former un réservoir de médicament, b) du bopindolol à travers un polymère hydrophile ou d) du bopindolol dans un excipient transdermique approprié, et éventuellement l'application d'une couche adhésive.

6. Un procédé selon la revendication 4 ou 5, dans lequel le polymère contient des groupes ester triméthylaminoéthyliques.

7. Un procédé selon l'une quelconque des revendications 3 à 6, dans lequel le polyacrylate est un copolymère acrylate/méthacrylate.

8. Un procédé selon l'une quelconque des revendications 1 à 7, dans lequel on mélange un tensioactif compatible avec la peau.

9. Un procédé selon l'une quelconque des revendications 1 à 8, dans lequel on mélange un élastomère hydrophobe.

10. L'utilisation du bopindolol comme substance active pour la préparation d'un médicament approprié pour l'administration systémique transdermique.

11. L'utilisation selon la revendication 10, dans laquelle le médicament est une composition préparée comme défini à l'une quelconque des revendications 1 à 9.

FIG. 1

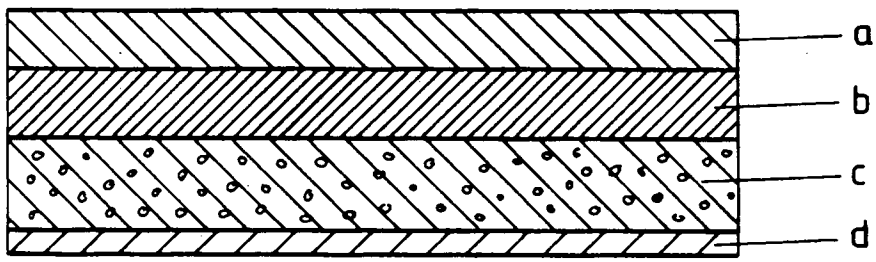
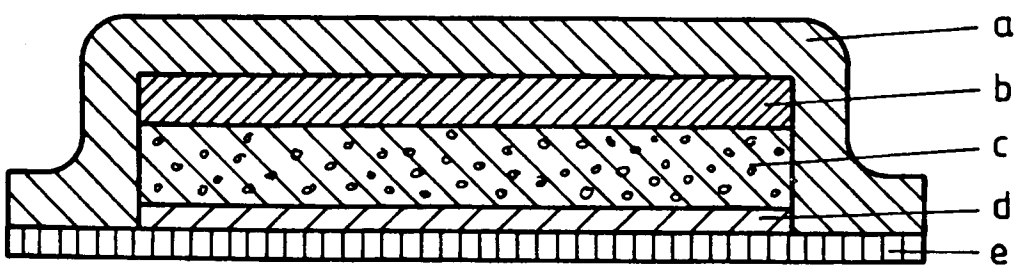


FIG. 2



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