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(54) **Pharmaceutical compositions.**

(57) The present invention provides a pharmaceutical composition for the transdermal systemic administration of an active agent characterised in that the active agent is bopindolol or methysergide. Also the present invention provides a pharmaceutical composition for the transdermal systemic administration of a pharmacologically active agent characterised in that it contains bopindolol, tizanidine, clemastine, ketotifen or methysergide as active agent in a reservoir comprising a hydrophilic polymer. Furthermore a pharmaceutical composition for the transdermal systemic administration of pharmacologically active agents characterised in that the pharmacologically active agent is in a reservoir comprising a polyacrylate polymer containing cationic ester groups.

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PHARMACEUTICAL COMPOSITIONS

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 into 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, and methysergide (9,10-didehydro-N-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8-carboxamide, a known serotonin antagonist e.g. for the prophylaxis of migraine, have especially interesting properties for transdermal administration. These are hereinafter referred to as the active agents of the invention.

The penetration of these active agents 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.

Typically using rat skin a penetration flux of from 0.1 to 10 microgram/cm^2/hour over 24 hours is observed for the active agents.

In one aspect the present invention provides a method of systemically administering the active agent bopindolol or methysergide which comprises administering the active agent to the skin. In a further aspect the present invention provides the use of bopindolol or methysergide 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 or methysergide.

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

The active agents 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 the contents of which are incorporated herein by reference. 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 the above active agents, bopindolol and methysergide, as well as the following pharmacologically active agents tizanidine, ketotifen and clemastine may be advantageously administered transdermally from a drug reservoir comprising a hydrophilic polymer having the pharmacologically active agent dispersed throughout.

Tizanidine, ketotifen and clemastine have previously been disclosed for transdermal administration. GB 2098865 A discloses topical microemulsions containing these pharmacologically active agents The microemulsions are to be applied to the skin as a cream.

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