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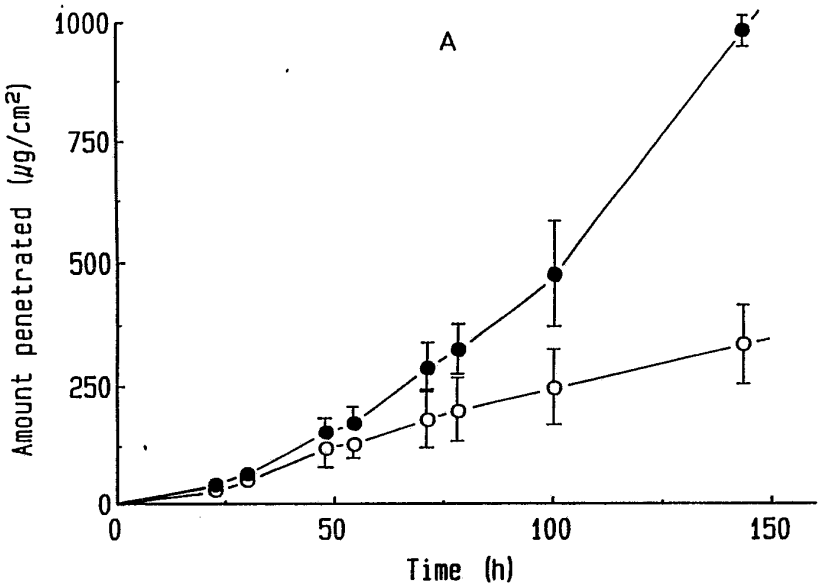
(54) Title: TOPICAL COMPOSITIONS FOR TRANSDERMAL DELIVERY OF PRODUG DERIVATIVES OF MORPHINE




(57) Abstract

The invention relates to topical composition for transdermal delivery of morphine. The composition comprises an effective amount of a morphine ester in association with a topical pharmaceutical carrier which gives solutions, suspensions, ointments, lotions, creams, gels, pastes, jellies, sprays and aerosols and/or together with a medical device. The invention also relates to the use of the morphine esters for the manufacture of a topical medicament for transdermal delivery for relieving pain or tranquilizing a mammal.

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# Topical compositions for transdermal delivery of prodrug derivatives of morphine

## BACKGROUND OF THE INVENTION

### Field of the Invention

The present invention relates to the use of prodrug derivatives of morphine in effecting transdermal delivery of morphine to the systemic circulation of a mammal.

For purposes of this specification, the term "prodrug" denotes a derivative of morphine which, when administered topically to warm-blooded animals, e. g. humans, is converted into the proven drug, i. e. morphine.

The prodrug forms of morphine of this invention are certain derivatives of morphine which possess a desirable high lipophilicity and biphasic solubility in comparison to the parent compound, morphine, and which are cleaved enzymatically to morphine.

### Description of the Prior Art

It is generally known and an accepted practice to administer morphine to control chronic pain. Morphine plays a prominent role in the control of pain associated with chronic diseases, especially the chronic pain of cancer, and acute pain, especially the acute pain experienced post-operatively. However, such prior art uses of morphine are subject to serious problems. In addition to the obvious problems associated with potential abuse and addiction, the oral and parenteral administration of morphine for pain control frequently involve wide swings in the pharmacodynamics of the drug over each dosing interval. Furthermore, morphine has a short duration of action and is inefficiently and variably absorbed orally due to first-pass metabolism in the intestine and liver.

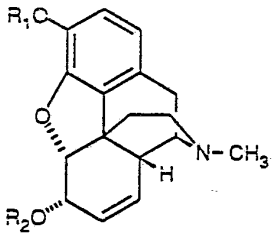
During recent years much attention has been paid to the development of transdermal delivery systems as a means of mitigating many of the drawbacks associated with the parenteral or oral route of administration. (Sloan K B, Adv. Drug Delivery Rev. (1989), 67-101) A prerequisite for the development of a transdermal delivery system of morphine and other opioids is, however, that the drugs are capable

of penetrating the skin at a sufficiently high rate and are not metabolized during the percutaneous absorption. Morphine which remains the analgesic drug of choice for the treatment of severe pain, unfortunately exhibits, a very limited skin permeability which makes it unsuited for transdermal delivery. For instance, the steady-state flux of morphine through human skin in vitro has been reported to be only 6 ng/cm$^2$/h when applied in the form of a saturated solution (pH 7.4). (Roy, S.D., and Flynn, G.L.,Transdermal delivery of narcotic analgesics: comparative permeabilities of narcotic analgesics through human cadaver skin.Pharm. Res. 6 (1989) 825-832). These poor skin-penetration properties of morphine led to the conclusion that morphine is totally unsuited for transdermal delivery. The very poor ability of morphine to permeate into and through the skin can mainly be ascribed to its poor lipophilicity. Thus, the log P value for morphine is only -0.15 where P is the partition coefficient between octanol and aqueous buffer of pH 7.4 (Roy and Flynn 1989) It has now surprisingly been found that transdermal delivery of morphine can be achieved by the prodrug approach proposed in accordance with the present invention.

## SUMMARY OF THE INVENTION

The present invention provides novel topical compositions for transdermal delivery comprising an effective amount of a compound represented by the following general Formula I

(I)




where $R_1$ and $R_2$ are the same or different and are hydrogen and a member selected from the group of physiologically hydrolyzable chemical groups consisting of alkylcarbonyl, alkenylcarbonyl arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, aryloxycarbonyl and heteroaryloxycarbonyl groups wherein the alkyl moiety consists of unsubstituted or substituted, straight-chain and branched-chain and cyclic alkyl groups having 1-20 carbon atoms, wherein the alkenyl

moiety consists of unsubstituted and substituted, straight-chain and branched-chain and cyclic alkenyl groups having 2-20 carbon atoms, wherein the aryl moiety consists of unsubstituted and substituted phenyl, and phenalkyl groups wherein the alkyl moiety contains 1-3 carbon atoms and the phenyl moiety is unsubstituted or substituted, and the heteroaryl moiety is an aromatic 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur;
and nontoxic pharmaceutically acceptable acid addition salts thereof, with the proviso that if $R_1$ = hydrogen then $R_2 \neq$ hydrogen, and if $R_2$ = hydrogen then $R_1 \neq$ hydrogen
in association with a topical pharmaceutical carrier for solutions, suspensions, ointments, lotions, creams, gels, pastes, jellies, sprays and aerosols and/or together with a medical device.
The invention also provides a composition containing a non-toxic additive acting as a skin penetration enhancer.
Another subject of the invention is topical dosage forms consisting of a matrix type or reservoir type patch system containing a compound as defined in Formula I or this compound in combination with a penetration enhancing delivery device/process such as iontophoresis. Reservoir type patch systems and iontophoresis are both well known systems for transdermal delivery.
The composition according to the invention can also be combined with an additional drug delivery device such as patches, gauze or compresses.
The invention further includes the use of the esters according to Formula I in the manufacure of a topical medicament for transdermal delivery with the intention of for relieving pain or tranquilizing a mammal and the use of these esters for transdermal delivery.
Also claimed is a process for achieving transdermal delivery of morphine, which comprises applying to mammalian skin an effective amount of a composition according to Formula I.
Examples of suitable straight-chain alkyl groups in Formula I include methyl, ethyl, propyl, butyl, hexyl, heptyl, octyl, dodecyl, palmityl and the like groups.

Examples of suitable branched-chain alkyl groups include isopropyl, sec-butyl, t-butyl, 2- methylbutyl, 2-pentyl, 3-pentyl and the like groups.

Examples of suitable cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups.

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