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(54) ALKALOID FORMULATIONS

ALKALOID-FORMULIERUNGEN

FORMULATIONS ALCALOIDES

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- **DATABASE WPI Week 199621 Derwent Publications Ltd., London, GB; AN 1996-205427 XP002421394 & JP 08 073338 A (NOEVIR KK) 19 March 1996 (1996-03-19)**
- **PATENT ABSTRACTS OF JAPAN vol. 017, no. 644 10 August 1993 & JP 05 201 858 A (SS PHARMACEUT CO LTD) 03 November 1993**

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Description

Field of the invention

[0001] The present invention is directed to specific topical alkaloid formulations comprising one or more alkaloids and one or more phosphate derivatives of electron transfer agents.

Background of the invention

[0002] In this specification, where a document, act or item of knowledge is referred to or discussed, this reference or discussion is not an admission that the document, act or item of knowledge or any combination thereof was at the priority date: part of common general knowledge, or known to be relevant to an attempt to solve any problem with which this specification is concerned.

Alkaloids

[0003] There is a long history of the use of alkaloids for medicine. These compounds were originally extracted from plants and include nitrogenous compounds having physiological actions on humans as drugs and poisons. The term "alkaloids" as used in this description and in the claims includes all natural and synthetic active compounds containing primary, secondary or tertiary amine substituents. The amine may be incorporated into one or two rings, but non-cyclic structures are also included. For example, this includes:

- tertiary amines which:-
    - are alicyclic with the nitrogen atom as a common member of three rings (eg.) morphine, atropine, quinine); or
    - are cyclic where the nitrogen is incorporated into a single ring and alkylated (eg. nicotine, fenspiride); or
    - have no cyclic structure incorporating the nitrogen (eg. flurazepam);
    - secondary amines where the nitrogen is incorporated into an alicyclic structure (eg conline, fendiline) or a linear structure (eg. epinephrine);
    - primary amines (eg. ephidrine);
    - pyridines (eg nicotine);
    - methamidine derivatives;
    - quinolines (eg. cinchonine); and
    - guanidines (eg. arginine).

[0004] Most alkaloids are not water soluble but are soluble in organic solvents. However, all alkaloids are basic and will combine with acids to form crystalline salts which are usually at least partially water soluble. Typically, alkaloids are administered as salts either orally or by intravenous injection. The alkaloids are a class of drugs that are not commonly administered transdermally because the hydrophilic nature of the salts usually limits transdermal transport. Morphine and atropine are examples of clinically useful alkaloids that are not administered transdermally. Further, it is desirable to improve oral delivery of alkaloids since some of them are thought to act through the lymphatic system.

Topical administration

[0005] Topical administration refers to the application of a drug directly to a part of the body and includes transdermal administration (application to the skin) and buccal administration (application to the inside of the mouth).

[0006] The skin is the largest organ of the body and functions to protect the internal organs from external chemical, physical and pathological hazards. Normal skin is divided into three layers: the epidermis, the dermis, and subcutaneous tissue. The outer cornified layer of the epidermis, the stratum corneum, possesses properties of strength, flexibility, high electrical impedance and dryness that retards penetration and proliferation of micro-organisms. The stratum corneum is also the principle barrier to transdermal drug absorption.

[0007] The art of transdermal delivery includes the application of drugs in the pure state or as formulations which typically include substances that enhance the rate of transport through the skin. Historically transdermal delivery was as ointments, creams, poultices and plasters to give effective contact with the skin. More recently, the technology has been improved by making the plaster into a "patch" which has better adhesion to the skin and improved control over the rate of transport.

[0008] Transdermal delivery has been recognized to offer several potential benefits including achieving blood levels similar to those achieved by slow intravenous infusion but without the inconvenience; better control of absorption and

metabolism compared to oral administration; continuity of drug effect especially of drugs with short half lives; equivalent efficacy with reduced drug dosage due to by-pass of hepatic first pass elimination; lower risk of under/or overdosing; and better patient compliance through simplification of a dosage regime.

[0009] Not every drug can be administered transdermally at a rate sufficiently high enough to achieve blood levels that are therapeutically beneficial for systemic medication. Drugs with similar molecular weights and sizes for example may absorb across the skin at different rates. Skin enhancers and various formulation techniques have been developed to improve drug absorption through the skin. But concern has been raised with respect to long term risk because increased drug permeability is achieved at the cost of damaging a fundamentally important protective layer of the skin.

[0010] Current strategies to improve transdermal therapy have not been universally successful and there is scope for further improvement. In particular, there is a need for use of transdermal delivery systems capable of delivering alkaloids.

[0011] There has also been increased interest in buccal delivery since this method of delivery avoids metabolism by the liver which can be a problem when drugs are administered orally. Typically, the drug is formulated in a lozenge which is placed under the tongue. The lining of the mouth does not have an equivalent of the stratum corneum on the skin so it is not as difficult to administer drugs by buccal delivery, but this method of administration is not commonly used because the rate of transport may be low, achieving an ineffective result if the buccal membranes do not allow permeation or active transport. Efforts have been made in the past to improve the topical administration of drugs. For example, international patent application no. PCT/AU03/00998 discloses a carrier for pharmaceuticals wherein the carrier comprises a complex of a phosphate derivative of a pharmaceutically acceptable compound, for example, laurylaminodipropionic acid tocopheryl phosphates. PCT/AU03/00998 discloses that the tocopheryl phosphate is complexed to a complexing agent selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids. This carrier has been shown to improve the topical administration of testosterone, estrogen, atropine and morphine. However, in relation to morphine and atropine, further improvement in skin penetration was desired.

Oral administration

[0012] Many drugs are administered orally, but a large number of potentially useful drugs are rejected because they are unable to pass through the intestinal walls. It is understood that substances such as fats are efficiently transported through the intestines, but many others such as tocopherol are poorly transported. There is thus a need for systems which enable improved oral administration of alkaloids.

Prior art

[0013] WO 2004/091636 refers to a complex of a pharmaceutical compound selected from the group consisting of opioids, hormones, anaethetics and chemotherapeutic agents comprising the reaction product of: (a) one or more phosphate derivatives of one or more opioids, steroid hormones, thyroid hormones, anaesthetics or chemotherapeutic agents having a phenolic, primary alcohol, secondary alcohol or tertiary hydroxyl group; and (b) a complexing agent selected from the group comprising amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

[0014] WO 02/40034 discloses a composition comprising the reaction product of: (a) one or more phosphate derivatives of one or more hydroxylated actives; and (b) one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

[0015] A dietary or health supplement comprising an effective amount of a micronutrient selected from the group consisting of phosphate derivatives of ubiquinol, ascorbic acid, tocotrienol, retinol and mixtures thereof delivered with an acceptable carrier is discussed in WO 03/013550.

[0016] WO 03/026673 relates to a method for increasing levels of a storage form of a vitamin selected from the group consisting of tocopherol, retinol, vitamin K1 and mixtures thereof in a target tissue of a subject, the method comprising administering to the subject an effective amount of a phosphate derivative of the vitamin so as to cause an accumulation of stored vitamin in the target tissue.

Summary of the invention

[0017] It has been found that there is a significant improvement in administration when an alkaloid compound is complexed directly to a phosphate derivative of an electron transfer agent. For example, the administration of morphine was improved when it was complexed directly to tocopheryl phosphate.

[0018] According to the present invention, there is provided a topical alkaloid formulation comprising the reaction product of :

(i) an alkaloid having a tertiary amine group; with
(ii) one or more phosphate derivatives of one or more electron transfer agents which is a mixture of mono-tocopheryl phosphate and di-tocopheryl phosphate, wherein the term "phosphate derivatives" does not include complexes of the phosphate derivatives with a complexing agent selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

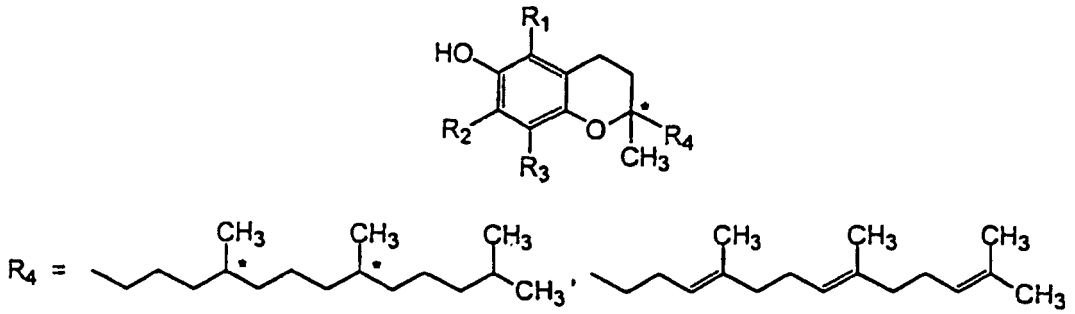
[0019] The present invention further relates to a method for the preparation of the topical alkaloid formulation according to the invention, said method comprising the step of reacting the alkaloid with one or more phosphate derivatives of one or more electron transfer agents which is a mixture of mono-tocopheryl phosphate and di-tocopheryl phosphate, wherein the term "phosphate derivatives" does not include complexes of the phosphate derivatives with a complexing agent selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

[0020] In another embodiment the present invention refers to a pharmaceutical composition comprising the alkaloid formulation according to the invention.

[0021] Preferably, the alkaloid is selected from the group consisting of tertiary amines which are (1) alicyclic with the nitrogen atom as a common member of three rings (eg. morphine, atropine, quinine); (2) are cyclic where the nitrogen is incorporated into a single ring and alkylated (eg. nicotine, fenspifide); or (3) have no cyclic structure incorporating the nitrogen (eg. flurazem). More preferably, the alkaloid is selected from the group consisting of atropine, quinine, opioids such as morphine, fentanyl, nicotine, fenspiride, flurazepam and codeine.

[0022] The term "electron transfer agents" is used herein to refer to the class of chemicals which may be phosphorylated and which (in the non-phosphorylated form) can accept an electron to generate a relatively stable molecular radical or accept two electrons to allow the compound to participate in a reversible redox system.

[0023] General types of electron transfer agents are tocols and mixtures thereof. The tocols include all isomers of derivatives of 6:hydoxy 2:methyl chroman (see structure below) where R_1, R_2 and R_3 may be hydrogen or methyl groups, that is, the α-5:7:8 tri-methyl; β-5:8 di-methyl; γ-7:8 di-methyl; and δ-8 methyl derivatives. In the tocopherols, R_4 is substituted by 4:8:12 tri-methyl tridecyl group and includes various stereoisomers and optical isomers (chiral centres are indicted by the *). In the tocotrienols, R_4 is substituted by 4:8:12 tri-methyl trideca-3:7:11 triene group and the 2-position may be stereoactive as R or S stereoisomers.



[0024] The term "phosphate derivatives" is generally used herein to refer to compounds covalently bound by means of an oxygen to the phosphorus atom of a phosphate group thus forming a carbon - oxygen-phosphorous bond. The oxygen atom is typically derived from a hydroxyl group on the electron transfer agent. The term includes the acid forms of phosphorylated electron transfer agents, salts of the phosphates including metal salts such as sodium, magnesium, potassium and calcium and any other derivative where the phosphate proton is replaced by other substituents such as ethyl or methyl groups or phosphatidyl groups. The term includes mixtures of phosphate derivatives, especially those which result from phosphorylation reactions, as well as each of the phosphate derivatives alone. In the present invention the one or more phosphate derivatives of one or more electron transfer agents is a mixture of mono-tocopheryl phosphate (TP) and di-tocopheryl phosphate (T2P). Most preferably, the electron transfer agent is α-tocopherol. Suitable mixtures are described in international patent application no. PCT/AU01/01475.

[0025] The term "phosphate derivatives" does not include complexes of the phosphate derivatives with a complexing agent selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

[0026] The alkaloid formulation is administered to humans or animals topically. Possible dose forms include dermal delivery including patches and creams as well as buccal delivery forms. Buccal delivery may specifically suit alkaloids

which have low water solubility.

[0027] The dose form may further include any additives routinely used in preparation of that dose form such as starch or polymeric binders, sweeteners, coloring agents, emulsifiers, coatings and the like. Another suitable additive is a complex of a phosphate derivative of an electron transfer agent. It may also be utilized where additional properties such as improved stability or deliverability may be useful. The term "complexes of phosphate derivatives" refers to the reaction product of one or more phosphate derivatives of electron transfer agents with one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids as disclosed in international patent application no. PCT/AU01/0 1476. If such an additive was used, it would be important to ensure that there was excess electron transfer agent present in the formulation. Other suitable additives will be readily apparent to those skilled in the art.

Brief Description of the Drawings

[0028]

Figure 1: Effect of various atropine formulations on heart rate in pigs. Data are cumulative averages over 10 minute periods and have been corrected for basal (average of 1 h before application) using covariate analyses.
Figure 2: Typical differential of heart rate versus time curve. Data are from pig 1 during replicate 1 who was treated with preparation C (i.e, the very first pig used). The treatment application commenced at 0 minutes and continued for 6 minutes. The period over which differentials were averaged is indicated by the straight lines.
Figure 3: Effect of various base creams on heart rate in pigs. Data are cumulative averages over 10 minutes periods and have been corrected for basal (average of 1 h before application) using covariate analyses.
Figure 4: Typical heart rate versus time curve. Data are from pig 1 during replicate 1 who was treated with preparation C (i.e, the very first pig used). The treatment application commenced at 0 minutes and continued for 6 minutes. The period over which differentials were averaged is indicated by the straight lines.
Figure 5: Effect of treatment and time flinch response after heat probe application.
Figure 6: Effect of morphine 1.35, 2.7 and 5.4 mg/kg in TPM-01/M formulation on paw withdrawal latency, tested up to 8 hours.

Examples

[0029] Various embodiments/aspects of the invention will now be described with reference to the following non-limiting examples.

Example 1

[0030] This example investigates the transdermal delivery to pigs of atropine in various formulations.

[0031] This experiment investigated the effects of dermal penetration of atropine when applied in gel form on heart rate of pigs.

Methods and materials

[0032] Atropine (20 mg/kg) was formulated in the following base creams for testing. In addition to the components specified below, all of the creams contained the following: 12% Ultrez-10 Carbomer-3% solution, 0.25% triethanolamine, 0.1% Surcide DMDMH and Deionized Water up to 100%.

[0033] Compositions G and J when combined with atropine produce a formulation according to the invention. Compositions B, D and E produce formulations according to the prior art and compositions A, C and I illustrate the effect of the excipients. Compositions F and H are reference compositions.

Code	Composition
A	1.27% Deriphat 160
B	7.5% of 40% disodium lauryliminodipropionate monotocopheryl phosphate and lauryliminodipropionate ditocopheryl phosphate
C	0.77% arginine
D	7.5% of 40% arginine monotocopheryl phosphate and arginine ditocopheryl phosphate

(continued)

Code	Composition
E	7.5% of 40% arginine monotocopheryl phosphate
F	3% monotocopheryl phosphate
G	3% monotocopheryl phosphate and ditocopheryl phosphate
H	7.5% disodium lauryliminodipropionate monotocopheryl phosphate
I	1.5% triethanolamine
J	tocopheryl phosphate and ditocopheryl phosphate

[0034] Ten male crossbred (Large white x Landrace) pigs (initial average weight 51.5 kg and final average weight of 61.0 kg) were utilised in this experiment. Four days prior to the study fourteen pigs were weighed and randomly allocated to individual pens (1.75 m x 0.65 m) in the experimental facility for an acclimatisation period. During this period the hair on the back of the pigs was removed with animal clippers (Oster - U.S.A) followed by regular shaving with an electric human shaver (Philishave HQ5041 - Philips Aust Pty Ltd). Elastic belts were also placed around the chest of the pigs to accustom them to wearing the heart rate monitors. At the start of the experiment the ten pigs that adapted best to the environment and regular handling were selected and housed such that there were no pigs in adjacent pens. This physical separation of the pigs avoided any potential conflict between signals from the heart rate monitors which all operated at the same frequency. The ten pigs were divided into two groups of five (odd and even numbers) and utilised on alternate days in the experiment. An experimental replicate was therefore performed over two consecutive treatment days. Within each replicate the ten pigs were randomly assigned to one of the ten treatment groups, therefore each pig was used for data capture on five occasions, and each treatment was applied five times.

[0035] On each measurement day by about 08:00 the five pigs under experiment were weighed, fitted with heart rate monitors and recording of heart rate at 1-minute intervals commenced. Human heart rate monitors (Polar Sport Tester PE4000 - Polar Electro Finland) were used to capture heart rate data. Chest belts with in-built sensors and transmitters were fitted around the pig's chest just behind the front legs. These belts had a liberal coating of an ultra-sonic gel (Virbac Aust Pty Ltd) applied to the sensor contact areas to ensure a good heart rate signal was obtained. A second belt fabricated from 100 mm wide elastic and velcro was placed around the pigs over the transmitter belt. This belt protected the transmitter from physical damage and included a pocket for storage of the monitor recording unit (similar to a wristwatch) during the recording period. An area on the back of the pigs was then shaved with the electric human shaver. Within this shaved area a template and permanent marker was used to outline a rectangular treatment application area of 172.5 cm^2 (75 x 230 mm). Feed was then offered at 100 g/kg liveweight 0.75 (eg: 55 kg pig = 2020 g/d). Treatment application was begun at least 1 h after the commencement of heart rate recording. Three staff wearing protective rubber gloves applied each of the test formulations in 5 ml syringes. This involved rubbing the products into the skin of the pig while an assistant directed warm air from an electric hair dryer onto the treatment area. Rubbing was discontinued after approximately 8 to 10 minutes when the skin surface became tacky to touch. Three (10x12 cm) transparent dressings (Tegaderm - 3M Health Care U.S.A.) were then applied over the treatment area. Following treatment application the pigs were left undisturbed for the remaining 6 to 7 hours of the recording period. Syringes and gloves used in treatment applications were weighed before and after application to enable accurate calculation of the actual doses applied to the pigs. At the conclusion of the recording period, the heart rate monitors and the transparent dressings were removed and the treatment application area was washed down with warm water containing a small quantity of a liquid handwash.

Results

[0036]

Table 1. Effect of various atropine preparations on average heart rate over 60 minute intervals.

	A	B	C	D	E	F	G	H	I	J	sed	χ^2
Heart rate (bpm)												
-60-0min	148	147	148	154	148	152	151	149	150	146	5.52	0.916
0-60min	173	155	176	155	165	162	180	170	155	154	9.33	0.007
60-120mm	186	170	184	169	170	175	196	190	164	165	10.91	0.011

(continued)

	A	B	C	D	E	F	G	H	I	J	sed	χ^2
Heart rate (bpm)												
120-180min	161	156	162	154	148	165	168	171	144	153	10.46	0.124
180 - 240 min	145	148	146	149	139	156	152	164	144	149	9.87	0.353
240-300min	144	146	150	142	147	147	146	155	139	136	7.93	0.471
300-360min	143	142	144	131	137	142	147	150	135	136	7.60	0.271
Difference from baseline (bpm)												
0-60min	24.2	8.7	28.5	1.1	16.1	10.3	30.7	20.0	4.9	7.1	10.41	0.021
60-120min	37.8	22.8	35.6	14.1	21.7	22.6	46.8	40.9	13.2	19.0	12.58	0.045
120-180min	13.0	8.9	13.2	-1.4	-0.8	12.8	20.1	21.2	-6.8	8.0	11.71	0.196

Table 2. Effect of various atropine preparations on average heart rate over 60 minute intervals.

	A	B	C	D	E	F	G	H	I	J	sed	χ^2
Log peak rate (bpm)	2.341	2.307	2.33	2.29	2.313	2.326	2.351	2.321	2.301	2.288	0.0233	0.078
	(219)	(203)	(214)	(195)	(206)	(212)	(224)	(209)	(200)	(194)		
Log time to peak (min)	1.790	1.904	1.762	1.872	1.726	1.787	1.738	1.734	1.764	1.786	0.0953	0.452
	(61.7)	(80.2)	(57.8)	(74.5)	(53.2)	(61.2)	(54.7)	(54.2)	(58.1)	(61.1)		
Log ascending slope[I]	0.125	0.003	0.171	-0.060	0.061	0.229	0.434	0.250	0.211	0.117	0.1568	<0.001
	(1.33)	(1.01)	(1.48)	(0.87)	(1.15)	(1.69)	(2.72)	(1.78)	(1.62)	(1.31)		
Log descending slope[1,2]	-0.244	-0.312	-0.206	-0.124	-0.186	-0.393	-0.375	-0.427	-0.299	-0.049	0.1095	<0.001
	(0.57)	(0.49)	(0.62)	(0.75)	(0.65)	(0.40)	(0.42)	(0.37)	(0.50)	(0.89)		
Log ratio of slopes[2]	0.354	0.292	0.393	0.072	0.264	0.624	0.808	0.680	0.495	0.196	0.2052	<0.001
	(2.26)	(1.96)	(2.47)	(1.18)	(1.84)	(4.21)	(6.43)	(4.79)	(3.13)	(1.57)		
units are bpm per min^2 units should be negative but were multiplied by -1 so that a log transformation could be performed.												

Table 3. Effect of various base cream preparations on average heart rate over 60 minute intervals.

	A	B	C	D	E	F	G	H	I	J	sed	χ^2
Heart rate (bpm)												
-60-0 min	146	147	147	143	145	127	145	135	124	132	11.1	0.283
0-60min	139	140	129	144	138	123	142	120	123	128	10.7	0.141
60-120 min	125	132	124	137	134	122	139	120	120	132	10.9	0.587
120-180min	128	126	126	131	135	119	130	125	119	124	6.7	<0.001
180-240min	125	121	132	134	129	121	132	122	114	122	8.7	0.358
240-300 min	137	122	130	132	120	112	139	130	121	122	9.0	0.040
300-360min	131	120	132	127	116	110	134	126	110	125	6.0	<0.001
Difference from baseline (bpm)												
0-60min	-4.4	-5.1	-16.5	1.4	-6.6	-6.3	-2.7	-12.5	-0.9	-5.8	6.16	0.162
60 - 120 min	-16.7	-15.3	-20.1	-3.8	-10.3	-7.0	-6.5	-13.7	-5.5	-4.4	11.44	0.708
120 - 180 min	-15.0	-16.0	-21.1	-9.9	-9.8	-9.8	-15.8	-8.3	-4.1	-8.6	12.62	0.971

Discussion and conclusion

[0037] The data suggests that transdermal application of atropine will increase heart rate in the pig with the peak occurring approximately 60 minutes after application. The data also suggests that the base creams alone do not increase heart rate and that the affects of the preparations are due to the atropine itself.

[0038] Formulation G which contains the tocopheryl phosphate/ditocopheryl phosphate mixture provided the best delivery system for atropine. The heart rate increased and remained sustained for longer periods compared to the other formulations. This is shown in table 1, where under the heading "Differences from baseline" the values at the 0-60 min and 60-120 min are greatest with formulation G. Table 1 demonstrates that formulation G is consistently more effective than a similar concentration of atropine in compositions containing the lauryliminodipropionate tocopheryl phosphates.

[0039] The evaluation of the data in Table 2 shows that there is a consistent increased efficacy of formulation G versus formulation H for log peak rate, log time to peak and, importantly, log ascending slope and log descending slope.

[0040] Further, the formulation according to the invention caused no inflammation, thus it appears possible to allow prolonged dermal contact without causing irritation.

Example 2

[0041] This example investigated the effect of transdermal delivery to pigs of morphine. The skin of pigs has similar properties to human skin and as such the pig is an excellent model for studying dermal delivery of drugs.

[0042] This study was designed to assess the level of analgesia as measured by a delay in the tail flinch response to a heat (62°C) placed on the rump following the transdermal delivery to pigs of morphine.

[0043] Flinch test data were analysed by REML (Residual maximum likelihood) with treatment and time as the fixed model and pig, replicate and flinch time at time zero as the random model. Data were initially analysed raw but because there were some skewed data at 6 h they were also log-transformed for analyses. Either analyses provided essentially the same interpretation.

[0044] The following formulations were tested:

Code	Composition
AGM	Morphine in formulation G as per Example 1.
AG	Formulation G with no morphine
AHM	Morphine in formulation H as per Example 1.

(continued)

Code	Composition
AH	Formulation H with no morphine.

[0045] Overall, the flinch time for pigs treated with preparation AGM had a greater flinch time than any of the other treatments (2.63, 2.88, 4.82 and 3.17 seconds for treatments AG, AH, AGM and AHM, Table 4). Interestingly, the response was greatest at 6 h after treatment (Figure 5) suggesting a sustained effect, particularly when compared to the control AG. In this context the flinch test was 133% greater at 6 h in pigs treated with AGM compared to AG. There was an indication that AHM had a greater flinch time at 2 h after treatment when compared to the control AH, but this was not sustained. AHM did not provide the sustained results which were obtained with AGM.

[0046] In conclusion, the data demonstrates that transdermal delivery of morphine in a formulation according to the invention (AGM) provides rapid and sustained analgesia as measured by a delay in the tail flinch response to a heat treatment at 1 to 6 h. Further, the formulation according to the invention caused no inflammation, thus it appears possible to allow prolonged dermal contact without causing irritation.

Table 4. Effect of treatment and time flinch response after heat probe application (seconds)[1]

Time after treatment (h)						Significance (χ^2)		
	1	2	4	6	sed[1]	Treat	Time	Tr x Ti
AG	1.83	2.69	3.26	2.75	1.087	<0.001	0.062	0.45
AH	2.10	2.34	3.60	3.50				
AGM	3.96	3.40	5.49	6.42				
AHM	2.85	3.87	2.97	3.00				
AG	(0.260)	(0.411)	(0.461)	(0.413)	0.0858	0.003	0.011	0.85
AH	(0.313)	(0.335)	(0.465)	(0.438)				
AGM	(0.460)	(0.470)	(0.570)	(0.622)				
AHM	(0.410)	(0.466)	(0.440)	(0.458)				
[1]Values in parentheses are log transformed. [2]standard error of the difference for time x treatment. For treatment and time effects multiply by 0.511 and 0.497, respectively.								

Example 3

[0047] This example investigates the effect of different formulations according to invention when compared to a control using complexed tocopheryl phosphate on transdermal delivery of morphine to rats.

Methods

[0048] Animals: Conscious Sprague Dawley Rats (~ 280 g) n=6 per group.

[0049] Transdermal Formulation Preparation: Morphine HCl, Glaxo Australia Pty Ltd (catalogue number 22284). Morphine free base was derived from HCl form in aqueous solution by the addition of potassium carbonate. This process was completed at Monash University. (Morphine HCl could not be used with creams, so free base was used).

[0050] Morphine (10 mg/kg) was applied in each of the formulations set out in Table 5. The effect was measured by the delayed response of the rat to heat with the delay in time taken to withdraw the paw taken as the action of morphine.

Table 5: Formulations of tocopheryl phosphates

Ingredient	Purpose	Vital ET™	TP/T_2P	TPM-01	TPM-01/M
Disodium tocopheryl phosphate	Transdermal agents	2.00 %	2.00 %	2.00 %	7.20 %
Ditocopheryl phosphate		1.00 %	1.00 %	1.00 %	3.60 %
Lauryldiaminopropionic acid	Complexing agent	3.00 %	-	-	-

(continued)

Ingredient	Purpose	Vital ET™	TP/T_2P	TPM-01	TPM-01/M
Morphine HCl USP-NF	Active Ingredient	-	-	-	5.4 %
Ultrez-10 carbomer- 3% solution	Excipient	0.36%	0.36 %	-	-
Carbomer 934 USP-NF	-	-	-	0.36%	0.36%
Triethanolamine (trolamine) USP	Excipient	0.25%	0.25 %	0.25%	0.25%
Surcide DMDMH	preservative	0.10%	0.10 %	-	-
Germall 115	preservative	-	-	-	-
Methylparaben USP-NF, BP	preservative	0.10 %	-	0.10%	0.10 %
Purified water USP-NF	Solvent	QS 100 %	QS 100 %	QS 100 %	QS 100 %

[0051] The base gels used as controls contained all of the ingredients except for the tocopheryl phosphate. Vital ET was not used in this experiment and is listed here as a comparison of the components between Vital ET and the formulation of the invention.

Test Method:

[0052] The plantar analgesiometer is designed for rapid and efficient screening of analgesia levels in small laboratory animals. The device is used to apply a heat source (~45°C from an infrared light) to the animal's hind paw and the time taken to withdraw the paw is measured (paw withdrawal latency). The hot plate provides a constant surface temperature, with a built-in digital thermometer with an accuracy of 0.1 °C and a timer with an accuracy of 0.1 second. The animal is placed on a hot plate, confined by a clear acrylic cage which surrounds the plate and paw-lick response is monitored. An increased time period before paw-lick response indicating analgesia.

[0053] Rats had a hair removal cream applied to a dorsal hindquarter area of skin (under anaesthesia) at least 24 hours prior to any transdermal patch application. Conscious Sprague Dawley rats (~400 grams) received morphine at a dose of 10 mg morphine HCl per kg body weight. The formulation contained 10% w/w morphine HCl, and for a 0.2 kg rat the amount applied was 20 mg of formulation that contained 2 mg morphine HCl. A single application was used in the morning, with measures of the analgesia made at various time-points. The skin area exposed to drug/vehicle was then covered with a Tegaderm patch. All animals underwent analgesic testing before and after morphine administration.

Results:

[0054] Figure 6 illustrates the results achieved with each of the formulations. The results show an increase in response time, indicating analgesia, in a dose-dependant manner. The control test of gel with morphine but no TPM show the essential requirement of TPM for the transdermal route to work. Results are expressed as change in withdrawal time compared to controls, where control values are from rats treated with incomplete formulations (i.e., no morphine or no TPM), as well as the zero-time values for rats treated with complete the formulation, TPM-01/M)

Conclusion:

[0055] The formulation used in this study contains TP/T2P mix (or TPM), morphine HCl and other excipients as listed in table 5. The formulation did not contain any lauryldiaminoproprionic acid.

[0056] Figure 6 shows a clear dose-response and a sustained affect. When compared to the 2 types of control (i.e., a control gel with base excipients only, and no morphine and no TP/T2P mix, and a control gel with base excipients and morphine but no TP/T2P) the results show that morphine is best delivered when formulated with the TP/T2P mix.

Claims

1. A topical alkaloid formulation comprising the reaction product of:

(i) an alkaloid having a tertiary amine group; with
(ii) one or more phosphate derivatives of one or more electron transfer agents which is a mixture of mono-

tocopheryl phosphate and di-tocopheryl phosphate, wherein the term "phosphate derivatives" does not include complexes of the phosphate derivatives with a complexing agent selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

2. The alkaloid formulation according to claim 1 wherein the alkaloid is selected from the group consisting of atropine, quinine, opioids having a tertiary amine group, fentanyl, nicotine, fenspiride, flurazepam and codeine.

3. The alkaloid formulation according to claim 1 or 2 wherein the alkaloid is atropine or morphine.

4. The alkaloid formulation according to any one of claims 1 to 3 which is in a form selected from the group consisting of a dermal delivery form or transdermal formulation.

5. A method for the preparation of a topical alkaloid formulation according to any of claims 1 to 4, said method comprising the step of reacting the alkaloid with one or more phosphate derivatives of one or more electron transfer agents which is a mixture of mono-tocopheryl phosphate and di-tocopheryl phosphate, wherein the term "phosphate derivatives" does not include complexes of the phosphate derivatives with a complexing agent selected from the group consisting of amphoteric surfactants, cationic surfactants, amino acids having nitrogen functional groups and proteins rich in these amino acids.

6. A pharmaceutical composition comprising the alkaloid formulation as defined in any of claims 1 to 4.

Patentansprüche

1. Eine topische Alkaloidformulierung, umfassend das Reaktionsprodukt von:

   (i) einem Alkaloid mit einer tertiären Amingruppe; mit
   (ii) einem oder mehreren Phosphatderivaten von einem oder mehreren Elektronenübertragungsmitteln, die ein Gemisch aus Monotocopherylphosphat und Ditocopherylphosphat, wobei der Begriff "Phosphatderivate" keine Komplexe der Phosphatderivate mit einem Komplexbildner, ausgewählt aus der Gruppe bestehend aus amphoteren grenzflächenaktiven Mitteln, kationischen grenzflächenaktiven Mitteln, Aminosäuren mit funktionellen Stickstoffgruppen und Proteinen, die reich an diesen Aminosäuren sind, einschließen.

2. Die Alkaloidformulierung gemäß Anspruch 1, wobei das Alkaloid aus der Gruppe bestehend aus Atropin, Chinin, Opioiden mit einer tertiären Amingruppe, Fentanyl, Nikotin, Fenspirid, Flurazepam und Kodein ausgewählt ist.

3. Die Alkaloidformulierung gemäß Anspruch 1 oder 2, wobei das Alkaloid Atropin oder Morphin ist.

4. Die Alkaloidformulierung gemäß einem der Ansprüche 1 bis 3, die in einer Form vorliegt, die aus der Gruppe bestehend aus einer dermalen Darreichungsform oder transdermalen Formulierung ausgewählt ist.

5. Ein Verfahren zur Herstellung einer topischen Alkaloidformulierung gemäß einem der Ansprüche 1 bis 4, wobei das Verfahren den Schritt umfasst, bei dem das Alkaloid mit einem oder mehreren Phosphatderivaten von einem oder mehreren Elektronenübertragungsmitteln, die ein Gemisch aus Monotocopherylphosphat und Ditocopherylphosphat, wobei der Begriff "Phosphatderivate" keine Komplexe der Phosphatderivate mit einem Komplexbildner, ausgewählt aus der Gruppe bestehend aus amphoteren grenzflächenaktiven Mitteln, kationischen grenzflächenaktiven Mitteln, Aminosäuren mit funktionellen Stickstoffgruppen und Proteinen, die reich an diesen Aminosäuren sind, einschließen, zur Reaktion gebracht wird.

6. Ein Arzneimittel, umfassend die Alkaloidformulierung, wie in einem der Ansprüche 1 bis 4 definiert.

Revendications

1. Formulation d'alcaloïde à usage topique comprenant le produit de la réaction:

   (i) d'un alcaloïde ayant un groupe amine tertiaire ; avec

(ii) un ou plusieurs dérivés phosphate d'un ou de plusieurs agents de transfert d'électrons qui est un mélange de phosphate de mono-tocophéryle et de phosphate de di-tocophéryle, dans laquelle le terme « dérivés phosphate » ne comprend pas les complexes des dérivés phosphate avec un agent complexant choisi dans le groupe constitué par les tensioactifs amphotères, les tensioactifs cationiques, les acides aminés à groupes fonctionnels azotés et les protéines riches en ces acides aminés.

2. Formulation d'alcaloïde selon la revendication 1 dans laquelle l'alcaloïde est choisi dans le groupe constitué par l'atropine, la quinine, les opioïdes ayant un groupe amine tertiaire, le fentanyle, la nicotine, le fenspiride, le flurazépam et la codéine.

3. Formulation d'alcaloïde selon la revendication 1 ou 2 dans laquelle l'alcaloïde est l'atropine ou la morphine.

4. Formulation d'alcaloïde selon l'une quelconque des revendications 1 à 3 qui est sous une forme choisie dans le groupe constitué par une forme pour la délivrance dermique ou une formulation transdermique.

5. Procédé de préparation d'une formulation d'alcaloïde à usage topique selon l'une quelconque des revendications 1 à 4, ledit procédé comprenant l'étape de réaction de l'alcaloïde avec un ou plusieurs dérivés phosphate d'un ou de plusieurs agents de transfert d'électrons qui est un mélange de phosphate de mono-tocophéryle et de phosphate de di-tocophéryle, dans lequel le terme « dérivés phosphate » ne comprend pas les complexes des dérivés phosphate avec un agent complexant choisi dans le groupe constitué par les tensioactifs amphotères, les tensioactifs cationiques, les acides aminés à groupes fonctionnels azotés et les protéines riches en ces acides aminés.

6. Composition pharmaceutique comprenant la formulation d'alcaloïde telle que définie dans l'une quelconque des revendications 1 à 4.

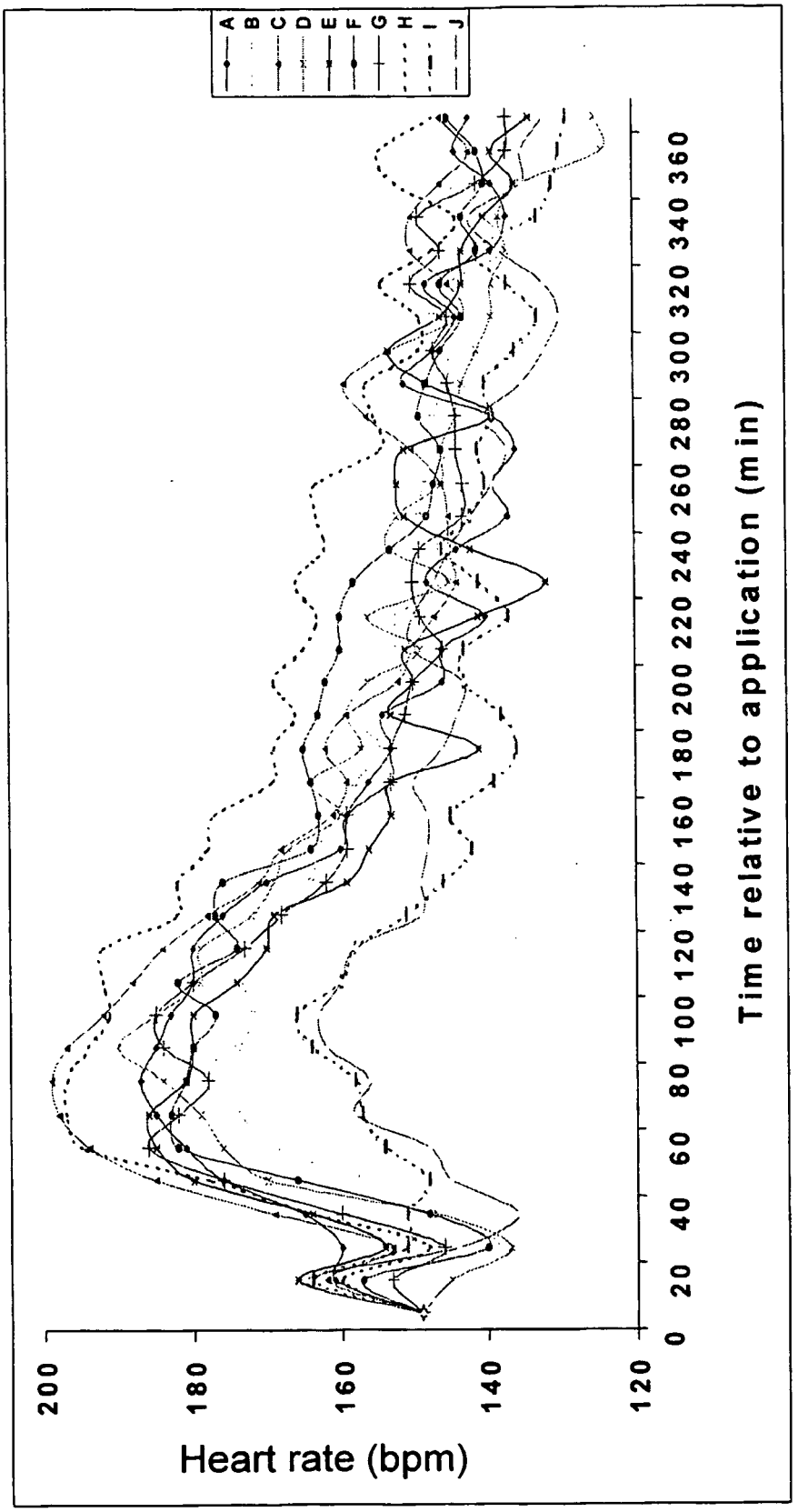

A
B
C
D
E
F
G
H
I
J
200
180
160
140
120
Heart rate (bpm)
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
Time relative to application (min)

Figure 1

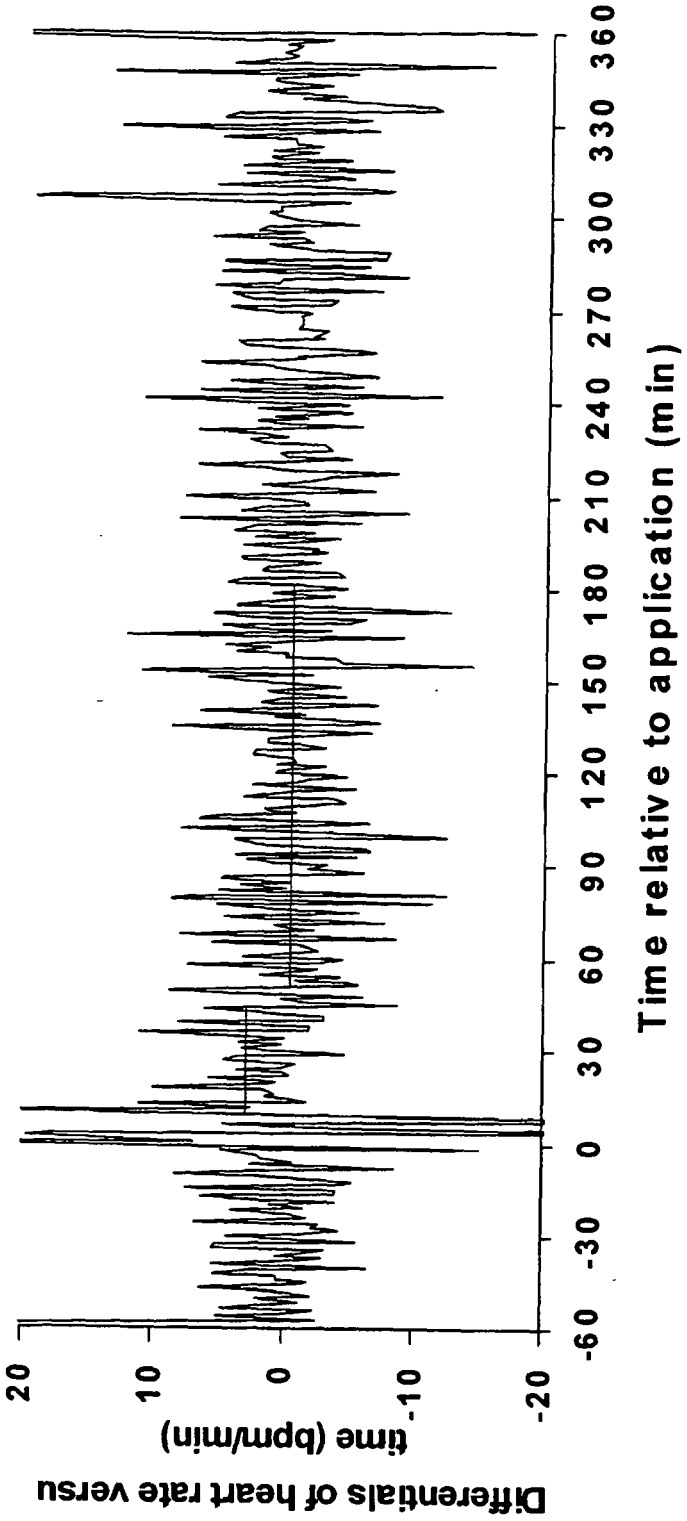

Differentials of heart rate versus time (bpm/min)
20
10
0
-10
-20
-60
-30
0
30
60
90
120
150
180
210
240
270
300
330
360
Time relative to application (min)

Figure 2

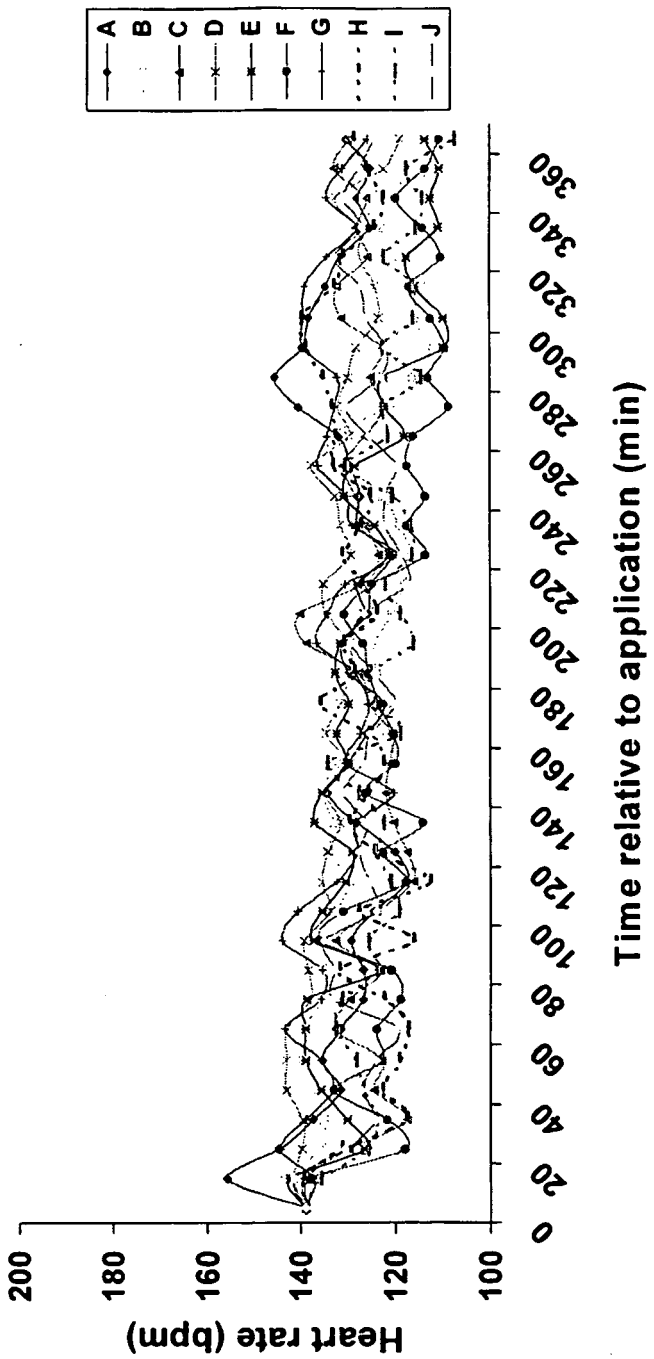

A
B
C
D
E
F
G
H
I
J
Heart rate (bpm)
200
180
160
140
120
100
Time relative to application (min)
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360

Figure 3

Figure 4

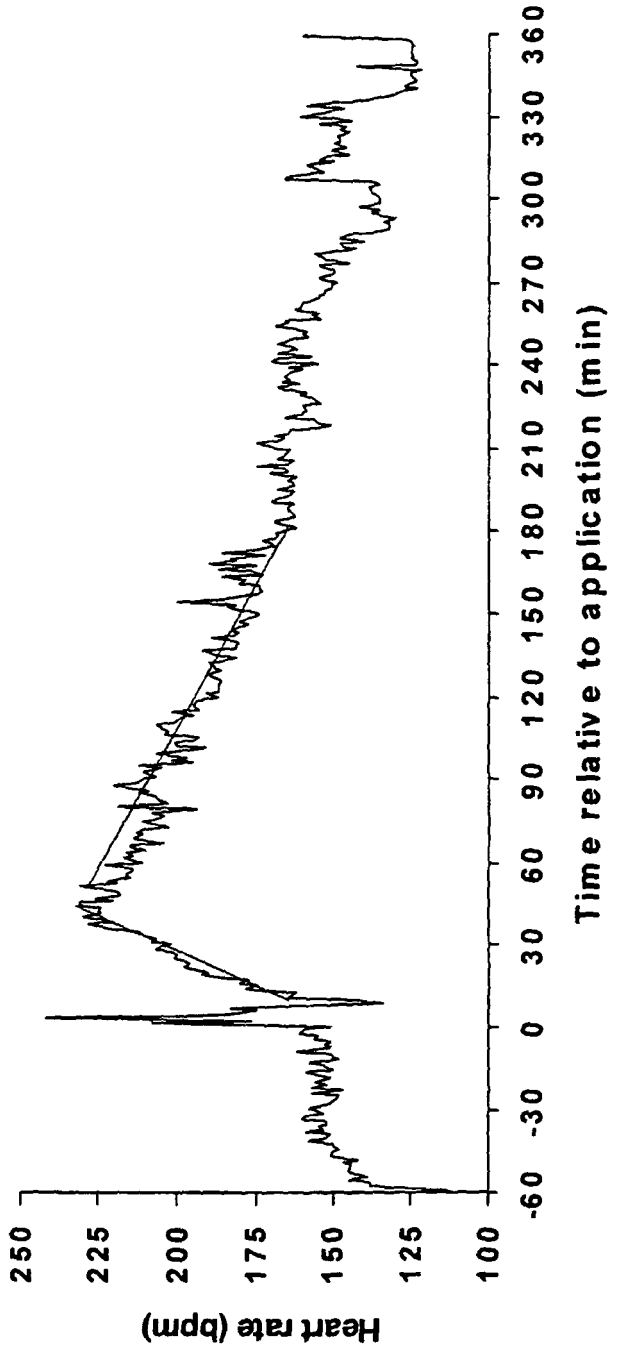

Heart rate (bpm)
250
225
200
175
150
125
100
-60
-30
0
30
60
90
120
150
180
210
240
270
300
330
360
Time relative to application (min)

Figure 5

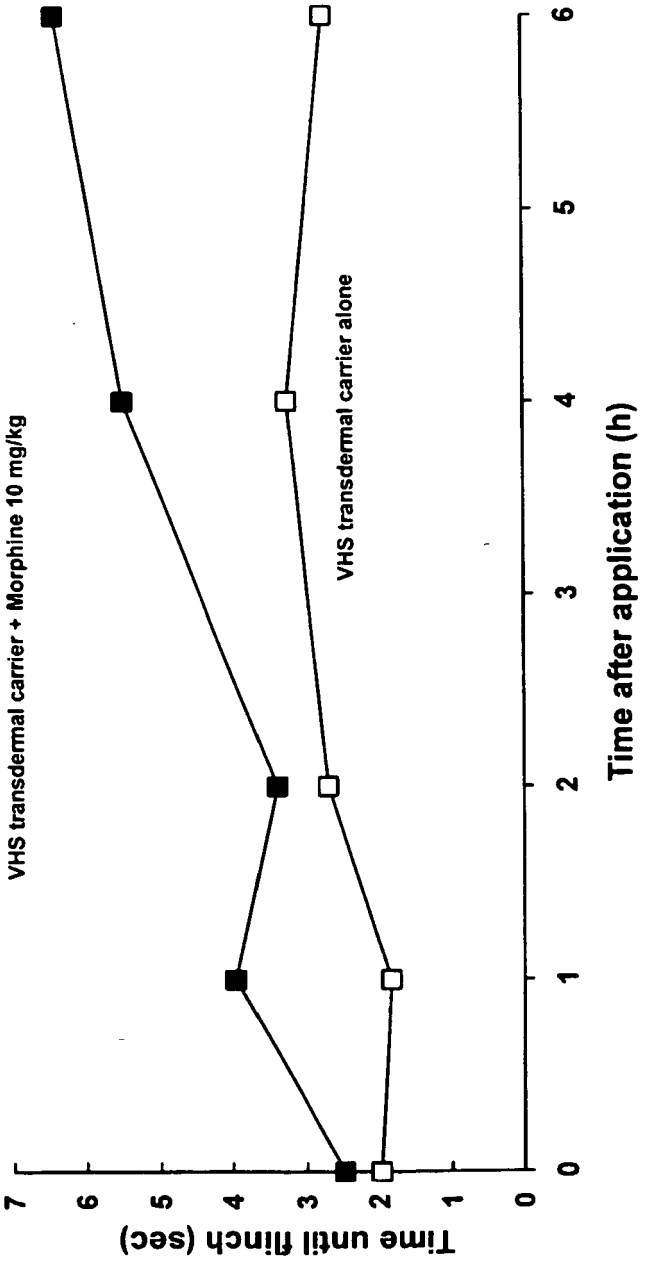
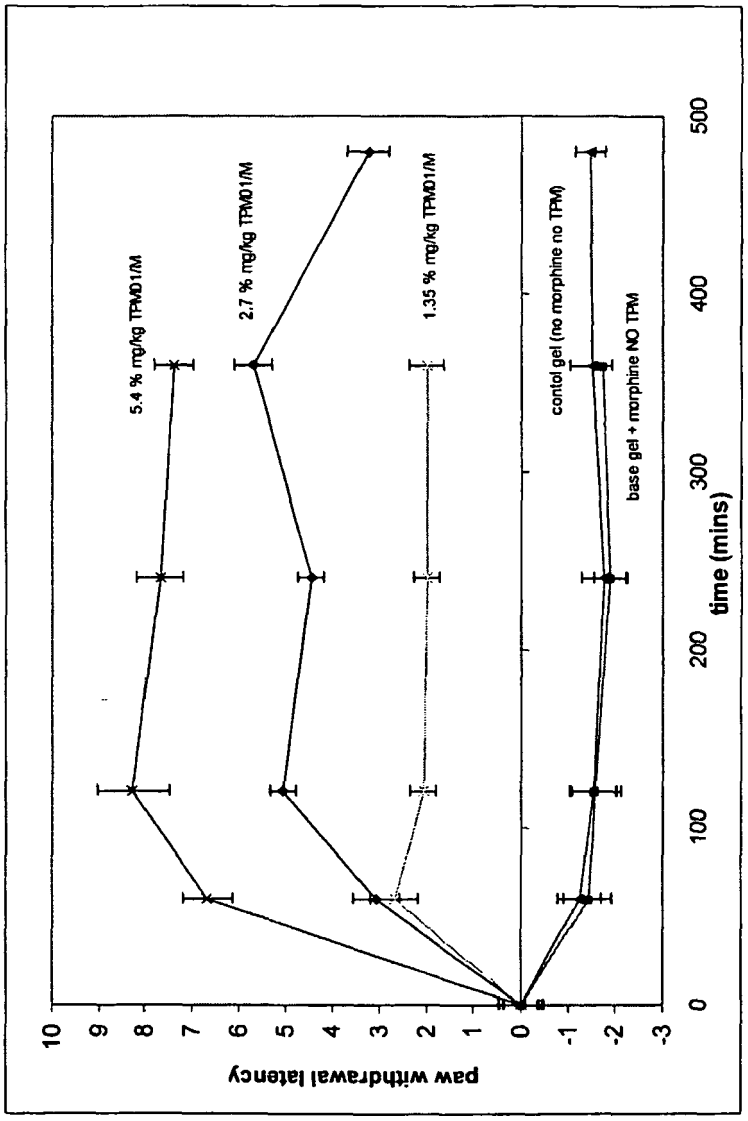

VHS transdermal carrier + Morphine 10 mg/kg
VHS transdermal carrier alone
Time until flinch (sec)
Time after application (h)
0
1
2
3
4
5
6
7

Figure 6


paw withdrawal latency
time (mins)
5.4 % mg/kg TPM01/M
2.7 % mg/kg TPM01/M
1.35 % mg/kg TPM01/M
contol gel (no morphine no TPM)
base gel + morphine NO TPM

REFERENCES CITED IN THE DESCRIPTION

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