Alkaloid Formulations

Field of the invention

The present invention is directed to formulations comprising one or more alkaloids. More specifically but not exclusively it relates to formulations comprising one or more alkaloids and one or more phosphate derivatives of electron transfer agents.

Background of the invention

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

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. Flurazepan);

- 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).

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

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).

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.

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.

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.

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.

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.

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

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.

Summary of the invention

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.

According to the present invention, there is provided an alkaloid formulation comprising the reaction product of one or more alkaloids with one or more phosphate derivatives of one or more electron transfer agents.

Preferably, the phosphate derivative of a electron transfer agent is selected from the group comprising one or more phosphate derivatives of tocopherol.

Preferably, the alkaloid formulation is administered topically or orally.

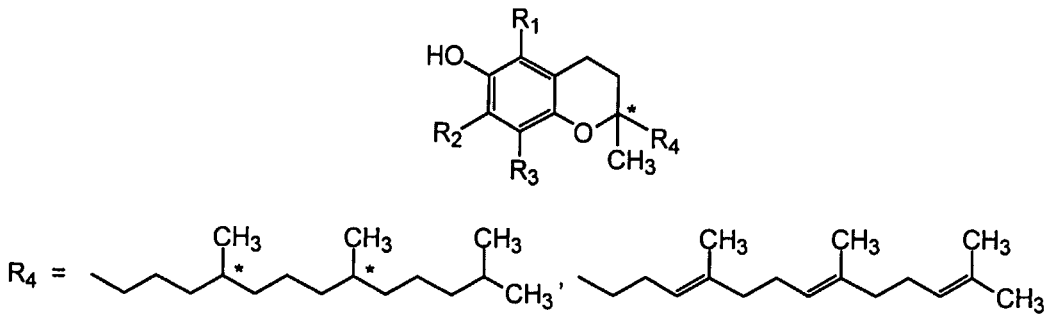
According to a second aspect of the invention, there is provided a method for improving the efficacy of an alkaloid, said method comprising the step of reacting the alkaloid with one or more phosphate derivative of one or more electron transfer agents.

The present invention also provides for the use of the reaction product of one or more alkaloids with one or more phosphate derivatives of one or more electron transfer agents, together with excipients in the manufacture of a formulation.

The present invention also provides a pharmaceutical composition comprising the reaction product of one or more alkaloids with one or more phosphate derivatives of one or more electron transfer agents, such as phosphate derivatives of tocopherol.

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, Fenspiride); or (3) have no cyclic structure incorporating the nitrogen (eg. Flurazepan). More preferably, , the alkaloid is selected from the group consisting of atropine, quinine, opioids such as morphine, fentanyl, nicotine, fenspiride, flurazepan and codeine.

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. Examples of classes of electron transfer agent compounds that may be phosphorylated include hydroxy chromans including alpha, beta, gamma and delta tocols in enantiomeric and racemic forms; quinols being the reduced forms of vitamin K1 and ubiquinone; hydroxy carotenoids including retinol; calciferol and ascorbic acid. Preferably, the electron transfer agent is selected from the group consisting of tocopherol and other tocols, retinol, vitamin K1 and mixtures thereof. More preferably, the electron transfer agent is selected from the group consisting of the 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. Most preferably, the electron transfer agent is α-tocopherol.



The term "phosphate derivatives" is 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. For example, the term includes a mixture of mono-tocopheryl phosphate (TP) and di-tocopheryl phosphate (T2P) as well as each of TP and T2P alone. Suitable mixtures are described in international patent application no PCT/AU01/01475.

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.

Preferably, the one or more phosphate derivatives of one or more electron transfer agents is selected from the group consisting of mono-tocopheryl phosphate, di-tocopheryl phosphate and mixtures thereof. Most preferably, the one or more phosphate derivatives of one or more electron transfer agents is a mixture of mono-tocopheryl phosphate and di-tocopheryl phosphate.

In some situations, it may be necessary to use a phosphate derivative such as a phosphatide where additional properties such as increased water solubility are preferred. Phosphatidyl derivatives are amino alkyl derivatives of organic phosphates. These derivatives may be prepared from amines having a structure of $R_1R_2N(CH_2)_nOH$ wherein n is an integer

between 1 and 6 and R_1 and R_2 may be either H or short alkyl chains with 3 or less carbons. R_1 and R_2 may be the same or different. The phosphatidyl derivatives are prepared by displacing the hydroxyl proton of the electron transfer agent with a phosphate entity that is then reacted with an amine, such as ethanolamine or N,N' dimethylethanolamine, to generate the phosphatidyl derivative of the electron transfer agent. One method of preparation of the phosphatidyl derivatives uses a basic solvent such as pyridine or triethylamine with phosphorous oxychloride to prepare the intermediate which is then reacted with the hydroxy group of the amine to produce the corresponding phosphatidyl derivative, such as P cholyl P tocopheryl dihydrogen phosphate.

The alkaloid formulation may be administered to humans or animals through a variety of dose forms such as supplements, enteral feeds, parenteral dose forms, suppositories, nasal delivery forms, dermal delivery including patches and creams, buccal delivery forms. Oral or buccal delivery may specifically suit alkaloids which have low water solubility. Preferably, oral alkaloid formulations according to the invention further comprise an enteric coating. The enteric coating protects the complexes from the acidic environment in the stomach. Oral formulations may take the form of tablets, powders, chewable tablets, capsules, oral suspensions, suspensions, emulsions or fluids, children's formulations, enteral feeds, nutraceuticals, and functional foods.

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 agents 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/AU01/01476, incorporated herein by reference. 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

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 (ie 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 (ie the very 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

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

Example 1

This example investigates the transdermal delivery to pigs of atropine in a formulation according to the invention. This experiment investigated the effects of dermal penetration of atropine when applied in gel form on heart rate of pigs.

Methods and materials

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%.

Compositions f, H 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.

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
E	7.5% of 40% arginine mono tocopheryl phosphate
F	3% mono tocopheryl phosphate
G	3% mono tocopheryl phosphate and ditocopheryl phosphate
H	7.5% disodium lauryliminodipropionate mono tocopheryl phosphate
I	1.5% Triethanolamine
J	Tocopheryl phosphate and di-tocopheryl phosphate

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.

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 (10 x 12 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

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 – 0 min	148	147	148	154	148	152	151	149	150	146	5.52	0.916
0 – 60 min	173	155	176	155	165	162	180	170	155	154	9.33	0.007
60 – 120 min	186	170	184	169	170	175	196	190	164	165	10.91	0.011
120 - 180 min	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 – 300 min	144	146	150	142	147	147	146	155	139	136	7.93	0.471
300 – 360 min	143	142	144	131	137	142	147	150	135	136	7.60	0.271
Difference from baseline (bpm)												
0 – 60 min	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 – 120 min	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 - 180 min	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[1]	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)		

[1] 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 – 60 min	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 - 180 min	128	126	126	131	135	119	130	125	119	124	6.7	<0.001
180 – 240 min	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 – 360 min	131	120	132	127	116	110	134	126	110	125	6.0	<0.001
Difference from baseline (bpm)												
0 – 60 min	-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

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.

Formulation G which contains the tocopheryl phosphate/di-tocopheryl 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 G. Table 1 demonstrates that Formulation G is consistently more effective than a similar concentration of atropine in compositions containing the lauryliminodipropionate-tocopheryl phosphates.

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.

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

Example 2

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.

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.

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.

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.
AH	Formulation H with no morphine.

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.

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

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

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

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).

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 pat taken as the action of morphine.

Table 5: Formulations of tocopheryl phosphates

Ingredient	Purpose	Vital-ET™	TP/T2P2	TPM-01	TPM-01/M
Disodium tocopheryl phosphate	Transdermal agents	2.00 %	2.00 %	2.00 %	7.20 %
Di-tocopheryl phosphate		1.00 %	1.00 %	1.00 %	3.60 %
Lauryldiaminoprop-ionic acid	Complexing agent	3.00 %	-	-	-
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 %

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:

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.

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:

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:

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.

Figure 6 shows a clear dose-response and a sustained affect. When compared to the 2 types of control (ie, 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.

The word 'comprising' and forms of the word 'comprising' as used in this description and in the claims does not limit the invention claimed to exclude any variants or additions.

Modifications and improvements to the invention will be readily apparent to those skilled in the art. Such modifications and improvements are intended to be within the scope of this invention.

The claims defining the invention are as follows:

1 An alkaloid formulation comprising the reaction product of one or more alkaloids with one or more phosphate derivatives of one or more electron transfer agents.

2 The alkaloid formulation according to claim 1 wherein the phosphate derivative of a electron transfer agent is selected from the group comprising one or more phosphate derivatives of tocopherol.

3 The alkaloid formulation according to claim 1 wherein the formulation is a topical formulation.

4 The alkaloid formulation according to claim 1 wherein the formulation is an oral formulation.

5 The alkaloid formulation according to claim 4 further comprising an enteric coating.

6 The alkaloid formulation according to claim 4 wherein the formulation is selected from the group consisting of tablets, powders, chewable tablets, capsules, oral suspensions, suspensions, emulsions or fluids, children's formulations, enteral feeds, nutraceuticals, and functional foods.

7 The alkaloid formulation according to claim 1 wherein the formulation is a buccal formulation.

8 The alkaloid formulation according to any one of the preceding claims wherein the electron transfer agent is selected from the group consisting of hydroxy chromans including alpha, beta, gamma and delta tocols in enantiomeric and racemic forms; quinols being the reduced forms of vitamin K1 and ubiquinone; hydroxy carotenoids including retinol; calciferol, ascorbic acid and mixtures thereof.

9 The alkaloid formulation according to claim 8 wherein the electron transfer agent is selected from the group consisting of tocopherol and other tocols, retinol, vitamin K1 and mixtures thereof.

10 The alkaloid formulation according to claim 9 wherein the electron transfer agent is selected from the group consisting of the tocols and mixtures thereof.

11 The alkaloid formulation according to claim 10 wherein the electron transfer agent is α-tocopherol.

12 The alkaloid formulation according to claim 11 wherein the one or more phosphate derivatives of one or more electron transfer agents is selected from the group consisting of mono-tocopheryl phosphate, di-tocopheryl phosphate and mixtures thereof.

13 The alkaloid formulation according to claim 12 wherein the one or more phosphate derivatives of one or more electron transfer agents is a mixture of mono-tocopheryl phosphate and di-tocopheryl phosphate.

14 The alkaloid formulation according to any one of claims 1 to 11 wherein the one or more phosphate derivatives of one or more electron transfer agents is a phosphatide.

15 The alkaloid formulation according to any one of the preceding claims wherein the alkaloid is selected from the group consisting of tertiary amines which are alicyclic with the nitrogen atom as a common member of three rings; are cyclic where the nitrogen is incorporated into a single ring and alkylated; or have no cyclic structure incorporating the nitrogen; and mixtures thereof.

16 The alkaloid formulation according to claim 15 wherein the alkaloid is selected from the group consisting of atropine, quinine, opioids, fentanyl, nicotine, fenspiride, flurazepan and codeine.

17 The alkaloid formulation according to any one of the preceding claims wherein the alkaloid is atropine.

18 The alkaloid formulation according to any one of the preceding claims wherein the alkaloid is morphine.

19 A method for improving the efficacy of an alkaloid, said method comprising the step of reacting the alkaloid with one or more phosphate derivative of one or more electron transfer agents.

20 Use of the reaction product of one or more alkaloids with one or more phosphate derivatives of one or more electron transfer agents, together with excipients in the manufacture of a formulation.

21 A pharmaceutical composition comprising the reaction product of one or more alkaloids with one or more phosphate derivatives of one or more electron transfer agents.

22 A pharmaceutical composition according to claim 21 wherein the electron transfer agent is tocopherol.