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(54) **PARASITICIDAL FORMULATION**

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(57) **ABSTRACT**

The present invention provides a parasiticidal formulation comprising: Fipronil, or a veterinarily acceptable derivative thereof; at least one C_1-C_6 alcohol co-solvent, wherein the total amount of C_1-C_6 alcohol is up to 8% by weight of the formulation; at least one organic solvent which is not the C_1-C_6 alcohol co-solvent; and at least one crystallisation inhibitor, wherein the total amount of crystallisation inhibitor is from 2 to 20% by weight of the formulation. The formulations of the invention have higher flash points than known parasiticidal formulations comprising Fipronil and therefore provide safer formulations for use in the home, storage, manufacture and distribution.

PARASITICIDAL FORMULATION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 61/161,361, filed Mar. 18, 2009, the disclosure of which is herein incorporated by reference for all purposes.

TECHNICAL FIELD

[0002] This invention relates to a parasiticidal formulation comprising Fipronil, or a veterinarily acceptable derivative thereof. In particular, it relates to parasiticidal formulations comprising Fipronil having improved safety characteristics compared with known Fipronil formulations.

BACKGROUND ART

[0003] EP 295 217 A and EP 352 944 A describe a class of 1-N-arylpyrazole-based insecticides. A particular compound of this class is 5-amino-1-(2,6-dichloro-4-(trifluoromethyl) phenyl)-4-((trifluoromethyl)sulfinyl)-1H-pyrazole-3-carbonitrile, also known as Fipronil. Fipronil has proven to be particularly effective as a parasiticide against crop parasites and against mammal ectoparasites, in particular fleas, ticks, flies and myiases.

[0004] Fipronil formulations are disclosed in GB 2 331 242 A, which also discloses the combination of Fipronil with other parasiticides. Furthermore, GB 2 317 264 A discloses Fipronil formulations additionally comprising an IGR (insect growth regulator) compound, e.g. Methoprene.

[0005] Parasiticidal formulations comprising Fipronil are marketed for use in the home treatment of domestic 20 pets, e.g. cats and dogs. One such formulation is FRONTLINE® PLUS FOR DOGS.

[0006] However, a problem with these known formulations is their relatively low flashpoints, i.e. the lowest temperatures at which they can form an ignitable mixture in air. The Material Safety Data Sheet for the FRONTLINE® PLUS FOR DOGS formulation indicates the flashpoint for this formulation to be 36° C. (97° F.).

[0007] A liquid which forms an ignitable mixture at 36° C. presents a safety risk during use in the home, and during manufacture, distribution and storage, because temperatures in many countries exceed this level during summer. There is therefore a need for effective parasiticidal formulations comprising Fipronil which have higher flashpoints, and therefore improved safety profiles, but which still retain parasiticidal efficacy. Accordingly, the object of the present invention is to provide a parasiticidal formulation comprising Fipronil having improved safety while maintaining parasiticidal efficacy.

DISCLOSURE OF THE INVENTION

[0008] The present invention provides a parasiticidal formulation comprising:

[0009] Fipronil, or a veterinarily acceptable derivative thereof;

[0010] at least one C_1-C_6 alcohol co-solvent, wherein the total amount of C_1-C_6 alcohol is up to 8% by weight of the formulation;

[0011] at least one organic solvent which is not the C1-C6 alcohol co-solvent; and

[0012] at least one crystallisation inhibitor, wherein the total amount of crystallisation inhibitor is from 2 10 to 20% by weight of the formulation.

[0013] The parasiticidal formulations of the present invention surprisingly have a flashpoint of greater than 36° C. (97° F.). In particular, formulations of the present invention have been shown to have flashpoints between 47° C. and 52° C. and are therefore safer than the known formulations of the prior art. The formulations of the present invention also retain parasiticidal efficacy.

[0014] The present invention further provides the use of a formulation according the present invention as a parasiticide, particularly for controlling parasites on a mammal (e.g a cat or a dog) in need thereof:

[0015] The present invention further provides a process for controlling parasites on mammals in need thereof, in particular cats and dogs, said process comprising treating the mammal by application to the skin of a parasiticidally effective dose of a formulation according to the present invention.

EMBODIMENTS OF THE INVENTION

[0016] In one embodiment, the amount of Fipronil, or a veterinarily acceptable derivative thereof, in the formulation is from 5% to 20%, alternatively from 5% to 15%, alternatively from 8% to 12%, alternatively about 10% by weight of the formulation.

[0017] The term "veterinarily acceptable derivative" of Fipronil includes any veterinarily acceptable salt, solvate or hydrate of Fipronil. The term "veterinarily acceptable salt" includes a salt prepared from veterinarily acceptable non-toxic acids or bases including inorganic or organic acids and bases.

[0018] In one embodiment, the formulation of the present invention comprises an IGR (insect growth regulator) compound, e.g. S-Methoprene. In one embodiment, the amount of S-Methoprene in the formulation is from 5% to 25%, alternatively from 5% to 20%, alternatively from 5% to 15%, alternatively from 8% to 12% by weight of the formulation.

[0019] The amount of the at least one C_1-C_6 alcohol co-solvent in the formulation is up to **8**% by weight of the formulation. In one embodiment, the amount of at least one C_1-C_6 alcohol co-solvent in the formulation is from 2% to 8%, alternatively about 5% by weight of the formulation.

[0020] Examples of the C_1 to C_6 alcohol co-solvent are methanol, ethanol, propanol, isopropanol or butanol, and combinations thereof. In one embodiment, the C_1 to C_6 alcohol is ethanol.

[0021] In one embodiment, the formulation comprises at least one antioxidant. In one embodiment, the amount of antioxidant in the formulation is from 0.005 to 1%, alternatively from 0.01 to 0.05%, alternatively from 0.02 to 0.03%, alternatively about 0.03% by weight of the formulation.

[0022] Examples of the antioxidant are butylated hydroxylanisole, butylated hydroxyltoluene, alpha tocopheral, ascorbic acid, ascobyl palmitate, fumeric acid., malic acid, citric acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, monothioglycerol and combinations thereof. In one embodiment, the antioxidant is butylated hydroxylanisole, butylated hydroxyltoluene or combinations thereof. In one embodiment, the at least one antioxidant consists of butylated hydroxylanisole (e.g. in amount of about 0.02% by weight) and butylated hydroxyltoluene (e.g. in amount of 0.01% by weight).

[0023] The amount of the at least one crystallisation inhibitor in the formulation is from 2 to 20% by weight of the formulation. In one embodiment, the amount of crystallisation inhibitor in the formulation is from 4% to 15%, alternatively 6% to 12%, alternatively about 10% by weight of the formulation.

[0024] The at least one crystallization inhibitor satisfies the following test having steps (i)-(iii): (i) 0.5 ml of a formulation of the invention comprising the at least one crystallisation inhibitor in an amount of 10% by weight is deposited in an open Petri dish at 20° C.; (ii) the deposited formulation is observed at 20 minute intervals; and (iii) no crystals are observed with the naked eye within 3 hours of depositing the formulation.

[0025] Examples of the crystallization inhibitor are polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters, polyoxyethylenated hydrogenated castor oil (e.g. PEG-60 hydrogenated castor oil), lecithin, sodium carboxymethylcellulose, or acrylic derivatives such as methacrylates.

[0026] Alternatively, or in addition, the crystallization inhibitor may be an anionic surfactant such as alkaline stearates, in particular sodium, potassium or ammonium stearate; calcium stearate; triethanolamine stearate; sodium abietate; alkyl sulphates, in particular sodium lauryl sulphate and sodium cetyl sulphate; sodium dodecylbenzenesulphonate, sodium dioctylsulphosuccinate; fatty acids, in particular those derived from coconut oil.

[0027] Alternatively, or in addition, the crystallization inhibitor may be a cationic surfactant such as water-soluble quaternary ammonium salts such as cetyltrimetylammonium bromide, octadecylamine 5 hydrochloride.

[0028] Alternatively, or in addition, the crystallization inhibitor may be a nonionic surfactant such as polyoxyethylenated sorbitan esters, in particular polysorbate 80, polyoxyethylenated alkyl ethers; polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, copolymers of ethylene oxide and propylene oxide.

[0029] Alternatively or in addition, the crystallization inhibitor may be an amphoteric surfactant such as a substituted lauryl compound of betaine.

[0030] In one embodiment, the at least one crystallization inhibitor is polyethylene glycol (e.g. polyethylene glycol 1000), polyethylene glycol hydrogenated castor oil (e.g. polyethylene glycol 60 hydrogenated castor oil, e.g. Nikkol HCO 60), or combinations thereof.

[0031] In one embodiment, the at least one crystallisation inhibitor consists of two crystallisation inhibitors.

[0032] In one embodiment, the at least one crystallization inhibitor is polyethylene glycol (e.g. polyethylene glycol 1000) and polyethylene glycol hydrogenated castor oil (e.g. polyethylene glycol 60 hydrogenated castor oil, e.g. Nikkol HCO 60). In one embodiment, the amount of polyethylene glycol is about 5% by weight of the formulation and the amount of polyethylene glycol hydrogenated castor oil is about 5% by weight of the formulation.

[0033] As used herein, "polyethylene glycol" includes combinations of polyethylene glycols having different molecular weights.

[0034] The formulation of the invention comprises at least one organic solvent which is not C_1-C6 alcohol.

[0035] Typically, the total amount of the at least one organic solvent which is not C_1-C_6 alcohol makes up the balance of the formulation. Examples of the at least one organic solvent which is not C_1-C6 alcohol are diethylene glycol monoethyl ether, ethylene glycol monoethyl ether, dipropylene glycol n-butyl ether, dipropylene glycol monomethyl ether, or combinations thereof. In one embodiment, the at least one organic solvent which is not C_1-C_6 alcohol is diethylene glycol monoethyl ether (e.g. Transcutol P).

[0036] In one embodiment, the formulation of the present invention consists of:

[0037] 9.7 wt % Fipronil;

[0038] 5.0 wt % ethanol;

[0039] 0.02 wt % butylated hydroxylanisole;

[0040] 0.01 wt % butylated hydroxyltoluene;

[0041] 5.0 wt % polyethylene glycol 1000;

[0042] 5.0 wt % polyethylene glycol 60 hydrogenated castor oil;

[0043] balance diethylene glycol monoethyl ether.

[0044] In another embodiment, the formulation of the present invention consists of

[0045] 9.8 wt % Fipronil;

[0046] 11.8 wt % S-Methoprene;

[0047] 5.0 wt % ethanol;

[0048] 0.02 wt % butylated hydroxylanisole;

[0049] 0.01 wt % butylated hydroxyltoluene;

[0050] 5.0 wt % polyethylene glycol 1000;

[0051] 5.0 wt % polyethylene glycol 60 hydrogenated castor oil;

[0052] balance diethylene glycol monoethyl ether.

[0053] This formulation is particularly suitable for cats.

[0054] In another embodiment, the formulation of the present invention consists of

[0055] 9.8 wt % Fipronil;

[0056] 8.8 wt % S-Methoprene;

[0057] 5.0 wt % ethanol;

[0058] 0.02 wt % butylated hydroxylanisole;

[0059] 0.01 wt % butylated hydroxyltoluene;

[0060] 5.0 wt % polyethylene glycol 1000;

[0061] 5.0 wt % polyethylene glycol 60 hydrogenated castor oil;

[0062] balance diethylene glycol monoethyl ether.

[0063] This formulation is particularly suitable for dogs.

[0064] The formulations of the present invention may be manufactured by mixing the desired components in the desired amounts.

[0065] The formulations of the present invention are intended for mammals, in particular cats and dogs, and are generally deposited onto the skin ("spot-on" or "pour-on" application). The deposition is generally a localised application over a surface area of less than 10 cm^2, especially of between 5 and 10 cm^2, in particular at one point or two points which may be located between the mammal's shoulders. Once deposited, the formulation diffuses over the mammal's body and dries without crystallising or modifying the appearance or feel of the fur.

[0066] As mentioned above, the present invention provides a process for controlling parasites on mammals, in particular cats and dogs, said process comprising treating the mammal by application to the skin of parasiticidally effective doses of a formulation according to the present invention.

[0067] The object of the application of the formulations of the present invention may be non-therapeutic in that it relates to the cleaning of mammal hairs and skin by elimination of

parasites, as well as their residues and dejections. The treated mammals will therefore have hair which is more pleasant to look at and feel.

[0068] The object of the application of the formulations of the present invention may be therapeutic if the intention is to treat and prevent parasitoses having pathologic consequences.

[0069] The process of the present invention may treat the mammal by local point application to the skin of "spot-on" type. Spot-on formulations are particularly advantageous due to their efficacy, their speed of action and the pleasant appearance of the mammal's fur after application and drying.

[0070] The process, formulations and use of the present invention is particularly suitable when the parasites are ectoparasites, in particular ticks or fleas.

[0071] Treatment of mammals, in particular cats and dogs, with the formulation of the present invention may be carried out every two or three months.

[0072] The treatment may be carried out so as to administer to the mammal a does from 0.1 to 80 mg/kg, alternatively from 1 to 40 mg/kg, alternatively from 1 to 30 mg/kg of the parasiticidal component, wherein the parasiticidal component is either Fipronil or the combination of Fipronil and S-Methoprene when S-Methoprene is present.

[0073] It is to be understood that these dosage values are average values which may vary because the formulation will be administered to mammals having relatively different body weights. Consequently, the doses applied may be smaller or larger than the doses provided above.

MODES FOR CARRYING OUT THE INVENTION

[0074] The invention is further illustrated by the following examples. It will be appreciated that the examples are for illustrative purposes only and are not intended to limit the invention as described above. Modification of detail may be made without departing from the scope of the invention.

Example 1

[0075] A formulation of the following composition is prepared by mixing ingredients in the following amounts:

[0076] 9.7 wt % Fipronil;

[0077] 5.0 wt % ethanol;

[0078] 0.02 wt % butylated hydroxylanisole;

[0079] 0.01 wt % butylated hydroxyltoluene;

[0080] 5.0 wt % polyethylene glycol 1000;

[0081] 5.0 wt % polyethylene glycol 60 hydrogenated castor oil (Nikkol HCO 60);

[0082] balance diethylene glycol monoethyl ether (Transcutol P).

Example 2

[0083] A formulation of the following composition particularly useful for cats is prepared by mixing ingredients in the following amounts:

[0084] 9.8 wt % Fipronil;

[0085] 11.8 wt % S-Methoprene;

[0086] 0.02 wt % butylated hydroxylanisole;

[0087] 0.01 wt % butylated hydroxyltoluene;

[0088] 5.0 wt % polyethylene glycol 1000;

[0089] 5.0 wt % polyethylene glycol 60 hydrogenated castor oil (Nikkol HCO 60);

[0090] balance diethylene glycol monoethyl ether (Transcutol P).

Example 3

[0091] A formulation of the following composition particularly useful for dogs is prepared by mixing ingredients in the following amounts:

[0092] 9.8 wt % Fipronil;

[0093] 8.8 wt % S-Methoprene;

[0094] 5.0 wt % ethanol;

[0095] 0.02 wt % butylated hydroxylanisole;

[0096] 0.01 wt % butylated hydroxyltoluene;

[0097] 5.0 wt % polyethylene glycol 1000;

[0098] 5.0 wt % polyethylene glycol 60 hydrogenated castor oil (Nikkol HCO 60);

[0099] balance diethylene glycol monoethyl ether (Transcutol P).

Example 4

Flash points

[0100] The flashpoints of the compositions of Examples 1-3 were measured and were found to be between 15 47-52° C., some 11-18° C. higher than the flashpoint of the marketed product FRONTLINE® PLUS FOR DOGS.

[0101] The formulations of the invention therefore have a reduced propensity to form ignitable mixtures with air. They therefore provide a safer formulation for use, storage, distribution and manufacture.

Example 5

Parasiticidal activity

[0102] The compositions of Examples 1-3 have been shown in trials to have parasiticidal activity.

1-19. (canceled)

20. A parasiticidal formulation comprising:

Fipronil, or a veterinarily acceptable derivative thereof;

at least one C_1-C_6 alcohol co-solvent, wherein the total amount of C_1-C_6 alcohol is up to 8% by weight of the formulation; and

at least one organic solvent which is not the C_1-C_6 alcohol co-solvent.

21. The formulation of claim **20**, further comprising at least one crystallisation inhibitor, wherein the total amount of the crystallisation inhibitor is from 2 to 20% by weight of the formulation.

22. The formulation of claim **20**, wherein the Fipronil or a veterinarily acceptable derivative thereof, is Fipronil.

23. The formulation of claim **22**, wherein the amount of Fipronil is from 5% to 20% by weight of the formulation.

24. The formulation of claim **20**, which further comprises S-Methoprene.

25. The formulation of claim **24**, wherein the amount of S-Methoprene is from 5% to 25% by weight of the formulation.

26. The formulation of claim **20**, wherein the at least one C_1-C_6 alcohol co-solvent is methanol, ethanol, propanol, isopropanol, butanol, or combinations thereof.

27. The formulation of claim **26**, wherein the at least one C_1-C_6 alcohol co-solvent is ethanol.

28. The formulation of claim **21**, wherein the at least one crystallisation inhibitor is polyethylene glycol, polyethylene glycol hydrogenated castor oil, or combinations thereof.

29. The formulation of claim **28**, wherein the at least one crystallisation inhibitor is polyethylene glycol and polyethylene glycol hydrogenated castor oil.

30. The formulation of claim **29**, wherein the amount of polyethylene glycol is about 5% by weight of the formulation and the amount of polyethylene glycol hydrogenated castor oil is about 5% by weight of the formulation.

31. The formulation of claim **20**, wherein the at least one organic solvent which is not the C_1-C_6 alcohol co-solvent is diethylene glycol monoethyl ether, ethylene glycol monoethyl ether, dipropylene glycol n-butyl ether, dipropylene glycol monomethyl ether, or combinations thereof.

32. The formulation of claim **31**, wherein the at least one organic solvent which is not the C1-C6 alcohol co-solvent is diethylene glycol monoethyl ether.

33. A method for controlling parasites on mammals in need thereof, in particular cats and dogs, said method comprising treating the mammal by application to the skin of parasiticidally effective dose of a formulation of claim **20**.

34. The method of claim **33**, wherein the mammal is treated by local point application to the skin of "spot-on" type.

35. The method of claim **33**, wherein the parasites are ectoparasites, in particular ticks or fleas.

36. A parasiticidal formulation consisting of:
about 9.7 wt % Fipronil;
about 5.0 wt % ethanol;
about 0.02 wt % butylated hydroxylanisole;
about 0.01 wt % butylated hydroxyltoluene;
about 5.0 wt % polyethylene glycol 1000;
about 5.0 wt % polyethylene glycol 60 hydrogenated castor oil;
balance diethylene glycol monoethyl ether.

37. A parasiticidal formulation consisting of:
about 9.8 wt % Fipronil;
about 11.8 wt % S-Methoprene;
about 5.0 wt % ethanol;
about 0.02 wt % butylated hydroxylanisole;
about 0.01 wt % butylated hydroxyltoluene;
about 5.0 wt % polyethylene glycol 1000;
about 5.0 wt % polyethylene glycol 60 hydrogenated castor oil;
balance diethylene glycol monoethyl ether.

38. A parasiticidal formulation consisting of:
about 9.8 wt % Fipronil;
about 8.8 wt % S-Methoprene;
about 5.0 wt % ethanol;
about 0.02 wt % butylated hydroxylanisole;
about 0.01 wt % butylated hydroxyltoluene;
about 5.0 wt % polyethylene glycol 1000;
about 5.0 wt % polyethylene glycol 60 hydrogenated castor oil;
balance diethylene glycol monoethyl ether.

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