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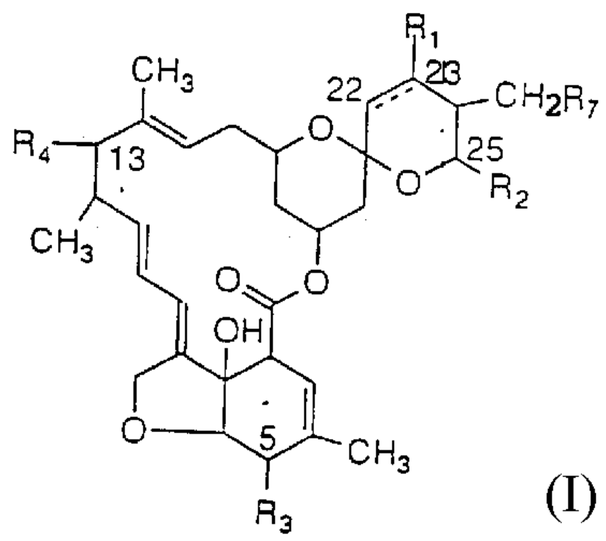
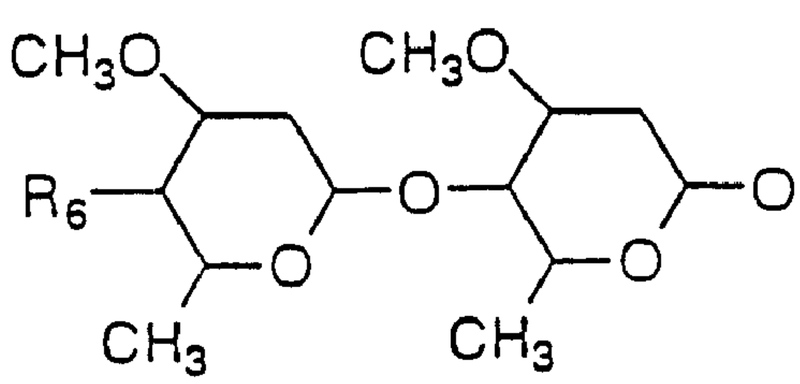
(54) **FORMULATIONS TOPIQUES CONTENANT DES MATERIAUX POLYMERIQUES**

(54) **TOPICAL FORMULATIONS CONTAINING POLYMERIC MATERIAL**



(I)

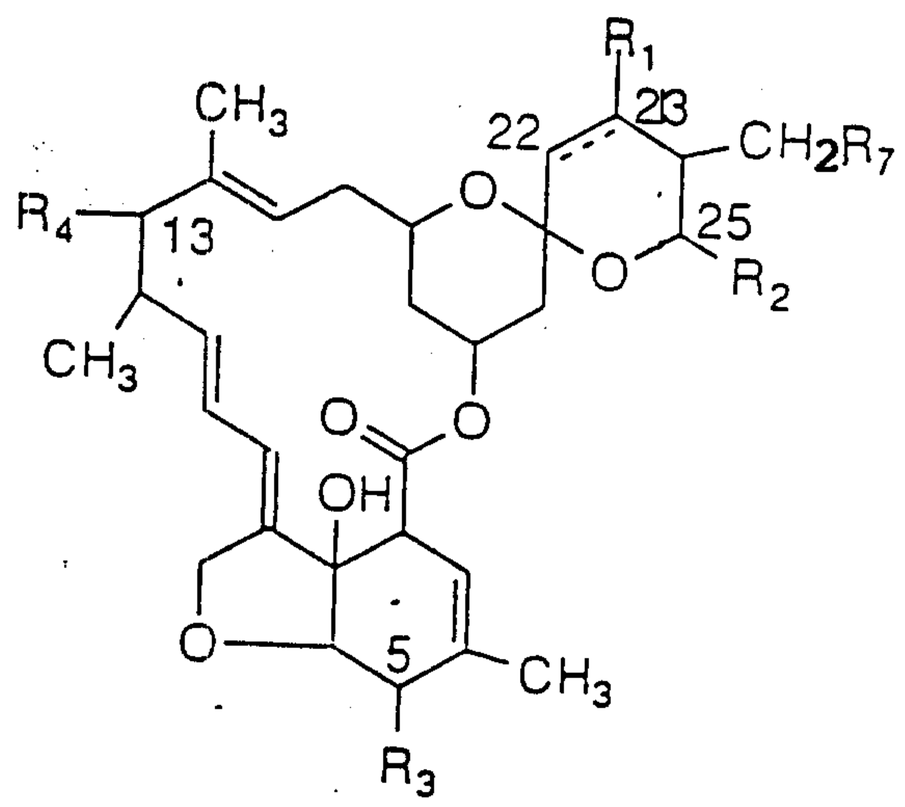


(II)

(57) A topical formulation for direct application to the skin of an animal, effective for treatment and prevention of ectoparasitic and endoparasitic infestations for four weeks, consists of from about 0.01 to about 20% w/v of a polymeric material, from about 1 to about 95% v/v of ethanol, 100% v/v obtained with addition of water, and from about 0.05 to about 10% w/v of an avermectin compound having the formula: (see formula I) where the broken line indicates a single or a double bond at the 22,23- positions; R_1 is hydrogen or hydroxy, provided that R_1 is presently only when the broken line indicates a single bond; R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms; R_3 is hydroxy, methoxy, or =NOR$_5$, where R_5 is hydrogen or lower alkyl; R_7 is hydrogen, hydroxy or lower alkyl; and R_4 is hydrogen, hydroxy, poly C(1-6) alkoxy, or: (see formula II) where R_6 is hydroxy, amino, mono- or di-C_1-C_6 alkylamino or C_1-C_6 alkanolylamino.

ABSTRACT

A topical formulation for direct application to the skin of an animal, effective for treatment and prevention of ectoparasitic and endoparasitic infestations for four weeks, consists of from about 0.01 to about 20% w/v of a polymeric material, from about 1 to about 95% v/v of ethanol, 100% v/v obtained with addition of water, and from about 0.05 to about 10% w/v of an avermectin compound having the formula:



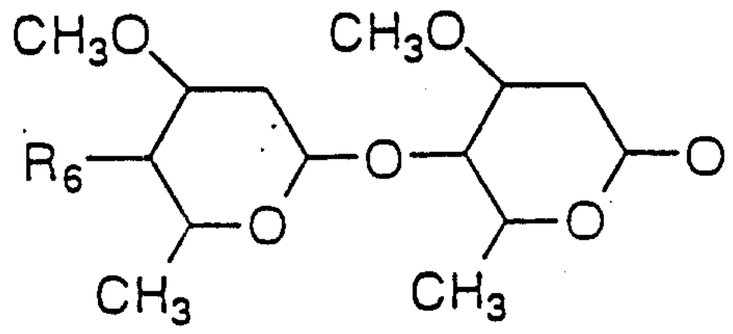
where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy, provided that R_1 is presently only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

R_3 is hydroxy, methoxy, or $=NOR_5$, where R_5 is hydrogen or lower alkyl;

R_7 is hydrogen, hydroxy or lower alkyl; and R_4 is hydrogen, hydroxy, poly C(1-6) alkoxy, or:



where R_6 is hydroxy, amino, mono- or di-C_1-C_6 alkylamino or C_1-C_6 alkanolyl-amino.

TOPICAL FORMULATIONS CONTAINING POLYMERIC MATERIAL

Background of the Invention

The avermectin series of compounds are potent anthelmintic and antiparasitic agents against internal and external parasites.

This application is a division of Canadian Application Serial No. 2,161,703 filed April 28, 1994.

The natural product avermectins are disclosed in U.S. 4,310,519 to Albers-Schonberg et al., and the 22,23-dihydroavermectin compounds are disclosed in Chabala et al., U.S. 4,199,569. Administration of the avermectin compounds occur orally, parenterally or topically.

However, the conventional topical formulations do not provide acceptable efficacy against ectoparasites, especially against Chorioptes, fleas and ticks. Often times these formulations fail due to the lack of extended efficacy. The animals are readily reinfested by fleas, ticks and the like after treatment with the above-noted formulations simply by returning to a flea infested environment. Further, topical formulations of currently available medicinal agents have not demonstrated efficacy against endoparasites, such as heartworms and nematodes.

It is known in the pet care industry that sustained release of an insecticide is obtained by incorporation of the insecticide into a polymeric system. However, conventional polymer based formulations rely on the vaporization of the active compounds, which means this type of system may not be used for non-evaporable drugs. See U.S. Pat. Nos. 3,852,416 and 4,172,904. Additionally, conventional formulations of current medicinal agents require a withdrawal period of a few weeks after application of the active compound before any milk can be withdrawn from dairy animals for human consumption.

Summary of the Invention

This invention is concerned with avermectin topical pour-on formulations which effectively eliminate both ectoparasites, especially Chorioptes, fleas and ticks, and endoparasites, especially heartworms and nematodes, of animals such as cattle, swine, etc. for an extended period up to a full four weeks, particularly household pets such as cats and dogs. The instant formulations also

unexpectedly provides a zero milk withdrawal time for topically applied antiparasitic agents with regard to dairy animals. The formulations are prepared using solvents such as water, alcohols such as ethanol, methanol, isopropanol and the like, propylene glycol esters, glycerides, or their derivatives as the carrier.

The formulations in particular contain in addition to the active avermectin ingredient and solvent, a polymer such as polyvinylpyrrolidone. The drug is bound to the skin with the aid of the polymer which remains on the skin surface after the solvents have evaporated following application. Thus it is an object of this invention to describe such ectoparasitic and endoparasitic efficacy. Another object is to describe the avermectin compounds which may be employed in the formulation. A still further object is to describe how the concentration of the active compound in the milk of dairy animals is maintained below a concentration level that provides for a zero withdrawal period for human consumption. A still further object is to describe how extended efficacy against ticks, fleas and heartworms is obtained. Additional objects will become apparent after a reading of the following description.

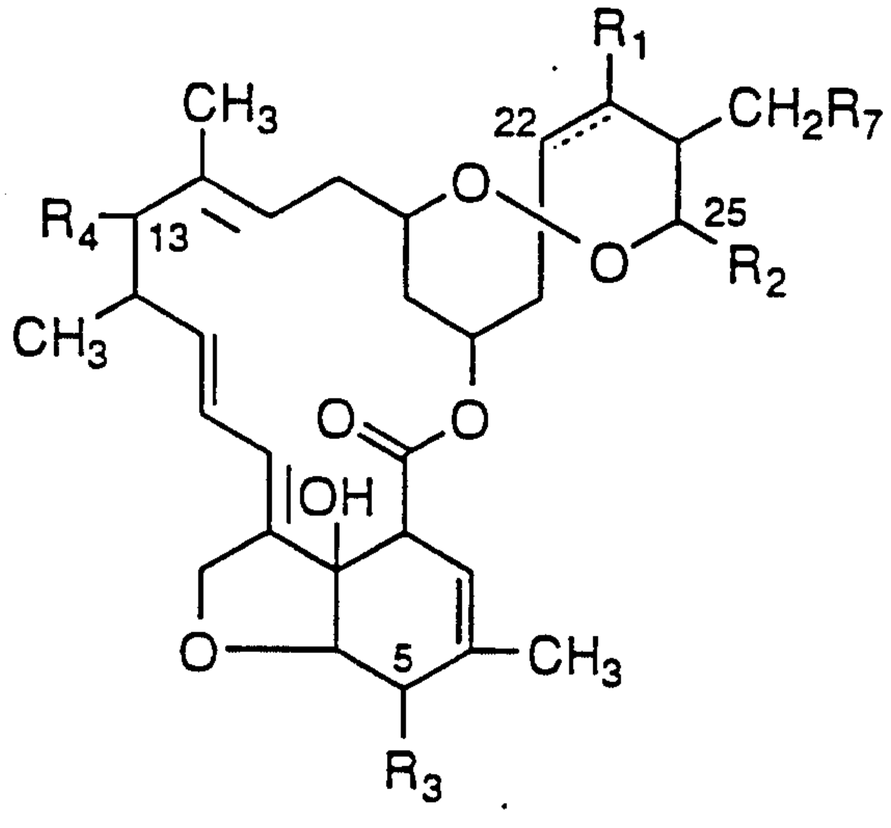
Description of the Invention

In accordance with the invention there is provided a topical formulation for direct application to the skin of an animal, effective for treatment and prevention of ectoparasitic and endoparasitic infestations for four weeks, consisting of from about 0.01 to about 20% w/v of a polymeric material, from about 1 to about 95% v/v of ethanol, 100% v/v obtained with addition of water, and from about 0.05 to about 10% w/v of an avermectin compound.

Also disclosed herein is a topical formulation of a glyceride, glycol, or a derivative thereof and an avermectin compound which has been found to effectively eliminate both ectoparasites and endoparasites. The formulation can optionally contain in addition to the glyceride, glycol or derivative thereof and avermectin, an antioxidant such as BHA, BHT and the like, additives such as Crodamol CAP(™), glycerol formal, Tween 80(™) and the like, a solvent mixture of water and/or solvents with high vapor pressure such as ethanol, methanol,

isopropanol and the like, and a polymeric material such as polyvinyl pyrrolidone, polyvinyl alcohol and the like.

The avermectin compounds used in the instant formulations have the following general structure:



where the broken line indicates a single or a double bond at the 22,23-positions.

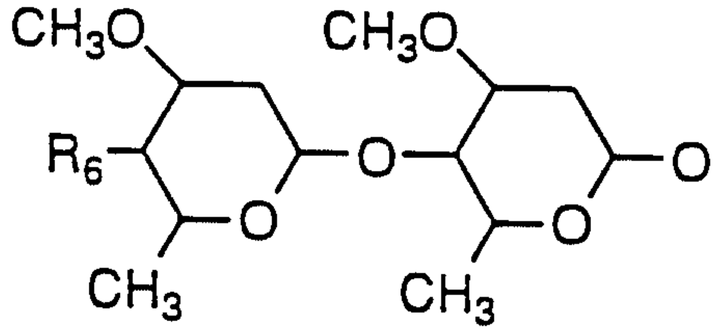
R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;

R_3 is hydroxy, methoxy or $=NOR_5$ where R_5 is hydrogen or lower alkyl;

R_7 is hydrogen, hydroxy, or lower alkyl; and

R_4 is hydrogen, hydroxy, poly C(1-6) alkoxy or



where R_6 is hydroxy, amino, mono- or di-C_1 to C_6 alkylamino or C_1 to C_6 alkanoylamino.

The term "loweralkyl" when used in the instant application is intended to represent those alkyl groups either straight or branched chain which have from 1-5 carbon atoms. Examples of such alkyl groups are methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, pentyl, and the like.

The term "loweralkanoyl" is intended to include those alkanoyl groups containing from one to five carbon atoms in either a straight or branched chain. Examples of such alkanoyl groups are formyl, acetyl, propenyl, butyryl, valeryl, and the like.

The term "halogen" is intended to include those halogen atoms, fluorine, chlorine, bromine and iodine.

The term "polyalkoxy" is intended to include methoxymethoxy, 2-methoxyethoxy, (2-methoxyethoxy)-methoxy, [2-(2-methoxyethoxy)ethoxy]-methoxy; and the like.

A related family of natural products also useful in the present invention is known as the milbemycins. The milbemycins have the same macrocyclic ring structures as the avermectins but have no substitution at position 13 (R_4 = hydrogen) and have a methyl or ethyl group at position 25 R_2 = methyl or ethyl rather than isopropyl or secbutyl as in the avermectins). The milbemycins and the fermentation conditions used to prepare them are described in U.S. Pat. No. 3,950,360. Closely related 13-deoxyavermectin aglycones are prepared by chemical modification of the natural avermectins and have been described in U.S. Pat. No. 4,173,571.

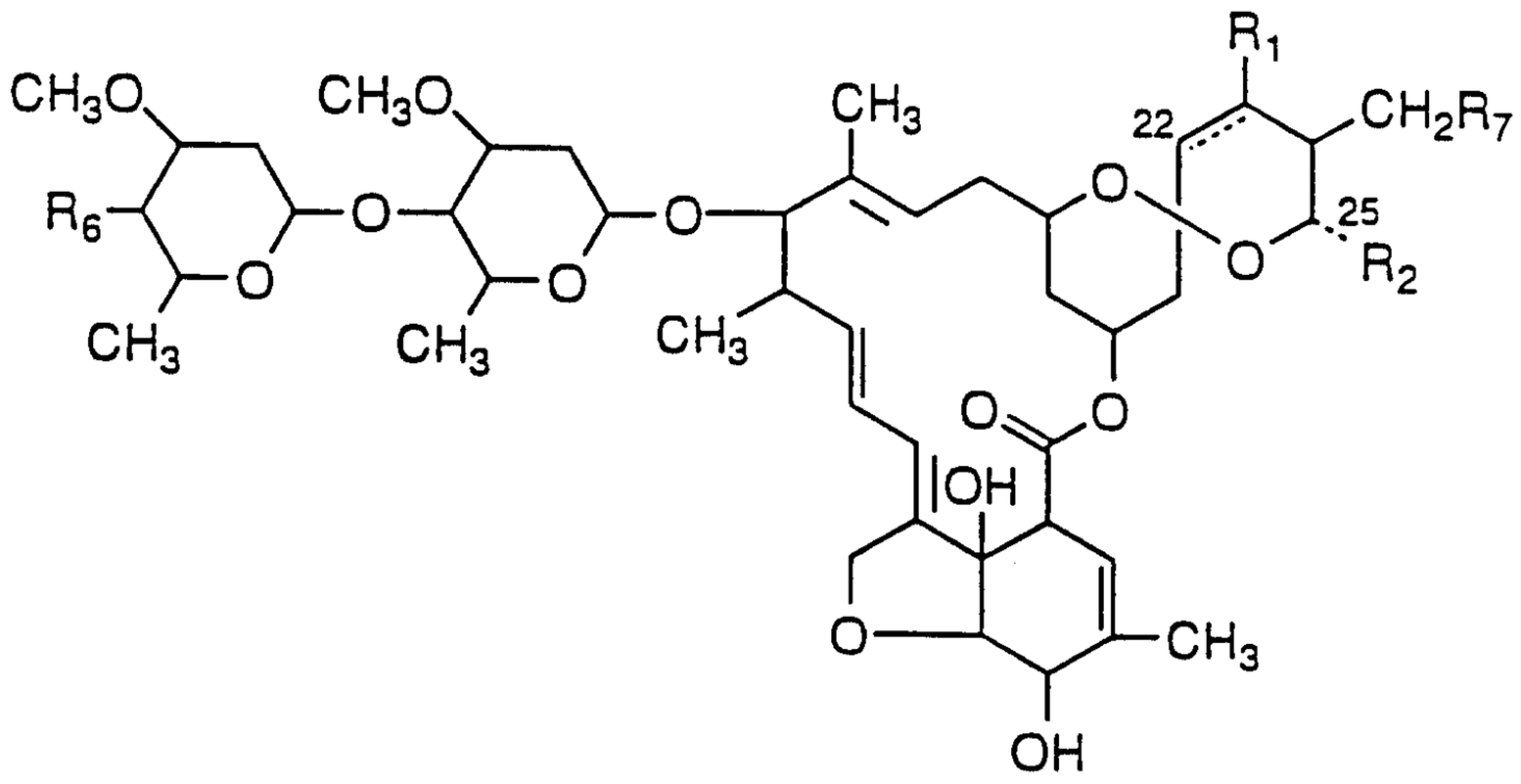
There is disclosed herein a composition which is a topical pour-on formulation of a glyceride, glycol, or a derivative thereof as a carrier and an avermectin compound which has been found to effectively eliminate both ectoparasites, especially Chorioptes, and endoparasites, while simultaneously maintaining the concentration of the active compound in the milk of dairy animals below an adequate concentration period for human consumption to provide a zero milk

withdrawal time for topically applied endectocides [milk concentration of 4"-acetylamino-4"-deoxyavermectin B1 (L-653,648) for zero milk withdrawal is 48 ng/ml] .

The carriers are oleyl alcohol, propylene glycol and its esters such as propylene dicaprylate/dicaprate, propylene glycol laurate, and the like, glycol ethers such as diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol diethyl ether and the like, and glycerides such as PEG-6 caprylic/capric triglyceride, caprylic/capric diglyceryl succinate, polyglycolysed glycerides, and the like, preferrably propylene caprylate/caprate or caprylate caprate glyceride, and is available under such Trademarks as Miglyol 810, 812, 818, 829 and 840, Softigen and Labrasol®. The (/) in propylene dicaprylate/dicaprate and PEG-6 caprylic/capric triglycerides indicates a mixture of the two components in a ratio of 65-80/15-30.

The above carriers impart to the formulation good penetration and spreadability of the active compound even at cold temperatures.

The preferred avermectin compounds of E1 have the following structural formula:



wherein the broken line represents a single bond; R_1 is hydrogen; R_2 is isopropyl of sec-butyl; R_6 is hydroxy, amino, mono-or di-C_1 to C_6

alkyl-amino or C_1 to C_6 alkanoylamino; and R_7 is hydrogen, hydroxy, or loweralkyl.

Examples of preferred compounds of the instant E1 formulation are:

4"-keto avermectin B1;
4"-keto avermectin B2;
4"-keto-22,23-dihydro avermectin B1;
4"-keto-22,23-dihydro avermectin B2;
4"-deoxy-4"-amino avermectin B1;
4"-deoxy-4"-amino avermectin B2;
4"-deoxy-4"-amino-22,23-dihydro avermectin B1;
4"-deoxy-4"-amino-22,23-dihydro avermectin B2;
4"-deoxy-4"-acetylamino avermectin B1;
4"-deoxy-4"-acetylamino avermectin B2;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-dimethylamino avermectin B1;
4"-deoxy-4"-dimethylamino avermectin B2;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B1;
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B2.

The "b" compounds, those with a 25-iso-propyl group, are not necessarily separated from the corresponding "a" compound with a 25-sec-butyl group and the compounds are generally isolated as

mixtures of the two compounds, consisting of at least 80% of the secbutyl compound and no more than 20% of the isopropyl compound. Thus references in the instant application to "a" compounds such as Bla, Ala, and the like, are construed to actually contain a certain proportion of the corresponding "b" compound. Alternatively, this representation of a mixture is sometimes done by referring to the B1 or B2 compounds or by separating the "a" compound from the "b" compound by a slash (/) such as Bla/Blb, B2a/B2b and the like. Additionally, the products of synthetic procedures such as racemization or epimerization, procedures known to those skilled in the art, can be a mixture of stereoisomers. In particular, the stereoisomers of the 13- and 23-positions may be oriented either α- or β- representing such groups being below or above the general plane of the molecule, respectively. In each case, and at other positions in the molecule, both the α- and β- configurations are intended to be included within the ambit of the invention.

In the topical forms of the avermectin formulation it has not been possible to provide a formulation which provides an acceptable efficacy against ectoparasites, especially Chorioptes. Additionally, currently available topical formulations do not provide a zero milk withdrawal time with the application of endectocides which thus precludes the use of such compounds on milk producing animals.

E1 gives the advantages of a pour-on topical formulation which provides the animal with effective treatment and protection against endoparasites and ectoparasites, especially Chorioptes and at the same time maintains the concentration of the active compound in the milk of dairy animals below a safe concentration for human consumption. Additional advantages of this invention are that the formulation is non-flammable, it is not readily washable by rain, it has good spreadability and cold temperature usage and has good compatibility with currently available dosing devices.

E1 can contain the avermectin compound and the glycol or glyceride carrier as the only ingredients. The formulations will generally be prepared to administer a safe and effective amount from 0.005 to 10% by weight of the avermectin component, most preferably from 0.01 to 5% by weight. Most

preferably a formulation containing about 0.5% of the avermectin is employed. At a preferred dose volume of about 5 ml to treat 50 kg of animal body weight the formulation contains from about 1.0 to 50 mg of avermectin compound per ml of solution. The glycol or glyceride carrier is added to the formulation from about 40 to 100% (q.s.v/v).

The most preferred formulation for E1 contains in addition to the glycol, glyceride, or derivatives thereof and avermectin compound, an antioxidant such as propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like, preferably BHT. The antioxidants are generally added to the formulation at rates of from 0.005 to 1.0% (w/v). Additives such as Crodamol CAP, glycerol formal, Tween 80 propylene glycol and the like, preferably Crodamol CAP, may also be used. The additives are generally added to the formulation at volumes of up to 60% of the volume of glycol or glyceride carrier, preferably up to 40% of the volume of carrier.

E1 is preferred by dissolving avermectin compound in approximately 50-100% of the intended volume of the above mentioned carriers and then adjusting the volume to 100% by the addition of the final volume of the carrier or additive. The antioxidant and additive may be combined with the above mentioned carriers prior to mixing the avermectin or added as the final volume of solvent.

The following example is provided in order that the E1 embodiment might be more fully understood.

Example of E1

The formulations described herein depend upon the particular avermectin compound and treatment. The avermectin is dissolved in approximately 50% of the glycol or glyceride carrier. When dissolved, the antioxidant and/or additive are optionally added and the volume adjusted to 100% with the final volume of glycol or glyceride carrier. The solution is mixed until it becomes homogeneous. Generally, mixing at room temperature (15-25°C) is adequate, however,

if necessary, warming up to 50°C may be helpful. The following are nonlimiting examples of the composition of the present invention, which are conventionally formulated by mixing all components as stated above.

Composition I

4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Crodamol CAP	10.0 % v/v
Miglyol 840 (q.s.)	100.0 % v/v

Composition II

4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Miglyol 840 (q.s.)	100.0 % v/v

Composition III

4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Isopropyl Myristate	10.0 % v/v
Miglyol 840 (q.s.)	100.0 % v/v

Composition IV

4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
Triacetin	50.0 % v/v
Miglyol 840 (q.s.)	100.0 % v/v

Composition V	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
Softigen 767	65.0 % v/v
Miglyol 840	25.0 % v/v
Ethanol (q.s.)	100.0 % v/v

Composition VI	
4"-acetylamino-4"-deoxyavermectin	0.5 % w/v
Softigen 767	65.0 % v/v
Isopropanol (q.s.)	100.0 % v/v

Composition VII	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Dowanol DB (q.s.)	100.00% v/v

Crodamol CAP is a Trademarkmixture of isopropyl myristate, cetyl octanoate and stearyl octanoate and Dowanol DB is a trademark for diethylene glycol butyl ether.

E1 EXAMPLE II

The data below are results indicating the avermectin concentration (ng/ml) in the milk of lactating cows after topical application with some of the above formulations and that the avermectin concentration is maintained below 48 ng/ml which is the milk concentration of avermectin required for a zero milk withdrawal.

4"-ACETYLAMINO-4"-DEOXYAVERMECTIN B1 CONCENTRATIONS (ng/mL) IN MILK OF LACTATING COWS DOSED TOPICALLY

TREATMENT A: MIGLYOL 840/BHT/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5950	0.0	1.5	5.0	6.4	9.5	8.7	8.1	6.3
5931	0.0	6.0	23.2	13.0	7.1	4.2	2.5	1.7
5932	0.0	3.4	4.8	3.4	3.1	2.0	1.6	3.4
5938	0.0	5.6	15.5	9.6	8.5	4.5	3.7	3.1
MEAN	0.0	4.1	12.1	8.1	7.1	4.9	4.0	3.6
STD. DEV.		2.1	8.9	4.1	2.8	2.8	2.9	1.9

TREATMENT B: TRIACETIN/MIGLYOL 840 (50/50)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5946	0.0	1.2	2.9	4.0	5.0	4.7	4.1	2.9
5949	0.0	2.7	13.3	11.4	8.6	5.3	3.5	2.8
5929	0.0	1.3	2.8	4.1	5.8	5.7	4.2	3.0
5928	0.0	4.9	14.6	9.4	5.4	3.1	2.0	1.4
MEAN	0.0	2.5	8.4	7.2	6.2	4.7	3.5	2.5
STD. DEV.		1.7	6.4	3.8	1.6	1.1	1.0	0.8

TREATMENT C: SOFTIGEN 767/MIGLYOL 840 (70/30)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5948	0.0	1.1	4.5	6.4	6.6	7.1	5.4	3.8
5930	0.0	1.4	3.8	3.9	5.8	9.0	7.6	4.9
5927	0.0	2.7	6.0	7.0	7.6	5.5	4.6	3.7
5934	0.0	1.9	4.7	10.6	15.0	8.3	4.9	3.2
MEAN	0.0	1.8	4.8	7.0	8.8	7.5	5.6	3.9
STD. DEV.		0.7	0.9	3.9	4.2	1.5	1.4	0.7

TREATMENT D: Miglyol/Crodamol CAP (90/10)-500 µg/Kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
6384	0.0	2.1	4.8	6.8	7.6	5.7	5.4	3.8
6385	0.0	7.3	7.1	6.1	4.8	3.3	2.7	2.3
6379	0.0	10.0	10.6	7.8	5.4	2.9	1.9	1.7
6386	0.0	2.7	6.0	6.0	5.8	4.1	5.4	5.2
6377	0.0	5.2	9.7	8.7	9.8	4.8	2.9	2.5
6382	0.0	7.7	15.5	11.8	8.7	4.7	3.3	2.3
MEAN	0.0	5.8	9.0	7.9	7.0	4.3	3.6	3.0
STD. DEV.		3.1	3.9	2.2	2.0	1.0	1.5	1.3

TREATMENT E: Miglyol/Crodamol CAP (90/10)-250 µg/Kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
6389	0.0	1.2	2.7	2.8	2.6	1.9	1.7	1.4
6381	0.0	1.0	1.6	1.8	2.8	2.5	2.6	2.0
6380	0.0	2.8	5.5	4.4	3.5	2.0	1.5	0.0
6378	0.0	2.4	4.8	4.0	2.9	1.6	1.1	0.0
6376	0.0	1.8	4.2	4.3	4.3	3.1	2.4	1.9
6388	0.0	0.0	1.3	1.7	2.8	2.3	2.0	1.9
MEAN	0.0	1.5	3.4	3.2	3.2	2.2	1.9	1.2
STD. DEV.		1.0	1.7	1.2	0.6	0.5	0.6	1.0

TREATMENT F: TRIACETIN/MIGLYOL 840 (50/50)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5977	0.0	1.4	6.8	6.9	4.3	3.4	3.0	2.2
5976	0.0	2.1	10.8	13.8	5.7	5.6	2.9	1.8
MEAN	0.0	1.8	8.8	10.4	5.0	4.5	3.0	2.0
STD. DEV.		0.5	2.8	4.9	1.0	1.6	0.0	0.3

TREATMENT :G IPA/SOFTIGEN 767 (40/60)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5984	0.0	0.0	0.0	0.6	0.6	0.7	1.0	1.6
5980	0.0	0.5	0.8	1.6	1.3	2.9	2.3	2.8
5987	0.0	0.0	0.5	0.9	3.1	6.3	4.6	5.0
5982	0.0	0.0	2.0	3.8	3.8	3.5	2.2	1.6
MEAN	0.0	0.0	0.8	1.7	2.2	3.4	2.5	2.8
STD. DEV.		0.0	0.9	1.5	1.5	2.3	1.5	1.6

NOTE: Samples with 4"-acetylamino-4"-deoxyavermectin B1 concentrations equal to or less than 0.4 ng/ml are reported as 0 ng/ml:

E1 EXAMPLE III

Efficacy trials with Chorioptes and key endoparasites were conducted to evaluate some of the above formulations. For each trial evaluating Chorioptes, four cattle were infested with *Chorioptes bovis* on Day -1 and treatment was given on Day 0. Respecting the trials evaluating endoparasites, the animals were challenged with Oesophagostamum, Trichuris and Dictyocaulus 17, 7, and 7 days before treatment with the formulation. The results are below.

CHORIOPTES MITE COUNTS

An. No.	Day -1	Day 7	Day 14	Day 21	Day 27	Day 35
Trt. 1 - Untreated Control						
H215	32	3	0	10	0	0
H208	6	19	15	3	4	17
H229	708	5024	2546	601[a]	11477[b]	6835
H233	511	875	1430	889[a]	1432[b]	1339
Trt. 2 - 4"-aa-4" deoxy in Miglyol 840/Crodamol CAP/BHT at 500 mcg/kg						
H224	22	1	79	2	0	0
H223	17	0	0	0	0	0
H234	2018	1007	895	0[a]	0[b]	0
H230	378	265	2	5[a]	0[b]	150
Trt. 3 - 4"-aa-4" deoxy in Miglyol 840/BHT at 500 mcg/kg						
H226	182	3	0	1	0	0
H218	3	0	0	0	0	0
H228	1644	659	16	0[a]	0[b]	0
H231	233	358	603	133[a]	89[b]	5

[a] Day 20

[b] Day 28

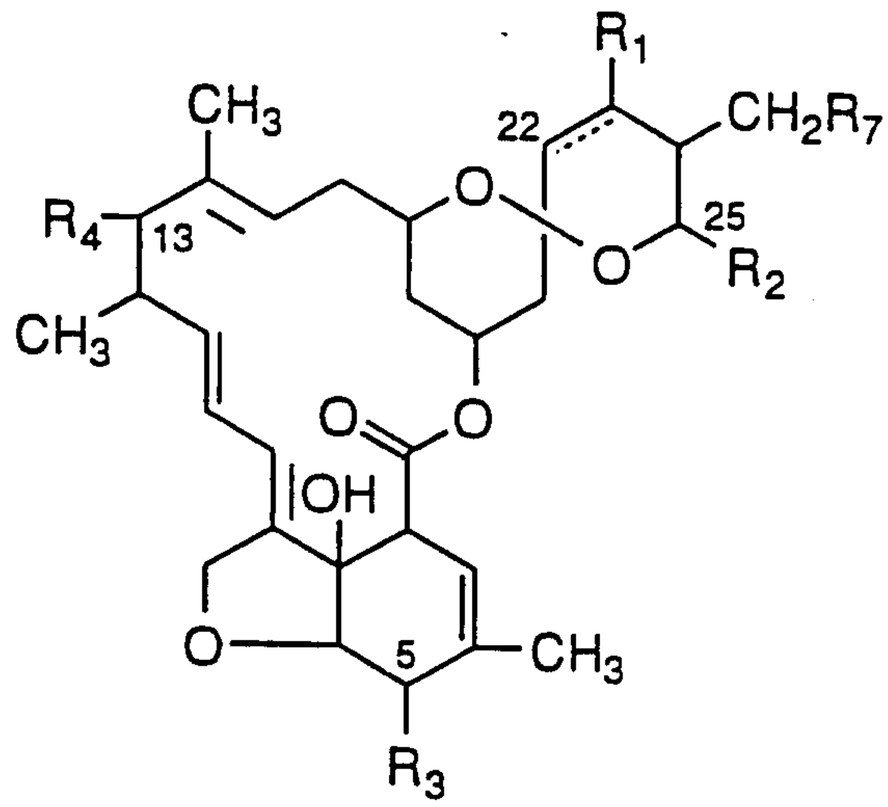
4"-aa-4" deoxy = 4"-acetylamino-4"-deoxy avermectin B1

4"-aa-4" deoxy Nematode Counts
Total Counts based on 10% aliquots
(*Dictyocaulus* counts are total counts)

Animal Number	*Oesophagost* spp. Adult	*Oesophagost* spp. L4	*Trichuris* spp. Adult	*Dictyocaulus* spp.
Trt. 1 - Untreated Control				
2477	0	0	20	3
2374	50	0	0	0
2259	0	0	50	17
41	240	0	80	14
Trt. 2 - 4"-aa-4" deoxy in Miglyol 840 Crodamol CAP/BHT (0.5%/q.s./10%/0.01% at 500 mcg/kg				
2456	0	0	0	0
2478	0	0	0	0
5	0	0	0	0
2254	0	0	0	0
Trt. 3 - 4"-aa-4" deoxy in Miglyol 840 BHT (0.5%/q.s./0.01%) at 500 mcg/kg				
2510	0	0	0	0
2358	0	0	0	0
40	0	0	0	0
2258	0	0	0	0
Trt. 4 - 4"-aa-4" deoxy in Miglyol 840/Lauroglycol/BHT (0.5%/q.s./10%/0.01%) at 500 mcg/kg				
2528	0	0	0	0
2443	0	0	0	0
44	0	0	0	0
2298	0	0	0	0

The invention is more especially concerned with a composition (E2) which is a topical pour-on formulation of a solvent mixture of water and/or solvents with relative high vapor pressure such as ethanol, methanol, isopropanol, acetone, and the like most preferably ethanol, a polymeric material such as polyvinyl pyrrolidone, polyvinyl alcohol, cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxy methyl cellulose, and hydroxyethyl cellulose, and the like, most preferably polyvinyl pyrrolidone (MW from about 20,000 to 65,000, preferably about 45,000), skin or hair subtantantive protein derivatives such as hydrolyzed wheat protein, hydrolyzed animal protein, gelatin derivatives, collagen derivatives, and the like, hydroalcoholic soluble copolymers such as acrylates/t-octylpropenamide copolymer and the like, and cationic quaternary amine salts and the like, which has been found to extend the efficacy of the formulation for up to a full four weeks. The polymeric material helps to keep the drug at the skin level longer by remaining on the skin surface after the solvents have evaporated following application. The remaining avermectin and polymer does not change the appearance of the animal's hair coat and the avermectin is released by diffusion and/or erosion of the polymer

The preferred avermectin compounds of E2 have the following structural formula:



wherein R_1, R_2, and R_3 are as described above, and R_4 is hydrogen, hydroxy, or polyalkoxy, and the broken line indicates a single or double bond at the 22,23-position, provided that R2 is hydroxy only when the broken line indicates a single bond.

Examples of preferred compounds of the instant invention are:

4"-keto avermectin B1;
4"-keto avermectin B2;
4"-keto-22,23-dihydro avermectin B1;
4"-keto-22,23-dihydro avermectin B2;
4"-deoxy-4"-amino avermectin B1;
4"-deoxy-4"-amino avermectin B2;
4"-deoxy-4"-amino-22,23-dihydro avermectin B1;
4"-deoxy-4"-acetylamino avermectin B1;
4"-deoxy-4"-acetylamino avermectin B2;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-dimethylamino avermectin B1;
4"-deoxy-4"-dimethylamino avermectin B2;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro-13-O-[(2-methoxyethoxy)methyl] avermectin B1 aglycone (hereinafter referred to as 13-O-MEM AVM);
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B1;
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B2
13-epi-O-(methoxymethyl)-22,23-dihydro avermectin B1 aglycone (hereinafter referred to as 13-O-MOM AVM).

The most preferred compound is 22,23-dihydro-13-O-[(2-methoxyethoxy)methyl] avermectin B1 aglycone (hereinafter referred to as 13-O-MEM AVM).

In the topical forms of the avermectin formulation it has not been possible to provide a formulation which provides superior extended efficacy against ectoparasites, especially fleas and ticks. Additionally, currently available topical formulations do not provide adequate efficacy against endoparasites, especially heartworms and nematodes.

The E2 embodiment of the instant formulation gives the advantages of a pour-on topical formulation which provides the animal with extended effective treatment and protection against endoparasites and ectoparasites, especially fleas, ticks, mange mites, hookworms, ascarids, and heartworms. Additional advantages of this invention are that the formulation is not readily dislodgeable by petting the animals, it has good spreadability and cold temperature usage.

The E2 embodiment of the instant formulation can contain the avermectin compound, alcohol, water and the polymer as the only ingredients. The formulations will benerally be prepared to administered the avermectin from about 0.005 by weight to about 30% of the total composition, preferrably from 0.1 to 10% by weight and most preferrably about 5% by weight of the active ingredient. At a preferred dose of about 0.5 to 50 mg/kg the formulation is applied at a dose volume of 0.05 to 4.0 ml/kg body weight. The polymer is present in the compositions of the present invention in amounts ranging from about 0% to 20% w/v and preferrably from about 0.5 to 10% w/v by weight of the total composition and up to 95% by volume of alcohol, q.s. to 100% with water.

The preferred E2 embodiment contains in addition to the polymer, alcohol, water and avermectin compound, additional ingredients such as antioxidants and the glycol, glycerides, glycol ethers, and the derivatives thereof mentioned above. The anti-oxidants are generally added to the formulation at rates of from 0.005 to 1.0% (w/v)

and can be propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene), monothioglycerol and the like, preferrably BHT.

The E2 formulation is prepared by dissolving the avermectin compound in the intended volume of alcohol. The anti-oxidant and one of the polymeric materials listed above are then dissolved in the alcohol/avermectin mixture. The volume is then adjusted to 100% by the addition of the final volume of water, with the solution being mixed until it becomes homogeneous. Alternatively, either the BHT or the polymer, or both can be added prior to the addition of the avermectin compound.

The following example is provided in order that the E2 emobodiment of the invention might be more fully understood. It is not to be construed as a limitation of the invention.

EXAMPLE OF E2 OF THE INVENTION

The E2 formulations of this invention which are employed depend upon the particular avermectin compound and treatment. To test the effective killing power of the E2 formulations against fleas and ticks, the following compositions were prepared:

Composition VIII

13-O-MEM AVM	0.3 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Cremophor RH-40	1.0 % w/v
Anhyd. (Denatured) Ethanol	40.0 % v/v
Softigen 767	20.0 % v/v
Water (q.s.)	100.0 % v/v

Composition IX

13-O-MEM AVM	0.3 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Anhydrous Ethanol	75.0 % v/v
Water (q.s.)	100.0 % v/v

BHT	0.01% w/v

Composition X

13-O-MOM AVM	5.0 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Anhydrous Ethanol	90.0 % v/v
Water (q.s.)	100.0 % v/v
BHT	0.01% w/v

Composition XI

13-O-MEM AVM	0.6 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Anhydrous Ethanol	75.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

Composition XII

13-O-MEM AVM	0.6 % w/v
hydrolyzed wheat protein	3.0 % w/v
Anhydrous Ethanol	90.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

Composition XIII

13-O-MEM AVM	0.6 % w/v
Ethocel	2.0 % w/v
Anhydrous Ethanol	90.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

Composition XIV

13-O-MEM AVM	0.6 % w/v
polyvinyl pyrrolidine	5.0 % w/v
Anhydrous Ethanol	80.0 % v/v

Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v
Miglyol	0.5 % v/v

Composition XV

13-O-MEM AVM	0.6 % w/v
acrylates/t-octylpropenamide copoly	1.0 % w/v
polyvinyl pyrrolidone	2.0 % w/v
Anhydrous Ethanol	80.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

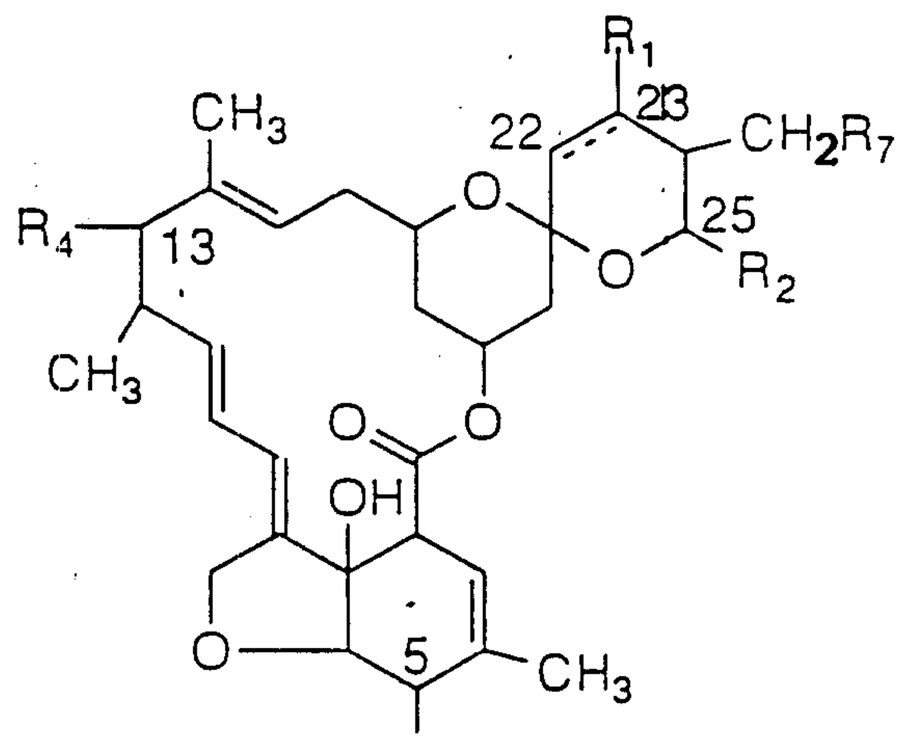
Softigen 767 is a trademark for PEG-6 caprylic/caprate glyceride, Cremophor RH-40 is a trademark for a mixture of glycerol polyethylene and glycol oxysteasrate, and Ethocel is a trademark for ethyl cellulose.

Composition X above was topically applied in multiple locations, typically 2 to 6 points spaced equidistant between the back of the neck and the head of the tail of a flea infested dog. Counts were made by combing the hair, removing and counting the live parasites on the dog at a specified time. The observed flea kills varying the amount of 13-O-MEM AVM, is given in Table No. 1 below, where 60 dogs were allocated to four treatment groups. The dogs were infested with 100 unfed, adult fleas at times indicated by the down arrow ( ), which is equivalent to three days before a flea count is conducted. Treatment was applied on day zero. Table No. 2 summarizes the results of a similar test evaluating the efficacy of the composition, containing 13-O-MEM AVE (termed 2-MEM) in various vehicles, in the treatment of ticks.

The instant formulations can be topically administered to warm blooded animals to provide long acting treatment and protection against endoparasites and ectoparasites either locally at the site of infestation or at multiple points, typically 2 to 6 points (multiple-point-application) along the back of domesticated animals and household pets such as cattle, sheep, cats, dogs and the like.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A topical formulation for direct application to the skin of an animal, effective for treatment and prevention of ectoparasitic and endoparasitic infestations for four weeks, consisting of from about 0.01 to about 20% w/v of a polymeric material, from about 1 to about 95% v/v of ethanol, 100% v/v obtained with addition of water, and from about 0.05 to about 10% w/v of an avermectin compound having the formula:



R3

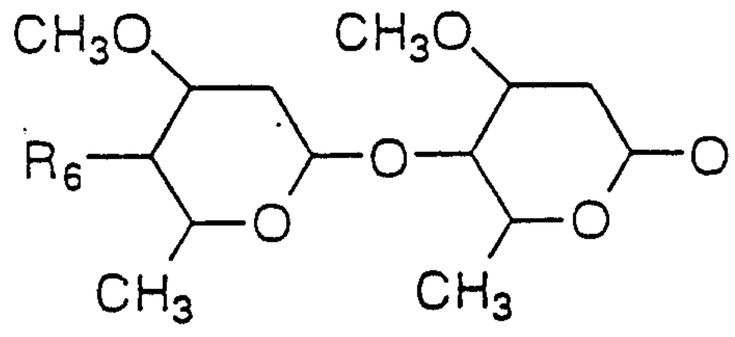
where the broken line indicates a single or a double bond at the 22,23-positions;

R_1 is hydrogen or hydroxy, provided that R_1 is presently only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

R_3 is hydroxy, methoxy, or $=NOR_5$, where R_5 is hydrogen or lower alkyl;

R_7 is hydrogen, hydroxy or lower alkyl; and R_4 is hydrogen, hydroxy, poly C(1-6) alkoxy, or:



where R_6 is hydroxy, amino, mono- or di-C_1-C_6 alkylamino or C_1-C_6 alkanolyl-amino.

2. The formulation of claim 1, wherein R_4 is hydrogen, hydroxy or polyC(1-6)alkoxy.

3. The formulation of claim 1, which contains from 0.1 to 5.0% w/v of the avermectin compound and 5.0 to 10% w/v of the polymeric material and wherein R_4 of the avermectin compound is $CH_3OCH_2CH_2OCH_2O$.

4. The formulation of claim 1, 2 or 3, wherein the polymeric material is selected from the group consisting of polyvinyl pyrrolidone, polyvinyl alcohol, methyl cellulose, ethyl cellulose, carboxy methyl cellulose, hydroxyethyl cellulose, hydrolyzed wheat protein, hydrolyzed animal protein, gelatin derivatives, collagen derivatives, acrylates/t-octylpropenamide copolymer and cationic quaternary amine salts.

5. The formulation of claim 1, 2 or 3, wherein the polymeric material is polyvinyl pyrrolidone.

6. The formulation of claim 5, wherein the polyvinyl pyrrolidone has a molecular weight of about 20,000 to about 65,000.

7. The formulation of claim 5, wherein the polyvinyl pyrrolidone has a molecular weight of 45,000.

8. The formulation of claim 1, 2 or 3, which further contains an anti-oxidant selected from the group consisting of n-propyl gallate, BHA, BHT and monothioglycerol from about 0.005 to 1.0% w/v and an additive selected from the group consisting of propylene glycol, Tween 80(TM), Crodamol/CAP(TM), Vitamin E or glycerol formal, at up to 50% v/v.

9. A topical formulation for direct application to the skin of an animal for effective treatment of parasitic infestations consisting of 5.0% w/v of polyvinyl pyrrolidone, molecular weight 45,000, 5.0% w/v of 22,23-dihydro-13-0-[(2-

methoxyethoxy)methyl]avermectin B1 aglycone, 90% v/v ethanol q.s. to 100% with water and 0.01 w/v BHT.