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(54) ANTHELMINTIC PREPARATIONS

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to anthelmintic preparations containing 4 - (4 - nitroanilino)-phenylisothiocyanate.

It is known that 4 - (4 - nitroanilino)-phenylisothiocyanate has anthelmintic activity: see British Patent Specification No. 1,280,887 and corresponding patent specifications of other countries. Nematodes, inter alia *Strongylidae* and *Ancylostomatidae*, as well as *Cestoda* and *Trematoda* such as *Fasciolidae*, are mentioned as being classes of worms that can be combatted with the substance mentioned. In test examples there are given, inter alia, the favourable results of tests on mice infested with *Hymenolepis nana* (dwarf tapeworm) as well as on rats infested with *Fasciola hepatica* (liver fluke); that is, therefore, favourable results also with regard to combatting helminthes, which are of importance from the point of view not only of veterinary medicine but also of human medicine.

It has now been found that particularly in the combatting of helminthes, which are important in human medicine, in the intestinal tract, such as hookworm (especially *Ancylostoma* or *Necator*), and particularly in the blood stream, such as *Schistosoma* (especially *S. haematobium*, *S. mansoni* and *S. japonicum*), by means of 4 - (4 - (nitroanilino) - phenylisothiocyanate a degree of fineness of the 4 - (4-nitroanilino) - phenylisothiocyanate (m.p. 204—206° C) that is unattainable with normal grinding is of great importance for obtaining a strong and reliable anthelmintic action, and renders possible a surprisingly large reduction of the therapeutically necessary amount of active ingredient. In conformity with these findings, the present invention relates to anthelmintic preparations for oral or rectal administration to warm-blooded animals, which preparations contain an anthelmintically effective amount of 4 - (4 - nitroanilino) - phenylisothiacyanate in solid form having a median of particle size of at most 10 mμ, and particularly of at most 5 mμ, together with suitable pharmaceutical carriers and/or auxiliaries. The active ingredient can be contained in solid preparations, such as in tablets, dragées, capsules or powders, for example as a mixture with other solid substances; or it can be contained in liquid or semi-solid preparations as a suspension, which may also be emulsified. Of particular importance are preparations which consist of the suspensions of the active ingredient in triglycerides or of mixtures of the active ingredient with starches, which are described hereinafter, or preparations which contain such suspensions or mixtures.

The particle size necessary according to the invention can be obtained with the aid of grinding processes known per se; the present invention is not limited in any way to the use of a specific type of mill, such as that mentioned hereinafter as an example, or even to the use of a specific make. A mean particle size of about 10 mμ is obtainable, for example, by grinding the crystallised active ingredient in various known mills, for example in dowelled disc mills. A mean particle size of 10 mμ, and optionally down to 5 μm, can be obtained for example by grinding in jet mills, especially in counter-jet mills. There may be mentioned, merely as examples of such mills, those of George W. Helme Co., Drost-jet Mill Division, Helmetta, New Jersey 08828, USA, see in this respect U.S. Patent Specifications 2,704,635 and 3,229,918, as well as the journal 'Chemie-anlagen + Verfahren' (Chemical plant + Processes) 1970, Issue 7, pages 50—54. Still smaller particle sizes can be attained by wet grinding in stirrer ball mills, for example in water, also in paraffin oil or in triglycerides of higher (above C_{12}) fatty acids, and particularly in triglycerides of C_8—C_{12} saturated fatty acids. As examples of such mills, there may be mentioned the Dyno®-mills, registered trademark of W. A. Bachofen, CH—4005 Basle, see Chemische Rundschau *28* (1975), No. 10,

pages 3—7; Experientia *27* (1971), No. 9, pages 1103—1104; Biotechnology and Biotechnology and Bioengineering *15*, (1973), 125—142 and *16* (1974), 623—634; as well as the Swiss Patent Specification No. 550,024.

The surprising increase in effectiveness as a result of the reduction of particle size according to the invention and optionally of further measures according to the invention is shown, for example, from the results of animal tests summarised below in Tables I and II. In Table I there are given the ED_{50} and ED_{99} values determined on mice infested by *Schistosoma mansoni* and on hamsters infested by *Schistosoma haematobium* in the case of a single administration orally of several preparations which differ from each other in the particle size and in some cases in the type of carrier used.

TABLE I

Test No.	Parasite	Host	Preparation	Median of particle size in μm	ED_{50} mg/kg	ED_{99} mg/kg
1	*S. mansoni*	mouse	aqueous suspension	50	200	300×5**
2	*S. mansoni*	mouse	aqueous suspension	23.2	90	160
3	*S. mansoni*	mouse	aqueous suspension	10	20	80
4	*S. mansoni*	mouse	suspension in triglyceride*	2	9	25
5	*S. haematobium*	hamster	aqueous suspension	50	110	not determined
6	*S. haematobium*	hamster	aqueous suspension	23.2	43	90
7	*S. haematobium*	hamster	suspension in triglyceride*	2	20	20

*) 20% active-ingredient suspension in a synthetic triglyceride mixture of saturated fatty acids C_8 to C_{12} = Miglyol ®, Dynamit Nobel A.G.

**) Treatment on 5 successive days.

On the basis of the ED_{50} and ED_{99} values given in Table I with respect to effectiveness against *Schistosoma mansoni* in the mouse, a reduction of particle size from 23.2 mμ to 10mμ results in a lowering of the doses of equivalent efficacy to about 2/9 to 1/2; and a reduction from 23.2 mμ to 2 mμ, together with administration as a 20% (by weight) suspension in triglycerides of C_8—C_{12} fatty acids, results in a lowering of the values even to 1/10 to 1/6. Also in the case of *Schistosoma haematobium*, a reduction of particle size from 23.2 μm to 2 μm results in a very considerable lowering of the doses of equivalent efficacy.

Table II contains a summary of the results of tests on a primate, the green long-tailed monkey *(Cercopithecus Aethiops)*, infested with *Schistosoma mansoni*. Fifteen long-tailed monkeys were each simultaneously infested, by subcutaneous injection in the cervical region, with 600 cercaria of *Schistosoma mansoni*. The test animals were divided into 5 groups each of three, of which one group served as a control group. The 4 remaining groups were used for testing two test preparations each administered in two doses. The test preparations consisted of 4 - (4 nitroanilino) - phenylisocanate having a median of partical size of 4.23 μm, which in the one case had been processed into the form of tablets in a manner analogous to that of Example 2, and in the other case had been mixed with the 9-fold amount of

maize starch in the manner described in Example 4. The tablets were administered directly per os; the mixture with maize starch was administered as a suspension in the 9-fold amount of water containing 0.1% of Tween 80 (polyoxyethylenesorbitanmonooleate, registered trade-mark, ICI United States Inc., Wilmington DE 19897). The test preparation were administered 53 days after infestation with cercaria. After a further 30 days, the test animals were killed and the total number of male and female *Schistosoma* present in the portal system were determined.

From the autopsy findings given in Table II, obtained from tests made on the animals treated with the two test preparations and on the control animals, there can be seen the effectiveness of the tablets produced according to the invention particularly with respect to the female *Schistosoma* which alone are important regarding the further course of the infestation, and the effectiveness — still further enhanced compared with that of the tablets, of the mixtures produced with maize starch according to the invention.

TABLE II

Preparation	Animal No.	Dose of active ingredient in mg/kg per os	Autopsy findings Number of Schistosoma			Reduction in % compared with control		
			male	female	total	of male	of female	or of all parasites
tablets	791	40	61	33	94			
	792	40	29	19	48	0	25%	0
	793	40	39	21	60			
	794	80	62	32	94			
	796	80	6	7	13	39%	46%	42%
	799	80	3	13	16			
mixture with maize starch	797	20	26	22	48			
	798	20	2	1	3	60%	73%	66%
	800	20	17	3	20			
	801	40	34	1	35			
	804	40	16	0	16	31%	91%	62%
	805	40	29	8	37			
	790		35	33	68			
	795	control	36	32	68			
	803		43	32	75			

The active ingredient of the particle size as defined can be processed with pharmaceutical carrier substances in a manner known per se, e.g. by means of conventional mixing, granulating, coating, suspending and encapsulating methods, into the customary preparations for oral or rectal administration. Thus, anthelmintic preparations for oral application can be obtained by combining the active ingredient of the defined particle size with solid carrier substances; optionally granulating the resulting mixtures; and processing the mixture or granulate, if desired and/or optionally after the addition of suitable auxiliaries, into the form of tablets or dragée cores.

Suitable carrier substances for solid prepara-

tions are, in particular, fillers such as sugar, e.g. lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate; also binding agents, such as starch paste, with the use, e.g., of maize, wheat, rice or potato starch, gelatine, tragacanth, methyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxymethyl cellulose and/or polyvinylpyrrolidone, esters of polyacrylates or polymethacrylates with partially free functional groups; and/or, if required, effervescent agents, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are primarily flow-regulating agents and lubricating agents, e.g. silicic acid, talcum, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, mixtures of mono-, di- and triesters of palmitic and stearic acid with glycerin and/or polyethylene glycol. Dragée cores are provided with suitable coatings, optionally resistant to gastric juices, whereby there are used, inter alia, concentrated sugar solutions optionally containing gum arabic, talcum, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in aqueous solvents or in suitable organic solvents or in mixtures of solvents; or, for producing coatings resistant to stomach juices, solutions of esters of polyacrylates or polymethacrylates having partially free functional groups, or of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate, with or without suitable softeners such as phthalic acid ester or triacetin. Dyestuffs or pigments may be added to the tablets or dragée coatings, e.g. for identification or marking of the various doses of active ingredient.

Further anthelmintic preparations which can be administered orally are hard gelatine capsules, as well as hard or soft closed capsules made from gelatine and, if required, a softener such as glycerin or sorbital. The hard gelatine capsules can contain the active ingredient in the form of a granulate, e.g. in admixture with fillers such as maize starch, optionally granulated wheat starch, binders or lubricants such as talcum, magnesium stearate or colloidal silicic acid, and optionally stabilisers. In closed capsules the active ingredient is in the form of a powder or granulate; or it is preferably suspended in suitable liquids such as paraffin oil, liquid polyethylene glycols, or preferably triglycerides of C_8—C_{12} or higher fatty acids whereby for stabilising the suspensions there can be added, e.g., glycerin monostearate.

Other anthelmintic preparations to be administered orally are, for example, aqueous suspensions prepared in the usual manner, which suspensions contain the active ingredient in the suspended form and at a concentration rendering a single dose sufficient. The aqueous suspensions either contain at most small amounts of stabilisers and/or flavouring substances, for example sweetening agents such as saccharin-sodium, or as syrups contain a certain amount of sugar and/or sorbitol or similar substances. Also suitable are, for example, pulverulent concentrates or concentrated suspensions for the prepartion of shakes. Such concentrates can also be packed in single-dose amounts.

Suitable anthelmintic preparations for rectal administration are, for example, suppositories consisting of a combination of the active ingredient with a suppository foundation substance. Such substances are, for example, natural or synthetic triglyceride mixtures, paraffin hydrocarbons, polyethylene glycols or suitable alkanols. Also suitable are gelatine rectal capsules consisting of a combination of the active ingredient with a foundation substance. Suitable foundation substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Of particular importance among the above-mentioned preparations are those which contain the active ingredient as a suspension in an oily carrier substance, especially in triglycerides of fatty acids, particularly of C_8—C_{12} saturated fatty acids, as well as a small amount of a suspension stabiliser such as glycerin monostearate. There may be mentioned, merely as examples of corresponding triglycerides available commercially, Miglyol 812 and Miglyol 810, registered trade-marks of Dynamit Nobel A.G. for triglyceride mixtures of saturated fatty acids C_8—C_{12} and C_8—C_{10}, respectively; as well as Myritol 318 and Syndermin GTC, registered trade-marks for octanoic acid/decanoic acid triglycerides of the series of Dehydag products of Henkel u. Co., G.m.b.H. The triglycerides mentioned are very suitable as grinding liquids for wet grinding, and at the same time they facilitate also the absorption of the active ingredient in the intestines. By virtue of the last-mentioned property, the stated triglycerides are particularly advantageously used for producing preparations for combatting helminthes present in the blood stream, such as *Schistosoma*. The suspensions most suitable for grinding are those having a content of active ingredient of 10 to 30% (by weight), preferably about 20% (by weight). A lower concentration of active ingredient desired for specific preparations can be obtained by subsequent addition of the natural or synthetic triglycerides mentioned or of others.

Likewise of particular interest are preparations containing the finely ground active ingredient, preferably that having a median of particle size of 5 mμ or less, in admixture with a starch, especially with maize starch or wheat starch, also, for example, with potato

starch or rice starch. Such admixtures preferably have a content of active ingredient of 5 to 20% (by weight), particularly 10% (by weight). They are produced preferably by means of a brief mixing in a high-speed mixer having a propeller-like, sharp-edged stirring device at a speed of at least 15,000 rpm, for example with a mixing time of from 3 to 10 minutes, and in the case of larger amounts of constituents with cooling if necessary. In this mixing process, the particles of the active ingredient are uniformly deposited, with a continuing reduction of the size of some particles, onto the starch particles. The mixtures of the active ingredient with starches, especially the mixtures obtained in the aforesaid manner, are characterised, as seen from, inter alia, the described tests on the green long-tailed monkey, by a particularly high degree of effectiveness, which moreover is subject to less variation from one host animal to another. The mixtures mentioned can be processed with the customary, e.g. the aforementioned, auxiliaries into the form of solid dosage units; i.e., pressed for example into the form of tablets or dragées or filled into capsules. They can however also be used directly, or after the addition of auxiliaries, e.g. pharmaceutically acceptable wetting agents and distributing agents, such as esters of polyoxyethylene sorbitans with fatty acids above C_{12} or sodium lauryl sulphate, and/or flavouring substances, as concentrates for the preparation of aqueous suspensions, e.g. with the approx. 5- to 20-fold amount of water. Instead of combining the active ingredient/starch mixture with a surface-active substance or with other auxiliaries, these substances may also be added to the water used to prepare the suspension. The concentrates for producing suspensions, consisting of the active ingredient/starch mixtures and optionally auxiliaries, can be packed in single-dose amounts, if required in an airtight and moistureproof manner.

Anthelmintic preparations according to the invention contain the active ingredient at a concentration suitable for administration of the following doses to warm-blooded animals, which concentration is, depending on the mode of administration, from 5% to 95% (by weight), preferably from 10% to 90% (by weight). In the case of suspensions, the concentration is usually not higher than 30% (by weight), preferably about 20% (by weight), and conversely in the case of tablets, dragées and capsules with a pulverulent active ingredient the concentration is preferably not lower than about 40% (by weight) in order to ensure an easy ingestion of the required doses of active ingredient. Tablets, dragées and capsules having a pulverulent active ingredient contain 100 to 1000 mg, preferably 200—500 mg, of active ingredient; and capsules filled with suspensions contain for example 50—300 mg, preferably 100—200 mg, of active ingredient.

The treatment of warm-blooded animals infested with parasitic helminthes with the preparations according to the invention is carried out preferably by a single oral or rectal administration of an amount which contains a dose of 4 - (4 - nitroanilino) - phenylisothiocyanate sufficient to practically completely free the warm-blooded animal from the parasitic helminthes, that is to say, an amount which contains a curative dose. If required, the curative dose can be divided into several partial doses which are administered at intervals of several hours, but all on the same day. The administered dose of the active ingredient, 4 - (4 - nitroanilino) - phenylisothiocyanate, is dependant both on the species and general condition of the warm-blooded animal to be treated and on the genus and species of the helminthes to be combatted, with their specific pattern of life and manner of reproduction, and is preferably from 5 to 80 mg/kg, especially from to 5 to 30 mg/kg. For a fairly large warm-blooded animal of 50—70 kg body weight for example, the dose to be administered is 250 to 2100 mg.

4 - (4 - Nitroanilino) - phenylisothiocyanate is effective, with very good compatibility, e.g. in experimental animals such as the mouse, rat, hamster, Mongolian Jird *(Meriones unguiculatus)*, dog, monkey or fowl, against nematodes such as *Ascaridia*, e.g. *Ascaridia galli*, *Trichostrongylidae*, e.g. *Nippostrongylus brasiliensis* or *Nematospiroides dubius*, *Ancylostomatidae*, e.g. *Necator americanus* and *Ancylostoma ceylanicum*, and *Strongylidae;* against *Cestoda* such as *Hymenolepsis nana*, *Anoplocephalidae* and *Taeniidae;* and particularly against Trematoda such as *Fasciolida*, e.g. *Fasciola hepatica*, and especially *Schistosoma*, e.g. *Schistosoma mansoni*, *Schistosoma japonicum* and *Schistosoma haematobium;* also against the pathogens of filariasis, e.g. *Dipetalonema witei* and *Litomosoides carinii*. The anthelmintic preparations according to the invention can be used therefore for the treatment of warm-blooded animals in the case of infestation with parasitic helminthes such as the aforementioned, especially for the treatment of warm-blooded animals affected by schistosomiasis, hookworm infestation or filariasis.

The following Examples further illustrate the invention but in no way do they limit the scope thereof.

Example 1.

200 g of 4 - (4 - nitroanilino) - phenylisothiocyanate of a medium particle size of about 50mμ or less is mixed with 800 ml of a mixture of triglycerides of saturated fatty acids of the chain length C_8—C_{12}, and the suspension is ground in a DYNO® mill until the median of the particle size of the active ingredient is 1—3 mμ. An addition is made of 5 g of glycerin monostearate to stabilise the suspension, and the volume is made up with the em-

ployed triglyceride to 1000 ml. The resulting suspension can be filled into gelatine capsules, in amounts of 0.50 ml and 0.75 ml, corresponding to 100 mg and 150 mg, respectively, of active ingredient, or, after the addition of flavouring substances, in amounts of, e.g., 2.5 ml and 5.0 ml, corresponding to 500 mg and 1000 mg, respectively, of active ingredient; or, for individual needs, the suspensions can also be administered dropwise.

Example 2.

To produce 10,000 tablets each containing 500 mg of active ingredient, 5.0 kg of 4 - (4-nitroanilino) - phenylisothiocyanate is mixed with agglutinated wheat starch obtained by agglutination of 0.55 kg of wheat starch with about 1.3 kg of demineralised water, and the mixture is uniformly moistened with a further 0.5 kg of demineralised water; it is then kneaded into the form of a slightly plastic mass and subsequently pressed through a sieve having a mesh size of about 3 mm. The granulate is afterwards dried and again put through a sieve. To the dry granulate, the gramular size of which has been made uniform, there are added 50 g of magnesium stearate, 30 g of talcum and 270 g of maize starch, 30 g of colloidal silicon dioxide, 900 g of a mixture of microcrystalline cellulose and carboxymethylcellulose, e.g. Avicel®, FMC Corp., American Viscose Division, and 100 g of sodium lauryl sulphate. The resulting mixture is pressed into the form of tablets.

4 - (4 - nitroanilino) - phenylisothiocyanate is used in the form of the ground substance having a median of particle size of at most 10 mμ, especially of at most 5 mμ, for example 4.23 mμ.

Example 3.

To produce 10.0 litres of a 10% aqueous suspension, 1.0 kg of 4 - (4 - nitroanilino)-phenylisothiocyanate, ground in a counter-jet mill until the median of the particle size is about 10 mμ, is suspended in a solution of 300 g of sodium carboxymethylcellulose, 20 g of sodium lauryl sulphate, 60 g of a mixture of the sodium salts of p-hydroxybenzoic acid methyl ester and p-hydroxybenzoic acid propyl ester in 5.0 kg of demineralised water; and the suspension is made up to the desired volume of 10.0 litres. To the aqueous suspension there can also be added saccharin sodium, sugar and/or sorbitol, as well as the customary flavouring substances. The suspension can be measured out in the way that a syrup is by means of a measuring vessel or tea-spoon, or for individual dosage requirements it can be measured out dropwise.

It is also possible to further grind the active ingredient ground in a counter-jet mill, or another pre-ground active ingredient, together with 5.0 kg of demineralised water containing 30 g of sodium lauryl sulphate, in a stirrer ball mill, e.g. in a Dyno® mill, to give a median of particle size of about 5 mμ, to subsequently add the remaining substances mentioned above; and to then make up the suspension to 10.0 litres.

Example 4.

5.0 g of 4 - (4 - nitroanilino) - phenylisothiocyanate having a median of particle size of 4.23 mμ is physically mixed under normal room conditions for 5 minutes with 45.0 g of maize starch. The mixing apparatus employed is a high-speed mixer having a propeller-like, sharp-edged stirring mechanism and a rotary speed of at least 15,000 r.p.m. There is obtained a homogeneous mixture having the properties described hereinbefore, cp. Table II.

The resulting powder mixture, as such or filled into capsules or suspended in an aqueous medium, can be administered perorally in dosages adapted to individual needs.

WHAT WE CLAIM IS:—

1. Anthelmintic preparations for oral or rectal administration to warm-blooded animals, which preparations contain an anthelmintically effective amount of 4 - (4 - nitroanilino)-phenylisothiocyanate in solid form having a median of particle size of at most 10 mμ together with suitable pharmaceutical carriers and/or auxilliaries.

2. Anthelmintic preparations according to Claim 1, wherein the solid 4 - (4 - nitroanilino) - phenylisothiocyanate has a median of particle size of at most 5 mμ.

3. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in admixture with a starch.

4. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in combination admixture with maize starch, wheat starch, potato starch or rice starch.

5. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in the form of a mixture with maize starch.

6. Anthelmintic preparations according to any one of Claims 3, 4 and 5, which preparation contains 5 to 20% by weight of 4 - (4-nitroanilino) - phenylisothiocyanate.

7. Anthelmintic preparations according to any one of Claims 3, 4, 5 and 6 which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in admixture with a starch which can be obtained by mixing in a high-speed mixer having a propeller-like, sharp-edged stirring device at a speed of at least 15000 rpm.

8. Anthelmintic preparations according to any one of Claims 3, 4, 5, 6 and 7, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in admixture with a starch,

ployed triglyceride to 1000 ml. The resulting suspension can be filled into gelatine capsules, in amounts of 0.50 ml and 0.75 ml, corresponding to 100 mg and 150 mg, respectively, of active ingredient, or, after the addition of flavouring substances, in amounts of, e.g., 2.5 ml and 5.0 ml, corresponding to 500 mg and 1000 mg, respectively, of active ingredient; or, for individual needs, the suspensions can also be administered dropwise.

Example 2.

To produce 10,000 tablets each containing 500 mg of active ingredient, 5.0 kg of 4 - (4-nitroanilino) - phenylisothiocyanate is mixed with agglutinated wheat starch obtained by agglutination of 0.55 kg of wheat starch with about 1.3 kg of demineralised water, and the mixture is uniformly moistened with a further 0.5 kg of demineralised water; it is then kneaded into the form of a slightly plastic mass and subsequently pressed through a sieve having a mesh size of about 3 mm. The granulate is afterwards dried and again put through a sieve. To the dry granulate, the granular size of which has been made uniform, there are added 50 g of magnesium stearate, 30 g of talcum and 270 g of maize starch, 30 g of colloidal silicon dioxide, 900 g of a mixture of microcrystalline cellulose and carboxymethylcellulose, e.g. Avicel®, FMC Corp., American Viscose Division, and 100 g of sodium lauryl sulphate. The resulting mixture is pressed into the form of tablets.

4 - (4 - nitroanilino) - phenylisothiocyanate is used in the form of the ground substance having a median of particle size of at most 10 mμ, especially of at most 5 mμ, for example 4.23 mμ.

Example 3.

To produce 10.0 litres of a 10% aqueous suspension, 1.0 kg of 4 - (4 - nitroanilino)-phenylisothiocyanate, ground in a counter-jet mill until the median of the particle size is about 10 mμ, is suspended in a solution of 300 g of sodium carboxymethylcellulose, 20 g of sodium lauryl sulphate, 60 g of a mixture of the sodium salts of p-hydroxybenzoic acid methyl ester and p-hydroxybenzoic acid propyl ester in 5.0 kg of demineralised water; and the suspension is made up to the desired volume of 10.0 litres. To the aqueous suspension there can also be added saccharin sodium, sugar and/or sorbitol, as well as the customary flavouring substances. The suspension can be measured out in the way that a syrup is by means of a measuring vessel or tea-spoon, or for individual dosage requirements it can be measured out dropwise.

It is also possible to further grind the active ingredient ground in a counter-jet mill, or another pre-ground active ingredient, together with 5.0 kg of demineralised water containing 30 g of sodium lauryl sulphate, in a stirrer ball mill, e.g. in a Dyno® mill, to give a median of particle size of about 5 mμ, to subsequently add the remaining substances mentioned above; and to then make up the suspension to 10.0 litres.

Example 4.

5.0 g of 4 - (4 - nitroanilino) - phenylisothiocyanate having a median of particle size of 4.23 mμ is physically mixed under normal room conditions for 5 minutes with 45.0 g of maize starch. The mixing apparatus employed is a high-speed mixer having a propeller-like, sharp-edged stirring mechanism and a rotary speed of at least 15,000 r.p.m. There is obtained a homogeneous mixture having the properties described hereinbefore, cp. Table II.

The resulting powder mixture, as such or filled into capsules or suspended in an aqueous medium, can be administered perorally in dosages adapted to individual needs.

WHAT WE CLAIM IS:—

1. Anthelmintic preparations for oral or rectal administration to warm-blooded animals, which preparations contain an anthelmintically effective amount of 4 - (4 - nitroanilino)-phenylisothiocyanate in solid form having a median of particle size of at most 10 mμ together with suitable pharmaceutical carriers and/or auxilliaries.

2. Anthelmintic preparations according to Claim 1, wherein the solid 4 - (4 - nitroanilino) - phenylisothiocyanate has a median of particle size of at most 5 mμ.

3. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in admixture with a starch.

4. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in combination admixture with maize starch, wheat starch, potato starch or rice starch.

5. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in the form of a mixture with maize starch.

6. Anthelmintic preparations according to any one of Claims 3, 4 and 5, which preparation contains 5 to 20% by weight of 4 - (4-nitroanilino) - phenylisothiocyanate.

7. Anthelmintic preparations according to any one of Claims 3, 4, 5 and 6 which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in admixture with a starch which can be obtained by mixing in a high-speed mixer having a propeller-like, sharp-edged stirring device at a speed of at least 15000 rpm.

8. Anthelmintic preparations according to any one of Claims 3, 4, 5, 6 and 7, which contain the solid 4 - (4 - nitroanilino) - phenylisothiocyanate in admixture with a starch,

* C L M S *

which mixture is suspended in water.

9. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4-nitroanilino) - phenylisothiocyanate in the form of a suspension in triglycerides of C_8—C_{12} saturated fatty acids.

10. Anthelmintic preparations according to Claim 9, which contain the solid 4 - (4-nitroanilino) - phenylisothiocyanate having a median of particle size of at most 5 μm in the form of a suspension in triglycerides of C_8—C_{12} saturated fatty acids.

11. Anthelmintic preparations according to any one of Claims 9 and 10, which preparations contain 10 to 30% by weight of 4 - (4 - nitroanilino) - phenylisothiocyanate.

12. Anthelmintic preparations according to any one of Claims 9 and 10, which preparations contain about 20% by weight of 4 - (4-nitroanilino) - phenylisothiocyanate.

13. Anthelmintic preparations according to Claim 1, which contain the solid 4 - (4-nitroanilino) - phenylisothiocyanate in the form of an aqueous suspension.

14. Anthelmintic preparations according to Claim 8 or 13 which preparations contain 5 to 20% by weight of 4 - (4 - nitroanilino)-phenylisothiocyanate.

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