Convention Application for a Patent

73612/81

We MERCK & CO., INC.

of 126 East Lincoln Avenue
Rahway, New Jersey
United States of America

hereby apply for the grant of a Patent for an invention entitled

"STABILIZED FORMULATION OF IVERMECTIN IN WATER"

which is described in the accompanying complete specification.

This application is a Convention Application and is based on the
application numbered 174,957

for a patent or similar protection made in
the United States of America

on 4 August 1980.

My address for service is:

Care: SPRUSON & FERGUSON
PATENT ATTORNEYS
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AUSTRALIA.

Dated May 12, 1981 MERCK & CO., INC.

James F. Naughton
Manager-Administration
Off. of V.P. & Gen. Counsel

To: The Commissioner of Patents

The Common Seal of MERCK & CO., INC. was hereto
affixed in the presence of:-
In support of the Convention Application made for a patent for an invention entitled "STABILIZED FORMULATION OF IVERMECTIN IN WATER"

1. I, JAMES F. NAUGHTON, Manager-Administration, of MERCK & CO., Inc., 126 East Lincoln Avenue, Rahway, New Jersey, United States of America do solemnly and sincerely declare as follows:—

2. The basic application as defined by Section 141 of the Act was made in the United States of America on 4th August, 1980 by PAK-KAN ALBERT LO and JAMES B. WILLIAMS.

3. PAK-KAN ALBERT LO and JAMES B. WILLIAMS
17 Lombardi Street, Edison, New Jersey 08817
4 Coventry Drive, Freehold, New Jersey 07728 both in United States of America, respectively

4s/are the actual inventor/s of the invention and the facts upon which the said Company is entitled to make the application are as follows:

The said Company is the assignee of the inventor/s.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

Declared at Rahway, New Jersey, U.S.A. this ___ day of May 1981.

To:
The Commissioner of Patents,
Commonwealth of Australia.

[Signature]
James F. Naughton
Manager-Administration
Off. of V.P. & Gen. Counsel
Claim 1. A stabilized aqueous formulation which comprises Ivermectin in a solution of a surface active agent and water and including one or more of a co-solvent selected from a water miscible organic solvent suitable for parenteral or oral administration, and one or more of a substrate also suitable for parenteral or oral administration.
The following statement is a full description of this invention, including the best method of performing it known to us:

"STABILIZED FORMULATION OF IVERMECTIN IN WATER"
TITLE OF THE INVENTION

Stabilized Formulation of Ivermectin in Water

ABSTRACT OF THE DISCLOSURE

Ivermectin, an antiparasitic agent which is 5 insoluble and unstable in water, is solubilized by the formation of colloidal particles, called micelles, with surface active agents as solubilizers and stabilized by using cosolvents and/or appropriate substrates in the aqueous formulation. The liquid formulations are 10 suitable for use as parenteral or oral administration for the treatment of parasitic infections.
TITLE OF THE INVENTION

Solubilization of Ivermectin in Water

BACKGROUND OF THE INVENTION

Ivermectin is a new and very potent anti-parasitic agent which is useful against a broad spectrum of endoparasites and ectoparasites in mammals as well as having agricultural uses against various parasites found in and on crops and in soil. Ivermectin is disclosed in U.S. Patent 4,199,569, issued 22 April, 1980 to Chabala and Fisher. Ivermectin is a mixture, in the ratio of approximately 80:20 of 22,23-dihydro C-076 Bla and Blb. In administering Ivermectin to animals it is most convenient for parenteral formulations to use an aqueous solution. Non-aqueous solutions tend to cause irritation and tissue damage at the injection site; precipitate the active ingredient at the injection site; have higher viscosity and poorer syringability; and generally have a higher cost. Aqueous liquid formulations for oral use are also preferred over non-aqueous formulations because non-aqueous solvents tend to have an unacceptable taste.
Thus, it is desirable to prepare an aqueous liquid formulation of Ivermectin. However, Ivermectin has very poor solubility in water, at a level of about 0.005 mg per ml at room temperature.

Ivermectin can be solubilized using surface active agents as solubilizers. This results in the formation of micelles, or minute colloidal particles which surround the Ivermectin molecule, isolating it from the water, but forming a clear solution in the water. Such a solution does contain sufficient active ingredient in order to prepare liquid formulations, for oral or parenteral use. However, it was discovered that such micelle formulations were unstable and the Ivermectin degraded at such a rate as to render the shelf life inadequate for a commercial preparation.

It was unexpectedly discovered during the investigation of this instability that the use of certain cosolvents and/or substrates would reduce the instability and result in an aqueous liquid solution which is suitable for parenteral or oral administration, and which had adequate shelf life such that a viable commercial preparation was afforded.

SUMMARY OF THE INVENTION

The instant invention concerns the solubilization and stabilization of Ivermectin, a new anthelmintic agent using surface active agents to dissolve the Ivermectin, and certain cosolvents and substrates to stabilize the thus formed micelle solution. Thus, it is an object of this invention to describe such a solution. A further object is to describe the parenteral and oral formulations which can be prepared using such a solution. A still further object is to describe the solubilizing agents, cosolvents
and substrates which are employed in such solutions and formulations. Further objects will become apparent from a reading of the following description.

**DESCRIPTION OF THE INVENTION**

The instant invention resides in the unexpected stabilization of an aqueous solution of Ivermectin prepared from water and a surface active agent, wherein one or both of a cosolvent and a substrate are added. The cosolvent and the substrate individually reduce the instability of the Ivermectin solution, however, the combination of both the cosolvent and the substrate are found to surprisingly increase the stability of the solution even further.

The aqueous Ivermectin solution is initially formed by dissolving the Ivermectin in a pharmacologically acceptable surfactant. A different surfactant will be employed depending upon the parenteral or oral acceptability of the final formulation.

For parenteral use a pharmacologically acceptable non-ionic surfactant will be employed. Examples of such non-ionic surfactants will be polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisoesterate polyoxyethylene sorbitan monostearate polyoxyethylene sorbitan monoleate (also known as polysorbate 80 or Tween 80) and the like. The preferred surface active agent is polysorbate 80.

For oral use, a pharmacologically acceptable non-ionic surfactant or an anionic surfactant will be employed. The non-ionic surfactants used for the parenteral formulation may also be employed for the oral formulation, and again polysorbate 80 is preferred. For anionic surfactants examples of such will be, diocylsodium sulfosuccinate (also known as Aerosol OT) and the like.
The preferred anionic surfactant is diotylsodium sulfosuccinate. The most preferred of the non-ionic and anionic surfactants is polysorbate 80.

The aqueous solution of Ivermectin and the surface active agent is prepared by dissolving the Ivermectin in the surface active agent such that the surface active agent will constitute from 4 to 25% w/v of the final solution. The Ivermectin is present in different amounts for parenteral and oral uses. For parenteral formulations the Ivermectin is present at from 0.1 to 7.5% w/v and for oral formulations the Ivermectin is present in from 0.01 to 2.0% w/v. Water may then be added to the surfactant solution to form a clear solution.

The cosolvents which are employed and which have been found to dramatically increase the stability of the Ivermectin are water miscible organic solvents which are suitable for parenteral or oral administration. Examples of such cosolvents are glycerol formal, propylene glycol, glycérine, polyethylene glycol and the like. The preferred cosolvent is glycerol formal for parenteral administration and propylene glycol for oral administration. The cosolvents are added to the final formulation to the extent of 10 to 40% v/v of the final formulation.

The substrates which are used to stabilize the formulation, either alone or in combination with the cosolvent are benzyl alcohol, lidocain, parabens, choline, and the like. Benzyl alcohol and lidocaine are the preferred substrates and both have been used in a single formulation with acceptable results. The substrates are present in the final formulations at a concentration of from about 1 to 5% w/v. Benzyl alcohol
is specifically present at about 1 to 5% v/v and lidocaine is present at about 1 to 4% w/v.

The preferred process for preparing the formulation is to combine the Ivermectin in a mixture of the surface active agent, the cosolvent and the substrate. At this time also buffering agents and other adjuvants which assist in the final formulation may be added. Water is then added to the desired volume, or almost the desired volume, and the pH adjusted, if necessary, to a range of 6.0 and 6.5 for optimum stability. The final volume is adjusted to the desired amount and the solution sterilized by autoclaving or membrane filtration.

The stability of the Ivermectin aqueous solution is thus greatly improved through the use of the above-described cosolvents and substrates. Without such cosolvents and substrates, the solution of Ivermectin formed by combining the drug in a surfactant and adding water, is observed to have a 50% stability per month at room temperature. That is 50% of the Ivermectin is lost after only one month. By combining a cosolvent or a substrate with the surfactant, the stability is seen to dramatically increase to about 10% in 2 to 3 months; or about 5% loss of Ivermectin activity per month. When both the cosolvent and the substrate are used in the surfactant formulation the stability of the resultant aqueous formulation is seen to even more dramatically increase its stability to less than 5% in 2 to 3 years.

The reason behind this dramatic and unexpected stabilizing effects resulting from the use of the cosolvent and the substrate are not completely understood.
While we do not wish to be bound by theory it appears that the initial micelle formation with the Ivermectin and the substrate, water is still able to penetrate the micelle, or otherwise contact the Ivermectin, even though it is surrounded by the surface active agent. The cosolvent and the substrate apparently displace the water of hydration of the micelle and further isolate the Ivermectin from the water which contacts the outside surface of the micelle, thus reducing the reaction of the water upon the Ivermectin and increasing the stability of the resultant solution.

The resultant solution avoids all of the disadvantages of non-aqueous formulations while retaining the required attributes of a parenteral or oral formulation. The solution is stable, both chemically and physically; it is low in viscosity, therefore its syringability is excellent; it does not cause any irritation or tissue damage at the injection site; its taste is not objectionable upon oral administration; the solution is totally dilutable with water without precipitating the Ivermectin; the Ivermectin is rapidly absorbed; and the solution is produced at low cost.

Thus, the unexpected stability of the instant aqueous solution as provided by the instant Ivermectin is seen to provide for a totally acceptable formulation for parenteral or oral administration.

The following examples of aqueous formulations using the instant invention are provided in order that the invention might be more fully understood. They are not to be construed as limitative of the invention.
EXAMPLE 1

Ivermectin Injectable Solution (10 mg/mL)

Formula

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-933</td>
<td>1.0%w/v</td>
</tr>
<tr>
<td>TWEEN 80</td>
<td>8%w/v</td>
</tr>
<tr>
<td>Glycerol Formal</td>
<td>20%w/v</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2%w/v</td>
</tr>
<tr>
<td>Benzyl Alcohol</td>
<td>1%v/v</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>q.s. 100%v/v</td>
</tr>
</tbody>
</table>

pH adjusted to 6.2 using 1N HCl

Procedure

1. Dissolve MK-933 and lidocaine in TWEEN 80, glycerol formal, and benzyl alcohol.
2. Add water for injection equal to 80% of final volume.
3. Adjust pH of the solution to 6.2 using 1N HCl.
4. Adjust the solution to volume with water for injection.
5. Sterilize by autoclave or membrane filtration and package aseptically.

EXAMPLE 2

Ivermectin Injectable Solution (20 mg/mL)

Formula

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-933</td>
<td>2.0%w/v</td>
</tr>
<tr>
<td>TWEEN 80</td>
<td>12%w/v</td>
</tr>
<tr>
<td>Glycerol Formal</td>
<td>25%v/v</td>
</tr>
<tr>
<td>Benzyl Alcohol</td>
<td>3% v/v</td>
</tr>
<tr>
<td>Sodium Phosphate Dibasic - Anhydrous</td>
<td>0.1%w/v</td>
</tr>
<tr>
<td>Sodium Phosphate Monobasic - Monohydrate</td>
<td>0.9w/v</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>q.s. 100%w/v</td>
</tr>
</tbody>
</table>
Procedure
1. Dissolve MK-933 in TWEEN 80, glycerol formal, and benzyl alcohol.
2. Disperse the buffer salts into the solution.
3. Add water for injection and agitate until a clear solution is obtained.
4. Adjust the solution to volume with water for injection.
5. Sterilize by autoclave or membrane filtration and package aseptically.

EXAMPLE 3
Ivermectin Oral Solution (0.8 mg/mL)

Formula

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-933</td>
<td>0.08% w/v</td>
</tr>
<tr>
<td>TWEEN 80</td>
<td>8.0% w/v</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>20% v/v</td>
</tr>
<tr>
<td>Benzyl Alcohol</td>
<td>3% v/v</td>
</tr>
<tr>
<td>Sodium Phosphate Dibasic - Anhydrous</td>
<td>0.1% w/v</td>
</tr>
<tr>
<td>Sodium Phosphate Monobasic - Monohydrate</td>
<td>0.9% w/v</td>
</tr>
<tr>
<td>Water, Purified</td>
<td>q.s. 100% w/v</td>
</tr>
</tbody>
</table>

Procedure
1. Dissolve MK-933 in TWEEN 80, propylene glycol, and benzyl alcohol.
2. Disperse the buffer salts into the solution.
3. Add purified water and agitate until a clear solution is obtained.
4. Adjust the solution to volume with purified water and package.
WHAT IS CLAIMED IS:

The claims defining the invention are as follows:

1. A stabilized aqueous formulation which comprises Ivermectin in a solution of a surface active agent and water and including one or more of a co-solvent selected from a water miscible organic solvent suitable for parenteral or oral administration, and one or more of a substrate also suitable for parenteral or oral administration.

2. The stabilized aqueous formulation of Claim 1 which contains from 0.1 to 7.5% w/v of Ivermectin; for parenteral administration or from 0.01 to 2.0% w/v of Ivermectin for oral administration; from 4 to 25% w/v of the surface active agent; from 10 to 40% v/v of the cosolvent; and from 1 to 5% w/v of the substrate.

3. The stabilized aqueous formulation of Claim 2 wherein the surface active agent is selected from polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate and polysorbate 80; the cosolvent is selected from glycerol formal, propylene glycol, glycerine, and polyethylene glycol; and the substrate is selected from benzyl alcohol, lidocaine, parabens, and choline.

4. The stabilized aqueous formulation of Claim 3 wherein the surface active agent is polysorbate 80; the cosolvent is glycerol formal or propylene glycol; and the substrate is benzyl alcohol or lidocaine.
5. The stabilized aqueous formulations of Claim 1 which comprises Ivermectin in a solution of a surface active agent and water and including a co-solvent selected from a water miscible organic solvent suitable for parenteral or oral administration.

6. The stabilized aqueous formulation of Claim 5 which contains from 0.1 to 7.5% w/v of Ivermectin for parenteral administration or from 0.01 to 2.0% w/v of Ivermectin for oral administration, from 4 to 25% w/v of a surface active agent selected from polyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate and polysorbate 80; and from 10 to 40% v/v of a cosolvent selected from glycerol formal, propylene glycol, glycerine, and polyethylene glycol.

7. The stabilized aqueous formulation of Claim 6 wherein the surface active agent is polysorbate 80 and the cosolvent is glycerol formal or propylene glycol.

8. The stabilized aqueous formulations of Claim 1 which comprises Ivermectin in a solution of a surface active agent and water and including one or more of a substrate suitable for parenteral or oral administration.
9. The stabilized aqueous formulation of Claim 8 which comprises from 0.1 to 7.5% w/v of Ivermectin; for parenteral administration or from 0.01 to 2.0% w/v of Ivermectin for oral administration; from 4 to 25% w/v of the surface active agent selected from polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monostearate and polysorbate 80; and from 1 to 5% w/v of a substrate selected from one or more of benzyl alcohol, lidocaine parabens, and choline.

10. The stabilized aqueous formulation of Claim 9 wherein the surface active agent is polysorbate 80 and the substrate is one or both of benzyl alcohol and lidocain.

11. A process for preparing a stabilized aqueous formulation containing Ivermectin, which comprises dissolving Ivermectin in a surface active agent containing one or both of 1) a cosolvent comprising one or more of a water miscible organic solvent suitable for parenteral administration and 2) one or more of a substrate suitable for parenteral or oral administration; adding water to the thus prepared solution to the desired volume and adjusting the pH if necessary.
12. The process of Claim 11 wherein the final solution contains from 0.1 to 7.5% w/v of Ivermectin for parenteral administration or from 0.01 to 2.0% w/v of Ivermectin for oral administration; a surface active agent present at from 4 to 25% w/v of polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, polyoxyethylene sorbitan monooleate or polysorbate 80; a cosolvent present at from 10 to 40%v/v of glycerol formal, propylene glycol, glycerine or polyethylene glycol; the substrate is present at from 1 to 5%w/v of one or more of benzyl alcohol, lidocaine, parabens or choline; and the pH is adjusted to from 6 to 6.5.

13. The process of Claim 12 wherein the surface active agent is polysorbate 80, the cosolvent is glycerol formal or propylene glycol and the substrate is one or both of benzyl alcohol or lidocaine.

DATED this EIGHTEENTH day of JUNE, 1981

MERCK & CO., INC.

Patent Attorneys for the Applicant
SPRUSON & FERGUSON