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2,735,798

ACYL AMINO-NITROTHIAZOLE COMPOSITIONS FOR ORAL ADMINISTRATION IN CONTROL OF TRICHOMONAS VAGINALIS VAGINITIS

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The present invention relates to a new and improved therapeutic tablet for the treatment of certain protozoan infections, and more particularly to a novel and highly effective pharmaceutical preparation designed for the treatment of *Trichomonas vaginalis* vaginitis.

Trichomonas vaginalis, a parasitic protozoon primarily infests the human vagina and is the ethological agent of a very troublesome and prevalent form of vaginal infestation known as *Trichomonas vaginalis* vaginitis.

Various medicaments and methods of treatment have heretofore been employed in the treatment of *Trichomonas vaginalis* vaginitis, particularly by topical application to the vaginal mucosa, but all have been subjected to numerous limitations and disadvantages. Organic acids such as acetic, lactic, and citric acids are commonly used topically but are characterized by very low trichomonadical action, and in many instances they fail satisfactorily to clear up the infestation, even when the therapy is continued for long periods of time. Silver picrate, another agent in common topical use, has good trichomonadical properties but is objectionable for it frequently gives rise to severe sensitizations, argyria and the like, and also because it produces aesthetically unacceptable stains. Phenyl mercuric nitrate or acetate are active trichomonadical compounds, but are reported to be unstable except at a limited pH range (7.4 to 7.6) which differs considerably from the pH of a human vagina moderately or heavily infested with *Trichomonas vaginalis*. Other preparations comprising various agents in powdered form such as boric acid, diiodoquinone, lactose, dextrose, and silver picrate, are commonly applied to an infested vagina by insufflation. However, vaginal insufflation of pregnant women has been reported to result in air embolisms and death, and this method is now seriously criticized and infrequently used. For these and other reasons, a more satisfactory trichomonadicide has long been desired and in particular a trichomonadicide effective by oral administration has been desired.

The object of the present invention is to provide a new and improved therapeutic tablet for the treatment of *Trichomonas vaginalis* vaginitis, with a view to obviating the disadvantages of the medicaments and modes of treatment heretofore employed.

A more particular object is the provision of a therapeutic tablet characterized by high trichomonadical power and capable of giving symptomatic relief to patients suffering from *Trichomonas vaginalis* vaginitis.

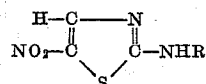
Still another object is the provision of a tablet which is free of adverse side reactions upon the patient and is characterized by a high degree of efficacy in the treatment of *Trichomonas vaginalis* vaginitis.

Other objects and advantages of the invention will become apparent as the description progresses.

The foregoing objectives may be attained in accordance with the present invention which is based on the discovery that therapeutic formulations in the form of tablets or capsules, or enteric coated tablets or capsules

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containing an acyl derivative of 2-amino-5-nitrothiazole as the active agent and an inert solid diluent have trichomonadical activity of a high order and upon oral administration result in prompt relief from the symptoms of *Trichomonas vaginalis* vaginitis and a high incidence of cures. Acyl derivatives of 2-amino-5-nitrothiazole are represented by the general formula



in which R is an acyl radical. Acyl derivatives of 2-amino-5-nitrothiazole in which the acyl radical is acetyl, propionyl, butyryl, isobutyryl, caproyl, or lauroyl have been found particularly effective trichomonadical agents for use in the formulations of this invention.

The in vitro trichomonadical activity of acyl derivatives of 2-amino-5-nitrothiazole has been established by a series of tests which established the minimal inhibitory concentration of these compounds. Minimal inhibitory concentration, as used above, is defined as the minimal concentration of a trichomonadical compound capable of preventing the growth of and killing *Trichomonas vaginalis* organisms introduced into a culture medium, capable alone of supporting a vigorous growth of the organisms, and containing the trichomonadical compound to be tested. The culture medium used in the tests is described in a publication of Kupferberg, Johnson and Sprince, Proceedings of the Society for Experimental Biology and Medicine, volume 67, pages 304-308, 1948.

In making the tests to determine minimal inhibitory concentrations, 0.05 ml. of a 48-hour culture of *Trichomonas vaginalis* was placed in a series of tubes containing 10 ml. of the culture medium and increasing amounts of the compound to be tested. The inoculated culture medium was then incubated at 37° C. for nine days and examined under magnification after two, five, seven, and nine days. The minimal inhibitory concentration of the compound tested is that concentration in the tube in which no viable organisms are present at the ninth day examination. If there are no viable organisms present on examination at a time less than nine days, the concentration of compound is greater than minimal and if there are viable organisms present at the ninth day examination, the concentration is less than minimal. The results of the tests are given in the table below:

Compound	Minimal Inhibitory Concentration, gamma per cc.
2-amino-5-nitrothiazole.....	13.80
2-acetyl-amino-5-nitrothiazole.....	0.33-1.20
2-propionyl-amino.....	2.30
2-butyryl-amino.....	0.47-0.94
2-caproyl-amino.....	0.93
2-iso-caproyl-amino.....	1.80
2-lauroyl-amino.....	1.10

In employing the trichomonadicides in the present invention for the treatment of *Trichomonas vaginalis* vaginitis, one or more of the active agents are uniformly distributed in a suitable vehicle that is chemically compatible with the particular trichomonadicide selected, formed into a tablet and in a specific embodiment of the invention, the tablet is coated or surrounded with an enteric coating in the nature of a layer or film of material which is substantially soluble in or disintegrated and removed by intestinal secretions but substantially insoluble in gastric juices and secretions or disintegrated and removed thereby.

Inert diluents or fillers are chosen which are chemically compatible with the trichomonadocidal agent. Satisfactory diluents include lactose, dextrose, sucrose, sodium chloride, glycine, kaolin and starch. It is desirable that a binder such as acacia, zein, tragacanth, gelatin, sodium carboxymethylcellulose, or methyl cellulose and also, in order that a tablet may be readily prepared, that a lubricant such as magnesium stearate, zinc stearate, mineral oil, stearic acid, stearyl alcohol or mono- and polyglycol esters also be intimately admixed with the filler and active agent. The above ingredients including the trichomonadocidal material, may be formed into a tablet by thoroughly mixing the ingredients in a moist condition, granulating and compressing the mixture into tablets by conventional methods.

It is preferred that an alkaline material also be present in the tablet formulation because the solubility of the acyl derivatives of 2-acetyl-amino-5-nitrothiazole is low at an acid pH but is substantially increased at an alkaline pH. 2-acetyl-amino-5-nitrothiazole has a solubility in water at pH 5.6 of about one part in 50,000 by weight, whereas the solubility in water at pH 7.0 by weight is about ten times as great. The presence in the formulation of an alkaline agent assists in solubilizing the active agent. Satisfactory alkaline agents include aluminum hydroxide, disodium phosphate, dipotassium phosphate, sodium carbonate, sodium bicarbonate and alkaline or alkaline earth salts of glycine.

In the preferred modification of the invention, the tablet or capsule is coated or surrounded with a composition which is substantially soluble in or disintegrated by intestinal secretions but substantially insoluble in and not disintegrated by the secretions of the stomach. The trichomonadocidal agents are more effective when administered in the form of an enteric or coated tablet or capsule and it is believed that this is due to the fact that the active ingredients are many times more soluble in an alkaline than in an acid medium. Because of the alkaline nature of intestinal fluids, the active ingredients are more readily solubilized and absorbed therein. There is also some possibility that the acyl group may be removed from the amino group of the active agents by prolonged contact with gastric juices by hydrolysis, and this would result in the conversion of the 2-acetyl-amino-5-nitrothiazole into 2-amino-5-nitrothiazole which, has been demonstrated to have less in vitro trichomonadocidal activity than its acyl derivatives.

Any conventional enteric coating is suitable for use in coating or surrounding the tablets or capsules of this invention. Examples of coatings which have been found satisfactory include acid-insoluble, alkali-soluble ion exchange resins, high-melting fats of both animal and vegetable origin, high-melting vegetable waxes such as carnauba wax and bees wax, lipid materials such as glyceryl esters of fatty acids, esters of polyhydric compounds such as long chain fatty acid partial esters of hexitol anhydrides and oxyalkylene derivatives of long chain fatty acid partial esters of hexitol anhydrides; natural resins such as gum mastic, shellac, and rosin; fat-soluble compounds such as abietic acid, bile acids and cholesterol; as well as cellulose derivatives such as cellulose nitrate, cellulose acetate, cellulose derivatives containing free carboxyl groups such as cellulose phthalate and cellulose acetate-phthalate, non-toxic water-soluble salts of polyvinyl phthalates and phenyl salicylate; or mixtures of any of the above compounds.

The enteric coatings may be formed into a capsule in which the active agents in association with an inert filler is contained. In general, a tablet may be coated by dipping directly into a solution of an enteric coating material capable of being put into solution in a suitable solvent. It is also contemplated that a powder or tablet containing the active agent in association with the inert ingredients may first be coated with or engaged in gelatin and then dipped into a solution in a suitable solvent of an enteric

coating material such as a solution of any one or a mixture of the cellulose derivatives listed above. The thickness of the coating of the tablet or capsule may be controlled by varying the concentration of the solution of the ester in the solvent. A plurality of immersions to form a plurality of coatings may also be used. Certain enteric coating materials, such as cellulose derivatives, are adapted to be formed into capsules composed of separate telescoping units into which the medicament may be placed and sealed therein by the application of a small amount of solution of the enteric coating material at the edge of the telescoping segments. The enteric coating material may be, for example, about five per cent to ten per cent of the weight of the tablet or other form of the medicament.

Acyl derivatives of 2-amino-5-nitrothiazole may be present in the formulations of the above examples in amounts ranging from 200 milligrams to 500 milligrams and be highly effective in the treatment of *Trichomonas vaginalis* vaginitis; however, it is preferred that about 300 milligrams of the trichomonadocidal agent be present.

In order to disclose more clearly the nature of the present invention several specific examples will hereafter be described in considerable detail. It should be understood that they are presented solely for purposes of illustration and not with the object of either delineating the scope of the application or restricting the scope of the appended claims. The amounts in the examples are expressed in milligrams.

Example I

2-acetyl-amino-5-nitrothiazole	300
Dipotassium phosphate	50
Acacia	50
Magnesium stearate	30
Lactose	70

Example II

2-acetyl-amino-5-nitrothiazole	300
Dipotassium phosphate	50
Acacia	50
Magnesium stearate	30
Lactose	70
Cellulose acetate-phthalate	50

Example III

2-propionyl-amino-5-nitrothiazole	350
Disodium phosphate	50
Gum tragacanth	50
Stearic acid	35
Dextrose	75

Example IV

2-propionyl-amino-5-nitrothiazole	350
Disodium phosphate	50
Gum tragacanth	50
Stearic acid	35
Dextrose	75
Phenylsalicylate	40

Example V

2-caproylamino-5-nitrothiazole	400
Aluminum hydroxide	45
Gelatin	55
Zinc stearate	30
Sucrose	70

Example VI

2-caproylamino-5-nitrothiazole	400
Aluminum hydroxide	45
Gelatin	55
Zinc stearate	30
Sucrose	70
Gum mastic	55

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Example VII

2-lauroylamino-5-nitrothiazole -----	425
Dipotassium phosphate -----	50
Acacia -----	50
Stearic acid -----	35
Dextrose -----	65

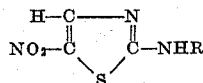
Example VIII

2-lauroylamino-5-nitrothiazole -----	425
Dipotassium phosphate -----	50
Acacia -----	50
Stearic acid -----	35
Dextrose -----	65
Cellulose acetate-phthalate -----	50

It will be apparent to those skilled in the art that numerous variations, modifications, and extensions of the principles involved may be made without departing from the spirit and scope of the invention. Thus, for example, the inert ingredients and enteric coating materials employed in the various examples are merely illustrative and it will be apparent that many others may be used in place of those illustrated in the examples. Likewise, acyl derivatives of 2-amino-5-nitrothiazole other than those specifically mentioned may be used either singly or in combination. All such variations, modifications, and extensions are to be understood as included within the ambit of the appended claims.

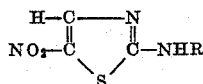
What is claimed is:

1. A composition of matter in dosage unit form for oral administration effective in the control of *Trichomonas vaginalis* vaginitis which comprises a compound of the formula



in which R is an acyl radical in intimate admixture with an inert solid diluent and surrounded by an enteric layer of substance which is substantially insoluble in acid stomach secretions and soluble in alkaline intestinal fluids.

2. A composition of matter in dosage unit form for oral administration effective in the control of *Trichomonas vaginalis* vaginitis which comprises a compound of the formula



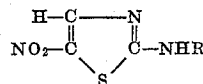
in which R is an acyl radical having not more than ten carbon atoms in intimate admixture with an inert solid diluent and surrounded by an enteric layer of a substance which is substantially insoluble in acid stomach secretions and soluble in alkaline intestinal fluids.

3. A composition according to claim 2 in which R is an acetyl radical.

4. A composition of matter in the form of a tablet for oral administration which is effective in the control

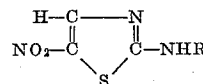
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of *Trichomonas vaginalis* vaginitis which comprises a compound of the formula



in which R is an acyl radical having not more than ten carbon atoms in intimate admixture with an inert solid diluent, a binder, an alkaline material, and a lubricant.

5. A composition of matter in the form of a tablet for oral administration which is effective in the control of *Trichomonas vaginalis* vaginitis which comprises a compound of the formula



in which R is an acyl radical having not more than ten carbon atoms in intimate admixture with an inert solid diluent, a binder, an alkaline material, and a lubricant; and surrounded by an enteric layer of a substance which is substantially insoluble in acid stomach secretions and soluble in alkaline intestinal fluids.

6. A composition according to claim 5 in which the enteric layer is composed of cellulose acetate-phthalate.

7. A composition according to claim 5 in which the enteric layer is composed of phenyl salicylate.

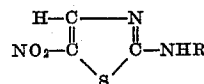
8. A composition according to claim 5 in which the enteric layer is composed of gum mastic.

9. A composition of matter in the form of a tablet for oral administration which is effective in the control of *Trichomonas vaginalis* vaginitis comprising 2-acetyl-amino-5-nitrothiazole intimately admixed with lactose, acacia, magnesium stearate and dipotassium phosphate.

10. A composition of matter in the form of a tablet for oral administration which is effective in the control of *Trichomonas vaginalis* vaginitis comprising 2-acetyl-amino-5-nitrothiazole intimately admixed with lactose, acacia, magnesium stearate, and dipotassium phosphate; and surrounded by an enteric layer of a substance which is substantially insoluble in acid stomach secretions and soluble in alkaline intestinal fluids.

11. A composition according to claim 10 in which the enteric layer is composed of cellulose acetate-phthalate.

12. A composition of matter in dosage unit form for oral administration effective in the control of *Trichomonas vaginalis* vaginitis which comprises the compound of the formula:



in which R is an acyl radical, in intimate admixture with an inert solid diluent and sealed in a gelatine capsule.

References Cited in the file of this patent

UNITED STATES PATENTS

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