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2,752,284

SPERMICIDAL COMPOSITION

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6 Claims. (Cl. 167—58)

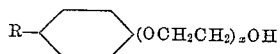
This invention relates to novel compositions of matter and more particularly to novel compositions which are intended for topical use. In its more specific aspect the invention is directed to novel compositions of matter useful chiefly for application to the mucous surfaces of the vaginal cavity where they act as spermicidal media.

A number of different spermicidal compositions have been proposed including those disclosed in U. S. Patent No. 2,330,846. This patent discloses spermicidal compositions wherein an aqueous vehicle is associated with an unsaturated higher fatty acid of ten or more carbon atoms and a surface tension depressant, the unsaturated fatty acid being suspended in the vehicle in the form of finely dispersed particles.

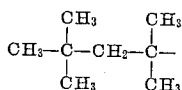
While spermicidal compositions disclosed in the said patent have found acceptance in the art, it has now been discovered that novel and highly spermicidal compositions having markedly high spermicidal power may be provided which include, as ingredients in the composition, an aliphatic organic mono- or dibasic acid, a surface tension depressant, and an acid buffer system.

Aliphatic acids suitable for use in the formulation are mono- and dibasic aliphatic acids having at least three but less than ten carbon atoms. The acids may be straight or branch chain acids. Acids such as propionic, butyric, isobutyric, caprylic, succinic and glutamic are particularly suitable; however succinic acid is the preferred acid.

The surface tension depressant employed in the formulation may be described as water-soluble alkylphenoxyethanols having the following general formula:



in which in the preferred form R is an alkyl radical having at least seven but not more than nine carbon atoms and in which x is at least seven but not greater than eleven. A mixture of water-soluble alkylphenoxyethanols may be used. In a specific preferred practice x has an average value of from 9.25 to 10.25, the average molecular weight of the water-soluble alkylphenoxyethanols is 595 to 639, and R is a diisobutyl radical having the following formula:



In the preferred specific embodiment of the invention, x is approximately 9.75 and R is a tertiary octyl radical.

The acid buffer system may be prepared with an aliphatic mono- or dibasic acid having at least two but less than ten carbon atoms. The acid may be a straight or branch chain acid. Particularly suitable acids having use as buffers include succinic, acetic, tartaric and citric acids.

A higher unsaturated fatty acid having at least ten carbon atoms may also be included in the formulation and has the effect of increasing the spermicidal power. Suitable

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higher unsaturated fatty acids include ricinoleic, oleic and linoleic. Ricinoleic acid is preferred. The surface-tension dispersant in the formulation enables a fine division of the unsaturated fatty acid to be obtained and this contributes substantially to the spermicidal power.

The vehicle employed in the formulation is preferably an aqueous vehicle and cellulose derivatives are preferred as gel-forming ingredients, although vegetable gums and materials such as synthetic gums may be used to produce satisfactory vehicles. A thickened mass comprising water and a vegetable gum such as tragacanth or acacia, a combination of these two vegetable gums, or other vegetable gums which are stable at a pH within the range of from 4.0 to 8.5 may also be used as vehicles. Cellulose derivatives such as cellulose ethers, specific examples of which are methyl cellulose, ethyl cellulose, and carboxymethyl cellulose, are stable at a pH within the range of from 4.0 to 8.5 and form excellent aqueous vehicles when mixed with water.

Combinations of one or more cellulose derivatives or combinations of a cellulose derivative and a vegetable gum may also be used in the aqueous vehicle.

In the practice of this invention there may be employed a vehicle, such as those described above, in association with one or more aliphatic mono- and dibasic acids, one or more alkylphenoxyethanols and one or more unsaturated fatty acids. The amount of aliphatic acid, alkylphenoxyethanol and fatty acid present in the aqueous vehicle is small, and it is preferable that the ratio of the quantity by weight respectively of the aliphatic acid, fatty acid and alkylphenoxyethanol to the vehicle be no greater than about 5 to 100 and 1.0 to 100, respectively. Also present may be one or more antiseptic agents such as boric acid, oxyquinoline sulfate, phenols, cresols, thymols, chlorinated thymols; an antimolding agent such as propyl para-hydroxy benzoate; a hygroscopic agent such as glycerine; and other substances such as perfumes and the like.

The invention accordingly comprises compositions possessing the characteristics, properties and relation of constituents which will be exemplified in the compositions hereinafter described. For a better understanding of the invention reference should be had to the following examples which are given as specific illustrations. It should be understood, however, that the invention is not to be limited to the specific details set forth in the examples but that the scope of the invention will be indicated in the claims.

The spermicidal compositions of the following examples are prepared according to the following general procedure in which two initial solutions are mixed to make the formulation, all the parts being given by weight.

The formulation of any of the following examples may be prepared as follows:

To prepare solution A, dissolve the para-hydroxybenzoic acid in about two-thirds of the hot deionized water, cool to about 170° F. and, while stirring well, add the gel-forming ingredient and glycerine or propylene glycol.

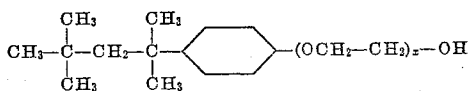
To prepare solution B, add the surface tension depressant to a solution of the higher unsaturated fatty acid in the remaining deionized water and then add the aliphatic mono- or dibasic acid; finally, add sufficient sodium hydroxide to adjust to the desired pH. The formulation results from adding solution B to solution A in a slow stream with good stirring; stirring is then continued for at least one hour.

EXAMPLE I

Deionized water	82.60
Sodium carboxymethylcellulose	3.50
Glycerine	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

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A mixture of para-diisobutylphenoxypolyethanols having the general formula:

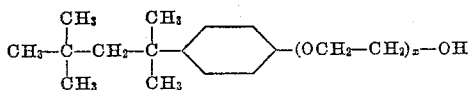


in which x has an approximate value of 9.75	1.00
Succinic acid	5.00
Ricinoleic acid	2.70

EXAMPLE II

Deionized water	89.30
Sodium carboxymethylcellulose	3.50
Propylene glycol	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

A mixture of para-diisobutylphenoxypolyethanols having the general formula:

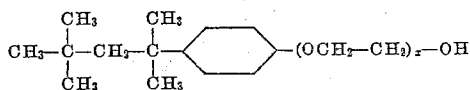


in which x has an approximate value of 9.75	1.00
Succinic acid	1.00

EXAMPLE III

Deionized water	89.06
Hydroxyethyl cellulose	3.50
Propylene glycol	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

A mixture of para-diisobutylphenoxypolyethanols having the general formula:

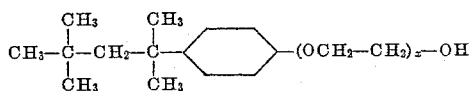


in which x has an approximate value of 9.75	1.00
Adipic acid	1.24

EXAMPLE IV

Deionized water	88.94
Methyl cellulose	3.50
Propylene glycol	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

A mixture of para-diisobutylphenoxypolyethanols having the general formula:

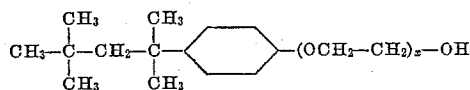


in which x has an approximate value of 9.75	1.00
Pimelic acid	1.36

EXAMPLE V

Deionized water	88.13
Sodium alginate	3.50
Propylene glycol	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

A mixture of para-diisobutylphenoxypolyethanols having the general formula:



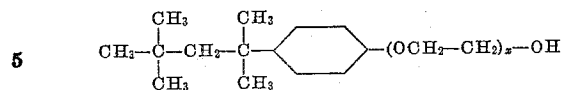
in which x has an approximate value of 9.75	1.00
Succinic acid	1.00
Oleic acid	1.17

EXAMPLE VI

Deionized water	87.89
Gum tragacanth	3.50
Propylene glycol	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

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A mixture of para-diisobutylphenoxypolyethanols having the general formula:

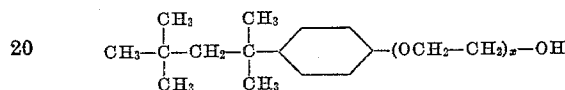


in which x has an approximate value of 9.75	1.00
Adipic acid	1.24
Linoleic acid	1.17

EXAMPLE VII

Deionized water	87.77
Sodium carboxymethylcellulose	3.50
Propylene glycol	5.00
Para-hydroxy-benzoic acid methyl ester	0.20

A mixture of para-diisobutylphenoxypolyethanols having the general formula:



in which x has an approximate value of 9.75	1.00
Pimelic acid	1.36
Ricinoleic acid	1.17

Spermicidal compositions were tested to determine their spermicidal power according to the following procedure: One gram of a spermicidal composition represented by Examples I to VII, inclusive, was placed in a test tube containing 99 grams of a physiological saline solution buffered at a pH of from 3.9 to 4.1. The saline solution contained 9.0 grams of sodium chloride per liter of water, and the buffer used in the saline was potassium acid phthalate and sodium phosphate. The buffered saline alone is not spermicidal and does not have the property of immobilizing sperm. The test tube was shaken vigorously until the jelly was uniformly distributed in the saline solution. One cc. of the jelly in saline solution was added to a second test tube containing 0.2 cc. of fresh human semen; the contents of the second tube were quickly mixed and examined microscopically to determine the activity of the spermatozoa. The time required for the mixing of the contents of the second test tube, the placing of a sample on a suitable slide, and its subsequent microscopic examination required a minimum of 20 seconds; therefore, results of tests listed as —20 seconds indicate that when first viewed under the microscope, the spermatozoa were immotile. In instances where the spermatozoa still showed motility when first examined under the microscope, the exact time when they became completely immobilized was found by constant observation of the test sample on the microscopic slide and this time is taken as killing time for immotile sperm are incapable of fertilizing an ovum or of regaining motility.

Three series of tests were made at intervals of a few days to determine the spermicidal activity of the formulations of the examples. Each formulation was tested three times. Each series of tests was made on a sample of human semen resulting from the pooling of individual specimens from three donors. The semen specimens were collected, pooled and used within a few hours to insure that the spermatozoa had full motility at the time the tests were made. In all cases spermatozoa were completely immotile in less than 20 seconds.

In order that the spermicidal power of the formulation be of a high order it is necessary that the aliphatic mono- or dibasic acid be present in a concentration sufficient that at least 20 millimols per liter of undissociated acid be present in the formulation. The concentration of acid required in order that this minimum amount of undissociated acid be present in the formulation varies with the acid used; the required minimum concentration of succinic acid is 0.085 molar. The greater the molecular weight of the acid, the less undissociated acid is required, but a minimum of 20 millimols of undissociated

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acid in the formulation is necessary in order that the formulation have a killing time of 20 seconds when tested according to the procedure given above. The spermicidal time of the formulations of the above examples is a function of the amount of residual undissociated acid present after the formulation and sperm have been mixed and a formulation having at least 20 millimols of undissociated acid will furnish sufficient undissociated acid on mixing with sperm to kill sperm in a maximum of 20 seconds when tested by the procedure given above. The formulation may be buffered over a wide pH range but this range is limited by the necessity to avoid irritation of the vaginal mucosa. Formulations having a pH within the range of from 4 to 8.5, and a concentration of buffer below the critical value given below, have a sufficiently low incidence of irritation to be satisfactory for use as contraceptive formulations. At pH values low in the non-irritation range, a lesser amount of undissociated acid is required than at pH values high in the acid range in order that the spermicidal time be less than 20 seconds according to the above tests.

The amount of undissociated acid required to be present when the formulation is mixed with sperm in order that the spermicidal time be less than 20 seconds is greater when the molecular weight of the aliphatic acid is lower than when the molecular weight of the acid is close to the upper limit. In a formulation in which the aliphatic acid has three carbon atoms, there must be present at least 35 millimols of undissociated acid in a formulation buffered at pH 4.5; however, when the aliphatic acid has nine carbon atoms it is only necessary that there be 20 millimols of undissociated acid present in a formulation buffered at pH 4.5.

It is necessary that the buffering capacity of the formulation be equivalent to the buffering capacity of any of the acids listed above as suitable for use in the preparation of the acid buffer system when the acid is present in a concentration of less than 0.775 molar but greater than 0.01 molar. The acid of the buffer system must be sufficiently water-soluble to be present in the solution in the concentration required to give a buffering capacity within the above range. If the buffering capacity is less than 0.01 molar, the undissociated acid present in the formulation will not be within the required range. If the buffering capacity is greater than 0.775 molar, the concentration of acid will be so high that undesirable incidences of irritation of vaginal mucosa will result. Buffering capacity may be defined as the concentration of the buffer present multiplied by its buffer index. Buffer index may be defined as the amount of alkali necessary to shift the pH one pH unit within a given pH range.

The results in Table I represent killing time in seconds, determined according to the above procedure, for a series of formulations corresponding to the formulation of Example I except that the amount of succinic acid was varied to give a series of jels with increasing acid concentration and buffering capacity, expressed in mols per liter. All formulations were adjusted to a pH of 4.5. The buffer index of succinic acid is 5.84.

Table I

Acid Concentration	Buffering Capacity	Killing Time
0.00359.....	0.021	315.
0.00616.....	0.036	185.
0.00856.....	0.050	75.
0.00975.....	0.057	61.
0.0103.....	0.060	less than 20.

The results in Table II represent killing time in seconds, determined according to the above procedure, for a series of formulations corresponding to the formulations of Example I except that the amount of acid is varied and succinic acid is replaced with designated acids

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in these formulations. Total acid concentration of each formulation is expressed in moles per liter. All formulations were adjusted to a pH of 4.5.

Table II

Acid	Concentration	Killing time
Succinic.....	0.0095	600.
Sebacic.....	0.009	40.
Lactic.....	0.001	800.
Pimelic.....	0.002	35.
Succinic.....	0.010	less than 20.

The results in Table III represent killing time in seconds, determined according to the above procedure except that in making the tests equal volumes of the formulation and semen were mixed, for a series of formulations corresponding to the formulation of Example I except that the concentration of undissociated succinic acid was varied to give a series of jels with increasing concentration of undissociated succinic acid, expressed in millimols per liter. All formulations were adjusted to a pH of 4.5.

Table III

Undissociated Acid	Killing Time
35.....	less than 20.
22.....	35.
12.....	310.
2.5.....	400.
0.2.....	7,200.

The results in Table IV represent killing time in seconds, determined according to the above procedure except that in making the tests equal volumes of the formulation and semen were mixed, for a series of formulations corresponding to the formulation of Example I except that in part of the formulations tested succinic acid was replaced with isocaproic acid and propionic acid and the concentration of undissociated acid was varied to give three series of gels, each with increasing amounts of undissociated acid expressed in millimols per liter. The pH values of Table IV are for the mixture of formulation and semen. The results show that for any particular acid the amount of undissociated acid required so that the formulation will have a killing time of less than 20 seconds increases as the pH increases from 4 to 7.4.

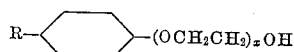
Table IV

Acid	pH	Undis-sociated Acid	Killing Time
Succinic.....	4.5	35	less than 20.
Do.....	7.2	35	210.
Do.....	7.4	42	less than 20.
Propionic.....	4.5	30	Do.
Do.....	7.4	30	500.
Do.....	7.4	40	less than 20.
Isocaproic.....	4.0	23	Do.
Do.....	5.0	24	300.
Do.....	5.0	25	200.
Do.....	5.0	30	less than 20.

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. 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 spermicidal composition comprising in combination with a vehicle, a water-soluble alkylphenoxyethanol having the formula



in which R is an alkyl radical having at least seven but

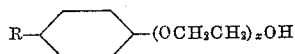
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not more than nine carbon atoms and x is at least seven but not greater than eleven, an aliphatic acid selected from the class consisting of mono- and dibasic aliphatic acids having at least three but less than ten carbon atoms in a concentration such that at least 20 millimols per liter of undissociated acid are present in the formulation, an acid buffer system, in which the acid is selected from the class consisting of mono- and dibasic aliphatic acids having at least two but less than ten carbon atoms, that maintains the pH of the formulation within the range of from about four to about eight and one-half and a higher unsaturated fatty acid having at least ten carbon atoms.

2. A composition according to claim 1 in which the aliphatic acid is succinic acid and the acid in the acid buffer system is succinic acid.

3. A composition according to claim 1 in which the aliphatic acid is succinic acid and the acid in the acid buffer system is acetic acid.

4. A spermicidal composition comprising in combination with a vehicle, a mixture of water-soluble alkylphenoxyethanols having the formula



in which R is a diisobutyl radical, the average value of x in said mixture is 9.25 to 10.25 and the average molecular weight is approximately 595 to 639, an aliphatic acid selected from the class consisting of mono- and dibasic aliphatic acids having at least three but less than

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ten carbon atoms in a concentration such that at least 20 millimols per liter of undissociated acid are present in the formulation, an acid buffer system, in which the acid is selected from the class consisting of mono- and dibasic aliphatic acids having at least two but less than ten carbon atoms, that maintains the pH of the formulation within the range of from about four to about eight and one-half and a higher unsaturated fatty acid having at least ten carbon atoms.

5. A composition according to claim 4 in which the aliphatic acid is succinic acid and the acid in the acid buffer system is succinic acid.

6. A composition according to claim 4 in which the aliphatic acid is succinic acid and the acid in the acid buffer system is acetic acid.

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