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THERAPEUTIC SULFONAMIDE COMPOSITIONS

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KILLING TIME IN MINUTES OF FORMULATIONS IN OIL-IN-WATER EMULSION BASE

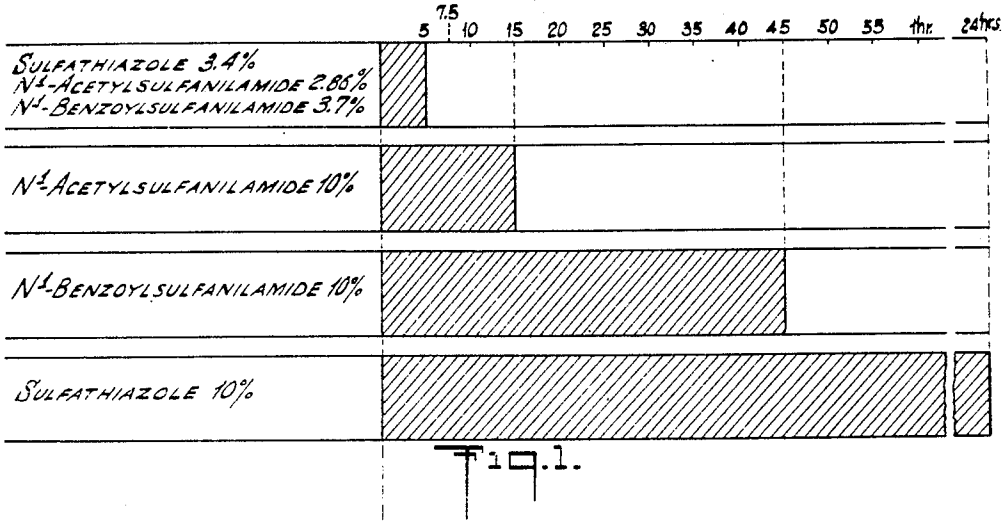

Fig. 1.

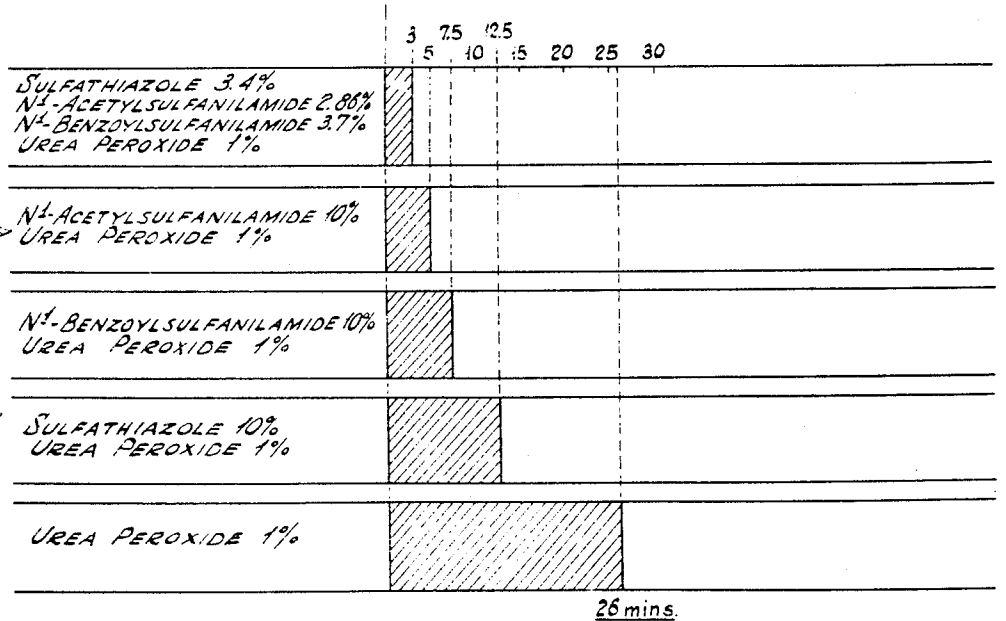

Fig. 2.

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THERAPEUTIC SULFONAMIDE COMPOSITIONS

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This invention relates to novel compositions of matter and more particularly those finding application in the therapeutic field. In its more specific aspects, the invention is directed to novel compositions especially useful as gynecic products which may be applied topically and generally useful for topical application to an infected area, or to an area in which infection is sought to be prevented.

It has been known that an abnormal bacterial flora in the vagina of an expectant mother provides a hazard in the form of an infection of the lining or wall of the uterus, which infection might progress to such a stage as to become a general peritonitis which may ultimately reach such a condition as to cause death from a septicemia. It is also known that an abnormal bacterial flora in the vagina produces an objectional condition during the healing process following minor cervical surgery, such as cautery and conization as well as following major cervical surgery, such as hysterectomy; and this is particularly true when the anaerobic streptococci are present, whose end products of protein metabolism are highly objectionable because these end products have a characteristically disagreeable odor. An abnormal bacterial flora in the vagina has been known to interfere with the normal healing process following minor cervical surgery, such as episitomy or cautery or conization to correct cervical erosion and/or endocervocitis and following major surgery, such as hysterectomy.

Prior to this invention it has been proposed to treat various forms of vaginitis with a topical medicament containing a sulfonamide. The sulfonamides generally proposed for this purpose have been one of the well known "sulfa" compounds, such as sulfanilamide or sulfathiazole. A medicament containing sulfanilamide has not been satisfactory mainly because its pKa value is outside of the range of 3.5 to 8, which is the pH range of the vaginal fluids. As pointed out in the table on page 2906 of the "Journal of American Chemical Society," volume 64, No. 12,2905–2917, December, 1942, in the article by Bell and Roblin, which lists a number of sulfonamides and the pKa of each the pKa value of sulfanilamide is 10.43. Philip B. Cowles in the "Yale Journal of Biology and Medicine," volume 14, pages 599–604, July, 1942, has established that in general the bacteriostatic power of a sulfonamide is at its maximum when its pKa approximates the pH of the culture medium and decreases progressively as the pH of the medium departs in either direction from that pH.

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A definition of the expression "pKa" is to be found in Kolthoft and Sandell's "Textbook of Quantitative Inorganic Analysis," 1937, and in Britton, "Hydrogen Ions," Third Edition, 1943. pKa may be defined as an expression representing the negative logarithm of the acid dissociation constant of a weak acid when the quantities of the components of the equilibrium are expressed as concentrations.

It has now been discovered that an effective medium for controlling the abnormal bacterial flora in the vagina may be provided by a combination of three sulfonamides whose pKa values differ from each other at least approximately by 1 and more specifically by a combination of three sulfonamides one of which has a pKa between 6 and 8, another having a pKa between 5 and 6, and a third having a pKa between 4 and 5. Such a combination of sulfonamides has been found to be synergistic in its action in that the action of the combination is superior to the sum of the actions of the individual sulfonamides. The specific combination of sulfonamides preferred is sulfathiazole, having a pKa of 7.12; N^1-acetylsulfanilamide, having a pKa of 5.38; and N^1-benzoylsulfanilamide, having a pKa of 4.37. In this preferred embodiment the difference in pKa's of the last two sulfonamides is 0.81. By employing these particular sulfonamides in combination, a medicament has been provided whose bacteriostatic activity is at least 80% of the maximum activity of the individual sulfonamides over a pH range of from 3.5 to 8, which is the pH range of the culture medium within the vagina depending upon the condition of the vagina at any particular time. This combination is particularly effective because during the reparative process of healing in the vagina with a pH of about 7 to 8, there is a regression of the pH toward a value of 3.5 to 4.5. These particular sulfonamides have maximum bacteriostatic activity at pKa's of approximately 7, 5.4, and 4.6 respectively. Sulfathiazole shows at least 80% of its maximum bacteriostatic activity in the pH range of from 6 to 8, N^1-acetylsulfanilamide in the pH range of from 4.5 to 6.5, and N^1-benzoylsulfanilamide in the pH range of from 3.5 to 5.5. While the ratio of these sulfonamides may vary, it is preferred that they be present in a mixture in which the molar ratio of these three components is approximately 1 to 1 to 1.

It is preferred that the combination of sulfonamides have pKa values in the range of from 3.5

to 8, and that their combined bacteriostatic action over the entire pH range of 4 to 7.5 be at least about 70% of the maximum bacteriostatic activity of any one of the individual sulfonamides. The preferred combination is free of any sulfonamide whose pKa is outside the range of from 2.5 to 9.

It has also been discovered that the above combination of three specific sulfonamides will kill the vegetative form of *Bacillus anthracis* in a shorter period of time than is required by any individual one of these three sulfonamides, and this is true even when the pH during the tests is substantially constant.

The three sulfonamides may be employed without any further additions, but it is preferred to combine therewith urea peroxide which acts to reduce the sulfonamide inhibiting activity of such compounds as para-amino benzoic acid and methionine which are normally present in body fluids and exudates at wound surfaces and also because urea peroxide reduces the tendency of sulfonamides to injure the kidneys by preventing crystal growth. Urea peroxide in the said combination has the added function of acting as a bactericidal agent complementing the sulfonamides in their therapeutic action. A still further function of the urea peroxide is that it assists in sterilizing the finished product as it leaves the manufacturing assembly.

The sulfonamides used are preferably in such comminuted form that the particle size thereof is no greater than four microns. The optimum particle size range is from 0.1 to 4.0 microns. When sulfonamides having a larger particle size are used, irritation of wound surfaces with a consequent retardation of wound healing and the production of a local area of chemical irritation which produces scar tissue often occurs.

While the various combinations of this invention may be applied in the form of a dry powder or a solution, it is preferred to incorporate them in a water-soluble or dispersible vehicle in which the active ingredients are readily and easily available. The vehicle should preferably possess a degree of tackiness such that it is aesthetically acceptable and will not leak out of the vagina, making it unnecessary for the patient to use a sanitary napkin for more than the minimal period during which lymph and other fluids might be escaping from the wound surfaces.

A satisfactory and preferred vehicle is an oil-in-water dispersion. Among vehicles of this type, which may be employed, are those known as "vanishing creams," examples of which are hereby given merely by way of illustration, all parts being given by weight:

Vanishing cream—Example I

Stearic acid	80.0
Potassium hydroxide	5.0
Glycerine C. P.	30.0
Deionized water	300.1

Vanishing cream—Example II

Stearic acid	20.0
Spermaceti	20.0
Glyceryl monostearate	50.0
Potassium hydroxide	0.6
Deionized water	354.5

The three sulfonamides may be uniformly distributed in the oil-in-water dispersion vehicle without, but preferably with, urea peroxide. The ratio by weight of the three component sulfonamides to the said vehicle may be in the range of from 3 to 100 and 12 to 100. The ratio by weight of urea peroxide to the combined weights of the three sulfonamides may be in the range of from 1 to 2 and preferably within the range of from 1 to 10.

The following are specific and preferred examples illustrating the active components and the ratio of active components in oil-in-water dispersions, all parts being given by weight:

Example III

Sulfathiazole	17.1
N^1-acetylsulfanilamide	14.3
N^1-benzoylsulfanilamide	18.5
Urea peroxide	5.0
Stearic acid	80.0
Glycerin C. P.	30.0
Potassium hydroxide	5.0
Deionized water	330.1

Example IV

Sulfathiazole	17.1
N^1-acetylsulfanilamide	14.3
N^1-benzoylsulfanilamide	18.5
Urea peroxide	5.0
Stearic acid	20.0
Spermaceti C. P.	20.0
Glyceryl monostearate	50.0
Potassium hydroxide	0.6
Deionized water	354.5

The pH of the formulation of Example III was 5.57 and that of Example IV was 4.25.

Tests have been made using a formulation containing the three preferred sulfonamides in a base such as that of Examples III and IV as well as formulations of each of the three individual sulfonamides in the same base to determine the killing time in minutes for the vegetative form of *Bacillus anthracis*. Additional tests have been made with urea peroxide present in the formulations. These results are graphically presented in Figure 1 and Figure 2, of which Figure 1 is a graphic presentation of the results wherein a combination of three sulfonamides in the base and individual sulfonamides in the base were tested, and Figure 2 is a graphic presentation of the results wherein urea peroxide was added to the formulations of Figure 1.

In making the tests graphically presented in Figures 1 and 2, 0.8 cc. of the formulation containing sulfonamides in an oil-in-water dispersion were placed in a sterile test tube and 0.1 cc. of sterile human serum, previously adjusted to pH 6.0, was added. One-tenth cubic centimeter of a broth culture of *Bacillus anthracis* was added to the material to be tested, and the whole was thoroughly mixed for 60 seconds with a sterile glass rod. Transfers from this mixture were made to 8.0 cc. of a thioglycollate culture medium containing para-amino benzoic acid. The culture medium was prepared by adding 350 cc. of the thioglycollate culture medium to 50 cc. of a 0.1% solution of para-amino benzoic acid. Para-amino benzoic acid was present to inhibit any of the sulfonamides which may have been carried over in the course of the transfer. Transfers to the culture medium were made at frequent intervals during the first 15 minutes and at less frequent intervals thereafter. The culture tubes containing the transferred bacteria were incubated and examined for the presence of living *Bacillus anthracis*. In cases where no living organisms were found, the tubes were reincubated with

Bacillus anthracis to insure that the absence of living organisms was not due to any non-inactivated sulfonamides from the original transfer; in all such cases, reincubated media showed vigorous growth of *Bacillus anthracis*.

The pH of the formulations tested with urea peroxide absent and with urea peroxide present was within the range of from 3.4 to 4.0, and the pH during the tests did not go above 4.5 at any time.

The results of the tests as presented in Figure 1 show that the formulation tested which contains all three sulfonamides has a killing time of 5 minutes, whereas the shortest killing time of any one of the formulations containing only one sulfonamide is 15 minutes, and that the longest killing time for a single sulfonamide, sulfathiazole, is 24 hours. This indicates that the combination of the three sulfonamides is superior in killing time, when tested against *Bacillus anthracis*, to any one of the individual sulfonamides.

The results of the tests as presented in Figure 2 were obtained from the same formulations as those of Figure 1 but with the addition of urea peroxide and these results indicate that the combination of the three sulfonamides with urea peroxide present has a shorter killing time, 3 minutes, for *Bacillus anthracis* than any one of the three individual sulfonamides with urea peroxide present.

Clinical experience with compositions embodying the present invention has shown that by employing them as topical vaginal medicaments the post-operative and post-conization leucorrheas may be reduced by nearly two-thirds and in addition, mucosal healing and the reversion to the more normal physiological balance may be accomplished within a period of 12 to 21 days in contrast to the usual 42 to 56 days.

The compositions of the present invention are particularly useful in those vaginal conditions caused by the overgrowth of secondary bacterial invaders in the presence of broken-down tissue. They have been found to be especially efficacious in the following vaginitides:

1. Post-operative vaginitis or cervicitis.
2. Post-cauterization of cervix.
3. Chronic adhesive vaginitis.
4. Ulcerative vaginitides.
5. Post-radiation vaginitis and cervicitis.
6. Post-conization cervicitis.
7. Antepartum vaginitis and cervicitis.
8. Postpartum vaginitis and cervicitis.

Dosages of about five grams of the compositions shown in Examples III and IV twice daily during the more serious extent of the condition and reducing the dose to one-half to one-quarter after 4 to 6 days have been particularly effective.

Although in its preferred embodiment the therapeutic compositions of this invention, in the form of oil-in-water emulsions, are used for topical application, it is also contemplated that the herein described combinations of three sulfonamides may be used orally or otherwise than topically.

This application is a continuation in part of my U. S. application Serial No. 675,325, filed June 8, 1946.

I claim:

1. A topical medicament showing synergism due to the differences in pKa values of the sulfonamides present comprising the combination of a sulfonamide having a pKa between 6 and 8, a sulfonamide having a pKa between 5 and 6, and a sulfonamide having a pKa between 4 and 5, the pKa values differing from each other at least approximately by one.

2. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising the combination of a sulfonamide having a pKa between 6 and 8, a sulfonamide having a pKa between 5 and 6, and a sulfonamide having a pKa between 4 and 5; the mole ratio of said sulfonamides to each other being approximately 1 to 1 to 1, the pKa values differing from each other at least approximately by one.

3. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising the combination of a sulfonamide having a pKa value of approximately 7, a sulfonamide having a pKa of approximately 5.5, and a sulfonamide having a pKa of approximately 4.5, the mole ratio of said sulfonamides to each other being approximately 1 to 1 to 1.

4. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising a combination of sulfathiazole, N^1-acetylsulfanilamide, and N^1-benzoylsulfanilamide.

5. A topical medicament comprising a combination of sulfathiazole, N^1-acetylsulfanilamide, N^1-benzoylsulfanilamide, and urea peroxide.

6. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water colloidal dispersion in combination with a sulfonamide having a pKa value of approximately 7, a sulfonamide having a pKa value of approximately 5.5, and a sulfonamide having a pKa value of approximately 4.5, the mole ratio of said sulfonamides to each other being approximately 1 to 1 to 1.

7. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water collodial dispersion in combination with urea peroxide and a plurality of sulfonamides, one of said sulfonamides having a pKa value between 6 and 8, another having a pKa value between 5 and 6, and another having a pKa value between 4 and 5, the pKa values differing from each other at least approximately by one; the particle size of said sulfonamides being no greater than 4 microns, and the ratio by weight of the sum of said sulfonamides to said dispersion being in the range of 2 to 100 and 10 to 100.

8. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water colloidal dispersion in combination with urea peroxide and a plurality of sulfonamides, one of said sulfonamides having a pKa value of approximately 7, another having a pKa value of approximately 5.5, and another having a pKa value of approximately 4.5, the mole ratio of said sulfonamides to each other being approximately 1 to 1 to 1, the particle size of said sulfonamides being no greater than 4 microns, and the ratio by weight of the sum of said sulfonamides to said dispersion being in the range of 2 to 100 and 10 to 100.

9. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water dispersion containing sulfathiazole, N^1-acetylsulfanilamide, and N^1-benzoylsulfanilamide.

10. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water dispersion containing sulfathiazole, N^1-acetylsulfanilamide, and N^1-benzoylsulfanilamide, the mole ratio of said sulfonamides to each other being about 1 to 1 to 1.

11. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water dispersion containing sulfathiazole, N^1-acetylsulfanilamide, and N^1-benzoylsulfanilamide, the mole ratio of said sulfonamides to each other being about 1 to 1 to 1, the ratio by weight of the sum of said sulfonamides to said dispersion being in the range of 2 to 100 and 10 to 100.

12. A topical medicament exhibiting a synergistic effect due to the differences in pKa's comprising an oil-in-water dispersion containing urea peroxide, sulfathiazole, N^1-acetylsulfanilamide, and N^1-benzoylsulfanilamide, the mole ratio of said sulfonamides to each other being about 1 to 1 to 1, the ratio by weight of the sum of said sulfonamides to said dispersion being in the range

of 2 to 100 and 10 to 100, the particle size of said sulfonamides being no greater than about 4 microns.

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