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THERAPEUTIC COMPOSITION OF MATTER

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This invention relates to a combination of antibacterial substances, and more particularly relates to the combination of erythromycin and the sulfonamides.

Among the greatest medical advances of the last quarter century is the development and use of antibacterial substances to combat infectious diseases. The medical art is in constant search of new and better antibacterial substances and combinations thereof. Since bacteria develop resistant strains to the commonly used antibacterial agents and since patients develop sensitivities to antibacterial agents which are used too often, the search for new agents is a continuing and ceaseless struggle for the medical art. Most combinations of antibacterial agents provide little advantage over the individual antibacterial agents used alone. Occasionally, an unusually good combination is discovered.

It is therefore an object of the present invention to provide novel preparations containing two different types of antibacterial agents which are admirably suited for the treatment of infectious diseases. Another object is to provide novel preparations containing erythromycin and sulfonamides which preparations possess an unusually broad antibacterial spectrum. Another object is to provide such antibacterial preparations possessing a hard hitting, reinforced antibacterial action against the organisms responsible for the majority of infections. Another object is to provide such novel preparations which are effective against strains of organisms resistant to other antibiotics. Another object is to provide such novel preparations which do not render organisms resistant to other antibiotics. Still another object is to provide such novel preparations which may be used in patients sensitive to other antibiotics. Still another object is to provide such novel preparations which forestall the development of resistant organisms. Still another object is to provide novel antibacterial preparations which are well tolerated and have negligible allergenic properties. Still another object is to provide such preparations which contain a combination of several sulfonamides in order to minimize possibility of crystalluria renal damage and lessen the incidence of allergic reactions. Other objects will be apparent to those skilled in the art to which this invention pertains.

The foregoing and additional objects are accomplished in the present invention by providing a composition of matter containing erythromycin as one essential active ingredient and at least one of the sulfonamides as a second essential active ingredient. In its most preferred embodiment the novel composition of the present invention consists of erythromycin and three sulfonamides, the most preferred sulfonamides being sulfadiazine, sulfamerazine, and sulfamethazine. In its broadest sense the present invention consists in the unexpected properties attributable to the combination of erythromycin with the sulfonamides. The antibacterial advantages of the combination have been clearly demonstrated for erythromycin with one sulfonamide drug, e. g., sulfadiazine. However, the sulfapyrimidines (sulfadiazine, sulfamerazine and sulfamethazine) are still regarded as outstandingly efficient in the treatment of bacterial infection. It is therefore that particular combination of sulfonamides which is most preferred for combination with erythromycin in the composition of the present invention. A combination of sevaral sulfonamides is used for reasons other than the broad concept of the present invention. The most outstanding attributes of mixed sulfonamide therapy are the same here as that known in the art, i. e., such a mixture lessens renal complications and decreases patient sensitivity.

The term "erythromycin" is used herein in its generic sense and denotes erythromycin itself, which is characterized as a nitrogenous base, erythromycin B, and the acid addition salts and esters thereof. It is more fully described in U. S. Patent 2,653,899, issued on September 29, 1953 and Pettinga et al. J. A. C. S. 76: 569–571 (1954).

The term sulfonamide drug includes sulfanilamide and the various sulfanilamide derivatives involving replacement of a hydrogen atom on the amino and/or amido groups by another group; for example, sulfamethazine, sulfacetamide, sulfamerazine, sulfadiazine, sulfadimetine, sulfisoxizole, sulfaguanidine, sulfapyridine, sulfathiazole, and phthalylsulfathiazole, succinylsulfathiazole, and the like.

In general the novel compositions of the present invention are prepared in a conventional manner, taking into account the pecularities of the components thereof. The preferred manner of administration is oral, and the preferred oral form is an enteric coated tablet. Palatable liquid diluents can be used but their use is not preferred since erythromycin is adversely effected by gastric secretion in the stomach. Therefore, a dry preparation can be protected by enteric coatings which do not dissolve in the stomach but which will dissolve in the upper intestine where there is no such adverse effect upon erythromycin. Typical examples of such enteric coating materials include salol (phenyl salicylate), tolu balsam, shellac, casein, keratin, cellulose acetate phthalate, carboxymethyl cellulose, shellac-ammonia, and the like. The amounts of the active materials useful in the present invention are not considered critical to the present invention, although the preferred amounts are illustrated in the examples given below.

In one embodiment of the present invention erythromycin and the triple sulfonamides are separated by preparation of a single enteric coated compressed tablet containing erythromycin and laminating it with the triple sulfonamides. The triple sulfonamides are rolled onto the enteric coated erythromycin tablet as in conventional pill making. Color coats and polish are applied.

More specifically, the erythromycin is granulated with suitable materials conventionally used in the art, screened and dried. The dried granules are lubricated and compressed into tablets of the proper size and weight. The compressed tablet of erythromycin is then coated with cellulose acetate phthalate coating solution. The enteric coated tablet is then air dried overnight. At this stage the tablet must resist artificial gastric juice (pH 1.2) for at least one hour and must disintegrate in pH 6.8 buffer solution is less than one hour. The tablets are then treated with a solution of sucrose in water and the mixed triple sulfonamides are dusted on between syrup applications. After all of the sulfonamide powder has been added, the tablets are colored with syrup containing suitable dyes. The finished tablets are polished with waxes.

In the laminated tablet described above, it has been found that the laminated sulfonamides are removed after approximately five minutes in artificial gastric juice. The enteric coated erythromycin core will resist the attack of

artificial gastric juice for at least two hours but will disintegrate upon transfer to an alkaline buffer solution of pH 6.8 or artificial intestinal juice (pH 6.9) within one hour. Usually the disintegration time in the alkaline buffer solution is more in the order of fifteen to thirty minutes.

Another embodiment similar to the above is an enteric coated tablet containing a mixture of both erythromycin and sulfonamides. In the first embodiment the sulfonamides were laminated on the enteric coated erythromycin tablet.

Another method of preparing an oral preparation having the same characteristics as the above consists of preparing an enteric coated compressed tablet or pill containing the erythromycin, placing it into a hard gelatin capsule, and powder filling the triple sulfonamides. The compressed tablet used here should be relatively small as compared to the compressed tablet of erythromycin described above; e. g., a one-quarter inch punch as compared with a three-eighth inch punch for the laminated tablet. The cellulose acetate phthalate coating is applied as previously described and the tablets or tablet inserts, as they are often called, are dried overnight. In this preparation, the gelatin capsule dissolves in the stomach exposing the sulfonamides to the action of the stomach juices. The enteric coated erythromycin is impervious to the hydrochloric acid in the stomach and remains unchanged until it passes into the intestinal tract where the erythromycin tablet or pill readily disintegrates. This tablet insert should have the disintegration specifications previously outlined.

For most liquid oral preparations it is preferred to use relatively insoluble esters and salts of erythromycin since these have a lesser tendency to be inactivated by the acid in the stomach, and they are usually more palatable. Even the free base of erythromycin could be used in such liquid oral preparations since the acid in the stomach does not prevent the attainment of therapeutic levels, but this is not the most preferable form by this means of administration. Among the insoluble esters preferred in liquid oral preparations are the stearate, cyclopentylpropionate, laureate and the ethyl carbonate. An illustrative salt which is also so useful is the stearic acid salt. Any of the conventional liquid vehicles used in pharmaceutical practice which are not incompatible with the active ingredients of the novel composition of the present invention can be used to prepare the liquid oral embodiment thereof.

Oil suspensions of the novel composition of the present invention can also be prepared. For these, as well as other oral embodiments, taste is an important factor. A soluble ester of erythromycin, i. e., the glutarate, has been found to be most useful in reducing the bitter taste of the free base. One example of such an oil suspension contains the following active ingredients for each five cubic centimeters of finished product:

	Milligrams
Erythromycin lactate	500
Sulfadiazine	167
Sulfacetamide	167
Sulfamerazine	167

The composition of the present invention can also be prepared as granules, especially for pediatric purposes. These granules can be dissolved in water or dispersed in foods immediately prior to use. These granules are generally prepared in packets containing a single dose. A typical pediatric formula contains the following amounts of active material as sugar coated granules:

	Milligrams
Erythromycin	50
Sulfadiazine	62.5
Sulfamerazine	62.5
Sulfacetamide	62.5
Sulfamethazine	62.5

The composition of the present invention can be prepared in a sterile vehicle for parenteral use, although this is not the preferred form of administration. The compositions can also be prepared in an ointment base or as a powder for topical use.

The following examples are illustrative of the compositions of the present invention but are not to be construed as limiting.

Example 1

Laminated enteric coated tablet

To make up a total of 100,000 enteric coated tablets of erythromycin for subsequent lamination with the sulfonamides, a homogeneous mixture of sixteen pounds, eight ounces of lactose U. S. P. and an equivalent amount of bolted starch is prepared and granulated with a sucrose-starch paste. The sucrose-starch paste consists of one part bolted starch; two parts fifty percent sucrose syrup, and seven parts deionized water. Each part equals one pound, six ounces and 175 grains. These granules are dried. Twenty-three pounds, twelve ounces of purified crystalline base of erythromycin is granulated with a mixture consisting of three parts of a 12½ percent sucrose-syrup and one part of denatured ethanol. This mixture amounts to eleven pounds, five ounces, and 56 grains. One pound, one ounce, and 63 grains of white mineral oil U. S. P. viscosity 180 is added during the wet granulating process. The granules are screened and dried. Both dried granulations are then screened again, mixed intimately and lubricated with eleven ounces, 188 grains of bolted starch; three pounds, nine ounces of bolted talc; and five ounces, 313 grains of a very fine powder of calcium stearate. This amount of material will then prepare 100,000 tablets by compressing on a rotary tablet machine with a three-eighth inch punch. The tablets are then assayed for potency and moisture.

After assaying, the tablets are given several coats of cellulose acetate phthalate in absolute denatured alcohol-acetone solution in accordance with U. S. Patent 2,196,768. Talc is used for dusting, and the tablets are air dried overnight.

The coating on the tablet must be thick enough at this stage so that at least eleven out of twelve tablets will resist artificial gastric juice (pH 1.2) for one hour at 37 degrees centigrade, and all twelve must disintegrate in pH 6.8 buffer in less than one hour.

Each group of ten thousands of these tablets are given several applications of a gelatin syrup, dusting with a powder containing the following ingredients:

	pounds	ounces	grains
Sulfadiazine, U. S. P.	2		145
Sulfamerazine, U. S. P.	2		145
Sulfamethazine	2		145
Lactose, U. S. P.		9	306
Acacia powder		4	372

These laminated tablets are then given several applications of a gelatin syrup, using talc for dusting. This is continued until smooth rounded tablets are obtained. These tablets are then coated with coloring material and polished with waxes. After assay, the tablets are bottled and properly labeled.

Example 2

Gelatin capsules

To make up 1000 capsules 100 grams of erythromycin and 83.3 grams of each of sulfadiazine, sulfamerazine and sulfamethazine are mixed thoroughly as dry powders until uniform and filled into hard gelatin capsules.

Inert diluents and lubricants such as lactose, starch, or talc, can be used in a manner well known to the art to adjust the volume of the capsule fill and to facilitate handling. If soft elastic gelatin capsules are desired, the

powders can be suspended in peanut oil gelled with two percent aluminum monostearate before capsulating.

EXAMPLE 3

Tablets

To make up 1000 tablets 100 grams of erythromycin, 125 grams of sulfadiazine, and 125 grams of sulfamerazine can be mixed and granulated with a sucrose-starch syrup. The dried granules are lubricated with mineral oil, talc, calcium stearate, or other suitable lubricants and compressed into tablets on a tablet machine. The amount of starch, sucrose syrup, mineral oil, talc and calcium stearate can be adjusted in accordance with practices well known to the tableting art depending upon the size of tablet desired.

EXAMPLE 4

Flavored granules for the extemporaneous preparation of a fluid

The following dry powdered ingredients are mixed in together: 2.3 grams of erythromycin glutarate, 2.0 grams of sulfadiazine, 2.0 grams of sulfamerazine, 2.0 grams of sulfaguanidine, 370 grains of sucrose and 8 grains of sodium citrate. The whole is granulated with an alcohol-water solution, containing the flavors and color, and dried. These dried granules are placed in a sixty-milliliter bottle and are then ready for dissolving in an aqueous vehicle prior to use.

It is to be understood that the invention is not to be limited to the exact details of operation or compounds shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

I claim:

1. A therapeutic composition comprising erythromycin and at least one sulfonamide drug.

2. A therapeutic composition comprising erythromycin and at least two sulfonamide drugs.

3. A therapeutic composition comprising erythromycin and at least three sulfonamide drugs.

4. A therapeutic composition comprising erythromycin and sulfadiazine.

5. A therapeutic composition comprising erythromycin, sulfadiazine and sulfamerazine.

6. A therapeutic composition comprising erythromycin, sulfadiazine, sulfamerazine and sulfamethazine.

7. An oral therapeutic composition comprising erythromycin glutarate, sulfadiazine, sulfamerazine and sulfaguanidine.

8. A therapeutic composition comprising erythromycin lactate, sulfadiazine, sulfacetamide, and sulfamerazine.

9. A therapeutic composition comprising erythromycin, sulfadiazine, sulfamerazine, sulfacetamide and sulfamethazine.

10. A therapeutic composition comprising an active salt of erythromycin and at least one sulfonamide drug.

11. A therapeutic composition comprising an active ester of erythromycin and at least one sulfonamide drug.

12. An oral therapeutic composition comprising enteric coated erythromycin and at least one sulfonamide drug.

13. An oral enteric coated composition comprising erythromycin and at least one sulfonamide drug.

14. An oral therapeutic composition comprising an enteric coated core containing erythromycin as the essential active ingredient and a mixture of sulfadiazine, sulfamerazine and sulfamethazine as the essential active ingredients outside the enteric coat.

15. An oral therapeutic composition comprising an erythromycin tablet coated with an enteric coating of cellulose acetate phthalate and the combination of sulfadiazine, sulfamerazine, and sulfamethazine laminated thereon.

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