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COMPOSITE ENTERIC TABLET OF ERYTHROMYCIN AND SULFONAMIDES

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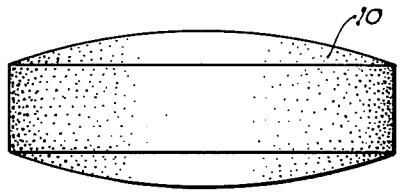

FIG. 1

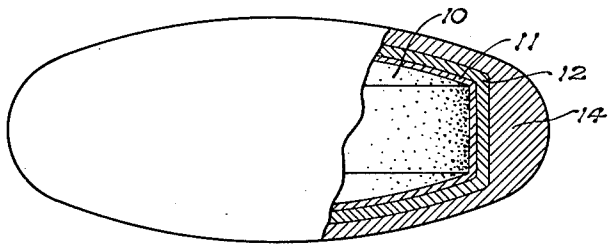

FIG. 2

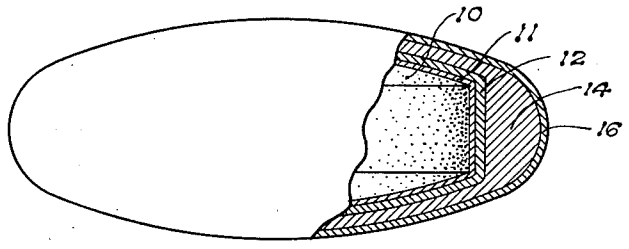

FIG. 3

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COMPOSITE ENTERIC TABLET OF ERYTHROMYCIN AND SULFONAMIDES

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5 Claims. (Cl. 167—82)

This invention relates to enteric-coated tablets and more particularly to tablets composed of two or more medicaments and having a dual function.

Erythromycin is an antibiotic compound having a broad antibacterial spectrum. The compound has a specific field of usefulness in the treatment of infections caused by certain Gram-positive and Gram-negative bacteria as well as some Rickettsial bodies. When ingested, erythromycin is absorbed from the gastro-intestinal tract, and is carried by means of the blood stream to the site of infection where it exerts its antibacterial action. However, the drug is readily destroyed by the acids and/or the acid-activated enzymes of the stomach. Consequently, oral administration of the drug results in the destruction of at least a part of the material administered. It has been found to be impossible to compensate for this destruction in the stomach by the simple expedient of increasing the dosage of erythromycin, for the reason that many variables such as presence or absence of food, amount of acid and/or enzyme in the stomach, and the like, render it impracticable to calculate a theoretical optimum dosage. It has therefore been proposed to coat tablets of erythromycin with a protective film of such character that the tablet will not be dissolved in the stomach but only in the intestine. Any enteric coating which dissolves or rapidly disintegrates within a few minutes after the tablet thus coated passes from the stomach to the intestine is suitable for the purpose of providing an enteric coating for erythromycin. Particularly useful enteric coatings have been found to be cellulose acetate phthalate and related substances of the type disclosed in U. S. Patent No. 2,196,768, issued April 9, 1940. The cellulose compositions disclosed in that patent provide films which are quite resistant to the acid stomach secretions, but which disintegrate very readily in the alkaline intestinal secretions.

It has heretofore been found that certain bacterial infections do not readily yield to the action of antibiotics such as erythromycin, either because the antibiotic may be merely bacteriostatic rather than bactericidal, or for some reason fails to affect the infective bacteria to the degree necessary to enable the body defenses to overcome the disease. Furthermore, it is not always possible to determine immediately what microorganisms may be responsible for any one infection, and consequently the most effective treatment may not be instituted. However, by combining sulfonamide drugs with erythromycin, the over-all therapeutic range and effect is markedly increased, and the combination can be more successfully and reliably used in combating mixed and/or unknown infections.

It has previously been proposed that an antibiotic such as penicillin be combined with sulfonamides in a single tablet to bring about a more rapid resolution of disease caused by a bacterial invasion. However, when sulfonamides and erythromycin are administered simultaneously in the form of a single non-enteric tablet, there is a

rapid absorption of sulfonamides from the stomach, but the erythromycin is mostly destroyed by the acid stomach contents as set forth hereinabove. Furthermore, and undesirably, the sulfonamide concentration in the blood appears as a peak substantially simultaneously with the peak concentration of that portion of the erythromycin which is not destroyed.

If a tablet consisting of erythromycin and a sulfonamide is coated with an enteric coating to prevent destruction in the stomach of the erythromycin, the appearances in the blood of the two medicaments occur as simultaneous peaks. This is less desirable than is the case if somewhat lower peak concentrations are prolonged in such a way that effective concentrations of erythromycin and sulfonamide are maintained between doses, whereby the disease-producing bacteria are subject to a substantially continuous attack by one or both of the bacterial medicaments.

It is an object of this invention to provide a novel tablet comprising erythromycin and one or more sulfonamides which exerts a particularly favorable therapeutic effect.

It is a further object of this invention to provide for oral medication a composite tablet combining erythromycin and one or more sulfonamides, which has the dual function of rapid release of sulfonamides in the stomach and the release of both erythromycin and sulfonamides after the tablet has reached the intestine whereby a relatively constant concentration of the sulfonamide component is maintained in the blood and the erythromycin is protected from the acid stomach contents.

It is a further object of this invention to provide a tablet comprising erythromycin and one or more sulfonamides which is compact and more easily ingested than a tablet prepared by conventional methods.

It is a further object to provide a tablet capable of affording the above-described therapy in a simple single-dose form.

Other objects of this invention will become apparent from the following description, appended claims, and acompanying drawing.

In the drawing,

Figure 1 is an enlarged side elevation of the improved base tablet of combined sulfonamides and erythromycin.

Figure 2 is a view similar to Figure 1 but partially sectioned and showing the enteric coating applied over the base tablet and the triple sulfonamide coating applied over said enteric coating.

Figure 3 is a view similar to Figure 2 but with an optional sugar coating applied over the triple sulfonamide coating.

It has been found that a particularly advantageous therapeutic result follows from the use of a single tablet containing as one portion an enteric-coated mixture of erythromycin and sulfonamides and as a second portion a non-enteric-coated sulfonamide or mixture of sulfonamides. Such a composite therapeutic dosage form is conveniently prepared by first forming an inner core or base tablet of a mixture of sulfonamides and erythromycin, providing said tablet with an enteric coating and forming an outer layer of sulfonamides upon the enteric-coated base tablet. When administered orally, the sulfonamide-containing outer layer disintegrates immediately and is rapidly absorbed in the stomach, whereby an initial high blood level of sulfonamide is produced. After the remainder of the tablet passes into the duodenum, the enteric coating dissolves and the erythromycin is absorbed. At the same time, the sulfonamide portion of the inner core is absorbed, thereby maintaining a continued high blood level of sulfonamide. A desirable therapeutic result follows.

The sulfonamides which are preferred for use with erythromycin in the tablets of this invention are 2-sulfanilamidopyrimidine and its homologues. These include sulfadiazine, or 2-sulfanilamidopyrimidine itself; sulfamerazine, or 2-sulfanilamido-4-methylpyrimidine; sulfamethazine, or 2-sulfanilamido-4,6-dimethylpyrimidine; and their equivalents. Other sulfonamide drugs such as sulfathiazole, sulfanilamide, and the like are equivalents of the foregoing, and can also be used as the sulfonamide portion of our composite tablet. Thus, for example, suitable combinations include erythromycin-sulfathiazole, erythromycin-sulfadiazine, erythromycin-sulfadiazine-sulfamerazine, erythromycin-sulfadiazine-sulfathiazole, and the like.

It has heretofore been found necessary in the tableting art, when forming enteric-coated tablets, to provide a smooth, rounded outer surface for the ordinarily sharp-edged compressed base tablet, so that no sharp edges remain from which the enteric coating might be removed through handling, transit, bottle-filling operations, etc. whereby the effectiveness of the coating could be destroyed. This preliminary preparation of the base tablet has been accomplished in the prior art by tumbling the compressed tablets in a barrel without a coating substance so as to cause the tablets to abrade each other and generally round off the sharp corners by attrition. Alternatively, the same object has been achieved by tumbling the base tablets in a tablet-coating pan or barrel together with large quantities of a filler such as calcium sulfate, talc, or the like, while concurrently adding a sugar solution, whereupon the sugar and filler are gradually built up upon the surface of the tablet to form a product whose exterior surface approximates an oblate ellipsoid.

Although these and similar methods have heretofore been available, it has been found that the use of the self-abrading method for rounding the edges of the inner base tablet containing erythromycin and sulfonamides leads to irregularity in the amounts of the doses contained therein, and may cause some destruction of the antibiotic. This method is generally not adaptable to producing a product of constant dose amount. On the other hand, the application of a filler over the surface of a tablet to an extent such that its initially sharp edges are sufficiently rounded out into a satisfactory end product, as was heretofore thought to be necessary for application of further coatings, results in an oversize or bulky tablet. Thus, after application of the required uncoated sulfonamide portion, the composite tablet is too large to swallow comfortably.

It has now been found that, surprisingly, the sulfonamide or mixture of sulfonamides can in itself be powdered and employed as a filler material in producing a tablet of rounded-edge configuration. In this way, the size of the tablet is kept at a minimum, and at the same time the sulfonamide becomes a protective coating for the enteric layer which surrounds the inner base tablet. The powdered sulfonamide mixture can be used alone as a filler, together with the usual gums and other ingredients of tablet coatings, or a hardening agent such as calcium sulfate may be incorporated to provide a more resistant coating, if desired. Because of the protection afforded by the relatively thick layer of sulfonamide, the enteric coating can be applied directly to the unmodified, compressed base tablet. Preferably, a thin subcoating of talc bound with acacia gum is applied whenever a solvent in which erythromycin is soluble is employed in making the application of the enteric coating.

Referring now to Figure 1 of the drawing, the base tablet **10** is comprised of erythromycin and a triple sulfonamide mixture prepared and formed by granulation according to the usual methods, and compressed in a conventional tableting machine to form the tablet as shown. A thin "solvent-proofing" subcoating **11** of talc bound with acacia is applied to prevent the organic solvent generally used for applying the enteric coating from leaching therapeutic substances out of the base tablet. Following application of the solvent-proofing subcoating, if employed, tablet **10** has applied thereto a protective enteric coating **12**, the coating being applied as a simple film as, for example, by dissolving an enteric coating substance, such as cellulose acetate phthalate, in a suitable solvent and applying the solution to base tablet **10**. Many suitable solvents for such application are available, ranging from the relatively volatile to the relatively nonvolatile solvents, including, for example, acetone, ether, ethyl acetate, methyl ethyl ketone, methanol, ethanol, ethylene dichloride, ethyl lactate, and mixtures thereof. The mode of application is dependent to an extent upon the volatility of the selected solvent. If the solvent employed is highly volatile, air and vacuum should not be applied to the coating pan prior to the time that the solution has completely moistened and coated the tablets, or the solution will evaporate so rapidly that uniform tablet coating cannot be secured. Conversely, the employment of a solvent of relatively low volatility will permit the use of air and vacuum on the coating pans throughout the coating process. As a matter of fact, warm air may be employed to advantage in such circumstances so as to hasten the drying of the coating composition.

Preferably a plasticizer is incorporated in the cellulose material to impart toughness to the film, to avoid brittleness and to lessen the likelihood of cracking of the film on drying, or upon handling before the outer layer of sulfonamides is applied. Illustrative suitable plasticizers include the mono- and di-alkyl esters of phthalic acid, adipic acid, and similar acids, and glycol and glycerol esters, for example, triethylene glycol dipropionate, triacetin, tributyrin, and the like.

Following the application of enteric coating **12**, the tablet has applied thereto a coating **14** of sulfonamides as shown in Figure 2. This coating can consist substantially only of the selected sulfonamide or sulfonamides, and is added in well-mixed powdered form to the coating pan in which the enteric-coated tablets are agitated at the usual speed. While the coating pan is revolving, a solution of gum acacia is added gradually, to cause the powdered mixture to adhere to the external surface of the enteric-coated tablet **10**. By accretion in this manner there is built up a layer or coating **14** of the desired thickness over and around the enteric-coated base tablet. The selected quantity or dose amount of sulfonamide or sulfonamides which is required in the medicament is determined by the quantity of the sulfonamide which is originally added to the pan. When all of the mixture has been aggregated upon the tablets in the form of coating **14**, the rotation of the pan is stopped and the tablets can then be removed and packaged in the usual manner.

Alternatively, before the tablets are removed from the coating pan, a sugar syrup containing, if desired, a permissible coloring agent is added to the rotating contents gradually to form accretively upon the coating or layer **14** a sugar coating **16** (as shown in Figure 3). Such coatings are desirable for purposes of elegance and the like. However, they are not necessary to the efficacy of the medication and are advantageously omitted in order to reduce the size of the tablets, since the coating layer **14**, when properly applied, is already of such a degree of smoothness and continuously curved oblate spheroidal contour as to be entirely acceptable as a finished product.

The following specific example illustrates the preparation of a representative tablet embodying the novel concepts of our invention.

Preparation of combination erythromycin and triple sulfonamide tablets

A mixture of 31.5 kg. of erythromycin having a potency of 1000 mcg./mg. and 100.4 kg. of a mixture of equal parts of sulfamethazine, sulfadiazine and sulfamerazine was thoroughly mixed to a homogeneous pawder, and granulated by the addition of 68 liters of 20 percent starch paste. The mixture was wet sieved, dried at about 55°

C. and then forced through a screen to obtain uniform granules. To the granulation was added a mixture of 1.37 kg. of magnesium stearate and 12.23 kg. of starch powder for the purpose of a lubricant and disintegrating agent. After through mixing of the granulation with the lubricating and disintegrating agent, the material was compressed on a 13/32" die using concave punches of suitable size so that 10 tablets weighed 2.5 g. The tablet was compressed to such a degree that it disintegrated in less than 10 minutes in water at 25° C. The moisture content was controlled to not more than 7.5 percent of the tablet weight, and chemical assays were carried out on representative tablets in order to determine the amount of erythromycin and total sulfonamides present therein. About 600,000 tablets were thus obtained. The compressed tablets were placed in a conventional coating pan and 13.68 kg. of a mixture of 12.168 kg. of talc and 1.512 kg. of acacia, and 2.365 liters of 20 percent acacia solution were added thereto, and the pan was rotated to apply the talc acacia mixture to the tablets as a thin uniform subcoating. The coated tablets were dried at about 37° C. for about 12 hours to remove any moisture present in the subcoating. The coated tablets were cooled to about room temperature and placed in a coating pan. About 15.1 liters of an acetone solution containing 12 percent cellulose acetate phthalate having from 17 to 22 percent of acetyl groups was added to the coating pans, which were revolved until a uniform coating of cellulose acetate phthalate had been applied to the tablets. An equal amount of the cellulose acetate phthalate solution was added to the pans and again they were rotated as before. A total of 12 applications of cellulose acetate phthalate was made in this way, the evaporated acetone being removed in each case by a draft of dry air. The tablets were removed from the coating pans and again dried at about 37° C. for about 12 hours. The dried enteric-coated tablets were replaced in the coating pan and 182.344 kg. of a coating powder consisting of a mixture of 109.4 kg. of equal parts of sulfadiazine, sulfamerazine, and sulfamethazine, 63.82 kg. of calcium sulfate, and 9.124 kg. of starch was added thereto. The pans were rotated and the powder was applied to the tablets as a coating by means of an 85 percent sugar syrup solution. A sufficient amount of coating powder was employed so that the final amount of sulfonamide present in the average tablet would be 334 mg. If, after assay, the tablets contained less than 334 mg. of total sulfonamides, additional applications of the sulfonamide-containing coating powder were made. The coated tablets were then dried for about 18 hours at about 37° C., and allowed to cool to room temperature before proceeding with further coatings. The tablets were replaced in the coating pans and a grey color coat was applied to them by the usual means using syrup and gum. The tablets were dried in air for about 12 hours and polished.

The yield of tablets was about 600,000 tablets containing in each tablet about 50 mg. of erythromycin and about 334 mg. of a mixture of equal parts of sulfadiazine, sulfamerazine and sulfamethazine.

We claim:

1. A medicinal tablet comprised of an inner base tablet consisting of a mixture of erythromycin and at least one sulfonamide drug, the amount of said sulfonamide being substantially less than the amount of sulfonamide required for a therapeutic dose in conjunction with said erythromycin; an enteric coating surrounding said inner base tablet, and a combination filler and medicament layer surrounding said enteric-coated inner base tablet, comprising at least one sulfonamide drug in amount sufficient to complete the amount of sulfonamide required for a therapeutic dose in conjunction with erythromycin.

2. A medicinal tablet comprised of an inner base tablet consisting of a mixture of erythromycin and at least one sulfonamide selected from the group consisting of 2-sulfanilamidopyrimidine and homologues thereof, the amount of said sulfonamide being substantially less than the amount of sulfonamide required for a therapeutic dose in conjunction with said erythromycin; an enteric coating surrounding said inner base tablet, and a combination filler and medicament outer layer comprising at least one sulfonamide selected from the group consisting of 2-sulfanilamidopyrimidine and homologues thereof, sufficient to complete the amount of sulfonamide required for a therapeutic dose in conjunction with erythromycin.

3. A medicinal tablet comprised of an inner base tablet consisting of a mixture of erythromycin and at least one sulfonamide drug, the amount of said sulfonamide being substantially less than the amount of sulfonamide required for a therapeutic dose in conjunction with said erythromycin; an enteric coating of cellulose acetate phthalate surrounding said inner base tablet; and a combination filler and medicament outer layer comprising at least one sulfonamide drug in amount sufficient to complete the amount of sulfonamide required for a therapeutic dose in conjunction with erythromycin.

4. A medicinal tablet comprised of an inner base tablet consisting of a mixture of erythromycin and at least one sulfonamide selected from the group consisting of 2-sulfanilamidopyrimidine and homologues thereof, the amount of said sulfonamide being substantially less than that required for a therapeutic dose in conjunction with said erythromycin; an enteric coating of cellulose acetate phthalate surrounding said inner base tablet; and a combination filler and medicament outer layer comprising at least one sulfonamide selected from the group consisting of 2-sulfanilamidopyrimidine and homologues thereof, in amount sufficient to complete the amount of sulfonamide required for a therapeutic dose in conjunction with erythromycin.

5. A medicinal tablet comprised of an inner base tablet, an enteric coating layer and an outer layer, said inner base tablet consisting of a mixture of erythromycin and at least one sulfonamide selected from the group consisting of 2-sulfanilamidopyrimidine and homologues thereof, the amount of said sulfonamide being substantially less than the amount required for a therapeutic dose in conjunction with said erythromycin; said enteric coating layer consisting of cellulose acetate phthalate having from about 17 to about 22 percent of acetyl groups; and said outer layer comprising in combination a filler and a medicament consisting of at least one sulfonamide selected from the group consisting of 2-sulfanilamidopyrimidine and homologues thereof in amount sufficient to complete the amount of sulfonamide required for a therapeutic dose in conjunction with erythromycin.

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