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GELATIN STABILIZED DRY TABLET STREPTOKINASE-STREPTODORNASE COMPOSITION

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This invention relates to a stable composition of streptokinase and streptodornase and more particularly is concerned with a composition of matter containing streptokinase and streptodornase, preferably in the form of a tablet, which is stabilized against losses in potency by the addition of gelatin thereto.

Streptokinase is well known as an enzyme elaborated by certain strains of beta-hemolytic streptococci, especially those of Group A and Lancefield Group C streptococci. The production of streptokinase by fermentation of these organisms is also accompanied by the formation of substantial amounts of streptodornase. Combinations of streptokinase and streptodornase have been in use for some years for the liquefaction of fibrinous and purulent accumulations in the treatment of suppurative surface tissues, infected wounds and burns, chronic suppurations and the like.

Until recently, it has been proposed to introdce streptokinase into the system by intravenous or intramuscular injection. Each of those modes of administration is subject, however, to serious disadvantages and limitations. Attendance by, or a visit to a physician is necessary and patient acceptance is very poor. Pain and tenderness are experienced at the site of injection and administration by either of these routes may be accompanied by such undesirable side effects as elevation of temperature, nodule formation and allergic reactions. The side effects attending intravenous administration are apt to be particularly serious and may include shock, chills and high fever. Evidently the side effects that accompanying the administration of streptokinase by injection result from the fact that, when a sufficient quantity is administered by this route to be effective at the site of an injury, there is also produced an undesirably high level in the blood.

Recently, it has been found possible to administer systemically streptokinase in buccal form, that is by absorption of the streptokinase through the mucous membrane, or even more recently by the oral route. The side effects previously noted with intramuscular and intravenous injection have been obviated by these newer dosage forms. Tablets for both oral and buccal administration containing streptokinase-streptodornase have been found to be useful therapeutic agents for accelerating the liquefaction of purulent exudates and lysis of blood clots as well as efficacious in the reversal of inflammatory processes of diverse origin.

The production of streptokinase-streptodornase tablets, however, has raised considerable stability problems in that the tablets are not as stable against losses in potency as are the parenteral grades of streptokinase-streptodornase. As the result, the shelf-life of a tablet must be reduced to a one year marketing period instead of the usual eighteen months. Additionally, in order to insure that the consumer buys a product up to label potency, it has been necessary to formulate the tablet using a 30% excess streptokinase-streptodornase powder. This, of course, is an unsatisfactory answer to the problem as among other things, it imposes higher operating costs.

The present invention is based upon the discovery that by mixing liquid streptokinase-streptodornase solution with a gelatin solution also in liquid form and which is equivalent to at least 5% by weight of the total solids content of the streptokinase-streptodornase and phosphate diluent being treated, the resulting streptokinase-streptodornase when compressed into tablets in the usual manner is rendered stable against losses in potency for extended periods of time. It is not known with certainty how the addition of liquid gelatin to the liquid streptokinase-streptodornase solution results in a product which, when dried, is much more stable than tablets produced by the current operating conditions but it is believed that in some manner the enzyme solutions have been gelatinized by the addition of gelatin which keeps the enzymes from undergoing loss in potency upon storage for extended periods of time.

It is essential that the gelatin be mixed with the enzyme solution while both are in a liquid phase. By this procedure the gelatin becomes more or less an integral part of the final powder particles setting up a protective coating for the enzyme. The powder is obtained in final form by vacuum drying the gelatinized enzyme solution in a standard manner and this powder is then used in subsequent tableting procedures in the usual way.

While as indicated above, preferably an amount of liquid gelatin is added to the liquid solution of the enzymes equivalent to 5% by weight of the total solids of the enzymes being treated plus phosphate diluent, it has been found that the desired stability may be obtained when the amount of gelatin is as little as 1.0% by weight of the enzymes plus phosphate diluent. The upper limit of gelatin does not appear to be especially critical and in general it has not been found necessary to exceed 5% by weight based on the weight of the enzymes plus phosphate diluent. In terms of a commercial oral or buccal tablet and which usually contains 12,500 units of active ingredient, the amount of gelatin in such tablets would be about 0.0001 to 0.0005% by weight. Obviously, the dosage quantity need not be limited to 12,500 units of streptokinase as the dosage quantity may range from about 500 to 12,500 units, a unit of streptokinase being that amount which activates sufficient plasmin to bring about dissolution of a standard fibrin cloth in 10 minutes at 35° C. Usually, however, a single dose ranging from about 10,000 to 20,000 units of streptokinase is satisfactory.

The dried enzyme solution containing the gelatin may be formed into water-soluble tablets by standard tableting procedures. Thus, the active ingredients may be incorporated with pharmaceutical excipients in a standard manner. Such compositions should contain at least 12,500 units of streptokinase and streptodornase. The potency of the active ingredient is normally in the range of 3000 to 6000 units of streptokinase per milligram of powder. Therefore, the weight of the active ingredient may be between 0.8% and 1.7% of the weight of the tablet. The amount of active ingredient in such compositions is such that a suitable dosage may be obtained.

The tablets may contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin, a disintegrating agent such as corn starch, potato starch, alginic acid, or the like; a lubricant such as stearic acid, magnesium stearate, talc, or the like; and a sweetening agent such as sucrose or saccharin may be added, as well as flavoring such as peppermint, oil of wintergreen, or cherry flavoring.

The invention will be described in greater detail in conjunction with the following specific examples.

EXAMPLE 1

The dried weight of purified streptokinase-streptodornase powder is computed and the total solids of the phosphate buffer diluent is known. Based on the combined

total solids, a gelatin solution is prepared which is equivalent to 5% by weight of the total solids of the enzyme solution and phosphate being treated. The gelatin is heated to form a solution and then cooled below 37° C. The gelatin solution is then transferred to the liquid bulk solution with thorough mixing. The so-treated solution is then vacuum dried to yield a white fluffy powder which is thoroughly mixed. The powder is then assayed for streptokinase and streptodornase content before being made into tablets.

EXAMPLE 2

The powder produced as in Example 1 is blended and compressed into tablets by appropriate tablet making procedures using the following formulation.

(a) An aqueous solution of 205 g. gelatin (150 Bloom) in 2 liters of hot water is prepared concurrently with

(b) A phosphate solution comprising 2648 g. of an equimolar mixture of monobasic sodium phosphate with 1 water of crystallization and dibasic sodium phosphate with 12 waters of crystallization (.067 mole of each), dissolved in water made up to 80 liters. Then 1489 g. of bulk SK/SD (13 billion units) is added to the phosphate solution with stirring (the SK/SD bulk powder is made up of about 20% SK) and the solution clarified by filtration.

(c) The gelatin solution (a) is added to the phosphate SK/SD solution (b) above, with stirring and the combined solutions lyophillized.

Weight of lyophillized product, 3.00 kg. Each mg. of this gelatinized product is equivalent to about 4200 units of SK/SD.

The above product was tableted in the following manner. About 1.5 kg. of the above gelatinized SK/SD, containing approximately 6.5 billion units of SK, was mixed with 89.5 kg. of sprayed-dried lactose and 1 kg. of magnesium stearate. The well-mixed blend was compressed into 500,000 tablets. Each tablet contained about 12,500 units of SK/SD (3 mg. per tablet).

At the same time a control lot of tablets is made from powder not treated with gelatin. The initial potencies of both lots of tablets are determined. The potencies of the tablets are then determined at various time intervals and temperatures, that is, at 1, 2, 4 and 5 months at room temperature and at 1, 3 and 4 months at 37° C. Table 1 below shows the results obtained (one bulk liquid split; one-half gelatin treated; the remaining half served as control portion).

TABLE 1

Lot	Initial Potency (SK units/tablet)	Months, R.T.				Months, 37° C.		
		1	2	4	5	1	3	4
Gelatinized	11,600	10,900	14,400	11,900	9,600	12,600	11,900	9,375
Non-gelatinized control	12,055	10,900	10,240	-------	8,800	8,550	6,700	6,675

It can readily be seen that at the end of five months at room temperature there was an 8% greater loss in the potency of the non-gelatinized control than was observed in the "gelatinized" tablets. The stabilizing effect of the gelatin is even more dramatic in the accelerated temperature tests. In this instance, 45% loss in potency was observed in the control lot whereas the gelatinized tablets showed a loss of only 20% from original potency during a period of 4 months at 37° C.

EXAMPLE 3

Example 2 is repeated with the exception that (1) the gelatinized powder and the tablets prepared therefrom are compared for stability purposes, as well as the control powder and tablets, and (2) two separate lots of bulk liquid streptokinase-streptodornase chosen at random are used in this experimental comparison. The testing intervals are 0 time, 9 months and 14 months at room temperature only.

It can readily be seen that at the end of the 14 month period at room temperature, the non-gelatinized powder and the tablets prepared therefrom show a loss of potency of 33% and 34% respectively, while the gelatinized powder and the corresponding lot of tablets show no loss of potency.

TABLE 2

Tablet Lot No.	Original Potency SK units/tablet	9 months R.T., SK units/tablet	14 months R.T., SK units/tablet	14 months R.T., SK units/tablet	Percent Loss from theoretical
I (gel)	12,735	13,125	12,000	13,035	0
II (control)	10,800	8,325	9,300	8,600	34

SK-SD Powder No.	Tablet No.	Initial Potency SK units/mg.	9 months R.T., units/mg.	14 months R.T., units/mg	Percent Loss Potency
I (5% gel)	I	3,867	[1] 3,720	3,875	0
II (control)	II	3,611	[2] 3,300	2,607	33

[1] 4% loss.
[2] 9% loss.

We claim:

1. The method of increasing the stability of streptokinase-streptodornase tablets which comprises adding a liquid gelatin solution to a liquid solution containing the enzymes streptokinase and streptodornase equivalent to about 5% based on the weight of the total solids in the enzyme solution, and thereafter heating the resulting solution to dryness.

2. The method according to claim 1 in which the resulting dried powder is compressed into tablets.

3. A stable streptokinase-streptodornase tablet containing at least about 0.01% by weight of gelatin.

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