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GASTRIC RESISTANT MEDICINAL PREPARATION
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This invention relates to a gastric resistant medicinal preparation, and more particularly to a medicinal preparation containing at least one medicinal component being substantially resistant to gastric disintegration.

There is contemplated by this invention a process for preparing a gastric resistant medicinal preparation, which includes the steps of intimately mixing a medicinal agent and a substantially solid gastric resistant material, then treating the resulting mixture to liquefy the gastric resistant material therein, and thereafter solidifying such mixture to obtain a powder in which the individual medicinal particles are substantially resistant to gastric disintegration. The further handling of this powder may involve the formation of medicinal granules of significantly increased density by compressing such powder in, for example, a slugging operation, and then comminuting and classifying the resulting slugs to produce granules of a selected size.

It will be appreciated that in a conventional "enteric coating" operation a medicinal agent, in the form of tablets, pills or pellets, is immersed in a liquid gastric resistant material to obtain surface coating of the medicinal agent with the gastric resistant material, and that the resulting preparation consists of a core of medicinal agent enveloped by laminations of the gastric resistant material. On the other hand, in the process of this invention the mixing of the medicinal agent and the substantially solid gastric resistant material, prior to liquefaction of such gastric resistant material, provides a medicinal preparation in which there is achieved a significantly increased intimacy between the medicinal particles and the gastric resistant material.

Although any substantially non-toxic material being substantially resistant to gastric disintegration may be employed in this medicinal preparation, better results may be achieved when this ingredient is an edible ester of a higher alcohol or fatty acid. For example, this gastric resistant material may be a fatty or waxy substance such as a hydrocarbon compound, e.g., paraffin; a glyceryl ester of a higher fatty acid, e.g., stearic or palmitic acid; beeswax or carnauba wax. Still better results can be obtained with a mixture of at least one hydrocarbon and a glyceryl ester of at least one higher fatty acid, e.g. a glyceryl ester of stearic acid, or beeswax or carnauba wax. Especially desirable results can be obtained when this gastric resistant material is a mixture of paraffin and glyceryl tristearate. This gastric resistant material may be employed in a concentration of from about 10 to 90% by weight of the medicinal preparation. When there is employed in this medicinal preparation a combination of gastric resistant materials such as paraffin and glyceryl tristearate, the relative proportions thereof may be, for example, 40% by weight of paraffin and 60% by weight of glyceryl tristearate. However, it will be understood that the solubility rate and gastric resistance of this medicinal preparation may be varied by increasing or decreasing the concentration of gastric resistant material in relation to the content of medicinal agent.

It will be apparent that this invention may be applied to any medicinal agent in a substantially solid form, although better results are to be obtained when the medicinal agent is in the form of a substantially dry powder. Consequently, it is appropriate to describe the invention

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in connection with pancreatin, a classical medicinal agent susceptible to destruction by gastric juice. Pancreatin is a dehydrated, defatted preparation of mammalian pancreas tissue containing a mixture of enzymes physiologically secreted by the pancreas gland into the duodenum, and thus pancreatin is both physiologically and therapeutically an enteric preparation.

The practice of this invention can be described generally in connection with pancreatin as the medicinal agent and a mixture of paraffin and glyceryl tristearate as the gastric resistant material. The paraffin and glyceryl tristearate may be combined in a proportion of 1.5 parts of paraffin to 1 part of glyceryl tristearate. If desired, in order to achieve a more thorough dispersion of the pancreatin in the gastric resistant material at this stage of the operation, the mixture of paraffin and glyceryl tristearate and the pancreatin may be milled to achieve a particle size thereof of less than about 50 mesh (297 microns). Similarly, the mixing of the pancreatin and a milled mixture of paraffin and glyceryl tristearate can be obtained at room temperature in a suitable mixing vessel to which is attached an agitator or blending apparatus. In general, this mixing operation should be obtained at a temperature at which the gastric resistant material is in solid form, and thus conveniently the operation is carried out at a temperature of from about 20 to 35° C. After completing the mixing operation, the resulting mixture is heated to a temperature at which the gastric resistant constituent thereof is liquefied, but below that temperature at which there is obtained decomposition of either the medicinal agent or gastric resistant material. Accordingly, this heating operation may be carried out by spreading the mixture on trays to a depth of about one-half to three-quarter inch, and introducing the filled trays into a circulating air oven. Thereupon, the mixture is heated at a temperature of about 155–165° F. for a period of about ¼ to 2 hours. Although the liquefaction of the gastric resistant constituent of the mixture by heating is preferred, this liquefaction step may also be obtained by combining such mixture with a solvent such as a chlorinated hydrocarbon, e.g., carbon tetrachloride, and, after completing the operation, removing the solvent by evaporation. However, since these solvents are generally toxic, it is necessary that the removal thereof, after the liquefaction operation, be substantially complete and performed under safe conditions.

After completing this liquefaction operation by heating the solidification of the mixture may be obtained by cooling to approximately room temperature or in a desirable aspect of this invention to a temperature at which the particle size of the resulting solid mass is reducible to less than about 20 mesh (840 microns). Thereafter the density of the medicinal particles in the mixture may be desirably increased to further reduce the solubility rate and disintegration thereof in the stomach by compressing such particles into slugs in a slugging operation. It will be apparent that the degree to which the density of the medicinal particles is increased may be varied according to the pressure applied in the compressing operation. Prior to this compressing operation, it may be desirable to combine with the medicinal preparation approximately 1 to 3% of a lubricant such as talc or magnesium stearate or a mixture thereof, e.g. a mixture of 1% by weight of talc and 0.5% by weight of magnesium stearate. Granulation of the resulting slugs may be obtained in a milling operation employing an oscillating granulator or other milling device to obtain granules of an average size of about 5 to 30 mesh (4000–590 microns). Standardizing of the granule size of the medicinal preparation may be achieved by classifying the

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milled product in a screening operation, and then reworking that portion of the product of undesirable mesh size.

These gastric resistant granules may be employed directly as a therapeutic agent or may be introduced into capsules or may be formed into tablets. In addition, the gastric resistant granules may be combined with granules of the same or other medicinal agents in a form which is disintegrated in the stomach.

This invention may be further illustrated by the following specific examples:

Example I

A gastric resistant preparation of pancreatin was prepared having the following composition:

	Percent
Pancreatin	75
Paraffin	10
Glyceryl tristearate	15

A mixture of paraffin and tallow flakes (glyceryl tristearate) was milled and classified to an average particle size of about 80 mesh (177 microns). The pancreatin was also separately milled and classified to an average particle size of about 80 mesh (177 microns). The mixture of paraffin and tallow flakes, in the total amount of 2.5 pounds, was combined in a mixing vessel with 7.5 pounds of dehydrated, defatted pancreatin, having a U.S.P. potency of 1:80 (proteolytic activity) and 1:70 (diastase activity). The ingredients were blended by agitation at room temperature for about one hour to obtain intimate mixing of the pancreatin and the gastric resistant material.

The resulting mixture was spread on trays to a depth of approximately $\frac{1}{2}$ to $\frac{3}{4}$ inch. The filled trays were heated in a circulating air oven at a temperature of approximately 155–165° F. for a period of one hour. After the heating operation had been completed, the trays were removed from the oven and the heated mixture was cooled to solidify the medicinal preparation. The cooled material was classified to an average particle size of less than about 25 mesh (710 microns). This operation was carried out by periodically classifying an aliquot of the cooling mass to ascertain whether or not the particles thereof would pass a 20 mesh (840 microns) screen.

After classifying of the mass had been completed, such mass was mixed in a suitable vessel with 0.1 pound of talc and 0.05 pound of magnesium stearate as a lubricant. The resulting material was compressed into very hard slugs in a slugging apparatus. The resulting slugs were granulated in an oscillating granulator to produce granules of an average size of from 10 to 20 mesh (2000–840 microns). Those granules which upon classifying passed a 10 mesh (2000 microns) screen but failed to pass a 20 mesh (840 microns) screen were of the desired particle size. On the other hand, those particles passing the 20 mesh (840 microns) screen were recompressed and reggranulated to obtain medicinal granules of the desired size.

The resulting preparation of medicinal granules was subjected to analysis, and the results were as follows:

Moisture	3.24%.
Petroleum benzene solubles	25.17%.
Solubility in gastric media	None in 1 hour.
Solubility in intestinal media	60% in 2 hours.
Proteolytic activity (NF)	1:70 (defatted).
Diastase activity (NF)	1:70 (defatted).

Example II

A medicinal composition including a gastric resistant component and a gastric soluble component was prepared by the following method:

The gastric resistant component of this composition was similar in formulation to and was prepared by the method of Example I.

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The gastric soluble granules had the following composition:

	Percent
Iron ox bile	47
Lactose	43
Cornstarch	10

The foregoing ingredients were thoroughly mixed and granulated according to conventional methods.

The gastric soluble granules, in the amount of 10 pounds, were combined with the gastric resistant granules, also in the amount of 10 pounds. Accordingly, there was added to such mixture 0.2 pound of talc and 0.2 pound of magnesium stearate as a lubricant, and 1 pound of cornstarch as a disintegrator. After thorough mixing of the two granulations, the mixture was formed into tablets.

Example III

A medicinal composition including a gastric resistant component and a gastric soluble component was prepared by the following method:

The gastric resistant component of this composition was similar in formulation to and was prepared by the method of Example I.

The gastric soluble granules had the following composition:

	Percent
Iron ox bile	25
Pepsin 1:10,000	30
Lactose	30
Cornstarch	15

The gastric soluble granules were combined with the gastric resistant granules in approximately equal quantities. To the resulting mixture was added 1% of talc and 1% of magnesium stearate as a lubricant, and 5% of corn starch as a disintegrator.

After thorough mixing of the ingredients, the formulation was formed into tablets.

While in the foregoing specification various embodiments of this invention have been set forth and specific details thereof elaborated for the purpose of illustration, it will be apparent to those skilled in the art that this invention is susceptible to other embodiments and that many of the details can be varied widely without departing from the basic concept and spirit of the invention.

I claim:

1. In a process for preparing a medicinal preparation containing at least one component being substantially resistant to gastric disintegration, the steps of intimately mixing a substantially solid medicinal agent and a substantially solid gastric resistant material, then heating the resulting mixture to liquefy the gastric resistant material therein, and thereafter cooling the resulting mass to obtain a substantially dry powder medicinal preparation being substantially resistant to gastric disintegration.

2. The product obtained by the process of claim 1.

3. In a process for preparing a medicinal preparation containing at least one component being substantially resistant to gastric disintegration, the steps of intimately mixing a substantially solid medicinal agent and a substantially solid gastric resistant material, then heating the resulting mixture to liquefy the gastric resistant material therein, then cooling the mixture to obtain a solid mass of the medicinal preparation, compressing the solid mass to increase the density of the particles therein, and milling the compressed mass to obtain granules substantially resistant to gastric disintegration.

4. In a process for preparing an enteric medicinal preparation, the steps of intimately mixing a substantially solid medicinal agent and a substantially solid mixture of at least one hydrocarbon and a glyceryl ester of at least one higher fatty acid substantially resistant to gastric disintegration, heating the resulting mixture to liquefy the

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gastric resisant material therein, then cooling the heated mixture to obtain a solid mass having an average particle size of less than about 40 mesh (420 microns), compressing the solid mass to increase the density of the medicinal particles therein, and milling the compressed material to obtain granules of an average size of the from about 5 to 30 mesh (4000-590 microns).

5. In a process for preparing an enteric pancreatin preparation, the steps of intimately mixing pancreatin and a substantially solid mixture of paraffin and glyceryl tristearate, heating the resulting mixture to liquefy the paraffin and the glyceryl tristerate, cooling the heated mixture to obtain a solid mass having an average particle size of less than about 40 mesh (420 microns), compressing the solid mass to increase the density of the medicinal particles therein, and milling the compressed material to obtain granules of an average size of from 5 to 30 mesh (4000-590 microns).

6. The product obtained by the process of claim 5.

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