United States Patent Office 2,852,433 Patented Sept. 16, 1958

2,852,433

METHOD OF MAKING ENTERIC MEDICAMENT COMPOSITIONS

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No Drawing. Application March 7, 1956 Serial No. 569,967

7 Claims. (Cl. 167—82)

This invention relates to products which are inherently enteric prepared by dissolving in a melt of a solid therapeutic agent, a dicarboxylic acid ester of a cellulose derivative or of polyvinyl alcohol or polyvinyl acetate, forming into the desired form and cooling or allowing to cool to solidify the same.

Ordinarily, enteric products consist of a medicament surrounded by a non-toxic material insoluble in acids and soluble in alkaline liquids. The medicament is preferably first formed into a tablet or pill and a material such as shellac, or cellulose acetate phthalate is built up by successive additions to the tablets such as by tumbling in a coating pan. An enteric coating may be thus applied to the tablet or pill. A properly applied enteric coating in desirably of uniform thickness as there should be no weak spots in the layer surrounding the medicament. As a practical matter, this is difficult to achieve because most medicinal tablets are irregular in shape and have sharp edges which take a very thin coating. As a result, there is the danger that the overcoating of the tablet may be ruptured and the medicament would be released in the stomack, rather than in the intestine. If, to avoid this possibility, the enteric coating applied is appreciably thick, it may be that that coating might not be completely dissolved and thus the medicament might pass through the body without ever being freed therein.

One object of my invention is to provide a medicament material having enteric properties coating of which is unnecessary. Another object of my invention is to provide a method of making medicament material having enteric properties in which the medicament in melt form acts as a solvent for the composition. A further object of my invention is to provide enteric medicaments which are not affected by moisture or weather conditions. Other objects of my invention will appear herein.

I have found that a medicament material having enteric properties may be prepared by dissolving polymeric acid type enteric material in molten medicament whereby a plastic mass is formed and is given a selected shape. Upon cooling, enteric medicament in the desired form is thereby obtained. The enteric materials which may be used are the dicarboxylic acid esters of cellulose, cellulose derivatives, polyvinyl alcohol or polyvinyl acetate. For instance, compounds which have been found to be ideally adapted for this purpose are cellulose phthalate, cellulose acetate phthalate, ethyl cellulose phthalate, polyvinyl phthalate and polyvinyl acetate phthalate. These materials are employed in the acid form.

The medicament materials which are susceptible to melting and in the melts of which the enteric material will dissolve without any detrimental effects are aspirin, acetanilide, mandelic acid and phenacetin. All of these medicament materials are characterized by the presence of acetyl groups therein. Compositions for preparing enteric products in accordance with my invention may be prepared either by first mixing the meltable medicament and the enteric material and forming a melt of the same or by melting the medicament material and incorporating the enteric material therein. Other medicament materials may, if desired, be included with the aspirin or like meltable medicament. Medicaments which may be added to the composition of the molten medicament and the enteric material are barium sulfate, yeast, egg albumen, starch, zein, sodium chloride, potassium chloride, magnesium sulfate, ferrous sulfate, sulfanilamide, phenobarbital, thyroid, pancreatin, bile salts, ovarian substances, digitalis, gentian violet and the like.

Compositions in accordance with my invention may be compounded for instance, by mixing the dry material together in powder form and working the same hot rolls whereby the material is thoroughly mixed together in a molten or plastic condition which upon coming off from the rolls can be formed into convenient units. This may be done, if desired, by cutting the material into long strips as it comes off the rolls and slicing the strips into pieces. In carrying out this operation, the rolls should preferably be at a temperature of 120–150° C. depending upon the conditions of operation. If it is desired to use rolls having a lesser temperature, it will be desirable to incorporate into the mass a latent solvent such as isopropyl alcohol which is not a solvent for this composition at room temperature but is a solvent at elevated temperatures. Other useful latent solvents are etheyl alcohol, normal propyl alcohol, ethyl acetate and methyl ethyl ketone. The latent solvent may be used in an amount up to equal the amount of the solid composition. This latent solvent is driven off during the actual fluxing operation so that the product finally resulting is essentially a mixture of medicament and an enteric material. When a latent solvent is used the rolls upon which the material is worked need not be so hot; for instance, a roll temperature of 80–120° C. would be sufficient.

A method of preparing materials in accordance with my invention is to mix together in finely divided, comminuted or powdered form the meltable medicament and the enteric material and applying heat to obtain a flowable mass which can be shaped and cooled in any desirable form. Less conveniently, the medicament may be melted first and the enteric material added thereto followed by shaping and cooling. If desired, extrusion may be used in which operation the materials may be mixed in the extruding operation, the resulting mixed composition being extruded such as in the form of rods, which may be cut into pieces by means of a rotary cutter. In any of the procedures described, other medicaments not meltable may be incorporated to lend their properties to the resulting units which are obained. My invention is not limited to any particular proportion, the meltable medicament, such as aspirin, or its mixture with some other meltable medicament, being used in sufficient amount to obtain a good melt of the composition thereof with the enteric material and with other medicament material, if any, which might also be incorporated in the composition. I have found that for convenient operation, equal parts of medicament and enteric material are useful. Aspirin being somewhat higher melting than the other meltable medicaments mentioned, it is desirable that a higher temperature of operation be used in the preparation of medicament units when aspirin is depended upon as the fluxing material therein.

The following examples illustrate my invention:

Example 1

One part of acetanilide in comminuted form was well mixed with one part of a powdered cellulose acetate phthalate having enteric properties. The mass was sub-

jected to heat to form a molten composition. The clear melt obtained was poured out onto a surface and allowed to cool. The cooled composition thus obtained was divided into small units whereby it could be employed as an enteric source of acetanilide.

A similar mixture was prepared except that two parts of acetanilide per part of cellulose acetate phthalate was employed. This mixture resulted in a less viscous solution which, upon cooling, gave an opaque brittle solid having enteric properties.

Example 2

Melts were prepared as described in the preceding example except that the medicament used was DL-mandelic acid. Melts were prepared with good mixing and upon cooling, the compositions remained compatible. The cooled mass thus obtained was divided into convenient pieces whereby units were formed which were useful as enteric medicaments.

Example 3

A mixture was formed of cellulose acetate phthalate having an acetyl content of 19% and a phthalyl content of 36% and pure acetyl salicylic acid (aspirin) both in powdered condition. This mixture was melted by subjecting to an elevated temperature, and a homogeneous light brown melt was obtained. Compositions of ratios 2:1 and 1:1 by weight of aspirin to cellulose acetate phthalate were prepared. The melting took place at 140–150° C. The 1:1 composition required strong stirring to obtain good mixing. It is preferred in a compounding of this type that a heated two-roll mill be used. On cooling, a hard plastic material resulted. The 2:1 composition upon cooling was relatively soft and rubber-like. Units thereof were tested in simulated gastric juice to ascertain their behavior in the body. Ten cubes thereof weighing a total of .8336 gram were soaked in 0.35% strength hydrochloric acid for 7.5 hours. At the end of this time, the cubes were thoroughly dried and were weighed. A loss of only 3.7% was found. The units, however, were found to slowly dissolve in 0.5% aqueous sodium bicarbonate whereby the medicament becomes eventually released.

Example 4

A mixture of cellulose acetate phthalate and aspirin in dry powder form was worked up on hot rolls having a temperature of 140–150° C. There was thus formed a white mass which, after solidifying, was divided into convenient units useful for medicinal purposes.

Example 5

Two parts of aspirin were melted in a vessel at a temperature of 145° C. When the melt was obtained, there was stirred therein one part of cellulose acetate phthalate which composition was thoroughly agitated until complete homogeneity was obtained. The melt was then poured out onto a surface and was allowed to cool. The cooled composition was cut into rods which rods were divided into convenient units for use for medicinal purposes.

Example 6

Aspirin was mixed in equal parts with nembutal sodium, the latter not melting when alone even when heated to a high temperature. This medicament mixture was melted up with cellulose acetate phthalate at a temperature of approximately 150° C. Compositions of both 1:1:1 and 2:1:1, aspirin: nembutal sodium: cellulose acetate phthalate were prepared by heating the materials together and then cooling until a solid material was formed. The molten material was then poured out onto a surface and was allowed to cool. The resulting slab of medicament material was divided into convenient units for use for medicinal purposes.

Example 7

A mixture of polyvinyl phthalate and aspirin in dry powder form was worked up on hot rolls having a temperature of 140–150° C. There was thus formed a plastic white mass which was spread out upon a surface and upon cooling hardened. After the mass had cooled, it was divided into convenient units useful for medicinal purposes.

Example 8

A mixture was formed of equal parts of cellulose acetate phthalate, aspirin and isopropanol. The resulting mixture was worked on hot rolls having a temperature of 110–120° C. until a plastic mass was obtained and the isopropanol had been substantially driven off. The material was then spread out onto a surface and allowed to cool. The cooled mass was divided into units of convenient size for medicinal purposes.

In making medicament units in accordance with my invention, the enteric material employed is in the acid form, such as cellulose acetate acid phthalate, polyvinyl acid phthalate or the like. Consequently, the units which are prepared are resistant to the effect of any moisure or water with which it might come in contact. Instead of the phthalates, other dicarboxylic acid esters of cellulose derivatives, of polyvinyl alcohol or of polyvinyl acetate may be employed, such as the succinates, the maleates or the like as the enteric material in compositions in accordance with my invention.

This application is a continuation in part of my application Serial No. 273,145, entitled "Enteric Products," filed February 23, 1952, now abandoned.

I claim:

1. A process of forming a material having enteric properties which comprises dissolving a substantial proportion of an enteric material selected from the group consisting of the dicarboxylic acid esters of cellulose derivatives, of polyvinyl alcohol and of polyvinyl acetate in a melt of a medicament selected from the group consisting of aspirin, mandelic acid, acetanilide, and phenacetin at 120–150° C. and cooling the molten mass in convenient form.

2. A process of forming a material having enteric properties which comprises dissolving a substantial proportion of cellulose acetate phthalate in a melt of a medicament selected from the group consisting of aspirin, mandelic acid, acetanilide, and phenacetin at 120–150° C. and cooling the molten mass in convenient form.

3. A proces of forming a material having enteric properties which comprises dissolving in a melt of a medicament selected from the group consisting of aspirin, mandelic acid, acetanilide, and phenacetin at 120–150° C., a substantial proportion of an enteric material selected from the group consisting of the dicarboxylic acid esters of cellulose derivatives, of polyvinyl alcohol and of polyvinyl acetate and incorporating therein a medicament non-meltable at said temperature followed by cooling the resulting mass in convenient form.

4. A process for forming a material having enteric properties which comprises dissolving a substantial proportion of a dicarboxylic acid ester of cellulose acetate in a melt of a medicament selected from the group consisting of aspirin, mandelic acid, acetanilide, and phenacetin at 120–150° C., followed by cooling the molten mass in convenient form.

5. A process of forming a material having enteric properties which comprises dissolving one part of an enteric material selected from the group consisting of the dicarboxylic acid esters of cellulose derivatives, of polyvinyl alcohol and of polyvinyl acetate in a melt of two parts of aspirin followed by cooling the molten mass in convenient form.

6. A process of preparing a material having enteric properties which comprises intimately mixing together equal parts of cellulose acetate phthalate and aspirin,

subjecting the mixture to an elevated temperature within the range of 120–150° C., whereby the aspirin melts and the cellulose acetate phthalate dissolves in the melt and cooling the resulting mass in convenient form.

7. A method of forming a material having enteric properties which comprises intimately mixing equal parts of cellulose acetate phthalate, aspirin, and nembutal sodium, subjecting the mixture to an elevated temperature within the range of 120–150° C., whereby the aspirin melts and the cellulose acetate phthalate and the nembutal sodium dissolves in the melt followed by cooling the resulting mass in convenient form.

References Cited in the file of this patent

UNITED STATES PATENTS

2,196,768	Hiatt	Apr. 9, 1940

FOREIGN PATENTS

514,047	Great Britain	Oct. 30, 1939
285,091	Great Britain	June 10, 1929

OTHER REFERENCES

Thompson et al.: "History, Literature and Theory of enteric Coatings," Jour. Am. Pharm. Assoc., Sci. Ed., vol. 34, No. 5, May 1945, pp. 135–37.

Gutman: "Modern Drug Encycl.," 5th Ed., Drug Publs., Inc., N. Y. C., 1952, p. 634.