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ENTERIC COATING

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This invention relates to an improved enteric coating for medicaments.

As is well known, the desiderata of enteric coating are to protect an orally ingested medicament against release in the stomach, under the action of the fluids of the stomach or agitation therein, and, at the same time, allow release of the medicament in the intestines, under the action of the fluids therein, before elimination from the body. Such an enteric coating is said to have integrity in the stomach.

Heretofore various enteric coatings comprising various materials have been suggested and used. However, the best of the prior enteric coatings have not proved satisfactory for various reasons, chief among which are that the coating material where resistant to attack by the fluids of the stomach and, at the same time, soluble in the fluids of the intestines, is permeable by the fluids of the stomach with the result that the medicament if soluble in the stomach fluids is largely leached out through the coating; and where the material is resistant to attack and impermeable by the fluids of the stomach, it becomes ruptured by the agitation in the stomach, thus allowing the stomach fluids to attack the medicament.

By way of illustration, heretofore an enteric coating comprising a cellulose derivative containing free carboxyl groups substantially insoluble in the fluids of the stomach and soluble in the intestinal fluids, as, for example, cellulose acetate phthalate (see U. S. Patent No. 2,196,768) has been widely used, but has proved unsatisfactory where the medicament is soluble in the stomach fluids since coatings thereof on a medicament, of a thickness to permit release of the medicament in the intestines before elimination, are permeable by the fluids of the stomach, which are thus enabled to leach out or extract the medicament variously to a greater or less extent depending upon the conditions existing in the stomach at the time of ingestion, the period of retention in the stomach and the solubility of the medication in the stomach juices.

As further illustrative, a heretofore used enteric coating has comprised a wax, as, for example, beeswax. However, such a coating of a thickness permitting release of the medicament in the intestines before elimination has proved unsatisfactory, since it becomes ruptured under agitation in the stomach and permits direct attack upon the medicament by the fluids of the stomach.

Now in accordance with this invention, it has been found that an enteric coating having integrity in the fluids of the stomach which will

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readily release a medicament in the intestines and which is substantially not soluble or dispersible in and impermeable by the fluids of the stomach and proof against rupture by agitation in the stomach, is provided by double coating, as for example, by first coating a medicament, in pellet, tablet, capsule, granular, or other form, with a cellulose derivative containing free carboxyl groups and which is substantially insoluble in stomach fluids and soluble in intestinal fluids, and then overcoating with a non-toxic wax.

The wax coating may be of a first type which will be dissipated under the action of intestinal fluids or of a second type which will be dissipated only under abrasive action in the gastro-intestinal tract.

The enteric coating according to this invention has been found to provide effective protection of the medicament in the stomach. When the wax coating is the outer coating, it acts to prevent penetration of the inner coating by stomach fluids and the inner coating acts to support and stay the outer wax coat against rupture from agitation in the stomach. When the wax coating is the inner of the two coatings, it acts to prevent stomach fluids which have permeated the outer coating from reaching the medicament while the outer coating protects the wax coating from being ruptured. Thus the two coatings interact uniquely to effectively protect the medicament in the stomach.

In proceeding for the preparation of enteric coated medicaments according to this invention, while any of the several compounds disclosed by U. S. Patent No. 2,196,768, the disclosure of which is made a part hereof, may be used for the function of one of the coats, it is preferred to use cellulose acetate phthalate. When this first coat is the inner coat, it may be, for example, but without limitation 2%–5% of the weight of the tablet or other form of the medicament and when used as the outer coat it may be, for example, without limitation 5%–10% of the weight of the tablet or other form of the medicament.

When the wax coat is to be of the first type which will be dissipated under the action of intestinal fluids, it may be formed by the use of any wax which is substantially not soluble or dispersible in the stomach fluids and rapidly soluble or dispersible in the intestinal fluids, as, for example, a glyceryl ester or a diglycol ester of a higher fatty acid such as glyceryl monostearate, diglycol stearate, diethylene glycol monostearate, glyceryl myristate, or the like, alone or in admixture with a wax which is insoluble and not dis-

persible in the gastro-intestinal tract such as, for example, beeswax, Japan wax, paraffin, carnauba wax, bayberry wax, hydrocarbon waxes, non-toxic synthetic waxes, higher solid non-toxic alcohols such as cetyl alcohol, palmitic alcohol stearyl alcohol or the like.

The second or wax coat formed by the use of a wax which is substantially not soluble or dispersible in the stomach fluids and rapidly soluble or dispersible in the intestinal fluids when used alone as an outer coat will be, for example, 2%–8% of the weight of the tablet, or other form of the medicament and when used as an under coat will be, for example, 1%–4% of the weight of the tablet, or other form of the medicament.

When the wax coat of the aforementioned first type is formed by the use of a wax which is substantially not soluble or dispersible in the stomach fluids and rapidly soluble or dispersible in the intestinal fluids admixed with a wax which is insoluble and not dispersible in the gastro-intestinal tract, the latter wax will preferably be 25%–50% by weight of the mixture forming the coating and in no case will exceed 75% by weight of the mixture. When such a coat is used as an outer coat it will be for example 1%–5% of the weight of the tablet or other form of medicament and when used as an under coat it will be for example ½%–3% of the weight of the tablet.

When the wax coat is to be of the aforementioned second type, the coat is formed by the use of a wax which is insoluble and not dispersible in the gastro-intestinal tract, such as, for example, those exemplified above. When such a coating is used, it will preferably be 1%–2% by weight of the tablet or other form of the medicament and will in no case be more than 5% or less than 0.5% by weight of the tablet or other form of the medicament.

We intend to include within the scope of the term "wax" when used herein and in the claims appended hereto all of the above-mentioned waxes and mixtures thereof.

All of the several coatings may be formed successively through the medium of solutions or dopes comprising the respective substances, by conventional procedure and with the use of conventional apparatus. Each coating throughout its extent will, of course, be of substantially uniform thickness.

The following examples are more specifically illustrative of this invention:

Example 1

A tablet containing 5 mg. amphetamine sulfate is coated, in any usual manner, with cellulose acetate phthalate, the weight of the coating being about 5% of the weight of the tablet. The thus coated tablet is then overcoated with a mixture comprising 75 parts by weight of glyceryl monostearate and 25 parts by weight of beeswax, the weight of the coating being about 2% of the weight of the tablet.

Example 2

A tablet containing 0.486 gm. of ammonium chloride is coated, in any conventional manner, with cellulose acetate phthalate, the weight of the coating being about 7% of the weight of the tablet. The thus coated tablet is then overcoated with a mixture comprising 90 parts by weight of diglycol stearate and 10 parts by weight of carnauba wax, the weight of the coating being about 4% of the weight of the tablet.

Example 3

A tablet containing 200 mg. of theophylline ethylenediamine is coated, in any conventional manner, with cellulose acetate phthalate, the weight of the coating being about 10% of the weight of the tablet. The thus coated tablet is then overcoated with a mixture comprising 85 parts by weight of glyceryl myristate and 15 parts by weight of Japan wax, the weight of the coating being about 3% of the weight of the tablet.

Example 4

A tablet containing 5 mg. amphetamine sulfate is coated, in any conventional manner, with cellulose acetate phthalate, the weight of the coating being about 9% of the weight of the tablet. The thus coated tablet is then overcoated with a mixture comprising 80 parts by weight of diethylene glycol monostearate and 20 parts by weight of bayberry wax, the weight of the coating being about 2% of the weight of the tablet.

Example 5

A tablet containing 200 mg. of theophylline ethylenediamine is coated, in any conventional manner, with cellulose acetate phthalate, the weight of the coating being about 10% of the weight of the tablet. The thus coated tablet is then overcoated with a mixture comprising 70 parts by weight of diglycolstearate and 30 parts by weight of paraffin, the weight of the coating being about 3% of the weight of the tablet.

Example 6

A tablet containing 0.486 gm. of ammonium chloride is coated, in any conventional manner, with cellulose acetate phthalate, the weight of the coating being about 7% of the weight of the tablet. The thus coated tablet is then overcoated with glyceryl monostearate, the weight of the coating being 5% of the weight of the tablet.

Example 7

A tablet containing 5 mg. amphetamine sulfate is first coated with cellulose acetate phthalate, the weight of the coating being 8% of the weight of the tablet. The thus coated tablet is then overcoated with beeswax, the weight of the coating being 1% of the weight of the tablet.

Example 8

A tablet containing 0.65 gm. of ammonium chloride is first coated with a mixture comprising 85 parts by weight of glyceryl myristate and 15 parts by weight of carnauba wax, the weight of the coating being 6% of the weight of the tablet. The tablet is then overcoated with cellulose acetate phthalate, the weight of the coating being 6% of the weight of the tablet.

Example 9

A tablet containing 10 mg. amphetamine sulfate is first coated with a mixture comprising 75 parts by weight diglycol stearate and 25 parts by weight of beeswax, the weight of the coating being 8% of the weight of the tablet. The tablet is then overcoated with cellulose acetate phthalate, the weight of the coating being 5% of the weight of the tablet.

Tests of tablets enteric coated according to the first example given above show no penetration by fluids of the stomach for a period of ten hours and disintegration in about one hour in intestinal fluids.

Thus, according to this invention an enteric coating is provided which is insoluble and not dispersible in and impermeable by the fluids of the stomach and non-rupturable by agitation in the stomach, while, at the same time, it is readily dissipated by the fluids of the intestines.

In the following claims, the word "soluble" is intended to comprise also dispersible, digestible and emulsifiable.

What we claim and desire to protect by Letters Patent is:

1. A new article of manufacture comprising a medicament, and a coating comprising a layer of a cellulose derivative containing free carboxyl groups substantially insoluble in the stomach fluids and soluble in the intestinal fluids, and a layer of wax, said wax layer being characterized by the fact that its integrity will be maintained in the stomach and will be lost in the intestines and by the fact that it is not less than ½% by weight of the medicament.

2. A new article of manufacture comprising a medicament, a coating comprising a cellulose derivative containing free carboxyl groups substantially insoluble in the stomach fluids and soluble in the intestinal fluids, and an undercoating of wax, said wax coating being characterized by the fact that its integrity will be maintained in the stomach and will be lost in the intestines and by the fact that it is not less than ½% by weight of the medicament.

3. A new article of manufacture comprising a medicament, a coating comprising a cellulose derivative containing free carboxyl groups substantially insoluble in the stomach fluids and soluble in the intestinal fluids, and an overcoating of wax, said wax coating being characterized by the fact that its integrity will be maintained in the stomach and will be lost in the intestines and by the fact that it is not less than 1% by weight of the medicament.

4. A new article of manufacture comprising a medicament, and a coating comprising an inner layer of cellulose acetate phthalate and an outer layer of wax, said wax layer being characterized by the fact that its integrity will be maintained in the stomach and will be lost in the intestines and by the fact that it is not less than 1% by weight of the medicament.

5. A new article of manufacture comprising a medicament, and a coating comprising a layer of a cellulose derivative containing free carboxyl groups substantially insoluble in the stomach fluids and soluble in the intestinal fluids and a layer comprising in admixture a wax insoluble in the stomach fluids and soluble in the intestinal fluids and a wax insoluble in the gastro-intestinal tract and by the fact that it is not less than ½% by weight of the medicament.

6. A new article of manufacture comprising a medicament, and a coating comprising a layer of a cellulose derivative containing free carboxyl groups substantially insoluble in the stomach fluids and soluble in the intestinal fluids and a layer of from 1% to 5% by weight of the medicament of a wax which is insoluble in the gastro-intestinal tract, said layer of wax being the outer layer of the coating.

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