

1

3,073,748

COATED MEDICAMENTS

Isamu Utsumi, Kyoto, Tadao Ida, Gose, Shuzo Kishi, Habikino, and Toshiyuki Hashimoto, Kobe, Japan, assignors to Tanabe Seiyaku Co., Ltd.

No Drawing. Filed Nov. 17, 1961, Ser. No. 153,238

Claims priority, application Japan Nov. 28, 1960

3 Claims. (Cl. 167—82)

This invention relates to a sealing coat for oral medicaments in the form of tablets, pills, granules and the like to protect their contents, and to articles sealed with the coat.

It is known to give a sealing coat to compressed tablets to protect their contents from moisture before the tablets are covered with a plurality of coatings of sugar syrup to which powdered filler is added during the intermediate drying after the application of each coating. A sealing coat is also required when tablets are coated with a water-soluble film-forming material such as gelatin. Sometimes, such a sealing coat is applied to a tablet containing unstable substances such as vitamins, hormones and antibiotics to prevent deterioration. Heretofore, such a sealing coat has consisted of a film forming material insoluble in water such as shellac, nitrocellulose or polyvinyl acetate. Such a coat is practically insoluble in water and dilute acid, and therefore sufficient thickness of the coat for elimination of absorption of moisture results in an increase in disintegration time in the gastric juices.

It is also known that medicinal tables are coated with a basic film forming polymer, which coating will disintegrate in the presence of dilute acid such as is encountered in the stomach. But if a patient to be medicated has an acidity, such coating will not disintegrate either in the stomach or the intestine and will be excreted in the stool without releasing the medicament.

The object of our invention is to provide a coating for medicament tablets and the like which can be applied thereto from a solution of a synthetic polymer in a low-boiling solvent, susceptible to rapid evaporation, whereby a smooth surface is formed on the tablets.

Another object of our invention is to provide coated medicaments in which the coating thereof is resistant to water.

A further object of our invention is to provide a synthetic film-forming polymer coating for medicaments, which coating will ordinarily disintegrate in the stomach; otherwise the coating will disintegrate in the presence of dilute aqueous alkali such as is encountered in the intestine.

Other objects of our invention will appear herein.

According to the invention, compressed tablets and similar articles are coated with a solution of an amphoteric film-forming polymer selected from the group consisting of copolymers of (A) vinylpyridines with (B) a lower aliphatic α , β -unsaturated monocarboxylic acid of 3 to 4 carbon atoms and copolymers of (A), (B) and a neutral co-monomer selected from the group consisting of methyl acrylate, acrylonitrile, vinyl acetate, methyl methacrylate and styrene.

Amphoteric polymers of this type are dissolved in volatile organic solvents such as lower alkanol, acetone or a low boiling chlorinated hydrocarbon and applied to compressed tablets. Upon subjecting the tablets to drying conditions such as an air blast, the coating quickly loses solvent and there results tablets having a smooth water-resistant surface which is also resistant to the ordinary handling to which tablets are subjected. Tablets or the like coated in this fashion remain unchanged in water, but the coating thereon readily disintegrates in dilute aqueous acid such as gastric juice which permits the release of the medicament shortly after its entrance into the stomach.

2

If a patient to be medicated has an acidity, such coating will not disintegrate in the stomach but will pass into the intestine as it is. However the coating finally disintegrates in any digestive juice of the patient even one with an acidity, since the coating is also soluble in dilute aqueous alkali such as intestinal juice.

Our invention also includes the use of said amphoteric polymers as a binder in the preparation of medicinal product for oral administration. For instance, some of the solution of the polymer may be milled or kneaded with medicament in solid form to form a mass of fairly uniform composition which is then given form or shape such as by extrusion, dried and then pressed.

The amphoteric film-forming polymers which are useful as coating material of the invention are vinylpyridine-acrylic acid copolymers, vinylpyridine methacrylic copolymers and copolymers of vinylpyridine with acrylic or methacrylic acid and the other polymerizable co-monomers such as methyl acrylate, acrylonitrile, vinyl acetate, methyl methacrylate or styrene. The polymers employed in this invention may be prepared by polymerizing said vinylpyridine monomer with said co-monomer according to the known method. Polymerization may be carried out under a standard condition which is known to those skilled in the art. Among many kinds of polymerization technique, emulsion or solution-polymerization is conveniently applicable. For instance, the composition which consists of the mixture of one of the vinylpyridines with the co-monomer, methanol and a small amount of benzoyl peroxide is heated at a temperature of 20° to 70° C. until the conversion is essentially completed and then is fractionated by partial precipitation with ether. The copolymers may also be prepared by mass-polymerization using α , α' -azo-bis-iso-butyronitrile as a catalyst.

Another example of preferred composition is that constituted by vinylpyridine, acrylic or methacrylic acid, a dilute acid such as hydrochloric acid or sulfuric acid, and a small amount of potassium persulfate. Alternatively, the polymers may be prepared by partly or completely hydrolyzing a copolymer of vinylpyridine with a monomeric derivative of acrylic acid or methacrylic acid such as ester, nitrile or amide thereby liberating free carboxylic groups in the polymer.

The production of such resins themselves is not a part of this invention and any of said vinylpyridine-acrylic or methacrylic acid copolymers which are soluble in either dilute acid or dilute alkali but insoluble in water may be used.

The tablets and similar articles so coated are free from tendency to spoilage whenever wet accidentally and show a high degree of stability on storage. The invention is therefore, particularly suitable for use in the manufacture of tablets and similar articles containing unstable active substances such as vitamins, antibiotics and similar substances.

The invention is illustrated by the following examples, which are not limitative.

EXAMPLE 1

A mixture containing 45% of starch, 43% of lactose, 7% of dextrine and 5% of talc is compressed into a table of 8 mm. diameter, 7.5 mm. radius of curvature and 4 mm. thickness. 15% solution of the polymers indicated in the Table 1 in chloroform was added portionwise to tablets which tablets were tumbled to distribute the solution thereon. At intervals an air blast at 40° C. was applied to remove the chloroform from the tablets. The application of the coating to the tablets is carried out until the amount of coating of each tablet reaches about 10 mg. The polymers used and the result of disintegration test both in distilled water and gastro-intestinal juices are shown in Table 1.

Table 1

Copolymers			Disintegration time		
Vinylpyridine, mole percent	Acid co-monomer, mole percent	Neutral co-monomer, mole percent	Distilled water (hrs.)	Artificial gastric juice (min.)	Artificial intestinal juice
2-vinyl, 20	Methacrylic, 21	Methyl acrylate, 59	>3	10-15	10-20
2-vinyl, 39	Methacrylic, 30	Acrylonitrile, 31	>3	5-10	10-20
2-vinyl, 44	Methacrylic, 31	Vinylacetate, 25	>3	5-10	10-20
4-vinyl, 59	Methacrylic, 51		>3	10-15	10-20
4-vinyl, 41	Methacrylic, 29	Acrylonitrile, 30	>3	5-10	10-20
4-vinyl, 21	Methacrylic, 22	Methyl acrylate, 57	>3	5-10	10-20
4-vinyl, 44	Methacrylic, 32	Vinyl acetate, 24	>3	5-10	10-20
4-vinyl, 43	Acrylic, 36	Acrylonitrile, 21	>3	5-10	10-20
2-methyl-5-vinyl, 61	Methacrylic, 39		>3	5-10	10-20
2-methyl-5-vinyl, 29	Methacrylic, 21	Methyl acrylate, 50	>3	5-10	10-20
2-methyl-5-vinyl, 34	Methacrylic, 31	Methyl methacrylate, 35	>3	5-10	10-20
2-methyl-5-vinyl, 33	Methacrylic, 31	Acrylonitrile, 31	>3	5-10	10-20
2-methyl-5-vinyl, 41	Methacrylic, 28	Styrene, 31	>3	5-10	10-20
2-methyl-5-vinyl, 44	Methacrylic, 32	Vinyl acetate, 24	>3	5-10	10-20
2-methyl-5-vinyl, 40	Acrylic, 31	Styrene, 29	>3	5-10	10-20
5-ethyl-2-vinyl, 60	Methacrylic, 40		>3	5-10	10-20
5-ethyl-2-vinyl, 35	Methacrylic, 26	Acrylonitrile, 39	>3	5-10	10-20
5-ethyl-2-vinyl, 23	Methacrylic, 17	Methyl acrylate, 60	>3	5-10	10-20
5-ethyl-2-vinyl, 41	Methacrylic, 28	Styrene, 31	>3	5-10	10-20
5-ethyl-2-vinyl, 45	Methacrylic, 31	Vinyl acetate, 24	>3	5-10	10-20
5-ethyl-2-vinyl, 34	Acrylic, 27	Acrylonitrile, 39	>3	5-10	10-20

EXAMPLE 2

5-ethyl-2-vinylpyridine, methacrylic acid and methyl methacrylate copolymer as described in Table 1 of Example 1 is dissolved in chloroform to give a solution of 20% concentration. 25 parts by weight of this solution is kneaded with 95 parts by weight of 1 to 1 mixture of starch and lactose to form a mass of uniform composition which is then extruded through a screen of 20 mesh to form a granule and then dried at 40° C. The granules are pressed with addition of 5% of talc into tablets, each of which weighing 120 mg. The tablet has a hardness of 4 to 6 kg. and disintegrates within a range of 10 to 15 minutes in artificial gastric juice and 5 to 15 minutes in artificial intestinal juice respectively.

EXAMPLE 3

Riboflavin	Mg.
Lactose	9.0
Starch	84.0
Dextrine	31.2
Magnesium stearate	5.0
	0.8

130.0

A mixture of above composition is compressed into a tablet. 15% solution of 5-ethyl-2-vinylpyridine, methacrylic acid and methyl methacrylate copolymer in chloroform is applied in the same manner as described in Example 1. Both types of coated and uncoated tablets are administered to the patients respectively and the excretion amount of riboflavin in urine is measured.

The results are shown in Table 2.

Table 2

Tablet	0-3 hours, mg.	3-6 hours, mg.
Uncoated	2.512	1.285
Coated	1.951	1.496

25 What we claim is:

1. A medicinal composition comprising tablets of a solid form medicament compounded with an amphoteric film-forming polymer selected from the group consisting of copolymers of (A) vinylpyridines with (B) a lower aliphatic α,β -unsaturated monocarboxylic acid of 3 to 4 carbon atoms and copolymers of (A), (B) and a neutral co-monomer selected from the group consisting of methyl acrylate, acrylonitrile, vinyl acetate, methyl methacrylate and styrene.

2. Medicinal tablets containing thereon a coating of an amphoteric film-forming polymer selected from the group consisting of copolymers of (A) vinylpyridines with (B) a lower aliphatic α,β -unsaturated monocarboxylic acid of 3 to 4 carbon atoms and copolymers of (A), (B) and a neutral co-monomer selected from the group consisting of methyl acrylate, acrylonitrile, vinyl acetate, methyl methacrylate and styrene.

3. A method of preparing a medicinal composition which comprised tumbling compressed units of medicament with a solution of an amphoteric film-forming polymer selected from the group consisting of copolymers of (A) vinylpyridines with (B) a lower aliphatic α,β -unsaturated monocarboxylic acid of 3 to 4 carbon atoms and copolymers of (A), (B) and a neutral co-monomer selected from the group consisting of methyl acrylate, acrylonitrile, vinyl acetate, methyl methacrylate and styrene in a volatile solvent and removing the volatile solvent from the composition.

References Cited in the file of this patent

UNITED STATES PATENTS

2,976,214	Ida	Mar. 21, 1961
2,987,445	Levesque	June 6, 1961

FOREIGN PATENTS

217,287	Australia	Sept. 16, 1958
---------	-----------	----------------