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ENTERIC COMPOSITION FOR TABLET COMPRESSION COATING

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The present invention relates to a process for coating tablets, and in particular to a process for the compression coating of tablets with an enteric coating containing a film-forming copolymer.

Prior to the development of tableting presses specifically designed for compression coating, the principle method of coating preformed tablets was in the customary coating pan. The coating pan is still widely used for applying sugar coatings, combination coatings consisting of an enteric inner coat and sugar outer coats, and film coatings of enteric and non-enteric properties. Many compositions of enteric coatings prepared by the pan coating method have been reported in the literature. The latter describes the use of liquid formulations incorporating the film forming materials with auxiliary substances as well as the use of the film former alone.

For the preparation of enteric coated tablets by pan coating the film forming material is applied in multiple layers onto the tablet surface from a solution of the coating formulation. Each application of the coating solution is poured or sprayed onto the tumbling tablets, then the solvents are evaporated with a stream of heated or non-heated air, leaving a residue of film deposited on the tablet surface. Finely divided powders, such as talcum and the like, may be dusted onto the tablets or suspended in the coating solution. Additional coatings are similarly cast until the deposited film is of sufficient durability and thickness to provide satisfactory protection to the core contents against the penetration of the gastric fluids of the stomach, but allowing disintegration of the coating and subsequent absorption of the active substances in the intestinal tract.

However, in the pan coating technique reproductibility of the structure of the coating wholly depends on the manipulative skill of the operator. Weight differences of the coating applied on the tablets vary from batch to batch and weight variance is found between tablets of the same batch. During the tumbling of the tablets, it is exceedingly difficult to control the amount of coating substance that each tablet will accept. Therefore, pan coating lacks the precision that is obtainable with compression methods.

Through the advent of compression coating equipment, a technological field has been opened, and unique formulations can now be devised to create new compositions which can be compressed around a preformed core and confer enteric properties to the finished tablet.

The compression of enteric coatings around a core has definite advantages over the pan method. Positive control of the weight of the coating can be maintained within close tolerances by weight adjustment devices on the compression equipment, and uniform coatings within specified tolerances are reproductible from batch to batch.

The technical problems inherent in developing compressed enteric coatings are quite different from those of the pan coating method. In the latter one is mainly concerned in the development of solutions of coating substances capable of forming smooth and uniform films on the tablet surface. A major objective in the compression coating method is the development of coating granulations that will uniformly fill the die cavities and yield upon compression, tablets with centrally positioned cores and a coating of strongly coherent granules with a minimum of void space or interstices throughout the coating. In both techniques the object is to obtain a coating impermeable to gastric fluids, which, however, erodes or yields the core contents in the intestinal tract.

Studies utilizing film formers in the preparation of enteric compressed coatings have been made. Granulations for compression coating containing as the film-former triethanolamine cellulose acetate phthalate are described by Blubaugh et al., J. Am. Pharm. Assoc., Sci. Ed. vol. 47, p. 857 (1958); Gruber et al., J. Am. Pharm. Assoc., Sci. Ed. vol. 47, p. 862 and p. 867 (1958); Ridolfo et al., J. Am. Pharm. Assoc., vol. 47, p. 869 (1958); and Stephenson, Pharm. Weekbl., p. 689 (1961), whereas cellulose acetate phthalate granulates for the same purpose are disclosed by James et al., Canad. Pharm. J., p. 467 (1958). However, it was found, that enteric compression coatings utilizing such granulates are not entirely satisfactory in the formulations described in the above literature reports. For example, tablets compressed coated with a granulation containing triethanolamine cellulose acetate phthalate as the film forming copolymer, together with lactose and magnesium stearate, show some loss of the soluble core contents; the coating appears to act as a semi-permeable membrance allowing diffusion of the soluble material into the surrounding medium. A compressed coating of triethanolamine cellulose acetate phthalate as the film former tends to swell and the soluble material is released by diffusion. Pan-coating with cellulose acetate phthalate solutions is widely employed with good results; however, it has been observed that tablets having compressed enteric coatings of granules containing cellulose acetate phthalate as described by James et al. tend to disintegrate rapidly (i.e. within one hour or less) in simulated gasteric fluid. We have found that cellulose acetate phthalate in the formulations described by James et al. imparts hardness and brittleness to the granulation; under the forces of compression, the granules crumble or fracture into smaller particles, which no longer give the necessary mutual cohesion to produce the desired continuous coating. The coating structure is weakened, and gastric or other fluids penetrate and moisten the coating mass, which upon agitation, disintegrates into the individual granules or small particles.

It is an object of the invention to provide a new process for the coating of tablets with an enteric coating.

It is a further object of this invention to provide a process for the compression coating of tablets with an enteric coating.

It is a further object of this invention to provide a process for the compression coating of tablets with an enteric coating by using a coating granulate containing a film-forming copolymer.

We have now found that tablets can be compressed coated with an enteric coating by using an enteric coating granulate composition containing a polyvinyl acetate copolymer as the film-forming copolymer and a substrate.

The process of enterically coating tablets by compression using a granulate composition containing a film-forming polyvinyl acetate copolymer is carried out according to known methods, preferably by using a machine capable of compressing a coating around a preformed core tablet. The latter contains the physiologically active components, which is intended to pass unaltered through the acidic medium of the stomach and to be absorbed in the alkaline medium of the lower intestine.

It is a further object of this invention to provide an enteric tablet having compressed onto the core with the physiologically active material an enteric coating containing a polyvinyl acetate copolymer as a film-forming agent and a substrate. Tablets of this type are prepared according to the above procedure using an enteric coat-

ing granulate composition containing a polyvinyl acetate copolymer.

It is a further object of this invention to provide an enteric coating granulate composition particularly suitable in the compression coating process of this invention. Such granulate composition comprises the polyvinyl acetate copolymer and a substrate.

The polyvinyl acetate copolymer, prepared according to known methods, is made up of two comonomers, one of which is, of course, the vinyl acetate monomer. The other comonomer may be selected from a variety of unsaturated compounds capable of copolymerizing with the vinyl acetate comonomer; preferably these compounds have a vinylogous carbon-carbon double bond, i.e. a double bond, in which at least one of the carbon atoms carries a functional group, e.g. a carboxyl group, an esterified carboxyl group, a carbamyl group, a halogeno atom and the like. Preferred compounds of this type are those having the acrylic acid moiety, as well as a functionally converted carboxyl group, i.e. an esterified carboxyl group, a carbamyl group and the like, in which a carboxyl group is attached to a carbon atom of the carbon-carbon double bond. Acids of this type are acrylic, methacrylic, maleic, fumaric, itaconic, citraconic acid and the like, above all crotonic acid. Other suitable comonomers are esters of the above acids containing the acrylic acid moiety, particularly the esters thereof with alkanols, i.e. the alkyl esters, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, n-hexyl, n-octyl esters and the like, of the above acids e.g. acrylic, methacrylic, fumaric, maleic, crotonic acid and the like. Also included as comonomers are the anhydrides or amides of the above acids having a vinylogous double bond, e.g. maleic acid anhydride, acrylic acid amide and the like. Other suitable esters having the vinylogous carbon-carbon double bond are the vinyl esters of alkanoic acids having at least three carbon atoms; esters of that type are, for example, vinyl propionate, vinyl butyrate, vinyl caprylate and the like; vinyl halides, e.g. vinyl chloride and the like, or any other suitable unsaturated compound having a vinylogous carbon-carbon double bond and being capable of forming a copolymer with the vinyl acetate may also be useful. In the compression coating granulate composition of this invention, the preformed polyvinyl acetate copolymer is employed.

If desired, a plasticizer is added to the granulate composition to give the enteric coating the desired plasticity. Suitable plasticizers are, for example, esters of carboxylic acids, such as lower alkyl citrates, e.g. triethyl citrate and the like, or other esters, such as diethyl phthalate, benzyl benzoate and the like. Although the presence of a plasticizer is not required, we have found, that an enteric compression coating granulate composition containing in addition to the polyvinyl acetate copolymer, a plasticizing agent, such as one of the above-mentioned compounds, provides certain advantages with respect to plasticity of the finished coating. Usually, the ratio between the platicizer and the polyvinyl acetate copolymer is from zero part per weight to about one hundred parts per weight, preferably from about thirty parts per weight to about one hundred parts per weight of the plasticizer, per one hundred parts per weight of the copolymer.

The substrate of the enteric coating granulate composition comprises a diluent or bulking agent and a lubricant agent. Any diluent or bulking material known in the pharmaceutical art may be suitable as part of the substrate. Especially useful are sugars, e.g. lactose, sucrose and the like, polyuronic acids, e.g. alginic acid and the like, metal salts, particularly alkali metal or alkaline earth metal salts, of inorganic or organic acids, e.g. calcium phosphate, calcium hydrogen phosphate, calcium lactate and the like, aluminum silicates, e.g. bentonite (colloidal clay) and the like, or any other analogous materials. Combinations of bulking materials may also be used, for example, a mixture of calcium lactate and lactose, or a mixture of calcium lactate and bentonite, or any other similar combinations.

A lubricating agent is required in the manufacture of tablets or compression coatings to prevent clogging of the machine and retention of the tablets, reduce friction during compression and ejection of the tablets and the like. Suitable lubricating agents are, for example, stearic acid or certain metal salts thereof, e.g. calcium stearate, magnesium stearate and the like, talc, hydrogenated castor oil, or any other analogous agents; mixtures of several lubricants, for example, a mixture containing magnesium stearate, stearic acid, hydrogenated castor oil and the like, may be used as well.

The raito of the polyvinyl acetate copolymer, together with any plasticizer, to the substrate in the enteric coating granulate composition of this invention is from about five parts per weight to about forty parts per weight, preferably from about fifteen parts per weight to about thirty parts per weight, of the polyvinyl acetate copolymer and any plasticizer to one hundred parts per weight of the substrate consisting of a mixture of at least a bulking material and of a lubricating agent.

A further object of this invention comprises a process for the manufacture of an enteric coating granulate composition containing a polyvinyl acetate copolymer and a substrate, which comprises mixing the substrate comprising a bulking material and a lubricant agent with a solution of the polyvinyl acetate copolymer and any plasticizer.

The granulate composition of this invention is prepared according to known methods. For practical reasons, a homogenous mixture of the bulking material and the lubricant agent, both screened through suitable screens, is first formed in one of the mixers usually employed in the pharmaceutical art to prepare the substrate. The latter is then granulated by adding a solution of the polyvinyl acetate copolymer and of any plastcizer while agitating. The solution is prepared by dissolving the polyvinyl acetate polymer and any plasticizer in a suitable organic solvent, particularly ethyl acetate and the like, or in a mixture of solvents containing preferably ethyl acetate and another miscible organic solvent, e.g. methanol, ethanol, isopropanol, acetone and the like; a preferred solvent is a 1:1-mixture of ethyl acetate and ethanol. The resulting wet granulation mass is preferably screened through a suitable screen and dried, usually while passing air over it, and, if necessary, at an elevated temperature. The dried granules are then passed through a mill and screened to yield granulate particles of a certain maximum size.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

Example 1

An enteric coating granulate composition suitable for a tablet compression coating procedure and containing 12.0 percent of a polyvinyl acetate copolymer consisting of vinyl acetate and crotonic acid as the comonomers, is prepared as follows:

Ingredients:	G.
Calcium lactate	630.0
Hydrogenated castor oil	70.0
Polyvinyl acetate copolymer	100.0
Triethyl citrate	30.0

The calcium lactate and the hydrogenated castor oil are sifted through a 30 mesh screen and mixed in a suitable mixer for thirty minutes. A solution of the polyvinyl acetate copolymer and the triethyl acetate plasticizer in a sufficient quantity of the 1:1-mixture of ethyl acetate and anhydrous ethanol is prepared, and added to the mixer to form the granulate. The wet mass is passed through a No. 8 sieve, dried at room temperature and ground through a mill using a screen with 0.063 inch (about 1.6 mm.) openings.

Example 2

An enteric coating granulate composition suitable for a tablet compression coating procedure and containing 15.7 percent of a polyvinyl acetate copolymer consisting of vinyl acetate and crotonic acid as the comonomers, is prepared as follows:

Ingredients:	G.
Calcium lactate	630.0
Hydrogenated castor oil	70.0
Polyvinyl acetate copolymer	151.0
Triethyl citrate	105.7

The enteric coating granulate composition is prepared as described in Example 1.

In the above example, the particular polyvinyl acetate copolymer may be replaced by another polyvinyl acetate copolymer using as comonomers vinyl acetate and acrylic acid, vinyl acetate and acrylic acid amide, vinyl acetate and maleic acid, vinyl acetate and itaconic acid, vinyl acetate and methyl acrylate, vinyl acetate and vinyl chloride, and the like. The triethyl acetate plasticizer may be replaced by another suitable plasticizer, e.g. diethyl phthalate, benzyl benzoate and the like.

Example 3

An enteric coating granulate composition suitable for a tablet compression coating procedure and containing 18.1 percent of a polyvinyl acetate copolymer consisting of vinyl acetate and crotonic acid as the comonomers, is prepared as follows:

Ingredients:	G.
Calcium lactate	630.0
Hydrogenated castor oil	70.0
Polyvinyl acetate copolymer	200.0
Triethyl citrate	200.0

The enteric coating granulate composition is prepared as described in Example 1.

In the above example, the calcium lactate may be replaced by other bulking materials, such as lactose, sucrose, alginic acid, calcium phosphate, bentonite and the like, or combinations of bulking materials, such as a mixture of calcium lactate and lactose, or calcium lactate and bentonite, and the like. Other lubricating agents than hydrogenated castor oil may be used, for example, stearic acid, magnesium stearate, talc and the like, or a mixture of several lubricants, such as stearic acid, magnesium stearate and hydrogenated castor oil and the like.

Example 4

Enteric tablets containing 0.3 g. of ammonium chloride as the physiologically active component and have a compressed enteric coating are prepared as follows (for 100,000 tablets):

Ingredients of the core:	G.
Ammonium chloride	30,000.0
Corn starch	1,700.0
Stearic acid	400.0
Methyl cellulose (100 cps.)	400.0
Alcohol, 3A	Q.s.
Water	Q.s.

The ammonium chloride, corn starch, stearic acid and methyl cellulose powders are sifted through a 30 mesh screen, mixed for thirty minutes and granulated with a sufficient quantity of 50 percent 3A alcohol. The granulate is screened, dried at 40° C. and broken through a 16 mesh screen.

On a suitable tablet pressing machine designed for compression coating, the above granulate is compressed into cores weighing 0.325 g., using 1⅞₂ inch punches. Around this core is then compressed the enteric coating granulate composition described in Example 2 using 1⅝₂ inch punches; the total weight of the enteric tablet is 0.65 g. and has a Strong Cobb Hardness of 22 units.

Example 5

Enteric tablets containing 0.3 g. of acetylsalicylic acid as the physiologically active component and having a compressed enteric coating are prepared as follows (for 20,000 tablets):

Ingredients of the core:	G.
Acetylsalicylic acid	6,000.0
Corn starch	340.0
Colloidal silica	80.0
Stearic acid	80.0

The acetylsalicylic acid, corn starch, colloidal silica and stearic acid powders are sifted through a 16 mesh screen and mixed for thirty minutes. The powder mass is made compact by slugging, and the slugs are broken through a 16 mesh screen. The resulting material is compressed into cores weighing 0.325 g. each, using 1⅞₂ inch punches.

An enteric coating is compressed around the resulting cores using the enteric coating granulate composition described in Example 2 and 1⅝₂ inch punches; the resulting enteric tablets weigh 0.65 g. each and have an average Strong Cobb Hardness of 20 units.

Example 6

An enteric coating granulate composition suitable for tablet compression coating compression coating procedure and containing 17.7 percent of a polyvinyl acetate copolymer consisting of vinyl acetate and crotonic acid as the comonomers, is prepared as follows:

Ingredients:	G.
Calcium lactate	630.0
Hydrogenated castor oil	70.0
Polyvinyl acetate copolymer	151.0

The enteric coating granulate composition is prepared as described in Example 1.

What is claimed is:

1. An enteric tablet having compressed onto the core with the physiologically active material an enteric coating containing (a) a polyvinyl acetate copolymer consisting of vinyl acetate comonomer and a comonomer having a vinylogous carbon-carbon double bond and (b) a substrate.

2. An enteric tablet according to claim 1, wherein the enteric coating contains (a) a polyvinyl acetate copolymer consisting of vinyl acetate comonomer and a comonomer having a vinylogous carbon-carbon double bond, (b) a plasticizer and (c) a substrate consisting of a bulking material and a lubricant.

3. An enteric tablet according to claim 2, wherein the enteric coating consists of from about five parts per weight to about forty parts per weight of the polyvinyl acetate copolymer and plasticizer per one hundred parts per weight of substrate.

4. An enteric tablet according to claim 2, wherein the enteric coating contains from zero part per weight to about one hundred parts per weight of a plasticizer per one hundred parts per weight of the polyvinyl acetate copolymer.

5. A solid enteric coating granulate composition for compression coating containing (a) a polyvinyl acetate copolymer consisting of vinyl acetate comonomer and a comonomer having a vinylogous carbon-carbon double bond and (b) a substrate.

6. An enteric coating granulate composition according to claim 5, wherein the composition contains (a) a polyvinyl acetate copolymer consisting of vinyl acetate comonomer and a comonomer having a vinylogous carbon-carbon double bond, (b) a plasticizer and (c) a substrate consisting of a bulking material and a lubricant.

7. An enteric coating granulate composition according to claim 6, wherein the composition contains from zero part per weight to about one hundred parts per weight of

a plasticizer per one hundred parts per weight of the polyvinyl acetate copolymer.

8. An enteric coating granulate composition for compression coating according to claim **6**, having as the plasticizer an ester of a carboxylic acid.

9. An enteric coating granulate composition for compression coating according to claim **8**, having as the plasticizer triethyl citrate.

10. An enteric coating granulate composition for compression coating consisting of the copolymer from vinyl acetate comonomer and crotonic acid comonomer, triethyl citrate as the plasticizer, calcium lactate as the bulking material, and hydrogenerated castor oil as the lubricant.

11. In the process for the preparation of enteric coated tablets the step which consists in compression coating with a solid granulate composition comprising (a) a polyvinyl acetate copolymer consisting of vinyl acetate comonomer and a comonomer having a vinylogous carbon-carbon double bond and (b) a substrate.

12. A process according to claim **11**, wherein the granulate composition comprises (a) a polyvinyl acetate copolymer consisting of vinyl acetate comonomer and a comonomer having a vinylogous carbon-carbon double bond, (b) a plasticizer and (c) a substrate consisting of a bulking material and a lubricant.

13. A process according to claim **12**, wherein the granulate composition contains from about five parts per weight to about forty parts per weight of the polyvinyl acetate copolymer and plasticizer per one hundred parts per weight of the substrate.

14. A process according to claim **12**, wherein the granulate composition contains from zero part per weight to about one hundred parts per weight of the plasticizer per one hundred parts per weight of the polyvinyl acetate copolymer.

15. An enteric coating granulate composition according to claim **6**, wherein the composition consists of from about five parts per weight to about forty parts per weight of the polyvinyl acetate copolymer and plasticizer per one hundred parts per weight of substrate.

16. An enteric coating granulate composition according to claim **5**, wherein the polyinyl acetate copolymer consists of vinyl acetate comonomer and a comonomer having the acrylic acid moiety.

17. An enteric coating granulate composition according to claim **5**, wherein the polyinyl acetate copolymer consists of vinyl acetate comonomer and crotonic acid comonomer.

18. An enteric coating granulate composition according to claim **6**, wherein the polyvinyl acetate copolymer consists of vinyl acetate comonomer and a comonomer having the acrylic acid moiety.

19. An enteric coating granulate composition according to claim **6**, wherein the polyvinyl acetate copolymer consists of vinyl acetate comonomer and crotonic acid comonomer.

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