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(54) Title: AQUEOUS ENTERIC COATING COMPOSITION WITH LOW GASTRIC PERMEABILITY**(57) Abstract**

Disclosed herein is an aqueous enteric coating composition comprised of a solution of a water-soluble salt of an enteric coating polymer, with a hydrophobic compound containing 12 to 20 carbon atoms and a water-insoluble solid flake material dispersed in the aqueous solution. The enteric coating formed from the present composition has good mechanical strength and shows superior resistance to attack by atmospheric moisture and simulated gastric fluid, while being readily broken down under the alkaline conditions which exist in the intestine.

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AQUEOUS ENTERIC COATING COMPOSITION WITH LOW GASTRIC PERMEABILITY

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FIELD OF THE INVENTION

The present invention relates to the field of enteric coating polymers. The present invention more particularly relates to the field of aqueous compositions of enteric coating polymers.

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BACKGROUND OF THE INVENTION

It is frequently desirable to coat oral pharmaceutical tablet cores with an enteric coating. An enteric coating 15 resists dissolution in acidic gastric media, but dissolves in the alkaline intestinal environment. Enteric coatings are useful for protecting the stomach wall from the effect of active ingredients in dosage form. For example, if aspirin is directly exposed to gastric mucosa, it can cause 20 corrosion of the stomach wall. Enteric coatings are also used to protect active ingredients in the tablet core from chemical attack from stomach acids and digestive enzymes. Enteric coatings can also be used to promote the delivery of active ingredients in the core tablet to a particular region 25 of the intestine such as the upper part of the small intestine, in order to enhance the bioavailability of the active ingredient.

Polymers useful as enteric coatings contain ionizable carboxylic groups and include cellulose acetate 30 phthalates (C-A-P), cellulose acetate trimellitates (C-A-T), hydroxypropyl methyl cellulose phthalates (HPMCP), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinyl acetate phthalate (PVAP), and certain acrylic polymers. In the low pH stomach environment, the carboxylic acid groups in the polymers remain un-ionized. Therefore, 35

the polymeric coating remains insoluble in gastric fluid. The polymeric coating disintegrates or dissolves in the higher pH intestinal environment to allow dissolution of the tablet core in the small intestine. The active ingredients 5 are absorbed through the intestinal wall for delivery to the blood stream.

Originally these polymers were applied to tablets as solutions in various organic solvents since the polymers are soluble in organic solvents. The use of organic solvents, 10 however, is objectionable from environmental, physiological, and safety standpoints, as well as for economic reasons.

The use of organic solvents has been avoided by applying the polymers as aqueous solutions or dispersions of their water-soluble salts. The enteric polymers are water- 15 solubilized with a water soluble base through neutralization of a sufficient number of carboxyl groups so that the polymer becomes water soluble or water dispersible. Useful water soluble bases include alkali metal hydroxides and ammonium hydroxide. The water soluble salts of enteric 20 cellulose esters have been found to be somewhat hydrolytically unstable, hydrolyzing slowly upon exposure to atmospheric moisture or gastric juices. A resulting film of partly hydrolyzed polymer is partially insoluble in intestinal fluid, causing the active ingredient to be 25 released too slowly in the intestinal tract.

Parker et al, J. Pharm. Sci. 63, 119-215 (1974); Okhamafe & York, Int. J. Pharm. 22 (2-3) (1984), and Okhamafe & York (1984) disclose that the presence of solid 30 filler material in film dispersed from a solution of a water soluble salt of an enteric polymer reduces polymer film hydrolysis.

Parker, et al disclose that the reduction in film hydrolysis is directly related to film thickness. However, a thicker film takes longer to disintegrate in the

intestine. Similarly, Porter, Pharm. Tech., March, 1980, pp 67-75, discloses that while low loadings of solid pigment material can somewhat increase film resistance to moisture, higher filler loading levels which would add more water 5 resistance detrimentally affect the mechanical strength of the film. High tensile strength is required for a useful tablet coating. Therefore, the amount of solid filler material used for increasing water resistance is limited by decreased mechanical strength.

10 In light of the above, it would be desirable to provide an aqueous enteric coating composition containing a water soluble salt of a film-forming enteric polymer wherein the film coating provides a higher water resistance than was previously achievable and maintains good mechanical 15 strength.

SUMMARY OF THE INVENTION

The present invention is an aqueous enteric coating composition which comprises a dispersion of 5 to 45 weight 20 percent of a hydrophobic compound having from 12 to 20 aliphatic carbon atoms and 5 to 50 weight percent of a water-insoluble flake material, dispersed in an aqueous solution of 35 to 70 weight percent of a water-soluble salt of an enteric polymer, with the weight percentages being 25 based on a total solids weight.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a triangular coordinate graph illustrating a preferred embodiment of the invention wherein the 30 composition contains HPMCP, stearyl alcohol, and talc. The apex of the graph represents 100 weight percent HPMCP enteric polymer. The lower right corner of the graph represents 100 weight percent talc. The lower left hand corner represents 100 weight percent stearyl alcohol.

Compositions containing various concentrations of those three components are represented graphically by the numerals 1-7 and correspond to coating compositions illustrated in Table 1.

5

DETAILED DESCRIPTION OF THE INVENTION

The applicants discovered that, while maintaining good mechanical strength, the water and acid resistance of an enteric polymer film coating is increased beyond that which 10 was previously achievable via solids loading by way of loading an aqueous solution of enteric polymer salt with a dispersion of a particular concentration of solid flake filler material and a hydrophobic compound containing aliphatic carbon atoms. Enteric coating compositions have 15 not previously been loaded with a combination of solid flake material and hydrophobic aliphatic compound.

It was found that the present combination of flake material and hydrophobic aliphatic compound, within a particular concentration range, adds a "shingle effect" to 20 the enteric coating. This shingle effect is evidenced by the fact that the moisture resistance provided is equivalent to that which would be provided by a coating containing a much higher percentage of solid filler. Since mechanical strength decreases with an increased concentration of solid 25 filler, the present invention is beneficial in providing an increased water resistance without decreasing the mechanical strength of the coating. Additionally, the water resistant composition of the present invention can usefully be applied to a tablet as a relatively thin coat for the purpose of 30 quick intestinal disintegration.

The aqueous enteric coating composition of the present invention comprises an aqueous dispersion of 5 to 45 weight percent of a hydrophobic compound having between 12 to 20 aliphatic carbons and 5 to 50 weight percent of a water-

insoluble flake, dispersed in an aqueous solution comprising 35 to 70 weight percent of a water soluble salt of an enteric polymer which dissolves only at a pH above 5.0. The above listed weight percentages are based on the total 5 weight of solids in the composition. The composition preferably contains a sufficient amount of water to provide a total solids content between 5 to 20 weight percent, preferably between 10 to 15 weight percent, based on the total weight of the composition.

10 The present composition comprises 35 to 70 weight percent enteric polymer salt. The presence of more than 70 weight percent polymer salt would provide a coating with insufficient resistance to water permeation in a gastric environment. But at least 35 weight percent enteric polymer 15 is needed in order for a sufficient protective film to be formed around the tablet core and to hold the flake material and hydrophobic compound onto the core. The preferred concentration range of the soluble enteric polymer salt is 40 to 55 weight percent.

20 An "enteric polymer" is herein defined as a polymer having a polystyrene equivalent weight average molecular weight (M_w) of approximately 50,000 to 150,000, and containing carboxyl groups which remain insoluble at a pH below 4 (gastric pH range), but which ionize, and thus cause 25 the polymer to dissolve, at a pH above 5.0 (intestinal pH range). The enteric polymer used in the present composition is preferably a film-forming polymer. The most useful film-forming enteric polymers are cellulose acetate phthalate (C-A-P), cellulose acetate trimellitate (C-A-T), hydroxypropyl-30 methylcellulose phthalate (HPMCP), copolymer of methacrylic acid and ethyl acrylate, hydroxypropylmethylcellulose acetate succinate (HPMCAS), and polyvinyl acetate phthalate (PVAP). The preferred M_w for HPMCP is between 80,000 and 110,000, most preferably between 95,000 and 100,000. The

preferred Mw for C-A-P is between 55,000 and 75,000, with a Mw between 68,000 and 80,000 being more preferred.

A concentration of 5 to 45 weight percent of a hydrophobic compound is dispersed throughout the present 5 aqueous composition. The hydrophobic compound is a compound having 12 to 20 aliphatic carbon atoms. This hydrophobic component chemically repels aqueous, acidic medium away from the enteric polymer. At least 5 weight percent is needed to provide the shingle effect. The presence of more than 45 10 weight percent hydrophobic aliphatic compound causes agglomeration in the coating process. A concentration of 20 to 35 weight percent hydrophobic compound is preferable.

The hydrophobic compound used may be any linear or branched chain compound having less than 1 percent 15 solubility in water, a hydrophile-lipophile balance (HLB) value less than about 6, and which does not interfere chemically with the other components of the composition. The hydrophobic compound may contain non-aliphatic groups. Examples of such useful C₁₂ to C₂₀ hydrophobic compounds 20 include alcohols, fatty acids and salts thereof, fatty amides and salts thereof, and lipids. A C₁₂ to C₂₀ alcohol is preferred, with stearyl alcohol being most preferred because of it's low toxicity.

The insoluble solid flake material dispersed throughout 25 the aqueous composition of the present invention is present at a concentration of 5 to 50 weight percent. More than 50 weight percent solid flake material reduces the mechanical strength too much. A concentration of 25 to 40 weight percent flake material is preferred.

30 The flake material (sheet-like) is water-insoluble, preferably an inorganic mineral. The more preferred flake material is one of the inert hydrous magnesium silicate materials referred to commonly as "talc" or pyrophyllite, which is essentially aluminum silicate having similar

crystal structure and other properties to the talc materials. Other inert, powders whose crystals have a sheet-like or flake structure include materials such as aluminum flake, TiO_2 flakes, and silicate flakes.

5 It is a critical aspect of the present invention that the solid filler material has a flake or sheet-like shape. The shingle effect is most enhanced when the solid filler material is a flake material.

10 The average particle size of the flake material is preferably less than 50 micrometers, with the average particle size being measured in equivalent circular diameters. It was a surprising aspect of the present invention to find that the water permeation barrier is further improved as the particle size of the solid flake 15 material is decreased, using the same concentration of flake material. The preferred particle size of the flake material is less than 10 micrometers, with a size less than 1 micrometer (1,000 nanometers) being more preferable.

20 An exemplary embodiment of the preferred composition of the present invention is an approximately 10 percent solids content aqueous composition containing 40 to 55 weight percent ammoniated HPMCP, with 20 to 35 weight percent stearyl alcohol and 25 to 40 weight percent talc dispersed therein, based on the total weight of solids. This 25 particular composition is shown graphically by the smaller, triangular area indicated within FIG. 1.

20 Besides the insoluble flake material and hydrophobic compound of the present composition, the composition may also contain additive materials within the size range of 0.1 to 100 micrometers. Additives used should be relatively hydrophobic. Plasticizers are especially useful for forming a flexible soft coating. Examples of suitable plasticizers include triacetin, diethyl phthalate (DEP), triethyl citrate (TEC), and dibutyl sebacate (DBS). Solid pigments may also

be used. The weight percent of such additives should be less than 15 weight percent, more preferably less than 5 weight percent, based on the total weight of solids in the composition.

5 The present invention further includes a process of making an aqueous enteric coating composition comprising reacting 35 to 70 weight percent of a enteric polymer with a solubilizing amount of a water-soluble base to provide an aqueous solution or dispersion of a salt of the enteric
10 polymer and, dispersing 5 to 45 weight percent of a hydrophobic compound having from 12 to 20 aliphatic carbon atoms and 5 to 50 weight percent of a water insoluble flake material in the aqueous polymer solution. The present process is preferably conducted under conditions providing a
15 total solids content of 5 to 20 weight percent solids. The water-insoluble components are preferably dispersed throughout the solution through high shear mixing using a homogenizer or a colloid mill.

20 The enteric polymer salt of the aqueous coating composition is preferably formed *in situ* by adding the non-ionized enteric polymer and a water-soluble base to the aqueous solution separately for reaction. Suitable water-soluble bases for neutralization of the polymer include NH₄⁺OH⁻, and alkali metal hydroxides, with ammonium hydroxide
25 being the preferred neutralizing agent.

25 The aqueous enteric coating solution of the present invention is applied to a core substrate by any traditional coating means such as by spray coating. Suitable core substrates to which the aqueous enteric coating solution of the present invention can be applied includes pharmaceutically active tablets, pellets, granules, and beads. A coating weighing 5 to 15 weight percent of the total coated core is preferable so that the core is fully coated, yet the coating is thin enough so that it dissolves

quickly in the intestines. In order to protect the tablet cores from reacting with the basic coating solution, it is often preferable to apply a subcoat of polymer prior to applying the basic aqueous enteric coating solution of the 5 present invention. For example, a polymer subcoat film weighing approximately 2 percent of the core table weight is useful.

In order for the polymer to demonstrate enteric properties in the gastric and intestinal media, a sufficient 10 amount of ionized carboxyl salt groups must be converted back to the non-ionized free acid form. This can be done via different routes, depending on the exact polymer salt used. Heat may be applied to the coated tablets to convert the carboxylic acid groups into the free acid form upon 15 evaporation of ammonia or water. Alternatively, the polymer carboxylic acid groups of the coated tablets can be re-protonated by treatment with an acid during production or by the gastric acid upon entry into the stomach environment.

The present invention further includes the enteric 20 coating formed from the composition of the present invention. The coating of the present invention is preferably a film coating formed from a film-forming enteric polymer. The present coating dissolves only at a pH above approximately 5.0. The coating of the present invention may 25 contain enteric polymer in the ionized salt form, enteric polymer in the protonated non-ionized enteric polymer form, or a combination thereof. The coating is formed upon evaporation of the water and other volatiles of the present aqueous composition. The components of the coating should 30 be dispersed evenly throughout the coating in order to provide the maximum benefit.

The present invention further includes an enterically active dosage form, meaning that the active ingredient is released according to an enteric profile. The active dosage

form of the present invention is a pharmaceutically active core enveloped by the enteric coating of the present invention. The core will typically contain an active ingredient and various excipients. Examples of useful 5 pharmaceutically active ingredients for use in the present invention include aspirin, ibuprofen, ivermectin, acetaminophen, naproxen sodium, indomethacin, theophylline, propanolol, sucrose, erythromycin, pharmaceuticals such as diclofenac sodium, and the like. It is necessary that the 10 tablet core is hard enough to resist attack by the coating solution and that it does not react with the components of the coating. Application of a sub-coating between the core and the enteric coating is useful in some situations so that the core does not react with the coating. The enterically 15 active solid dosage form of the present invention preferably has a coating weighing between about 5 to 15 weight percent of the total coated dosage form so that the active core is adequately protected from water permeation, yet the active ingredient is released quickly enough in the intestines

20 The following examples further illustrate the present invention, but should not be interpreted as a limitation thereon.

EXAMPLES

25 The materials and testing procedures used for the results shown herein are as follows:

Storage Stability Test -

Accelerated storage stability evaluations were performed by 30 placing the coated tablets in high density polyethylene bottles that contained a desiccant cartridge and were fitted with a tamper-proof seal. The bottles were placed in a glass desiccator over saturated sodium chloride solution. The desiccator and contents were stored in a 37°C oven. The

desiccator interior relative humidity was equilibrated at 75%.

Simulated Gastric Fluid Uptake Test-

5 This evaluation was carried out as described in U. S. Pharmacopoeia XXII, pages 1784-1785 (1990). A total of 12 tablets were weighed and placed in a disintegration basket (Hanson Research Co.) and immersed in a pH 1.2 United States Pharmacopoeia simulated gastric fluid ("SGF") for 60 minutes.

10 The tablets were then removed, surface dried, and weighed. The SGF uptake was calculated from the difference between the initial and final weight of the tablets divided by the initial weight.

15 Disintegration Time in Simulated Intestinal Fluid Test- After conducting the Simulated Gastric Fluid Uptake Test, the tablets were replaced in the baskets and immersed in USP simulated intestinal fluid of pH 6.8. The time to achieve disintegration of all twelve core tablets was recorded.

20 All parts and percentages in the examples were calculated on a weight basis unless otherwise stated.

Examples 1-7

To prepare the coatings for Examples 1-7, a stock coating solution was first prepared. To prepare the stock solution, HPMCP (polystyrene equivalent Mw 96,000) was added to water and mixed with a laboratory stirrer. Triacetin plasticizer was then added and the mixture was stirred for 5 minutes. Then, a fully neutralizing amount of ammonium hydroxide (approximately 28%, aqueous) was added and the mixture was stirred for 30 minutes. The resulting stock solution contained 25 weight percent plasticizer (triacetin) and 12.4 weight percent ammonium hydroxide, based upon polymer weight.

Talc and stearyl alcohol were added to the stock coating solution to prepare Examples 1-7. Talc ($3\text{MgO}\cdot4\text{SiO}_2\cdot\text{H}_2\text{O}$) having average particle size of about 40 to 50 micrometers was added to the stock solution and the 5 mixture was stirred for 5 minutes. Then a solution of stearyl alcohol in warm isopropyl alcohol was added with stirring. The mixture was passed through a colloid mill (Greerco, Model W200V). Each of the individual coating compositions prepared from the stock coating solution 10 contained 13.8 weight percent solids.

500 gram tablet cores (7.3 weight percent diclofenac sodium, 92.7 weight percent excipients (59.7 wt% lactose, 24.8 wt% microcrystalline cellulose, and 8.2 wt% lubricants and other disintegrants) were sub-coated with a 13 weight 15 percent solution of HPMCP in water to a level of 2 percent of the core tablet weight prior to application of the enteric coating, in order to protect the tablet cores from the basic coating solution. After the subcoat was allowed to dry, the aqueous enteric coating compositions prepared 20 above were applied. Each aqueous coating composition prepared was applied in two different thicknesses, providing coatings weighing approximately 6 percent and 11 percent, based on the total weight of the coated tablet. Both the subcoat and the enteric coatings were applied by means of a 25 fluid bed coater (STREA-1, manufactured by Niro-Aromatic, Inc., Columbia, Maryland). The coating conditions were as follows:

	<u>SUBCOAT</u>	<u>ENTERIC</u>
Container Charge	400 g	400 g
Atomizer Pressure	2.0 bar	3 bar
Inlet Temp	70° C	60° C
5 Outlet Temp	47° C	42° C
Spray Rate	14 mL/min	15 mL/min
Spray Time	4.3 min	11 min for 6% coat 22 min for 11% coat

10 The Storage Stability Test was conducted on the tablets coated as described above. All of the coated tablets passed the disintegration test in simulated intestinal fluid after 3 months of storage under the accelerated storage conditions. This shows that the coatings formed from the 15 aqueous composition of the present invention were stable under heat and humidity.

10 The coated tablets were tested to determine the effectiveness of films formed from the different aqueous enteric coating compositions. The effectiveness of the 20 coating in protecting the active pharmaceutical from the action of simulated gastric fluid was determined by the Simulated Gastric Fluid Uptake Test. The effectiveness of the coating in allowing ready disintegration of the active pharmaceutical in simulated intestinal fluid was determined 25 by conducting the Dissolution Test in Simulated Intestinal Fluid. The results of these tests are shown illustrated Table 1.

10 The test results in Table 1 show, at two different coating thickness levels, the number of tablet coatings (18 30 tablet samples were tested for each example) that completely failed in Simulated Gastric Fluid. "Failure" means that the coating broke away from the tablet so that the tablet was not protected. Failure is due to low mechanical strength.

A failure of more than 3 out of 18 was considered to be unacceptable. The % SGF Uptake results show the weight percent of simulated gastric fluid absorbed by the coated tablets. The higher SGF uptake causes the tablet to lose 5 efficacy. About 10 weight percent SGF uptake is acceptable.

The intestinal disintegration time after being exposed to gastric fluid is also shown. It is desirable for the intestinal disintegration time to be short.

The results shown in Table 1 indicate the boundaries of 10 the particular useful concentration of polymer, talc, and stearyl alcohol. The results show that both an approximately 6 weight percent coating and an approximately 12 weight percent coating are useful, depending specifically on the coating composition.

15 The importance of combining talc and stearyl alcohol in the particular concentration ranges of the present invention can be seen by comparing the Examples, as follows:

-Examples 1, 1a, 2, 2a, 6, and 6a illustrate coating compositions within the scope of the present invention and 20 provided tablet coatings having few failures in simulated gastric fluid. The gastric uptake in those examples was less than 10%. Example 6 illustrates that the 5.9 weight percent coating did not fully cover the core tablet.

-Example 5a illustrates that the lower concentration limit 25 for stearyl alcohol is near 5 weight percent. Since 0 tablets failed in the disintegration test yet the average uptake was 13%, this indicates that the stearyl alcohol concentration was not quite sufficient when combined with 50 weight percent HPMCP and 45 weight percent talc.

30 -Examples 3, 3a, 7, and 7a demonstrate that neither a 25% or 30% enteric polymer concentration is sufficient to hold the talc and stearyl alcohol.

-Examples 4 and 4a demonstrate that 75% talc reduced the mechanical strength of the coating, evidenced by the high

number of mechanical failures in simulated gastric fluid.

Example 8-

In an experiment similar to Examples 1-7, C-A-P was
5 used as the enteric polymer instead of HPMCP, and aspirin
was the substrate. A coating which contained 40% of C-A-P,
23% of stearyl alcohol, and 27% of talc exhibited lower SGF
uptake (4%) than coatings which contained 48% C-A-P, 12%
stearyl alcohol, and 27% talc (7% SGF uptake); 60% C-A-P,
10 12% stearyl alcohol, and 12% talc (8% SGF uptake); or 50% C-
A-P, 23% stearyl alcohol, and 12% talc (6% SGF uptake).

Table 1
RESULTS FROM EXAMPLES 1-7

Ex.	Coating Composition			Coating Weight (wt%)	Gastric		Intestinal
	HPMCP (wt%)	Stearyl Alcohol (wt%)	Talc (wt%)		SGF Failure (#tabs)	SGF Uptake (wt%)	Disintegration (minutes)
C-1	100	0	0	6.3	18/18	99	2
C-2	100	0	0	12.6	18/18	31	2
1	50	25	25	5.5	3/18	13.0	2.50
1a	50	25	25	11.54	0/18	7.5	2.75
2	40	35	35	7.0	3/18	6.0	2.5
2a	40	35	35	11.4	1/18	6	4.0
3	25	35	40	6.5	18/18	n/a	n/a
3a	25	35	40	10.9	6/18	1.71	8.0
4	25	5	70	6.3	18/18	n/a	n/a
4a	25	5	70	10.7	18/18	n/a	n/a
5	50	5	45	5.7	8/18	14.9	
5a	50	5	45	10.5	0/18	13.0	2.5
6	40	20	40	5.9	10/18	9.9	2.3
6a	40	20	40	11.1	0/18	7.1	4.0
7	30	10	60	6.8	18/18	n/a	n/a
7a	30	10	60	11.2	17/18	n/a	n/a

The data from Table 1 was compiled in a triangular coordinate graph shown in FIG 1. The data points were used to plot out an area within which the preferred composition concentrations of HPMPC, stearyl alcohol, and talc were outlined. The area mapped out in the triangular coordinate graph corresponds to a preferred composition comprising 40 to 55 weight percent HPMCP, between 20 to 35 weight percent stearyl alcohol, and between 25 to 40 weight percent talc.

We Claim:

1. An aqueous enteric coating composition comprising:
a dispersion of 5 to 45 weight percent of a hydrophobic
5 compound having 12 to 20 aliphatic carbon atoms and 5 to 50
weight percent of a water-insoluble flake material,
dispersed in an aqueous solution of 35 to 70 weight percent
of a water-soluble salt of an enteric polymer, wherein said
weight percentages are based on a total solids weight.
10
2. The enteric coating of claim 1 wherein the
concentration of said water-soluble salt of an enteric
polymer is 40 to 55 weight percent, the concentration of
said hydrophobic compound is 20 to 35 weight percent, and
15 the concentration of said flake material is 25 to 40 weight
percent, based on the total solids weight.
3. The composition of claim 1 wherein a sufficient amount
of water is present so that said composition has a total
20 solids content of 5 to 20 weight percent, based on the total
weight of said composition.
4. The composition of claim 1 wherein said enteric polymer
is a film-forming enteric polymer.
25
5. The composition of claim 4 wherein said film-forming
enteric polymer is selected from the group consisting of
cellulose acetate phthalate (C-A-P), cellulose acetate
trimellitate (C-A-T), hydroxypropyl methylcellulose
30 phthalate (HPMCP), methacrylic acid/ethyl acrylate
copolymer, hydroxypropyl methylcellulose acetate succinate
(HPMCAS), and polyvinyl acetate phthalate (PVAP).
6. The composition of claim 1 wherein said hydrophobic

compound is selected from the group consisting of alcohols, fatty acids and salts thereof, fatty amides and salts thereof, and lipids.

5 7. The composition of claim 1 wherein said flake material is a talc.

8. The composition of claim 1 wherein said flake material has an average particle size less than 50 micrometers.

10

9. The composition of claim 8 wherein said flake material has an average particle size less than 10 micrometers.

15

10. The composition of claim 9 wherein said flake material has an average particle size less than 1 micrometer.

20

11. The composition of claim 1 further comprising up to 15 weight percent of an additive having a particle size between 0.1 to 100 micrometers, wherein the summation of all solids weight percentages equals 100 weight percent.

12. A process of making an aqueous enteric coating composition comprising:

providing an aqueous solution of 35 to 70 weight percent of 25 a water-soluble salt of an enteric polymer; and dispersing 5 to 45 weight percent of a hydrophobic compound having 12 to 20 aliphatic carbon atoms and 5 to 50 weight percent of a water-insoluble flake material in said aqueous solution, with said weight percentages based on a final total solids 30 weight.

13. The process of claim 12 wherein said dispersing step is conducted in the presence of 80 to 95 weight percent water, based on a total composition weight.

14. An enteric coating comprising a blend of 35 to 70 weight percent of an enteric polymer, 5 to 45 weight percent of a hydrophobic compound having 12 to 20 aliphatic carbon 5 atoms, and 5 to 50 weight percent of a water-insoluble flake material.

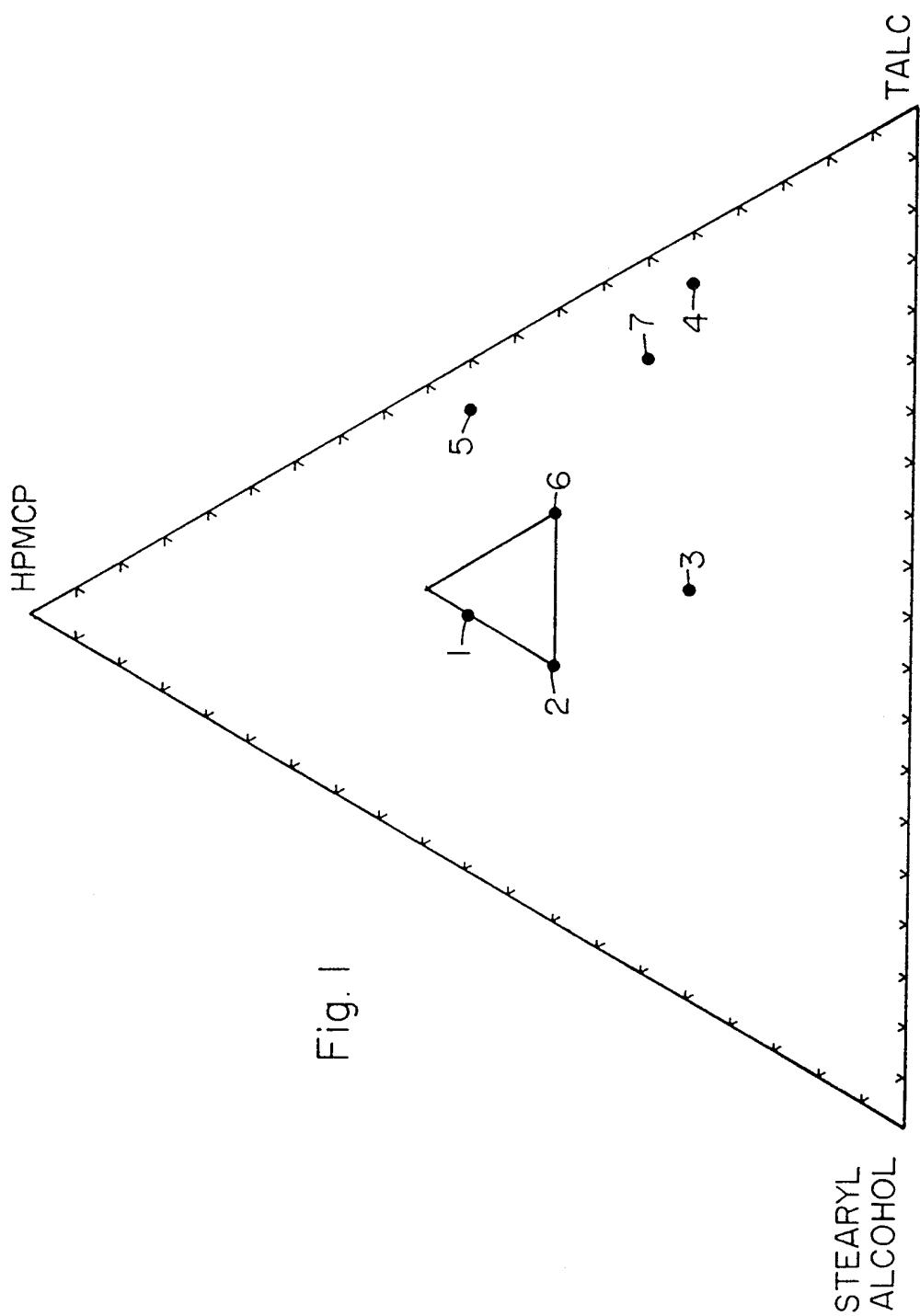
15. The enteric coating of claim 14 wherein said water-insoluble flake material has a particle size less than 50 10 micrometers.

16. The enteric coating of claim 15 wherein said water-insoluble flake material has a particle size less than 1 micrometer.

15

17. An enterically active solid dosage form comprising a pharmaceutically active core enveloped by the enteric coating composition of claim 14.

20 18. The solid dosage form of claim 17 wherein the weight of said enteric coating is 5 to 15 weight percent of the total weight of said solid dosage form.



INTERNATIONAL SEARCH REPORT

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PCT/US 99/21072

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 A61K9/28 A61K9/32 A61K9/34 A61K9/36		
According to International Patent Classification (IPC) or to both national classification and IPC		
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C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 199627 Derwent Publications Ltd., London, GB; Class A11, AN 1996-263781 XP002128219 & JP 08 109126 A (AMANO PHARM KK), 30 April 1996 (1996-04-30) abstract</p> <p>---</p> <p>US 5 733 575 A (MEHRA DEV K ET AL) 31 March 1998 (1998-03-31) column 3, line 4 -column 4, line 43; example 3 claims</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-18
X		1-18
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/21072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 48386 A (ANDRX PHARMACEUTICALS INC) 24 December 1997 (1997-12-24) page 4, line 26 -page 5, line 34 page 6, line 15 - line 38 ---	1-18
X	WO 95 16451 A (GOUCHET FRANCK ARNO ;FESSI HATEM (FR); PUISIEUX FRANCIS (FR)) 22 June 1995 (1995-06-22) page 7, line 14 - line 25; claims ---	1-18
Y	WO 97 03670 A (EDLER DAVID PHILIP ;LEONARD GRAHAM STANLEY (GB); SMITHKLINE BEECHAM) 6 February 1997 (1997-02-06) page 11, line 15 - line 20 ---	1-18
Y	DATABASE WPI Section Ch, Week 199709 Derwent Publications Ltd., London, GB; Class A96, AN 1997-095397 XP002128220 & JP 08 333240 A (SHINETSU CHEM IND CO LTD), 17 December 1996 (1996-12-17) abstract ---	1-18
A	GB 2 057 876 A (SANDOZ LTD) 8 April 1981 (1981-04-08) page 3, line 26 - line 62 ---	1-18
A	DATABASE WPI Section Ch, Derwent Publications Ltd., London, GB; Class A11, AN 1972-82834T XP002128221 & JP 47 049684 B (TAISHO PHARM CO LTD), 11 October 1970 (1970-10-11) abstract -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/21072

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
JP 8109126	A 30-04-1996	NONE			
US 5733575	A 31-03-1998	AU 684398 B		11-12-1997	
		AU 3951395 A		02-05-1996	
		CZ 9701059 A		14-01-1998	
		EP 0781125 A		02-07-1997	
		HU 77774 A		28-08-1998	
		JP 10506913 T		07-07-1998	
		TR 961003 A		21-12-1996	
		WO 9610995 A		18-04-1996	
		ZA 9508147 A		16-07-1996	
WO 9748386	A 24-12-1997	US 5830503 A		03-11-1998	
		AU 3302897 A		07-01-1998	
WO 9516451	A 22-06-1995	FR 2692484 A		24-12-1993	
		AU 5702194 A		03-07-1993	
WO 9703670	A 06-02-1997	AU 6659196 A		18-02-1997	
		BG 102259 A		30-09-1998	
		BR 9609857 A		16-03-1999	
		CN 1195986 A		14-10-1998	
		CZ 9800183 A		17-06-1998	
		EP 0839039 A		06-05-1998	
		HU 9900299 A		28-09-1999	
		JP 11509539 T		24-08-1999	
		NO 980240 A		20-01-1998	
		PL 324553 A		08-06-1998	
		SK 5398 A		08-07-1998	
JP 8333240	A 17-12-1996	NONE			
GB 2057876	A 08-04-1981	BE 884715 A		11-02-1981	
		CH 649216 A		15-05-1985	
		DE 3029745 A		26-03-1981	
		FR 2462911 A		20-02-1981	
		IE 50107 B		19-02-1986	
		IT 1194817 B		28-09-1988	
		JP 56030913 A		28-03-1981	
		NL 8004585 A		18-02-1981	
		SE 8005773 A		17-02-1981	
JP 47049684	B	NONE			