

(19) **DANMARK**



Patent- og
Varemærkestyrelsen

(12)

Oversættelse af europæisk patentskrift

(10) **DK/EP 2772250 T3**

-
- (51) Int.Cl.: **A 61 K 9/48 (2006.01)** **A 61 K 31/00 (2006.01)** **A 61 K 31/355 (2006.01)**
A 61 K 31/4402 (2006.01) **A 61 K 31/4439 (2006.01)** **A 61 K 31/663 (2006.01)**
A 61 P 1/04 (2006.01) **A 61 P 1/10 (2006.01)** **A 61 P 19/10 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2016-12-05**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-09-28**
- (86) Europæisk ansøgning nr.: **14170492.4**
- (86) Europæisk indleveringsdag: **2003-06-27**
- (87) Den europæiske ansøgnings publiceringsdag: **2014-09-03**
- (30) Prioritet: **2002-10-01 US 415187 P**
- (62) Stamansøgningsnr: **03742336.5**
- (84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR**
- (73) Patenthaver: **Banner Life Sciences LLC, 4125 Premier Drive, High Point, North Carolina 27265, USA**
- (72) Opfinder: **Hassan, EmadEldin M., 2748 Mount Carmel Road, Parkton, MD 21120, USA**
Fatmi, Aqeel A., 4125 Premier Drive, High Point , North Carolina 27265, USA
Chidambaram, Nachiappan, 8410 Handcart Circle, Sandy, UT 84070, USA
- (74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Rued Langgaards Vej 8, 2300 København S, Danmark**
- (54) Benævnelse: **Enterisk sammensætning til fremstillingen af blød kapselvæg**
- (56) Fremdragne publikationer:
EP-A- 0 092 908
EP-A- 1 184 033
WO-A-01/24780
WO-A2-2004/012701
DE-A- 3 222 476
US-A- 4 138 013
US-A- 4 790 881

DESCRIPTION

Field of the invention

[0001] The present invention relates to enteric preparations, More particularly, the invention relates to enteric solid dosage forms made using a gel mass comprising a film-forming, water-soluble polymer, an acid-insoluble polymer, and, optionally, other ingredients such as plasticizers, colors, and flavors. The invention further provides a direct method for manufacturing enteric preparations without need for coating.

Background of the invention

[0002] The use and manufacture of enteric dosage forms are well known to skilled personnel. Such dosage forms have been explained and reviewed in reference works, e.g., in Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Co., Easton, PA (1990). Enteric dosage forms are desirable, either to protect the content of the dosage form from the gastric conditions or to protect the gastric tissue from an irritant material contained in the enteric dosage form. A further use for enteric dosages is prevention of a lasting, unacceptable mouth odor resulting from ingestion of substances like garlic or fish oil. Enteric dosage forms are also used to provide slow or delayed release of a substance.

[0003] To fulfill the compendium definition requirement for enteric or gastro-resistant preparations, these preparations have to pass specific compendia tests. The enteric or gastro-resistant property is obtained only if the enteric dosage form does not dissolve or disintegrate in gastric acidity for a specified amount of time (usually two hours in 0.1 N hydrochloric acid at 37° C). Further, the enteric dosage forms must release their contents in simulated intestinal environments (e.g., in buffers of pH values at about 6.8 within certain time periods). Detailed evaluation techniques are described in national and international pharmacopoeia such as United States Pharmacopoeia.

[0004] The majority, if not all, of the enteric dosage forms currently in use are produced by a film-coating process, where a thin film layer of acid-insoluble (enteric) polymer is accumulated on the surface of an pre-manufactured dosage form. Dosage forms coated in this manner have been mainly tablets and, to a lesser extent, hard or soft capsules. The enteric coating method involves spraying of an aqueous or organic solution or a suspension of enteric polymers onto tumbling or moving tablets or capsules, accompanied by drying using hot air.

[0005] Enteric dosage forms made by coating suffer from various process-related problems and defects that affect their performance or appearance. For example, "orange peel" surface formation, also known as surface roughness, mottling, or lack of surface homogeneity may result. And more seriously, coat integrity failure may occur, such as in cases of cracking or flaking off of the coating. All coatings present inherent problems, including possible uneven distribution of the coating ingredients, which can easily happen under the multivariate coating process.

[0006] The foregoing problems of enteric coatings are shared by all enteric dosage forms such as tablets and capsules. However, the problems faced during coating of capsules are even more critical, due to the delicate and heat sensitive nature of the soft elastic capsule shell. Both hard and soft capsules can easily undergo agglomeration and distortion due to the heat-sensitive shell composition. Moreover, the smoothness and elasticity of the capsule surface make it difficult to form an intact adhering enteric coat without careful subcoating step to improve the surface for coating. A further disadvantage of enteric coating for soft capsules is the loss of the normally shiny and clear appearance of capsule gelatin shells. The elegant, clear gelatin shell has been a significant reason for soft capsule popularity and acceptance. In addition to the undesirable surface texture modifications usually caused by coating, most accepted aqueous enteric polymer preparations result in opaque capsules.

[0007] While different attempts have been tried to improve the manufacture of enteric soft gelatin capsules via coating, the inherent disadvantages in the coating process amplify the necessity for a better way of manufacturing enteric soft capsules, ideally, without coating. Enteric coatings (both sub-coating and over-coatings) and enteric polymers are discussed or suggested generally in U. S. Pat. Nos. 4,518,433, 4,816,259, and 5,330,759. None of these references, however, teach or suggest the invention as set forth herein.

[0008] WO01/24780 describes a soft gel capsule resistant to digestive juice comprising gelatin and an enteric polymer in the form of free acid or its salts.

[0009] US4,138,013 describes pharmaceutical capsules formed using a homogeneous film-forming mixture comprising (1) hydroxypropyl methylcellulose and an ammonium salt of cellulose acetate phthalate polymer, or (2) gelatin and an ammonium salt of a copolymer of methacrylic acid and methacrylic acid alkyl ester; optionally with the inclusion of a plasticizer and/or a coloring agent.

Summary of the invention

[0010] In a first aspect of the invention, there is provided an enteric soft shell capsule according to claim 1.

[0011] In a second aspect of the invention, there is a process according to claim 10.

[0012] Also described herein is a gel mass composition that can be used to manufacture enteric oral dosage forms such as tablets or capsules, without the need of coating. A second aspect of this invention is a filled enteric soft capsule that does not require enteric coating or cross-linking to gain its enteric character. Fill materials can be hydrophilic or hydrophobic in nature. Fill materials can also be liquid, solid or a combination thereof. Also described herein is a soft capsule enteric shell composition that contains a film-forming polymer, an acid-insoluble polymer, and, optionally, plasticizers, colours and/or other conventionally accepted pharmaceutical additives. The gel mass composition of the invention avoids significant loss of physical strength or viscosity of the film-forming polymer.

[0013] Also described herein is a process of preparing a gel mass from which the enteric capsule shell is made. According to this process, an alkali is used at a level allowing dissolution of the acid-insoluble polymer without negatively affecting the film-forming polymer integrity, its physical strength, or its viscosity. Also described herein is a process of manufacturing filled enteric soft capsules using cast gel mass and a rotary die encapsulation machine, such as that disclosed in U.S. Patents 5,146,730 and 5,459,983. Also described herein is production of clear enteric soft capsules. Also described herein is the production of transparent, yet colored, enteric soft capsules. Also described herein is the use of the foregoing aspects for delivering food and medicine.

[0014] The gel mass compositions of this invention are further useful to manufacture enteric solid oral dosage forms such as tablets, and hard and soft capsules without the conventional coating technique. A preferred method of manufacturing enteric tablets with this invention is to use enrobement techniques and a rotary die as described in US Patent Nos. 6,482,516 and 5,459,983, and 5,146,730. Gel compositions of this invention are also useful to make clear or opaque hard capsules using regular equipment known in the art.

[0015] Accordingly, also described herein is a gel mass composition comprising a film-forming, water-soluble polymer, an acid-insoluble polymer, and, optionally, at least one plasticizer, an optional coloring agent and an aqueous solvent. The gel mass is useful in manufacturing enteric soft or hard capsules, or enteric tablets without coating.

[0016] The film-forming, water-soluble polymer can be of proteinaceous nature, such as gelatin. In one embodiment, the gelatin is extracted from animal bones or skins, and has about 100 to about 250 blooms.

[0017] In another embodiment, the film-forming, water-soluble polymer can be of carbohydrate nature such as hydroxypropyl methylcellulose or methyl cellulose. The acid-insoluble polymer can also be selected from the group consisting of acyclic and methacrylic acid copolymers, cellulose acetate esters such as phthalate, butyrate, hydroxypropyl methyl cellulose phthalate, and salts thereof.

[0018] The shell composition of the invention can contain at least one plasticizer selected from the group consisting of sorbitol, glycerol, polyethylene glycol, poly-alcohols with 3 to 6 carbon atoms, citric acid, citric acid esters such as triethyl citrate, and combinations thereof.

[0019] The solvent used can be water or aqueous solution of alkalis, such as ammonia, sodium hydroxide, potassium hydroxide, ethylene diamine, hydroxylamine, tri-ethanol amine, or hydroalcoholic solutions of the same. The alkali can be adjusted such that the final pH of the gel mass is less than or equal to about 9.0 pH units. In another embodiment, the alkali is adjusted such that the pH does not exceed 8.5. In yet another embodiment, the alkali is adjusted such that the pH does not exceed 8.0. The alkali can be a volatile alkali such as ammonia or ethylene-diamine.

[0020] Generally, it is noted that the compositions of the invention are characterized by a consistency compatible with desirable

process handling, such as rotary die processing for capsule formation. Without wishing to be bound by a particular theory, it appears that the compositions of the invention avoid undue degradation of the film-forming, water-soluble polymer by avoiding excessively alkaline conditions during processing.

[0021] The invention also relates to a process of manufacturing a shell composition into soft capsules. The process includes preparing a solution comprising a film-forming, water-soluble polymer and an acid-insoluble polymer and mixing with appropriate plasticizers to form a gel mass; casting gel mass into films or ribbons using heat-controlled drums or surfaces; and manufacturing a soft capsule using rotary die technology. The thickness of the films or ribbons is from about 0.015 inches to about 0.050 inches. In one embodiment, the thickness is about 0.020 inches.

[0022] The moisture content of the shell composition can be from about 2% to about 10%. The moisture content can also be from about 4% to about 8%. The moisture content of particular embodiments is about 8%.

[0023] Also described herein is an enteric gel composition having an enteric polymer to film-former polymer ratio of from about 20:80 to about 45:55.

[0024] Also described herein is an enteric gel composition having a plasticizer to polymer ratio from about 10% to about 50% of the polymer weight. In one embodiment, the ratio is about 25%.

[0025] Capsules prepared in accordance with the methods of the invention can be used to contain a hydrophilic fill solution or suspension containing polyethylene glycol.

Alternatively, the fill composition can be a hydrophobic solution or suspension, such as vegetable oils or shortening, or waxes, or combinations thereof.

[0026] The present application describes enteric gel mass compositions that do not require cross-linking to achieve the desired enteric properties. Cross-linking treatments can cause potential toxicity concerns, and can lead to an uncontrolled process which lead to a product subject to deterioration over time. Further, such cross-linking adds an additional step to the manufacturing process.

Detailed Description of the Invention

[0027] This invention discloses a composition, process of manufacture and use of enteric oral solid dosage forms, namely tablets, and hard and soft capsules that do not require a coating or cross-linking in order to possess enteric properties. The gel mass of this invention can be made by mixing a film-forming polymer with an acid-insoluble polymer, and plasticizing materials to form a homogenous mixture, in presence of a solvent.

[0028] In a one embodiment, the invention provides an acid-insoluble polymer within the film-former mass that renders the total mass an enteric material, at relatively low concentrations of the acid-insoluble polymer (from about 8% to about 20% of the total wet gel mass) and without the need of excessive amounts of alkali, thus avoiding degradation or weakening of the film-forming polymer. In a described composition the ratio of acid-insoluble polymer to film-forming polymer is greater than about 1:4.

[0029] Films made by casting the final gel mass do not dissolve or disintegrate in acids, such as 0.1 M hydrochloric acid, despite the fact that the majority of shell ingredients (more than 50%) normally dissolve in, or are miscible with, acids. Enteric films made using the disclosed compositions remain substantially intact in hydrochloric acid. Further, enteric films of this invention reduce migration of small molecules such as methylene blue through them in acidic environments. In another embodiment, the final gel mass provides

[0030] Films of increased strength without substantially comprising film elasticity. Moreover, casting films according to the invention are able to be sealed at normal temperate range typically used for making softgel capsules (from about 80°F to about 105°F) or can be used to surround or enrobe tablets to make them enteric. The gel masses can also be cast around pins to form two-piece hard capsules as illustrated in Remington's Pharmaceutical Sciences, 18th edition, published by Mack Publishing Co., Easton, PA (1990)

[0031] Examples of film-former polymers that are useful in this invention can be of natural origin, preferably gelatin, or of synthetic nature such as hydroxypropyl methyl cellulose. Examples of acid-insoluble polymers are cellulose acetate phthalate (CAP), cellulose acetate butyrate, hydroxypropyl methyl cellulose phthalate, algenic acid salts such as sodium or potassium

alginate, shellac, acrylic acid-methacrylic acid copolymers (available under the trade name of EUDRAGIT (Rohm America Inc., Piscataway, NJ) as powder or 30% aqueous dispersion, or under the trade name of EASTACRYL as 30% dispersion (Eastman Chemical Company, Kingsport, TN) and sodium alginate. Acrylic-methacrylic acid copolymers are particularly stable and may be preferred in some embodiments. Acid-insoluble polymers specifications are detailed in the United States Pharmacopoeia.

[0032] Useful plasticizers according to the invention are glycerol, sorbitol, polyethylene glycol, citric acid, citric acid esters, such as tri-ethyl citrate, or combinations thereof. The composition ratio between the film-former and the acid-insoluble polymer is adjusted so that the gel mass can be made into soft capsules. Without being limited to any mechanism of performance, it has been discovered that enteric capsules can be made with an acid-insoluble polymer comprising as little as about 8% of the total content of the wet shell mass, and as high as about 30% of the total wet shell mass. The weight ratio range of acid-insoluble polymer/film-former polymer is from about 30% to about 40%.

[0033] In one embodiment of the process aspect of the invention, enteric gel masses can be made by dissolving the acid-insoluble polymer powder in aqueous solution of an alkali such as ammonia, sodium hydroxide, or potassium hydroxide, or liquid amines such as tri-ethanol amine or ethylene diamine. The amount of alkali is adjusted to give a final pH value of the gel mass less than or equal to about 9.0 pH units. In one embodiment, the final pH does not exceed 8.5. Volatile alkalis such as ammonia and ethylene diamine are preferred. The film-former can then be wetted by the plasticizer and mixed with the acid-insoluble gel to make a final homogenous mix in a heat-controlled vessel and can be degassed by using vacuum. The alkali concentrations do not require an additional step such as heating or neutralizing with acid in order to neutralize the gel mass or the finished capsules.

[0034] In another embodiment of the process aspect of the invention, the enteric gel can be made by using a ready-made aqueous dispersion of the acid-insoluble polymer by adding alkaline materials such as ammonium, sodium, or potassium hydroxides or other alkalis that will cause the acid-insoluble polymer to dissolve, such as triethanol amine or ethylene diamine or a combination thereof. The plasticizer-wetted, film-forming polymer can then be mixed with the solution of the acid-insoluble polymer. In a third embodiment of the process aspect of this invention, acid-insoluble polymers in the form of salts of the above-mentioned bases or alkalis can be dissolved directly in water and mixed with the plasticizer-wetted, film-forming polymer.

[0035] The enteric composition of the invention, comprising a film-forming polymer (e.g., gelatin or a synthetic polymer) and at least one enteric, acid, insoluble polymer, can be used to contain a fill that is liquid, semi-solid or solid.

EXAMPLES

Reference

Example 1 Enteric gel mass

[0036] A gel mass was made according to the formula below. The acid-insoluble polymer, EUDRAGIT L 100 was dissolved in the water-alkali vehicle, and triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol, and added to the enteric polymer solution, mixed for 2 hours and kept overnight at 60°C.

Gelatin	36.00%
EUDRAGIT L 100	9.00%
Glycerol	18.00%
Triethyl citrate	0.90%
Ammonium Hydroxide (30% w/v)	2.40%
Water	33.70%

Reference

Example 2 Enteric soft capsules with oil-based fill

[0037] Gel mass of Example 1 was cast as a ribbon with 0.03" thickness on a cold drum (10° C to 13° C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration testing as per the requirement of current USP.

Reference

Example 3 Enteric soft capsules with oil-based fill

[0038] Gel mass of Example 1 was cast into a ribbon with 0.03" thickness on a cold drum (10° C to 13° C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 12 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference

Example 4 Enteric soft capsules with oil-based fill

[0039] Gel mass of Example 1 was casted as a ribbon with 0.03" thickness on a cold drum (10° C to 13° C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 20 oblong die. The capsules were dried and subjected for dissolution / disintegration analysis as per the requirements of current USP.

Reference

[0040]

Example 5 Enteric soft capsules with oil-based fill containing a biphosphonate

Alendronate Sodium	1.54%
Hydrogenated Soybean Oil	7.45%
Soybean Oil	83.55%
Hydrogenated soybean oil was melted at 65°C with soybean oil and to this mixture, Alendronate sodium was added and mixed using homogenizer at 1000 rpm for 5 minutes.	

[0041] Gel mass of Example 1 was cast as a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of above mentioned fill using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference

[0042]

Example 6 Enteric soft capsules with hydrophilic fill

Alendronate Sodium	1.26%
Polyethylene glycol (3350)	4.94%
Polyethylene glycol (400)	93.80%
Polyethylene glycol was melted at 55°C with polyethylene glycol (400) and to this mixture, Alendronate sodium was added and mixed using a homogenizer at 1000 rpm for 5 minutes.	

[0043] Gel mass of Example 1 was cast into a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of above mentioned fill using 7.5 oval die. Capsules were dried and subjected to dissolution/disintegration analysis as per the requirements of current USP.

Reference

[0044]

Example 7 Enteric soft capsules with a hydrophilic/hydrophobic fill

Alendronate Sodium	1.26%
Water	10.00%
Hydrogenated Soybean Oil	7.47%
Vegetable Shortening	7.47%
Soybean Oil	73.50%
Alendronate sodium was dissolved in water (part 1). Hydrogenated soybean oil and vegetable shortening was melted at 65°C with soybean oil (part 2). Part 1 and 2 is mixed and passed five times through the MICROFLUIDIZER® at 10,000 psi.	

[0045] Gel mass of example 1 was casted as a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of above mentioned Alendronate fill using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference

Example 8 Enteric gel mass

[0046] A gel mass was made according to the formula below. The acid-insoluble polymer, EUDRAGIT L 100 was dissolved in the water-alkali vehicle, triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol. And added to the enteric polymer solution, mixed for 2 hours and was kept overnight at 60°C.

Gelatin	36.00%
EUDRAGIT L 100	9.00%
Glycerol	18.00%
Triethyl citrate	0.90%
Sodium Hydroxide	2.80%
Water	33.30%

Reference

Example 9 Enteric soft capsules with oil-based fill

[0047] Gel mass of Example 6 was cast into a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 12 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference

Example 10 Enteric soft capsules with oil-based fill

[0048] Gel mass of example 6 was cast into a ribbon with 0.025" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 12 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 11 Enteric soft capsules with oil-based fill**

[0049] Gel mass of example 6 was cast into a ribbon with 0.020" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 12 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 12 Enteric soft capsules with oil-based fill**

[0050] Gel mass of example 6 was cast into a ribbon with 0.015" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 12 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 13 Enteric gel mass**

[0051] A gel mass was made according to the formula below. The acid-insoluble polymer, EUDRAGIT L 100 was dissolved in the water-alkali vehicle, triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol. And added to the enteric polymer solution, mixed for 2 hours and was kept overnight at 60°C.

Gelatin	31.50%
EUDRAGIT L 100	13.50%
Glycerol	17.55%
Triethyl citrate	1.35%
Ammonium Hydroxide (30% w/v)	3.60%
Water	32.50%

Reference**Example 14 Enteric soft capsules with oil-based fill**

[0052] Gel mass of Example 13 was cast into a ribbon with 0.050" thickness on a cold drum (10°C to 13°C). This ribbon was

utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 15 Enteric soft capsules with oil-based fill**

[0053] Gel mass of Example 13 was cast into a ribbon with 0.045" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 16 Enteric soft capsules with oil-based fill**

[0054] Gel mass of example 13 was cast into a ribbon with 0.040" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 17 Enteric soft capsules with oil-based fill**

[0055] Gel mass of Example 13 was cast into a ribbon with 0.035" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 18 Enteric soft capsules with oil-based fill**

[0056] Gel mass of Example 13 was cast into a ribbon with 0.030" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 19 Enteric soft capsules with oil-based fill**

[0057] Gel mass of Example 13 was cast into a ribbon with 0.025" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference

Example 20 Enteric soft capsules with oil-based fill

[0058] Gel mass of Example 13 was cast into a ribbon with 0.020" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 21 Enteric soft capsules with oil-based fill**

[0059] Gel mass of Example 13 was cast into a ribbon with 0.015" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 22 Enteric soft capsules with oil-based fill containing garlic**

[0060] Garlic extract was mixed with soybean oil at 200 rpm using a propeller mixer.

Garlic extract	0.32%
Soybean Oil	99.68%

[0061] Gel mass of Example 13 was cast into a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of above-mentioned garlic fill using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference**Example 23 Enteric soft capsules with oil-based fill containing Omeprazole**

[0062] Vitamin E TPGS and CREMOPHOR RH40 were melted with medium chain triglyceride at 40°C. Omeprazole was added to the above mixture and mixed well.

Omeprazole	7.40%
Medium chain triglyceride	63.00%
Vitamin E TPGS	7.40%
Cremophor RH 40	22.20%

[0063] Gel mass of Example 13 was casted as a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of above mentioned Omeprazole fill using 3 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference

Example 24 Enteric gel mass

[0064] A gel mass was made according to the formula below. The acid-insoluble polymer, EUDRAGIT L 100 was dissolved in the water- alkali vehicle, triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol. And added to the enteric polymer solution, mixed for 2 hours and was kept overnight at 60°C.

Gelatin	27.00%
EUDRAGIT L 100	18.00%
Glycerol	17.10%
Triethyl citrate	1.80%
Ammonium Hydroxide (30% w/v)	4.80%
Water	31.30%

Reference**Example 25 Enteric soft capsules with oil-based fill**

[0065] Gel mass of Example 24 was cast into a ribbon with 0.030" thickness on a cold drum (10°C to 13°C). This ribbon is utilized for encapsulation of medium chain triglyceride oil using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirement of current USP.

Reference**Example 26 Hydrophilic enteric soft capsules containing Bisacodyl**

[0066] Acetic acid was added to polyethylene glycol (400) and mixed well. Bisacodyl was added to the polyethylene glycol/acetic acid mixture and mixed using a propeller mixture at 60°C for 30 minutes (till completely dissolved).

Bisacodyl	1.40%
Acetic acid	1.00%
Polyethylene glycol (400)	97.60%

[0067] Gel mass of Example 23 was cast into a ribbon with 0.03" thickness on a cold drum (10°C to 13°C). This ribbon was utilized for encapsulation of above-mentioned Bisacodyl fill using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference**Example 27 Hydrophobic enteric soft capsules containing bisacodyl**

[0068] Vegetable shortening, hydrogenated vegetable oil, and beeswax were melted with soybean oil at 65°C. To this wax mixture, Bisacodyl was added and mixed using a propeller mixer and the mix is cooled back to room temperature.

Bisacodyl	1.40%
-----------	-------

Vegetable Shortening	10.00%
Hydrogenated Soybean Oil	2.50%
Beeswax	2.50%
Soybean Oil	83.60%

[0069] Gel mass of Example 24 was cast into a ribbon with 0.03" thickness on a cold drum (10 to 13°C). This ribbon was utilized for encapsulation of above-mentioned Bisacodyl fill using 7.5 oval die. The capsules were dried and subjected for dissolution/disintegration analysis as per the requirements of current USP.

Reference

Example 28 Methylene blue permeation studies using dialysis chamber

[0070] Methylene blue (water soluble dye) was dissolved in 0.1 N HCl placed on one side of the chamber and plain 0.1 N HCl on the other side of the chamber separated using enteric gel mass according to Example 1. This setup was placed in shaking water bath at 15 37°C, samples were removed up to 2 hours at periodic time intervals of 10, 20, 30, 45, 60, 90 and 120 minutes.

[0071] Up to 60 minutes, no significant release of methylene blue was observed. After 60 minutes, the release was less than 10%.

Reference

Example 29 Gel masses having various ratios of gelatin-to-polymer and different ribbon thicknesses

[0072] Gel masses made based on Example 24 where the enteric polymer and gelatin comprise 45% by weight were manufactured having polymer to gelatin weight ratios of 1:19 (5%), 1:9 (10%) and 1:5.7 (15%). The resulting gel masses were cast as films and characterized for enteric properties using USP disintegration and dissolution apparatus: 5, 10, and 15% polymer films failed the enteric disintegration test

[0073] These experiments suggest that both 5 and 10% polymer concentration may not be enough to withstand the acidic pH (enteric properties) whereas 20% passes dissolution but really too weak for disintegration. Therefore 20% polymer may be minimum effective level of EUDRAGIT polymer to achieve acceptable enteric properties.

[0074] An 80:20 gelatin-to-polymer ratio gel mass was manufactured to verify the feasibility in the pilot gel reactor. The resulting gel mass was encapsulated at different ribbon thickness such as 0.015", 0.025" and 0.030" with two different speeds such as 3.0 and 3.5 RPM.

[0075] The 80:20 compositions with ammonium hydroxide, using EUDRAGIT formulations passed the enteric tests at. After 3 months stability at 40°C / 75% RH, the 80:20 composition were of border quality. The 70:30 ammonium hydroxide formulations with 0.035" 0.040", 0.045" and 0.050" ribbon thickness were attempted 0.035" ribbon thickness capsules, exhibited no swelling and stayed intact in SGF: they dissolved within 25 minutes in SIF. The 0.040" ribbon thickness capsules exhibited no swelling and stayed intact in SGF: they dissolved between 30 and 60 minutes in SIF. Thinner ribbons were also used for the same formula as shown in Table 1.

Table 1: Example Parameter and Testing Summary

No.	Parameters				USP Enteric Disintegration Test	
	Gelatin: Eudragit® [A to B]	Eudragit® solubilizer	Capsule size	Ribbon thickness	Acid	pH 6.8
1	70:30	NH ₄ OH	7.5 oval	0.030"	Pass Intact capsules	Pass Disappeared in 30 minutes

No.	Parameters				USP Enteric Disintegration Test	
	Gelatin: Eudragit® [A to B]	Eudragit® solubilizer	Capsule size	Ribbon thickness	Acid	pH 6.8
2	70:30	NH ₄ OH	7.5 oval	0.025"	Pass Intact capsules	Pass Disappeared in 30 minutes
3	70:30	NH ₄ OH	7.5 oval	0.015"	Pass Intact capsules	Pass Disappeared in 15 minutes

Reference**Example 30 Enteric gel mass containing cellulose acetate phthalate (CAP) and using ammonium hydroxide as the alkali solubilizer**

[0076] A gel mass was made according to the formula below. The acid-insoluble polymer, (CAP) was dissolved in the water-alkali vehicle, and triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol, and added to the enteric polymer solution, mixed for 2 hours and kept overnight at 60°C.

Cellulose Acetate Phthalate as 30% WN dispersion	
CPD - 30	13.30%
Gelatin	31.50%
Triethyl Citrate	1.35%
Glycerol	17.55%
Ammonium Hydroxide	1.48%
Water	34.82%

Reference**Example 31 Enteric gel mass containing cellulose acetate phthalate (CAP) and using sodium hydroxide as the alkali solubilizer**

[0077] A gel mass was made according to the formula below. The acid-insoluble polymer, CAP was dissolved in the water-alkali vehicle, and triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol, and added to the enteric polymer solution, mixed for 2 hours and kept overnight at 60°C.

Cellulose Acetate Phthalate as 30% W/V dispersion	
CPD - 30	13.18%
Gelatin	31.50%
Triethyl Citrate	1.35%
Glycerol	17.55%
Sodium Hydroxide	1.60%
Water	34.82%

Reference**Example 32 Enteric gel with shellac**

[0078] A gel mass was made according to the formula below. The acid-insoluble polymer shellac was dissolved in the water-alkali vehicle, and triethyl citrate was then added. The film-forming polymer, gelatin (lime bone, 150 bloom) was mixed with the plasticizer, glycerol, and added to the enteric polymer solution, mixed for 2 hours and kept overnight at 60°C.

Ammoniated Shellac (25% W/V solution)	36.00%
Gelatin	36.00%
Glycerol	18.00%
Triethyl citrate	0.90%
Water	9.10%

Reference

Example 33 Preparation of enteric aspirin

[0079] Enteric aspirin tablets were made using the enteric gel mass of Example 24 and a rotary die machine as per the process described in US Patent Nos. 5,459,983, 5,146,730 and 6,482,516.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- [US4518433A](#) [0007]
- [US4816259A](#) [0007]
- [US5330759A](#) [0007]
- [WO0124780A](#) [0008]
- [US4138013A](#) [0009]
- [US5146730A](#) [0013] [0014] [0079]
- [US5459983A](#) [0013] [0014] [0079]
- [US6482516B](#) [0014] [0079]

Non-patent literature cited in the description

- Remington's Pharmaceutical Sciences Mack Publishing Co. 19900000 [0002] [0030]

Patentkrav

1. En enterisk blød kapselskal dannet af gelmassesammensætning hvor gelmassen omfatter:

(a) en filmdannende, vand-opløselig polymer der er gelatine;

5 (b) en syre-uopløselig polymer der er en acrylsyre-methacrylsyre-copolymer;

(c) mindst ét plastificeringsmiddel; og

(c) et vandigt opløsningsmiddel;

10 hvor forholdet af syre-uopløselig polymer til filmdannende polymer er fra ca. 30 til ca. 40 vægtprocent.

2. Enterisk blød kapselskal ifølge krav 1, hvor den syre-uopløselige polymer omfatter ca. 8 til ca. 20 vægtprocent af den samlede gelmasse.

15 **3.** Enterisk blød kapselskal ifølge krav 1, hvor pH'en af gelmassen ikke overstiger pH 8,5.

4. Enterisk blød kapselskal ifølge krav 1, hvor fugtindholdet af den enterisk bløde kapselskalsammensætning er fra ca. 2% til ca. 10%.

20

5. Enterisk blød kapselskal ifølge krav 1, hvor gelatinen har en Bloom-værdi på ca. 100 til ca. 250.

6. Enterisk blød kapselskal ifølge krav 1, hvor plastificeringsmidlet omfatter
25 mindst én af sorbitol, glycerol, polyethylenglycol, citronsyre, triethylcitrat, eller kombinationer deraf.

7. Enterisk blød kapselskal ifølge krav 6, hvor plastificeringsmidlet er glycerol og triethylcitrat.

30

8. Enterisk blød kapselskal ifølge krav 1, hvor det vandige opløsningsmiddel omfatter en alkalisk vandig opløsning omfattende ammoniak, natriumhydroxid, kaliumhydroxid, ethylendiamin, hydroxylamin, eller tri-ethanolamin.

5 **9.** Enterisk blød kapselskal ifølge krav 8, hvor den alkaliske vandige opløsning er ammoniak.

10. Fremgangsmåde til fremstilling af en enterisk blød kapsel, hvilken fremgangsmåde omfatter

- 10 (a) fremstille en gelmassesammensætning som defineret i krav 1;
- (b) støbe gelmassen til film eller bånd under anvendelse af varme-styrede tromler eller flader; og
- (c) danne en enterisk blød kapsel under anvendelse af rotationsstanseteknologi.

15

11. Fremgangsmåden ifølge krav 10, hvor tykkelsen af filmene eller båndene er fra ca. 0,381 mm (0,015 inches) til ca. 1,27mm (0,050 inches).

12. Enterisk blød kapsel ifølge krav 1, hvor kapslen omfatter et fyld der er
20 flydende, fast, eller en kombination deraf.

13. Enterisk blød kapsel ifølge krav 1, hvor den enteriske bløde kapsel er klar eller transparent, endnu farvet.

25