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(54) **SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS**

LÖSUNGSMITTELSYSTEM ZUR ERHÖHUNG DER LÖSLICHKEIT PHARMAZEUTISCHER WIRKSTOFFE

SYSTEME DE SOLVANT DESTINE A AMELIORER LA SOLUBILITE DES AGENTS PHARMACEUTIQUES

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Description

FIELD OF THE INVENTION.

[0001] This invention is in the field of fill materials encapsulated in soft gelatin capsules.

BACKGROUND OF THE INVENTION

[0002] Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

[0003] Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

[0004] Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

[0005] Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

[0006] Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

[0007] Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu et al. discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer et al. discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel et al. describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley et al. describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

[0008] The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

[0009] There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

[0010] Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

[0011] The present invention provides a softgel capsule according to Claim 1 and a use according to Claim 13. Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The acid present in the compositions of the invention causes partial de-ionization (neutralization) of naproxen sodium resulting in enhanced bioavailability as well as decreased amounts of polyethylene glycol (PEG) esters. Thus, hereinafter the acid maybe referred to as the deionizing agent.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

[0012] In the present invention the fill material comprises naproxen sodium. Other formulations described herein may contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity-disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

[0013] Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

[0014] Some other drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the formulations described herein include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic acid, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine, Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

[0015] The fill material of the present invention comprises fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium. These acids act as deionizing agents.

[0016] The deionizing agent functions by causing partial deionization (neutralization) of the salt of the pharmaceutically active agent (in this invention naproxen sodium). As described herein when the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species such as an acid as described above or when the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species such as a metal hydroxide such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

[0017] Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

[0018] Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

[0019] A mixture of polyethylene glycol and water is used as a solvent for the naproxen sodium and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents described herein include surfactants and copolymers of polyethylene glycol. The fill material of the present invention also comprises a solubilizer selected from the group consisting of glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) and combinations thereof.

B. Shell Composition

1. Gelatin

[0020] Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime- processed gelatins of the same average molecular weight.

2. Other Shell Additives

[0021] Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

[0022] Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

[0023] Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

[0024] Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

[0025] Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

[0026] Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes

in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

[0027] The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

[0028] The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

[0029] The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

[0030] The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

[0031] Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

[0032] The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

[0033] The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

[0034] In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

[0035]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

[0036]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Reference Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

[0037]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

[0038]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15

(continued)

Ingredients	% (by weight)
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

[0039]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Reference Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

[0040]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

[0041]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

[0042]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

[0043]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

[0044]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

[0045]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

[0046]

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

[0047] It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0048] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described.

Claims

1. A softgel capsule comprising a fill material wherein the fill material comprises

   (a) naproxen sodium;
   (b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol;
   (d) water; and
   (e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

2. The capsule of claim 1 wherein (b) is citric acid or lactic acid.

3. The capsule of claim 2 wherein (b) is lactic acid.

4. The capsule of any one of the preceding claims wherein polyethylene glycol is present in an amount from 10% to 80% by weight.

5. The capsule of any one of the preceding claims wherein the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

6. The capsule of any one of the preceding claims wherein water is present in an amount from 1% to 18% by weight.

7. The capsule of any one of the preceding claims further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

8. The capsule of any one of the preceding claims wherein the solubilizer is present in amount from 1% to 10% by weight.

9. The capsule of any one of the preceding claims wherein the fill material is liquid.

10. A capsule of any of the preceding claims for use as a medicament.

11. A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and
(b) encapsulating the mixture in a softgel capsule.

12. The method of claim 11, wherein step (a) is conducted at a temperature of from 50°C to 70°C.

13. The use of

(a) naproxen sodium;
(b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
(c) polyethylene glycol;
(d) water; and
(e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof,

in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

Patentansprüche

1. Weichkapsel, umfassend ein Füllmaterial, wobei das Füllmaterial Folgendes umfasst:

(a) Naproxennatrium;
(b) Fumarsäure, Maleinsäure, Weinsäure, Citronensäure, Äpfelsäure, Essigsäure, Propionsäure, Brenztraubensäure, Buttersäure oder Milchsäure in einer Menge von 0,2 bis 1,0 Moläquivalenten pro Mol Naproxennatrium;
(c) Polyethylenglycol;
(d) Wasser; und
(e) einen Lösungsvermittler aus der Gruppe, bestehend aus Glycerin, Polyvinylpyrrolidon, Propylenglycol und Kombinationen daraus.

2. Kapsel nach Anspruch 1, wobei (b) Citronensäure oder Milchsäure ist.

3. Kapsel nach Anspruch 2, wobei (b) Milchsäure ist.

4. Kapsel nach einem der vorhergehenden Ansprüche, wobei das Polyethylenglycol in einer Menge von 10 Gew.-% bis 80 Gew.-% vorliegt.

5. Kapsel nach einem der vorhergehenden Ansprüche, wobei das Polyethylenglycol ein oder mehrere Polyethylenglycole mit einer Molekülmasse zwischen 300 und 1500 ist.

6. Kapsel nach einem der vorhergehenden Ansprüche, wobei Wasser in einer Menge von 1 Gew.-% bis 18 Gew.-% vorhanden ist.

7. Kapsel nach einem der vorhergehenden Ansprüche, ferner umfassend ein oder mehrere Hilfsstoffe, ausgewählt aus der Gruppe, bestehend aus Weichmachern, Kristallisationshemmern, Benetzungsmitteln, Massenfüllmitteln, Lösungsvermittlern, Bioverfügbarkeitsverstärkern, Lösungsmitteln, Farbstoffen, Konservierungsmitteln, Tensiden und Kombinationen daraus.

8. Kapsel nach einem der vorhergehenden Ansprüche, wobei der Lösungsvermittler in einer Menge von 1 Gew.-% bis 10 Gew.-% vorhanden ist.

9. Kapsel nach einem der vorhergehenden Ansprüche, wobei das Füllmaterial flüssig ist.

10. Kapsel nach einem der vorhergehenden Ansprüche zur Verwendung als ein Medikament.

11. Verfahren zum Herstellen der Kapsel nach Anspruch 1, Folgendes umfassend:

(a) Mischen der Komponenten (a), (b), (c), (d) und (e) nach Anspruch 1; und
(b) Einkapseln der Mischung in eine Weichkapsel.

12. Verfahren nach Anspruch 11, wobei Schritt (a) bei einer Temperatur von 50 °C bis 70 °C durchgeführt wird.

13. Gebrauch von

(a) Naproxennatrium;
(b) Fumarsäure, Maleinsäure, Weinsäure, Citronensäure, Äpfelsäure, Essigsäure, Propionsäure, Brenztraubensäure, Buttersäure oder Milchsäure in einer Menge von 0,2 bis 1,0 Moläquivalenten pro Mol Naproxennatrium;
(c) Polyethylenglycol;
(d) Wasser; und
(e) einem Lösungsvermittler aus der Gruppe, bestehend aus Glycerin, Polyvinylpyrrolidon, Propylenglycol und Kombinationen daraus,

bei der Herstellung eines Medikaments in der Form einer Kapsel zum Verabreichen von Naproxennatrium an einen Patienten, der dies benötigt.

Revendications

1. Capsule molle comprenant un matériau de remplissage dans laquelle le matériau de remplissage comprend :

(a) du naproxène sodique ;
(b) de l'acide fumarique, de l'acide maléique, de l'acide tartrique, de l'acide citrique, de l'acide malique, de l'acide acétique, de l'acide proprionique, de l'acide pyruvique, de l'acide butanoïque ou de l'acide lactique dans une quantité comprise entre 0,2 et 1,0 équivalent molaire par mole de naproxène sodique ;
(c) du polyéthylène glycol ;
(d) de l'eau ; et
(e) un solubilisant choisi dans le groupe constitué par la glycérine, la polyvinylpyrrolidone, le propylène glycol et des combinaisons de ceux-ci.

2. Capsule selon la revendication 1, dans laquelle (b) est de l'acide citrique ou de l'acide lactique.

3. Capsule selon la revendication 2, dans laquelle (b) est de l'acide lactique.

4. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le polyéthylène glycol est présent dans une quantité comprise entre 10 % et 80 % en poids.

5. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le polyéthylène glycol est un ou plusieurs polyéthylènes glycols ayant un poids moléculaire compris entre 300 et 1 500.

6. Capsule selon l'une quelconque des revendications précédentes, dans laquelle l'eau est présente dans une quantité comprise entre 1 % et 18 % en poids.

7. Capsule selon l'une quelconque des revendications précédentes, comprenant en outre un ou plusieurs excipients choisis dans le groupe constitué par les plastifiants, les inhibiteurs de cristallisation, les agents mouillants, les agents de remplissage en vrac, les solubilisants, les amplificateurs de biodisponibilité, les solvants, les colorants, les conservateurs, les tensioactifs et des combinaisons de ceux-ci.

8. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le solubilisant est présent dans une quantité comprise entre 1 % et 10 % en poids.

9. Capsule selon l'une quelconque des revendications précédentes, dans laquelle le matériau de remplissage est liquide.

10. Capsule selon l'une quelconque des revendications précédentes, pour une utilisation en tant que médicament.

11. Procédé de fabrication de la capsule selon la revendication 1, comprenant les étapes consistant à :

(a) mélanger les composants (a), (b), (c), (d) et (e) tels que définis dans la revendication 1 ; et
(b) encapsuler le mélange dans une capsule molle.

12. Procédé capsule selon la revendication 11, dans lequel l'étape (a) est effectuée à une température comprise entre 50°C et 70°C.

13. Utilisation

(a) de naproxène sodique ;
(b) d'acide fumarique, d'acide maléique, d'acide tartrique, d'acide citrique, d'acide malique, d'acide acétique, d'acide proprionique, d'acide pyruvique, d'acide butanoïque ou d'acide lactique dans une quantité comprise entre 0,2 et 1,0 équivalent molaire par mole de naproxène sodique ;
(c) de polyéthylène glycol ;
(d) d'eau ; et
(e) d'un solubilisant choisi dans le groupe constitué par la glycérine, la polyvinylpyrrolidone, le propylène glycol et des combinaisons de ceux-ci,

dans la fabrication d'un médicament sous la forme d'une capsule pour l'administration du naproxène sodique à un patient en ayant besoin.

REFERENCES CITED IN THE DESCRIPTION

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OLDÓSZERRENDSZER GYÓGYÁSZATI HATÓANYAGOK OLDHATÓSÁGÁNAK FOKOZÁSÁRA

Szabadalmi igénypontok:

1. Lágygél kapszula, amely töltőanyagot tartalmaz, ahol a töltőanyag a következőket tartalmazza:

(a) naproxén-nátrium;

(b) fumársav, maleinsav, borkősav, citromsav, almasav, ecetsav, propionsav, piroszőlősav, butánsav vagy tejsav 0,2 – 1,0 mol ekvivalens per mol naproxén-nátrium mennyiségben;

(c) polietilénglikol;

(d) víz; és

(e) szolubilizálószer, amelyet a glicerin, polivinilpirrolidon, propilénglikol és ezek kombinációi által alkotott csoportból választunk.

2. Az 1. igénypont szerinti kapszula, ahol (b) citromsav vagy tejsav.

3. A 2. igénypont szerinti kapszula, ahol (b) tejsav.

4. Az előző igénypontok bármelyike szerinti kapszula, ahol a polietilénglikol 10 tömeg% - 80 tömeg% mennyiségben van jelen.

5. Az előző igénypontok bármelyike szerinti kapszula, ahol a polietilénglikol egy vagy több polietilénglikol, amelyek molekulatömege 300 és 1500 közötti.

6. Az előző igénypontok bármelyike szerinti kapszula, ahol a víz 1 tömeg% - 18 tömeg% mennyiségben van jelen.

7. Az előző igénypontok bármelyike szerinti kapszula, amely tartalmaz még egy vagy több segédanyagot, amelye(ke)t a lágyítószerek, kristályosodást gátlók, nedvesítőszerek, térfogatnövelő szerek (bulk filling agents), szolubilizálószerek, biológiai hozzáférhetőséget fokozó szerek, oldószerek, színezékek, tartósítószerek, felületaktív anyagok és ezek kombinációi által alkotott csoportból választunk.

8. Az előző igénypontok bármelyike szerinti kapszula, ahol a szolubilizálószer 1 tömeg% - 10 tömeg% mennyiségben van jelen.

9. Az előző igénypontok bármelyike szerinti kapszula, ahol a töltőanyag folyadék.

10. Az előző igénypontok bármelyike szerinti kapszula gyógyszerként való alkalmazásra.

11. Eljárás az 1. igénypont szerinti kapszula előállítására, amely során

(a) összekeverjük az 1. igénypontban meghatározott (a), (b), (c), (d) és (e) komponenst; és

(b) az elegyet lágygél kapszulába kapszulázzuk.

12. A 11. igénypont szerinti eljárás, ahol az (a) lépést 50 °C – 70 °C hőmérsékleten végezzük.

13. A következők:

(a) naproxén-nátrium;

(b) fumársav, maleinsav, borkősav, citromsav, almasav, ecetsav, propionsav, piroszőlősav, butánsav vagy tejsav 0,2 – 1,0 mol ekvivalens per mol naproxén-nátrium mennyiségben;

(c) polietilénglikol;

(d) víz; és

(e) szolubilizálószer, amelyet a glicerin, polivinilpirrolidon, propilénglikol és ezek kombinációi által alkotott csoportból választunk;

alkalmazása gyógyszer előállítására kapszula formájában naproxén-nátrium olyan páciensnek való adagolására, aki ilyen adagolást igényel.