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(54) Title: INSTANTLY WETTABLE ORAL FILM DOSAGE FORM WITHOUT SURFACTANT OR POLYALCOHOL

(57) Abstract: An instantly wettable and rapidly disintegrating oral film dosage form without a surfactant and without a polyalcohol was achieved by combining at least one water soluble polymer that is not a copolymer of vinylpyrrolidone, at least one active agent, a copolymer of vinylpyrrolidone and titanium dioxide. In certain embodiments, the film comprises hydroxypropyl cellulose or a combination of hydroxypropyl cellulose and a polymer or copolymer of vinylpyrrolidone or a substituted vinylpyrrolidone as the water soluble polymer(s). A plasticizer, and optional additives selected from synthetic sweeteners, natural sweeteners, flavorants, antioxidants, colorants, and opacifiers, can be added to the disclosed film oral dosage forms.

INSTANTLY WETTABLE ORAL FILM DOSAGE FORM WITHOUT SURFACTANT OR POLYALCOHOL

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/860,345, filed July 31, 2013, which is incorporated herein by reference.

FIELD OF THE DISCLOSURE

[0002] This disclosure relates to rapidly disintegrating films for oral administration of an active agent, and more particularly to films of this type that exhibit instant wettability and excellent mouth feel due to the absence of noticeable particulate residues.

BACKGROUND OF THE DISCLOSURE

[0003] Film type oral dosage forms are often preferred by subjects that have difficulty swallowing a tablet. However, it is important that the film dissolves or disintegrates very rapidly without leaving a gritty residue. Thus, developing a film type oral dosage form that can achieve instant wettability and rapid disintegration, while exhibiting good mouth feel is desirable. This disclosure relates to rapidly disintegrating films for oral administration of an active agent, and more particularly to films of this type that exhibit instant wettability and excellent mouth feel due to the absence of noticeable particulate residues.

SUMMARY OF THE DISCLOSURE

[0004] It has been discovered that film oral dosage forms achieving instant wettability and rapid disintegration upon oral administration can be achieved without a surfactant and without a polyalcohol. Specifically, it has been determined that at least one water soluble polymer that is not a copolymer of vinylpyrrolidone can be combined with one or more active agents, a copolymer of vinylpyrrolidone, and titanium dioxide to provide an instantly wettable,

rapidly disintegratable film dosage form exhibiting good mouth feel and that is free of surfactants and polyalcohols.

[0005] A desirable combination of strength, stiffness, and disintegratability can be achieved by adding the copolymer of vinylpyrrolidone and titanium dioxide in a ratio by weight of from 3:1 to 5:1.

[0006] Also disclosed are particular embodiments in which desirable properties are enhanced by the addition of a food grade or pharmaceutically safe plasticizer.

[0007] These and other features, advantages and objects of the various embodiments will be better understood with reference to the following specification and claims.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0008] The term "instantly wettable" and variations thereof generally refers to the ability of the film dosage form to rapidly imbibe moisture upon oral administration to a subject and immediately soften, whereby the subject is prevented from experiencing a prolonged adverse feeling in the mouth, and with respect to certain aspects of the disclosure refers to embodiments in which moisture (i.e., water) applied to a surface of the film penetrates the thickness of the film (e.g., typically about 5 μm to 200 μm) within 5, 10 or 15 seconds.

[0009] The term "rapidly disintegrating" and variations thereof generally refers to the ability of the film dosage forms to break up into submicron particles or completely dissolve within an acceptable period of time (e.g., within 60 seconds, within 45 seconds, within 30 seconds, within 20 seconds, or within 15 seconds of being administered, i.e., placed in the oral cavity of a subject).

[0010] The term "good mouth feel" generally refers to a variety of perceived qualities relating to texture and consistency, and most notably within the context of this disclosure to graininess (i.e., the extent to which the films can be perceived to contain grainy particles), and to the overall subjective perception of the subject to which the film is orally administered.

[0011] Water soluble polymers that are not a copolymer of vinylpyrrolidone that can be employed in the disclosed films include water soluble cellulose derivatives, including hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose; polyvinyl pyrrolidone (PVP); polymers of substituted vinylpyrrolidone; derivatives of polyvinyl

pyrrolidone; polyethylene oxide, carboxymethyl cellulose; polyvinyl alcohol; natural gums, including xanthan, tragacanth, guar, acacia and arabic gums; and water soluble polyacrylates. Combinations of these water soluble polymers or other water soluble polymers can also be used. Examples of substituted vinyl pyrrolidones include N-vinyl-3-methyl-2-pyrrolidone, N-vinyl-4-methyl-2-pyrrolidone, N-vinyl-5-methyl-2-pyrrolidone, N-vinyl-5,5-dimethyl-2-pyrrolidone, N-vinyl-3,3,5-trimethyl-2-pyrrolidone and others.

[0012] The term "active agent" refers to any agent that is being administered orally to a subject and includes pharmaceutically active agents, nutraceutically active agents, and breath freshening agents. Examples of pharmaceutically active agents include ACE-inhibitors, antianginal drugs, anti-arrhythmics, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies such as sildenafil citrate, tadalafil, and vardenafil, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, anti-migraine preparations such as rizatriptan, eletriptan and zolmitriptan, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives such as lorazepam or diazepam, smoking cessation aids such as bromocryptine or nicotine, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents such as alprazolam, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic

drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spadmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-astmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof. Examples of nutraceutically active agents include various dietary supplements, vitamins, minerals, herbs and nutrients. Breath freshening agents include, for example, spearmint oil, cinnamon oil, peppermint oil, clove oil, menthol, etc.

[0013] The film oral dosage forms disclosed herein are free or substantially free of surfactants and polyalcohols. The term "substantially free" of surfactants and polyalcohols means that the film oral dosage forms contain no deliberately added surfactants or polyalcohols, and any unavoidable or incidental surfactants or polyalcohols are only present, if at all, as impurities in other ingredients in amounts that do not affect measurable properties relating to wettability (e.g., contact angle goniometer measurements), dissolution or disintegration rates by more than 10%, and do not adversely affect measurable stability properties. The term "free" of surfactants and polyalcohols means that incidental or unavoidable surfactants and polyalcohol impurities are present in only inconsequential amounts that affect water contact angle measurements and dissolution rate by less than 1%. In certain embodiments, the presence of surfactants and polyalcohols are each limited to less than 1000 ppm (w/w), less than 500 ppm (w/w), less than 100 ppm (w/w), less than 40 ppm (w/w), or less than 10 ppm (w/w).

[0014] The terms "surfactant" and "polyalcohol" are intended to have their ordinary meanings. Specifically, the term "surfactant" is intended to mean an amphophilic compound that lowers the surface tension of a liquid, the interfacial tension between two liquids, or the interfacial tension between a liquid and a solid. The term "polyalcohol" means a sugar alcohol, which is a hydrogenated form of a carbohydrate having a carbonyl group that has been reduced to a primary or secondary hydroxyl group. Polyalcohols are also distinguishable based on their chemical formula. Polyalcohols have the general formula $H(HCHO)_{n+1}H$, whereas sugars have the general formula $H(HCHO)_n$ HCO. Common examples of polyalcohols or sugar alcohols that are avoided or eliminated from the disclosed films include glycol, glycerol, erythritol, threitol, arabitol, xylitol, ribitol, mannitol, sorbitol, galactitol, fucitol, iditol, inositol, volemitol, isomalt, maltitol, lactitol, maltotritol and maltotetraitol.

[0015] The copolymer of vinylpyrrolidone can be generally any copolymer of vinylpyrrolidone. Commerically available vinylpyrrolidone-vinyl acetate copolymers (copovidones) that may be used in the films described herein include Kollidon® VA 64 copovidone, Kollidon® 25 copovidone, Kollidone® SR copovidone, and Plasdone® S-630 copovidone. The addition of copovidone increases the stiffness of the film, e.g., increasing flexural modulus, tensile strength, and hardness. Other examples of vinylpyrrolidone copolymers that could be used include poly (1-vinylpyrrolidone-co-2-dimethylaminoethyl methacrylate, poly (1-vinylpyrrolidone-co-styrene), poly (1-vinylpyrrolidone)-graft-(1-triacontene), poly (vinylpyrrolidone-co-methyl methacrylate), poly (vinylpyrrolidone-co-N,N'-dimethylacrylamide), and poly (vinylpyrrolidone-co-maleate). The copolymer of vinylpyrrolidone can be added in an amount that is effective to increase the stiffness or elastic modulus (Young's Modulus) of the film relative to a film that does not include copolymer of vinylpyrrolidone and is otherwise the same. Bending stiffness can be determined by applying a measured moment to the film and determining the quotient of the applied moment divided by the resulting curvature of the film. A suitable amount of copolymer of vinylpyrrolidone is from 0.1% to 25% of the weight (or mass) of the film, e.g., 0.2% to 20%, 0.5% to 20%, 1% to 15%, 2% to 15% or 5% to 15%.

[0016] Addition of a copolymer of vinylpyrrolidone can advantageously increase stiffness without adversely affecting wettability, disintegration rate or mouth feel by adding titanium dioxide in an amount such that the weight (or mass) ratio of copolymer of vinylpyrrolidone to titanium dioxide in the film is from 3:1 to 5:1. A suitable amount of titanium is, for example, from about 0.02% to about 8%, e.g., 0.04% to about 7%, 0.1% to about 7%, 0.2% to 5%, 0.4% to 5%, or 1% to 5%.

[0017] Within the disclosed ranges for the vinylpyrrolidone copolymer and the titanium dioxide, it is possible to achieve an advantageous balance or combination of improved stiffness or higher elastic modulus while concurrently achieving rapid disintegration and good mouth feel.

[0018] The titanium dioxide can be added in amounts from about 0.05% to 5%, 0.1% to 3%, or 0.5 to 2% of the weight of the film. The titanium dioxide acts as a disintegrant in the disclosed films, as well as a texture modifier that improves mouth feel, and an opacify or coloring agent. This amount is effective for increasing the rate at which the film will dissolve in

an aqueous medium. The amount of copovidone added can be an amount by weight that is from 3 to 5 times the weight of the titanium dioxide. The titanium dioxide provides an increased rate of disintegration relative to an otherwise identical composition that does not contain titanium dioxide. The increased rate of disintegration can be at least 5%, at least 10%, at least 20%, at least 50% or at least 75%.

[0019] In certain embodiments, the disclosed films may include a plasticizer. The term "plasticizer" refers to a component that reduces the glass-transition temperature of the film forming polymers (e.g., the water soluble polymer or water soluble polymers in the film). The plasticizer increases the flexibility, enhances elasticity and reduces brittleness of the film. Examples of plasticizers that can be used in the disclosed film oral dosage forms include triacetin, triethyl citrate, tributyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, trioctyl citrate, acetyl trioctyl citrate, trihexyl citrate, dibutyl sebacate, etc. Plasticizer may be added in an amount up to 25% of the total mass of the film oral dosage form, such as from 0.5% to 25%, 1% to 20%, 2% to 15% or 5% to 10%.

[0020] The amount of drug that can be incorporated in the film oral dosage forms disclosed herein is generally from 0.01% to 50% by total weight of the film, such as 1% to 40%, 2% to 30%, or 5% to 20% by total weight of the film.

[0021] Conventional film oral dosage form additives, other than surfactants and polyalcohols, can be added as needed or desired, generally in amounts conventionally employed. Examples of such additives include artificial sweeteners such as sucralose, aspartame, acesulfame potassium and monoammonium glycyrrhizinate, natural sweeteners such as sucrose and fructose; flavorants such as menthol, various fruit flavors (e.g., cherry, grape, orange, etc.) or various mint flavors (e.g., spearmint, peppermint, etc.); colorants; opacifiers (e.g., titanium dioxide); and antioxidants (e.g., butylhydroxytoluene). Other additives may also be incorporated in amounts that do not adversely affect film properties or film stability. Specifically, any such additives must not cause undesirable softening of the film and subsequent loss of dimensional stability, degradation of the active ingredient(s), or induce undesirable aesthetics such as discoloration of the film or noticeable segregation and agglomeration of film components.

[0022] In an embodiment, a method of forming a film of the present disclosure includes combining the various ingredients in generally any order, employing water, a combination of

water and water-miscible solvents such as lower alcohols (e.g., ethanol) or organic solvents alone or as a mixture. For example, the plasticizer and additives (e.g., sweetening agents, colorants, flavorants, and opacifying agents) can be dissolved or dispersed in a sufficient amount of solvent that is agitated to form a homogenous solution or suspension to which the water soluble polymer(s) is (are) added. Heat, vacuum and agitation may be applied as needed during addition of the water soluble polymer until a homogenous solution or homogenous suspension is obtained. Thereafter, the active ingredient(s) is (are) added, and the solution or suspension is cast or coated onto a carrier material and dried to form a film. Examples of suitable carrier materials include non-siliconized polyethylene terephthalate film, non-siliconized kraft paper, polyethylene-impregnated kraft paper and non-siliconized polyethylene film. The liquid film composition can be coated onto the carrier material using generally any conventional coating equipment, including knife-over-roll, extrusion die, reverse roll, or Meyer roll coating equipment.

[0023] Upon drying, the resulting solid film can have a thickness of generally 5 to 200 μm, such as 10 to 200 μm, 20 to 150 μm or 20 to 100 μm. The film can be cut into individual pieces having a suitable size to facilitate administration of a targeted dosage of active agent(s).

EXAMPLE 1

[0024] Rizatriptan film oral dosage forms are prepared using the above described processes and compositions listed in the following Table 1.

TABLE 1

Component	Function	Quantity per dry film [mg]		Quantity per dry film [%]
		2.58 cm²	5.16 cm²	
Hydroxymethyl ethyl cellulose	Film forming polymer	6.2 mg	12.400 mg	15.39
Copovidone	Film forming polymer	2.0 mg	4.0 mg	4.96
Hydroxypropylmethyl cellulose	Film forming polymer	20.203 mg	40.405 mg	50.14
Butylhydroxyltoluene	antioxidant	0.004 mg	0.008 mg	0.010
Monoammonium Glycyrrhizinate	sweetener	0.222 mg	0.443 mg	0.550
Sucralose	sweetener	0.439 mg	0.878 mg	1.090
Titanium dioxide	Opacifier/texture modifier	0.661 mg	1.322 mg	1.640
Menthol	flavour	0.439 mg	0.878 mg	1.090
Dibutyl sebacate	plasticizer	2.861 mg	5.722 mg	7.100
Rizatriptan benzoate	active	7.265 mg	14.530 mg	18.030
Total		40.294 mg	80.586 mg	100.000

[0025] The resulting rizatriptan films were stable for at least 18 months at 25°C and 65% relative humidity and for at least 6 months at 40°C and 75% relative humidity. Subjective testing, in which the subject was asked to moisten her mouth with a small amount of water and swallow the water before the film was placed on the tongue and the mouth was closed, indicated that the films had good mouth feel (i.e., was not unpleasant) and dissolved completely within a short period, typically within less than 15 minutes, less than 10 minutes, less than 5 minutes, less than 2 minutes, or even less than 1 minute. The subjects were advised that the film should not be chewed or swallowed but allowed to dissolve in available saliva. The time for disintegration is recorded as the time the film takes to completely disappear.

EXAMPLE 2

[0026] Palonosetron (a 5-HT_3 antagonist used to prevent or treat chemotherapy-induced nausea and vomiting) film oral dosage forms are prepared using the above described processes and compositions listed in the following Table 2.

TABLE 2

Component and Quality Standard (and Grade, if applicable)	**Function**	**Quantity per dry film [mg]**	**Quantity per dry film [%]**
Palonosetron	active	2.50	4.77
L-Cysteine	anti-oxidant	0.34	0.65
Sucralose	sweetener	0.52	0.99
Hydroxypropyl cellulose	Film forming polymer	23.10	44.12
Copovidone	Film forming polymer	2.5 mg	4.77
Hydroxypropylmethyl cellulose	Film forming polymer	15.02	28.69
Titanium dioxide	Opacifier/texture modifier	0.52	0.99
Polyvinyl pyrrolidone	Film forming polymer	6.72	12.83
Anhydrous citric acid	acidifier	1.14	2.18
Total		52.36 mg	100.0

EXAMPLE 3

[0027] Alprazolam film oral dosage forms are prepared using the above described processes and compositions listed in the following Table 3.

TABLE 3

Component and Quality Standard (and Grade, if applicable)	**Function**	**Quantity per dry film [mg]**	**Quantity per dry film [%]**
Alprazolam	active	2.00	4.68
Acesulfame potassium	sweetener	0.39	0.91
Copovidone	Film forming polymer	8.75	20.51
Hydroxypropyl cellulose	Film forming polymer	27.62	64.74
Triethyl citrate	Plastcizer	1.58	3.70
Titatnium dioxide	Opacifier/texture modifier	1.75	4.10
Menthol	Flavour	0.55	1.29
Yellow #6	Colour	0.02	0.05
Total		42.66 mg	100.0

[0028] The above description is considered that of the preferred embodiment(s) only. Modifications of these embodiments will occur to those skilled in the art and to those who make or use the illustrated embodiments. Therefore, it is understood that the embodiment(s) described above are merely exemplary and not intended to limit the scope of this disclosure, which is defined by the following claims as interpreted according to the principles of patent law, including the doctrine of equivalents.

IN THE CLAIMS

1. An instantly wettable, rapidly disintegrating film oral dosage form, comprising:

at least one water soluble polymer that is not a copolymer of vinylpyrrolidone;

at least one copolymer of vinylpyrrolidone in an amount that is effective to increase stiffness of the film as compared to a film without the at least one copolymer of vinylpyrrolidone;

titanium dioxide in an amount that is effective to increase a rate of disintegration of the film in an aqueous medium, wherein the ratio by weight of copolymer of vinylpyrrolidone to titanium dioxide in the film is from 3:1 to 5:1; and

at least one active agent;

wherein the film oral dosage form is substantially free of surfactants and polyalcohols.

2. The oral dosage form of Claim 1, further comprising a plasticizer.

3. The oral dosage form of Claim 1, further comprising a synthetic sweetener.

4. The oral dosage form of Claim 1, further comprising a natural sweetener.

5. The oral dosage form of Claim 1, further comprising a flavorant.

6. The oral dosage form of Claim 1, further comprising an antioxidant.

7. The oral dosage form of Claim 1, in which the at least one water soluble polymer that is not a copolymer of vinylpyrrolidone includes hydroxypropyl cellulose.

8. The oral dosage form of Claim 1, in which the at least one water soluble polymer that is not a copolymer of vinylpyrrolidone includes a combination of hydroxypropyl cellulose and polyvinylpyrrolidone.

9. The oral dosage form of Claim 1, in which the active agent is selected from the group consisting of rizatriptan, zolmitriptan, alprazolam, diazepam or lorazepam.

10. The oral dosage form of Claim 1, in which the active agent is rizatriptan benzoate.

11. The oral dosage form of Claim 1, in which the at least one water soluble polymer that is not a copolymer of vinylpyrrolidone consists of a combination of hydropropyl cellulose and polyvinylpyrrolidone and further comprising a plasticizer.

12. The oral dosage form of Claim 1 further comprising at least one plasticizer and at least one additive selected from the group consisting of synthetic sweeteners, natural sweeteners, flavorants, antioxidants, colorants, and opacifiers.

13. An instantly wettable, rapidly disintegrating film dosage form consisting of at least one water soluble polymer that is not a copolymer of vinylpyrrolidone, at least one copolymer of vinylpyrrolidone, at least one active agent, at least one plasticizer, titanium dioxide and optional additives.

14. The oral dosage form of Claim 13, in which the plasticizer is triacetin.

15. The oral dosage form of Claim 13, in which the at least one water soluble polymer includes hydroxypropyl cellulose.

16. The oral dosage form of Claim 13, in which the at least one water soluble polymer consists of a combination of hydroxypropyl cellulose and polyvinylpyrrolidone.

17. The oral dosage form of Claim 13, in which the at least one active agent is rizatriptan or rizatriptan benzoate.

18. An instantly wettable, rapidly disintegrating film dosage form consisting of hydroxypropyl cellulose, polyvinylpyrrolidone, triacetin, vinylpyrrolidone-vinyl acetate

copolymer, titanium dioxide, and at least one active agent, wherein the ratio of vinylpyrrolidone-vinyl acetate copolymer to titanium dioxide is from 3:1 to 5:1.

19. The oral dosage form of Claim 18, in which the at least one active agent is rizatriptan benzoate.

20. The oral dosage form of Claim 18, in which optional synthetic sweeteners are added and comprise sucralose and monoammonium glycyrrhizinate.

21. The oral dosage form of Claim 20, in which optional antioxidant is added and comprises butylhydroxytoluene.

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(57) Abstract: An instantly wettable and rapidly disintegrating oral film dosage form without a surfactant and without a polyalcohol was achieved by combining at least one water soluble polymer that is not a copolymer of vinylpyrrolidone, at least one active agent, a copolymer of vinylpyrrolidone and titanium dioxide. In certain embodiments, the film comprises hydroxypropyl cellulose or a combination of hydroxypropyl cellulose and a polymer or copolymer of vinylpyrrolidone or a substituted vinylpyrrolidone as the water soluble polymer(s). A plasticizer, and optional additives selected from synthetic sweeteners, natural sweeteners, flavorants, antioxidants, colorants, and opacifiers, can be added to the disclosed film oral dosage forms.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, US Patent Database, Questel Orbit (*FamPat*)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2,704,079 (Meyer et al.) 18 June 2009 (18-06-2009) Pages 17-19, Examples 1e, 1f, 2f	13-21

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search 18 February 2015 (18-02-2015)	Date of mailing of the international search report 25 February 2015 (25-02-2015)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Jad A. Nassif 819-994-3676

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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		CN101896172A	24 November 2010 (24-11-2010)
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		WO2009074552A3	21 January 2010 (21-01-2010)

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权利要求书2页 说明书7页

(54)发明名称

不含表面活性剂或多元醇的即时可湿性口服薄膜剂型

(57)摘要

一种不含表面活性剂且不含多元醇的即时可湿性速崩口服薄膜剂型，其通过组合至少一种不是乙烯吡咯烷酮共聚物的水溶性聚合物、至少一种活性剂、乙烯吡咯烷酮共聚物和二氧化钛制得。在某些实施方式中，所述薄膜包括作为水溶性聚合物的羟丙基纤维素、或羟丙基纤维素与乙烯吡咯烷酮聚合物或共聚物的组合、或取代的乙烯吡咯烷酮。可向所公开的薄膜口服剂型中添加增塑剂以及选自合成甜味剂、天然甜味剂、食用香料、抗氧化剂、着色剂和遮光剂的任选添加剂。

CN 105530921 A

1.一种即时可湿性速崩薄膜口服剂型,包括:

至少一种水溶性聚合物,该水溶性聚合物不是乙烯吡咯烷酮共聚物;

至少一种乙烯吡咯烷酮共聚物,与不含所述至少一种乙烯吡咯烷酮共聚物的薄膜相比,所述至少一种乙烯吡咯烷酮共聚物的量可有效提高薄膜的刚度;

二氧化钛,其量可有效提高薄膜在水性介质中的崩解速率,其中,薄膜中乙烯吡咯烷酮共聚物与二氧化钛的重量比为3:1至5:1;和

至少一种活性剂;

其中所述薄膜口服剂型基本上不含有表面活性剂和多元醇。

2.如权利要求1所述的口服剂型,进一步包括增塑剂。

3.如权利要求1所述的口服剂型,进一步包括合成甜味剂。

4.如权利要求1所述的口服剂型,进一步包括天然甜味剂。

5.如权利要求1所述的口服剂型,进一步包括食用香料。

6.如权利要求1所述的口服剂型,进一步包括抗氧化剂。

7.如权利要求1所述的口服剂型,其中,所述至少一种不是乙烯吡咯烷酮共聚物的水溶性聚合物包括羟丙基纤维素。

8.如权利要求1所述的口服剂型,其中,所述至少一种不是乙烯吡咯烷酮共聚物的水溶性聚合物包括羟丙基纤维素和聚乙烯吡咯烷酮的组合。

9.如权利要求1所述的口服剂型,其中,所述活性剂选自于由利扎曲坦、佐米曲坦、阿普唑仑、地西泮或劳拉西泮组成的组。

10.如权利要求1所述的口服剂型,其中,所述活性剂为苯甲酸利扎曲坦。

11.如权利要求1所述的口服剂型,其中,所述至少一种不是乙烯吡咯烷酮共聚物的水溶性聚合物由羟丙基纤维素和聚乙烯吡咯烷酮的组合组成,并且进一步包括增塑剂。

12.如权利要求1所述的口服剂型,进一步包括至少一种增塑剂以及选自于由合成甜味剂、天然甜味剂、食用香料、抗氧化剂、着色剂和遮光剂组成的组的至少一种添加剂。

13.一种即时可湿性速崩薄膜剂型,由至少一种不是乙烯吡咯烷酮共聚物的水溶性聚合物、至少一种乙烯吡咯烷酮共聚物、至少一种活性剂、至少一种增塑剂、二氧化钛和任选的添加剂组成。

14.如权利要求13所述的口服剂型,其中,所述增塑剂为三乙酸甘油酯。

15.如权利要求13所述的口服剂型,其中,所述至少一种水溶性聚合物包括羟丙基纤维素。

16.如权利要求13所述的口服剂型,其中,所述至少一种水溶性聚合物由羟丙基纤维素和聚乙烯吡咯烷酮的组合组成。

17.如权利要求13所述的口服剂型,其中,所述至少一种活性剂为利扎曲坦或苯甲酸利扎曲坦。

18.一种即时可湿性速崩薄膜剂型,由羟丙基纤维素、聚乙烯吡咯烷酮、三乙酸甘油酯、乙烯吡咯烷酮-乙酸乙烯酯共聚物、二氧化钛和至少一种活性剂组成,其中乙烯吡咯烷酮-乙酸乙烯酯共聚物与二氧化钛之比为3:1至5:1。

19.如权利要求18所述的口服剂型,其中,所述至少一种活性剂为苯甲酸利扎曲坦。

20.如权利要求18所述的口服剂型,其中,添加任选的合成甜味剂,并且包括三氯蔗糖

和甘草酸单铵盐。

21.如权利要求20所述的口服剂型,其中,添加任选的抗氧化剂,并且包括丁基羟基甲苯。

不含表面活性剂或多元醇的即时可湿性口服薄膜剂型

[0001] 相关申请的交叉引用

[0002] 本申请要求2013年7月31日提交的美国临时申请No.61/860,345的权益，其通过引用并入本申请中。

技术领域

[0003] 本发明涉及用于活性剂口服给药的速崩薄膜，特别涉及由于缺少明显的粒状残渣而表现出即时可湿性和优良口感的此类薄膜。

背景技术

[0004] 吞咽片剂有困难的受试者通常更喜欢薄膜型口服剂型。然而重要的是，薄膜非常迅速地溶解或崩解且不留有砂砾状残渣。因此，希望开发出一种可实现即时可湿性和迅速崩解、同时表现出良好口感的薄膜型口服剂型。本发明涉及用于活性剂口服给药的速崩薄膜，特别涉及由于缺少明显的粒状残渣而表现出即时可湿性和优良口感的此类薄膜。

发明内容

[0005] 已经发现，不用表面活性剂且不用多元醇，即可获得在口服给药时实现即时可湿性和迅速崩解的薄膜口服剂型。具体来说，已经确定，可将至少一种不是乙烯吡咯烷酮共聚物的水溶性聚合物与一种或多种活性剂、乙烯吡咯烷酮共聚物和二氧化钛组合，以提供一种表现出良好口感且不含表面活性剂和多元醇的即时可湿性速崩薄膜剂型。

[0006] 通过加入重量比为3:1至5:1的乙烯吡咯烷酮共聚物和二氧化钛，可得到理想的强度、刚度与崩解度的组合。

[0007] 本发明还公开了通过添加食品级或药学安全的增塑剂使得期望的性能得以加强的具体实施方式。

[0008] 参考以下说明书和权利要求书，可以更好地理解各个实施方式的这些和其它特征、优点和目标。

具体实施方式

[0009] 术语“即时可湿性”及其变形一般是指薄膜剂型在受试者口服给药时迅速吸收水分并且立即软化的能力，借以防止受试者经历口中长时间的不良感觉，并且关于本发明的某些方面，是指实施方式中施加至薄膜表面的水分(即，水)在5、10或15秒内渗入薄膜的厚度(如，通常约5μm至200μm)。

[0010] 术语“速崩”及其变形一般是指薄膜剂型在一段可接受的时间之内(如，给药(即放置于受试者的口腔中)60秒之内、45秒之内、30秒之内、20秒之内或15秒之内)分解为亚微米颗粒或完全溶解的能力。

[0011] 术语“良好的口感”一般是指多种与质地和稠度有关的感知质量，在本发明公开的内容中特别是指粒性(即，薄膜可被感知的含有粒状颗粒的程度)以及口服给予薄膜的受试

者的总体主观感觉。

[0012] 可用于所公开的薄膜中的不是乙烯吡咯烷酮共聚物的水溶性聚合物包括水溶性纤维素衍生物，包括羟丙基甲基纤维素、羟乙基纤维素、羟丙基纤维素；聚乙烯吡咯烷酮(PVP)；取代的乙烯吡咯烷酮的聚合物；聚乙烯吡咯烷酮的衍生物；聚环氧乙烷、羧甲基纤维素；聚乙烯醇；天然胶，包括黄原胶、黄芪胶、瓜尔豆胶、阿拉伯树胶和阿拉伯胶；以及水溶性聚丙烯酸酯。也可以使用这些水溶性聚合物或其它水溶性聚合物的组合。取代的乙烯吡咯烷酮的实例包括N-乙烯基-3-甲基-2-吡咯烷酮、N-乙烯基-4-甲基-2-吡咯烷酮、N-乙烯基-5-甲基-2-吡咯烷酮、N-乙烯基-5,5-二甲基-2-吡咯烷酮、N-乙烯-3,3,5-三甲基-2-吡咯烷酮及其它。

[0013] 术语“活性剂”是指口服给予受试者的任何药剂，包括药学活性剂、营养学活性剂和口气清新剂。药学活性剂的实例包括血管紧张素转化酶抑制剂、抗心绞痛药、抗心律失常药、抗哮喘药、抗胆固醇血症药、镇痛剂、麻醉剂、抗惊厥药、抗抑郁药、抗糖尿病剂、止泻制剂、解毒剂、抗组胺药、抗高血压药、抗炎剂、降脂剂、抗躁狂药、止呕药、抗中风剂、抗甲状腺制剂、抗肿瘤药、抗病毒剂、痤疮药、生物碱、氨基酸制剂、镇咳药、抗尿酸血症药、抗病毒药、合成代谢制剂、全身和非全身用抗感染剂、抗赘生剂、抗帕金森剂、抗风湿剂、食欲促进剂、生物学反应修饰剂、血液修饰剂、骨代谢调节剂、心血管药、中枢神经系统兴奋剂、胆碱酯酶抑制剂、避孕药、解充血药、膳食补充剂、多巴胺受体激动剂、子宫内膜异位管理剂、酶、勃起障碍治疗剂(如，枸橼酸西地那非、他达拉非和伐地那非)、生育剂、胃肠制剂、顺势疗法药、激素、高钙血症和低钙血症管理剂、免疫调节剂、免疫抑制剂、抗偏头痛制剂(如，利扎曲坦、依立曲坦和佐米曲坦)、晕动病治疗药、肌肉松弛药、肥胖症管理剂、骨质疏松症制剂、催产药、副交感神经阻滞药、拟副交感神经阻滞药、前列腺素、精神疗法制剂、呼吸道制剂、镇静剂(如，劳拉西泮或地西泮)、戒烟助剂(如，溴隐亭或尼古丁)、交感神经阻滞剂、震颤制剂、尿道制剂、血管扩张剂、泻药、解酸剂、离子交换树脂、解热剂、食欲抑制剂、祛痰剂、抗焦虑药(如，阿普唑仑)、抗溃疡药、抗炎物质、冠状血管扩张药、脑血管扩张药、外周血管扩张药、拟精神药物(psycho-tropics)、兴奋剂、抗高血压药、血管收缩剂、抗生素、镇静剂、抗精神病药、抗肿瘤药、阻凝剂、抗血栓药、安眠药、止吐药、止呕药、抗惊厥药、神经肌肉药、高血糖和低血糖制剂、甲状腺和抗甲状腺制剂、利尿剂、抗痉挛剂、子宫松弛剂、抗肥胖药、红细胞生成药、抗哮喘药(anti-astmatics)、镇咳药、粘液溶解药、DNA和基因修饰药、及它们的组合。营养学活性剂的实例包括多种膳食补充剂、维生素、矿物质、中草药和营养物。口气清新剂包括，如荷兰薄荷油、肉桂油、胡椒薄荷油、丁香油、薄荷醇等。

[0014] 在此公开的薄膜口服剂型不含或基本上不含表面活性剂和多元醇。术语“基本上不含”表面活性剂和多元醇的意思是所述薄膜口服剂型不含有意添加的表面活性剂或多元醇，即使含有，任何不可避免的或附带的表面活性剂或多元醇也仅作为杂质存在于其它成分中，其量对与可湿性(如，接触角测角仪测量)、溶解速率或崩解速率相关的可测量特性的影响不超过10％，且对可测量稳定性无负面影响。术语“不含”表面活性剂和多元醇的意思是附带的或不可避免的表面活性剂和多元醇杂质仅以对水的接触角测量和溶解速率低于1％影响的微不足道的量存在。在某些实施方式中，表面活性剂和多元醇的存在分别被限制为低于1000ppm(w/w)、低于500ppm(w/w)、低于100ppm(w/w)、低于40ppm(w/w)或低于10ppm(w/w)。

[0015] 术语“表面活性剂”和“多元醇”旨在具有其普通含义。具体来说，术语“表面活性剂”旨在意指一种降低液体表面张力、两种液体间界面张力或液体与固体间界面张力的两性化合物。术语“多元醇”意指一种糖醇，其为氢化形式的碳水化合物，该碳水化合物含有的羰基被还原为伯羟基或仲羟基。多元醇也可根据它们的化学式区分。多元醇具有通式$H(HCHO)_{n+1}H$，而糖具有通式$H(HCHO)_nHCO$。所公开的薄膜避开或排除的多元醇或糖醇的常见实例包括乙二醇、丙三醇、赤藻糖醇、苏糖醇、阿拉伯糖醇、木糖醇、核糖醇、甘露醇、山梨糖醇、半乳糖醇、岩藻糖醇、艾杜糖醇、肌醇、庚七醇、异麦芽酮糖醇、麦芽糖醇、乳糖醇、麦芽三糖醇和麦芽四糖醇。

[0016] 乙烯吡咯烷酮共聚物通常可为乙烯吡咯烷酮的任何共聚物。可用于此处所述薄膜中的市售乙烯吡咯烷酮-乙酸乙烯酯共聚物(共聚维酮)包括Kollidon®VA 64共聚维酮、Kollidon® 25共聚维酮、Kollidon®SR共聚维酮和Plasdone®S-630共聚维酮。共聚维酮的加入提高了薄膜的刚度，如提高了弯曲模量、抗张强度和硬度。其它可使用的乙烯吡咯烷酮共聚物的实例包括聚(1-乙烯吡咯烷酮-共-2-甲基丙烯酸二甲氨基乙酯)、聚(1-乙烯吡咯烷酮-共-苯乙烯)、聚(1-乙烯吡咯烷酮)-接枝-(1-三十烯)、聚(乙烯吡咯烷酮-共-甲基丙烯酸甲酯)、聚(乙烯吡咯烷酮-共-N,N’-二甲基丙烯酰胺)和聚(乙烯吡咯烷酮-共-马来酸酯)。与不含乙烯吡咯烷酮共聚物但在其他方面相同的薄膜相比，可以有效于提高薄膜的刚度或弹性模量(杨氏模量)的量添加乙烯吡咯烷酮共聚物。可通过向薄膜施加测量力矩(moment)并测定所施加力矩除以由此引起的薄膜曲率之商来确定弯曲刚度。乙烯吡咯烷酮共聚物的适宜量为薄膜重量(或质量)的0.1％至25％，如0.2％至20％、0.5％至20％、1％至15％、2％至15％或5％至15％。

[0017] 通过以薄膜中乙烯吡咯烷酮共聚物与二氧化钛的重量(或质量)比为3:1至5:1的量添加二氧化钛，加入的乙烯吡咯烷酮共聚物可有利地提高刚度而不会对可湿性、崩解速率或口感产生不利影响。例如，钛的适宜用量为约0.02％至约8％，如0.04％至约7％、0.1％至约7％、0.2％至5％、0.4％至5％或1％至5％。

[0018] 在乙烯吡咯烷酮共聚物和二氧化钛的公开范围内，能够得到改善的刚度或更高的弹性模量之间的有利平衡或组合，同时获得速崩和良好口感。

[0019] 二氧化钛可以约占薄膜重量的0.05％至5％、0.1％至3％或0.5至2％的量进行添加。二氧化钛在所公开的薄膜中充当崩解剂，还充当改善口感的质地修饰剂、以及遮光剂或着色剂。此量可有效提高薄膜在水性介质中的溶解速率。共聚维酮的添加量可以为二氧化钛重量的3至5倍。与另外不含二氧化钛的同样组合物相比，二氧化钛带来了崩解速率的提高。崩解速率可以提高至少5％、至少10％、至少20％、至少50％或至少75％。

[0020] 在某些实施方式中，所公开的薄膜可包含增塑剂。术语“增塑剂”是指降低薄膜形成聚合物(如，薄膜中的一种水溶性聚合物或多种水溶性聚合物)的玻璃化转变温度的组分。增塑剂提高薄膜的柔韧性、增强薄膜的弹性并且降低薄膜的脆性。可用于所公开的薄膜口服剂型中的增塑剂的实例包括三乙酸甘油酯、柠檬酸三乙酯、柠檬酸三丁酯、乙酰柠檬酸三丁酯、乙酰柠檬酸三乙酯、柠檬酸三辛酯、乙酰柠檬酸三辛酯、柠檬酸三己酯、葵二酸二丁酯等。增塑剂可以高达薄膜口服剂型总质量25％的量进行添加，如0.5％至25％、1％至20％、2％至15％或5％至10％。

[0021] 可加入到本文所公开的薄膜口服剂型中的药物量通常为该薄膜总重量的0.01％

至50％，如薄膜总重量的1％至40％、2％至30％或5％至20％。

[0022] 可根据需要或意愿，以常规用量添加除表面活性剂和多元醇之外的常规薄膜口服剂型添加剂。这些添加剂的实例包括人造甜味剂(如三氯蔗糖、阿司帕坦、乙酰磺胺酸钾和甘草酸单铵盐)、天然甜味剂(如蔗糖和果糖)；食用香料，如薄荷醇、各种果味香料(如樱桃、葡萄、桔子等)或各种薄荷香料(如荷兰薄荷、胡椒薄荷等)；着色剂；遮光剂(如二氧化钛)；以及抗氧化剂(如丁基羟基甲苯)。也可以不对薄膜特性或薄膜稳定性产生不利影响的量掺入其它添加剂。具体来说，任何此类添加剂均不应导致不期望的薄膜软化和由此带来的尺寸稳定性损失、活性成分降解或引起不良美感(如薄膜褪色或薄膜组分的明显分离和聚集)。

[0023] 在一种实施方式中，形成本发明所述薄膜的方法包括以一般任意顺序将多种成分组合，使用水、水和与水混溶性溶剂的组合，所述水混溶性溶剂例如单独的低级醇(如，乙醇)或有机溶剂或其混合物。例如，增塑剂和添加剂(如，甜味剂、着色剂、食用香料和遮光剂)可溶解或分散于足量的溶剂中，向其中加入水溶性聚合物，搅拌以形成均相溶液或悬浮液。在添加水溶性聚合物的过程中，可根据需要采用加热、抽真空和搅拌直至得到均相溶液或均质悬浮液。随后加入活性成分，将所述溶液或悬浮液浇铸或涂覆于载体材料上，干燥以形成薄膜。适宜的载体材料的实例包括非硅化聚对苯二甲酸乙二醇酯薄膜、非硅化牛皮纸、聚乙烯浸渍牛皮纸和非硅化聚乙烯薄膜。一般可使用任意的常规涂覆设备(包括辊式刮刀涂布设备、挤压模具涂布设备、逆转辊涂布设备或迈耶辊涂布设备)将液态薄膜组合物涂覆于载体材料上。

[0024] 经干燥，得到的固态薄膜通常可具有5至200μm的厚度，如10至200μm、20至150μm或20至100μm。所述薄膜可切割为具有合适尺寸的单片，以便于施用目标剂量的活性剂。

[0025] 实施例1

[0026] 采用上述工艺和如下表1所列组成制备利扎曲坦薄膜口服剂型。

[0027] 表1

[0028]

组分	作用	每片干薄膜的量[mg]		每片干薄膜的量[%]
		2.58 cm^2	5.16 cm^2	
羟甲基乙基纤维素	薄膜形成聚合物	6.2 mg	12.400 mg	15.39
共聚维酮	薄膜形成聚合物	2.0 mg	4.0 mg	4.96
羟丙基甲基纤维素	薄膜形成聚合物	20.203 mg	40.405 mg	50.14
丁基羟基甲苯	抗氧化剂	0.004 mg	0.008 mg	0.010
甘草酸单铵盐	甜味剂	0.222 mg	0.443 mg	0.550
三氯蔗糖	甜味剂	0.439 mg	0.878 mg	1.090
二氧化钛	遮光剂/质地修饰剂	0.661 mg	1.322 mg	1.640
薄荷醇	香料	0.439 mg	0.878 mg	1.090
癸二酸二丁酯	增塑剂	2.861 mg	5.722 mg	7.100
苯甲酸利扎曲坦	活性剂	7.265 mg	14.530 mg	18.030
总计		40.294 mg	80.586 mg	100.000

[0029] 得到的利扎曲坦薄膜在25℃、相对湿度65％下至少稳定18个月，在40℃、相对湿度75％下至少稳定6个月。在主观测试中，受试者被要求用少量水润湿其口腔，将水咽下，然后在舌头上放置所述薄膜，并闭上嘴，主观测试表明薄膜具有良好口感(即不会使人不愉快)且在短时间内完全溶解，通常在不到15分钟、不到10分钟、不到5分钟、不到2分钟或甚至不到1分钟。受试者被告知不要咀嚼或吞咽薄膜，但允许将其溶解于可用的唾液中。将薄膜完全消失所用时间记录为崩解所用时间。

[0030] 实施例2

[0031] 采用上述工艺和如下表2所列组成制备帕洛诺司琼(一种5-羟色胺拮抗剂，用于预防或治疗化疗引起的恶心和呕吐)薄膜口服剂型。

[0032] 表2

[0033]

组分和质量标准（及等级，如果适用）	作用	每片干薄膜的量［mg］	每片干薄膜的量［%］
帕洛诺司琼	活性剂	2.50	4.77
L-半胱氨酸	抗氧化剂	0.34	0.65
三氯蔗糖	甜味剂	0.52	0.99
羟丙基纤维素	薄膜形成聚合物	23.10	44.12
共聚维酮	薄膜形成聚合物	2.5 mg	4.77
羟丙基甲基纤维素	薄膜形成聚合物	15.02	28.69
二氧化钛	遮光剂/质地修饰剂	0.52	0.99
聚乙烯吡咯烷酮	薄膜形成聚合物	6.72	12.83
无水枸橼酸	酸化剂	1.14	2.18
总计		52.36 mg	100.0

[0034] 实施例3

[0035] 采用上述工艺和如下表3所列组成制备阿普唑仑薄膜口服剂型。

[0036] 表3

[0037]

组分和质量标准（及等级，如果适用）	作用	每片干薄膜的量［mg］	每片干薄膜的量［%］
阿普唑仑	活性剂	2.00	4.68
乙酰磺胺酸钾	甜味剂	0.39	0.91
共聚维酮	薄膜形成聚合物	8.75	20.51

[0038]

羟丙基纤维素	薄膜形成聚合物	27.62	64.74
柠檬酸三乙酯	增塑剂	1.58	3.70
二氧化钛	遮光剂/结构修饰剂	1.75	4.10
薄荷醇	香料	0.55	1.29
黄#6	着色剂	0.02	0.05
总计		42.66 mg	100.0

[0039] 上述说明仅被认为是优选的实施方式。本领域技术人员以及制造或使用所述实施方式的人员可想到这些实施方式的变形。因此，应当理解的是，上述实施方式仅为示例性的，并不意在限制本发明的范围，本发明的范围由以下根据专利法原则(包括等同原则)所解释的权利要求书来确定。