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(54) Title: STABILIZED POLYETHYLENE OXIDE COMPOSITIONS

(57) Abstract: The present invention is directed to stabilized compositions containing polyethylene oxide and calcium silicate and orally ingestible dosage forms prepared with these compositions. These compositions are less subject to oxidative degradation than compositions without calcium silicate.

STABILIZED POLYETHYLENE OXIDE COMPOSITIONS

1. Field of the Invention

5 The present invention relates to stabilized polyethylene oxide compositions, which are used in the preparation of orally-ingestible dosage forms.

2. Background of the Invention

10 Polyethylene oxide (PEO) is used as a release rate controlling polymer and binder in orally-ingestible dosage forms. Owing to its ability to swell upon contact with water, it has been used especially advantageously in osmotic pump dosage forms. While PEO has been used successfully in multiple dosage forms, it is susceptible to degradation via oxidation. When this occurs, the polymer chains are fragmented, and the physical properties, including the reduction of aqueous solution viscosity, of the polymer are
15 affected. This unfortunately necessitates that the shelf life of PEO be set at relatively short time intervals, for example 6 months, to maintain desired properties.

Accordingly, there is a need for compositions comprising PEO that have longer shelf lives to avoid costly disposal of materials upon shelf life expiration. The present
20 invention addresses this need.

3. Summary of the Invention

It has been surprisingly found that PEO compositions comprising calcium silicate have significantly greater stability than PEO alone. Use of stabilized PEO compositions in
25 orally-ingestible dosage forms results in the maintenance of desired drug release properties for longer periods of storage time when compared to compositions without calcium silicate.

In one aspect of the invention, there are provided blends of PEO and calcium silicate.
30 The preferably dry blend of PEO and calcium silicate may also contain other additives

used to prepare orally-ingestible dosage forms such as binders, osmogens, glidants, disintegrants, lubricants, pigments, other fillers and supplementary antioxidants.

In another aspect of the invention, there are provided orally-ingestible dosage forms
5 comprising the blend of PEO and calcium silicate and a pharmaceutically active ingredient, nutritional supplement or the like.

In the preferred aspects of this invention, the storage stability of compositions comprising PEO and calcium silicate is significantly increased versus similar compositions without
10 calcium silicate.

4. Detailed Description of the Invention

For purposes of the present invention, the following terms are given further clarification as to their meanings:

15

“dry” or “dry blend” shall be understood to refer to or describe PEO containing powders which are relatively dry to the touch rather than powders which are essentially without liquid content;

20

“ambient temperature” shall be understood to mean temperatures generally in the range of from about 20 °C (68 °F) to about 30 °C (86 °F) +/-3°C;

25

“orally-ingestible dosage form” shall be understood to mean any pharmaceutically or nutritionally acceptable dosage form, e.g. tablet, capsule, caplet, etc. or any other veterinary or confectionary product intended to be swallowed.

The inventive dry blends comprise PEO, calcium silicate and optionally one or more binders, osmogens, glidants, disintegrants, lubricants, pigments, other fillers and supplementary antioxidants.

30

The polyethylene oxide (PEO) of this invention is prepared by polymerization of ethylene oxide. Ethylene oxide may be polymerized to varying extents and thus many grades are commercially available that vary in molecular weight. Exemplary molecular weight grades range from about 100,000 to 8,000,000 grams/mole with 4,000,000 to 8,000,000
5 grams/mole being preferred in some aspects. Some preferred grades of PEO are sold under the POLYOX™ brand. It is known that PEO is susceptible to oxidative degradation at ambient storage conditions and that the tendency for PEO to degrade increases with polymer molecular weight. However, in certain embodiments, high molecular weight grades are preferred.

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In preferred aspects of the invention, calcium silicate functions as a water sequestrant and indirectly as an antioxidant. While not wishing to be bound by any particular theory, it is believed that, owing to its high surface area, calcium silicate can absorb and sequester water when it is formulated in a dry blend with PEO. Without otherwise higher
15 concentrations of adsorbed water on the PEO surface, PEO is less prone to undergo a phase change that would make it more susceptible to oxidation. Calcium silicate is not known as an antioxidant that can react directly with active forms of oxygen thereby preventing reaction of active oxygen with other materials. Therefore, it is surprising that adding calcium silicate to PEO compositions results in a reduced amount of oxidative
20 degradation by the aforementioned mechanism of sequestering water, which could otherwise facilitate oxidative degradation.

Preferred grades of calcium silicate have a surface area of 50 m²/gram or greater. More preferred grades of calcium silicate have a surface area of 120 m²/gram or greater. The
25 most preferred grades of calcium silicate have a surface area of 250 m²/gram or greater.

In most embodiments, the amount of calcium silicate included in the dry blends is an amount which is sufficient to reduce the oxidative degradation rate of PEO. This amount is also defined as a shelf-life prolonging amount. The extent of oxidative degradation can
30 be determined indirectly by measuring the viscosity of aqueous solutions containing PEO. Aqueous solution viscosity decreases with decreasing molecular weight; therefore,

if oxidative degradation occurs over time, the aqueous solution viscosity of the PEO will decrease. Generally, the amount of calcium silicate included in PEO compositions sufficient to reduce oxidative degradation, as measured indirectly by aqueous solution viscosity, is from about 0.1 to about 5% with respect to the amount of PEO in the composition. In some preferred embodiments, the amount ranges from about 0.25 to about 3% and, more preferably, ranges from about 0.5 to about 2% with respect to the amount of PEO in the composition. It should be appreciated that in some embodiments the amount of calcium silicate included is preferably as close as reasonably possible to the minimum amount required to enhance stability while still preserving the function of PEO as a release-rate controlling polymer or binder.

Other materials used in the production of tablets may also be included in the dry blend comprising PEO and calcium silicate. For example, binders such as cellulosic polymers including microcrystalline cellulose (MCC), pregelantized starches, polyvinyl pyrrolidone (PVP) and PVP copolymers may be included. Amounts will range from about 1 to 20%wt with respect to the amount of PEO in the composition. Osmogens, which when dissolved in water create a desirable osmotic pressure gradient between an osmotic dosage form and its surrounding medium, can also be included in the dry blend. Sodium chloride is a preferred osmogen. Amounts will range from about 10 to 50%wt with respect to the amount of PEO in the composition. A glidant may also be included to aid the flow of the dry blend through a tablet press. Talc and fumed silica are preferred glidants. It may also be desirable to add disintegrants to the dry blend. Native, partially-pregelatinized starch (such as Starch 1500) and modified starches are preferred disintegrants. Lubricants, useful to ensure that tablet presses run efficiently may also be included. Preferred lubricants are magnesium stearate and stearic acid. The amount of glidant, disintegrants, lubricants will range from about 0.25 to about 30% with respect to the amount of PEO in the composition. Fillers used commonly to produce pharmaceutical or dietary supplement tablets may also be included in amounts of from about 10 to about 50% with respect to the amount of PEO in the composition. Preferred fillers are saccharides such as lactose and mannitol and inorganic materials such as calcium phosphate. Supplementary antioxidants in amounts of from about 100 ppm to about 5%

with respect to the amount of PEO in composition may be added to extend the stability of dry blends comprising PEO and calcium silicate even further. Preferred supplementary antioxidants include butylated hydroxytoluene (BHT) and vitamin E.

5 Pigments are also optionally added and may be any food or pharmaceutically approved colors, opacifiers or dyes. For example, the pigments may be aluminum lakes, iron oxides, titanium dioxide, natural colors or pearlescent pigments (e.g. mica based pigments sold under the Candurin trade name). Examples of such pigments are listed in US 4543570, which is incorporated herein by reference. It will be understood that the amount of pigment employed in the dry blends of the invention is an amount which is sufficient or effective to impart the required appearance of the dosage form. Generally, amounts will range from about 0.25 to about 0.30% with respect to the amount of PEO in composition.

15 The PEO blends are prepared using standard dry blending or mixing techniques known to those of ordinary skill. For example, the ingredients are individually weighed, added to a suitable apparatus and blended for a sufficient time until a substantially uniform mixture of the ingredients is obtained. The time required to achieve such substantial uniformity will, of course, depend upon the batch size and apparatus used. A preblend may also be utilized, wherein the PEO and calcium silicate are first combined. The preblend may be prepared in bulk and used as needed to reduce the mixing time required for smaller batches that may contain other optional ingredients.

As mentioned above, batch sizes will vary upon need. A non-limiting list of suitable blending devices include diffusion blenders such as a cross flow, V-blender, or hub blenders, available from Patterson-Kelly, or convection blenders, such as Ruberg/Azo, Readco/CVM or Servolift blenders may be used. Blending of the aforementioned formulations may also be achieved by processing ingredients into a granular form to produce a non-dusting granular composition by methods including, but not limited to, wet massing, fluid bed granulation, spray granulation and dry compaction, roller compaction or slugging. Other manners of blending will be apparent to those of ordinary skill.

Regardless of the method employed or the specific materials included in the compositions, the dry blends of the present invention will include a PEO and calcium silicate. Preferably, the amount of calcium silicate blended with the PEO is an amount which is sufficient to reduce the viscosity loss of a 1% PEO solution after 6 months of storage at either a) 30° C, 65% RH (relative humidity) or b) 40° C, 75% RH by at least 10% when compared to a 1% PEO solution which does not contain calcium silicate.

The PEO-calcium silicate blend can be used in the preparation of any pharmaceutically-acceptable dosage form for which PEO is included. Formation of the dosage forms will be apparent to those of ordinary skill and no undue experimentation is required. For example, the PEO blend can be blended with any orally acceptable active pharmaceutical ingredient and desired auxiliary excipients and directly compressed into a solid tablet. The PEO blend can also be used in the formation of PEO-based tamper resistant tablets containing an opioid such as hydrocodone, oxycodone, oxymorphone, etc. See, for example, US Patent No. 8,323,889, the contents of which are incorporated herein by reference.

5. Examples

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention. All ingredients are expressed as being by weight %.

Example 1

A preferred formulation for an inventive composition with enhanced stability is the following:

<i>Component</i>	<i>Parts by Weight</i>
POLYOX Coagulant Grade (PEO MW = 5,000,000 g/mol)	99.0
Calcium silicate	<div style="border-top: 1px solid black; display: inline-block; width: 100px; margin: 0 auto;">1.0</div>
	100.0

The dry blend was prepared by adding the POLYOX Coagulant grade and calcium silicate into a laboratory blender and blending for 5 minutes until a homogenous mixture was produced. A small portion of the dry blend was taken to prepare a 1% solution in purified water. The viscosity of the 1% aqueous solution of the dry blend was
5 determined to be 6,940 centipoise (cP) using a Brookfield viscometer (spindle #2 operating at 2 rpm after 5 minutes). The dry blend was then stored for a period of 6 months at 40°C and 75% relative humidity. After this time, another small portion of the dry blend was taken to prepare a 1% aqueous solution. The viscosity of the 1% aqueous
10 solution of the dry blend was determined to be 2,400 cP using the same analytical procedure (a 65% reduction).

Comparative Example A

The same lot of POLYOX Coagulant grade was used in this example, but no calcium
15 silicate was added to it, and no blending took place. The viscosity of a 1% aqueous solution of this POLYOX Coagulant grade, determined as described in Example 1, was 7,420 cP. After storage of the POLYOX Coagulant Grade at 40°C and 75% relative humidity, the viscosity of a 1% aqueous solution decreased to 540 cP (a 93% reduction).

Examples 2-3

Dry blends of POLYOX Coagulant grade and calcium silicate were prepared as described
20 in Example 1 but with varying levels of calcium silicate. The viscosity of 1% aqueous solutions was measured immediately after blending the components and again after 6 months storage at 40°C and 75% relative humidity as described in Example 1. The
25 formulations and viscosity results are shown in the following table.

Example	2	3
<i>Component</i>	%	%
POLYOX Coagulant grade	99.5	99.75
Calcium silicate	0.5	0.25
Totals	100	100
<i>Viscosity of 1% Aqueous Solutions (cP)</i>		
Immediately after blending	6,860	7,261
After storage for 6 months at 40°C and 75% relative humidity	2,550	1,430
%Viscosity reduction	63	80

Examples 1-3 all showed significantly less viscosity loss than the POLYOX Coagulant grade (without added calcium silicate) after storage at 40°C and 75% relative humidity.

- 5 Even though the 40°C storage condition is well above the recommended maximum storage temperature of 30°C for POLYOX products, it was selected to accelerate the degradation process and differentiate the impact of varying levels of calcium silicate at shorter time intervals than might have been possible at lower temperatures. However, the following examples show that the inclusion of calcium silicate in dry blends comprising
- 10 PEO can slow the degradation process at 30°C as well.

Examples 4-5

Dry blends comprising POLYOX Coagulant grade and calcium silicate were prepared as described in Example 1 with the compositions shown in the following table. The

15 viscosity of 1% aqueous solutions was measured as described in Example 1 immediately after blending the components and again after 9 months storage at 30°C and 65% relative humidity. Comparative Example B was again pure POLYOX Coagulant grade. Comparative Example C was analogous to Example 5 but without calcium silicate.

20

Example	4	5	B	C
<i>Component</i>	%	%	%	%
POLYOX Coagulant grade	99.0	74.25	100	75
Calcium silicate	1.0	1.00		
Sodium chloride		24.255		24.5
Red iron oxide		0.495		0.5
Totals	100	100	100	100
Viscosity of 1% Aqueous Solutions (cP)				
Immediately after blending	5,885	5,240	5,830	5,440
After storage for 9 months at 30°C and 65% relative humidity	3,465	3,490	2,100	2,030
%Viscosity reduction	41	33	64	63

Examples 6-7

These examples were explored to show that the benefits of calcium silicate inclusion can be extended to PEO grades of varying molecular weights. Dry blends comprising either POLYOX 301 or POLYOX 303 grade and calcium silicate were prepared as described in Example 1 with the compositions shown in the following table. The viscosity of 1% aqueous solutions was measured as described in Example 1 immediately after blending the components and again after 6 months storage at 30°C and 65% relative humidity. Comparative Example D and E correspond to pure POLYOX 301 and 303, respectively, and were used without blending.

Example	6	7	D	E
<i>Component</i>	%	%	%	%
POLYOX 301 (PEO MW = 4,000,000 g/mol)	99.0		100	100
POLYOX 303 (PEO MW = 7,000,000 g/mol)		99.0		
Calcium silicate	1.0	1.0		
Totals	100	100	100	100
Viscosity of 1% Aqueous Solutions (cP)				
Immediately after blending	4,180	7,640	4,180	7,740
After storage for 6 months at 30°C and 65% relative humidity	2,360	4,040	1,800	2,120
%Viscosity reduction	44	47	57	73

Again, the rate of oxidative degradation, as measured indirectly by a decrease in the viscosity of a 1% aqueous solution, decreased when calcium silicate was included in the compositions.

5

SUMMARY TABLE

Ex No.	Composition	Storage Conditions	Storage Duration (months)	% Viscosity Loss	Absolute Charge in Viscosity Loss vs. Control (%)
A	100% Coagulant PEO	40 C° 75% RH	6	93	
1	99% Coagulant PEO- 1% calcium silicate	40 C° 75% RH	6	65	-28
2	99.5% Coagulant PEO- 0.5% calcium silicate	40 C° 75% RH	6	63	-30
3	99.75% Coagulant PEO- 0.25% calcium silicate	40 C° 75% RH	6	80	-13
B	100% Coagulant PEO	30 C° 65% RH	9	64	
4	99% Coagulant PEO- 1% calcium silicate	30 C° 65% RH	9	41	-23
C	75% Coagulant PEO 24.5% sodium chloride 0.5% red iron oxide	30 C° 65% RH	9	63	
5	74.25% Coagulant PEO 24.255% sodium chloride 0.495% red iron oxide 1% calcium silicate	30 C° 65% RH	9	33	-30
D	100% PEO 301 grade	30 C° 65% RH	6	57	
6	99% PEO 301- 1% calcium silicate	30 C° 65% RH	6	44	-13
E	100% PEO 303 grade	30 C° 65% RH	6	73	
7	99% PEO 303- 1% calcium silicate	30 C° 65% RH	6	47	-26

10

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention. It is intended to claim all such changes and modifications that fall within the true scope of the invention.

5

WHAT IS CLAIMED IS:

1. A blend comprising polyethylene oxide and calcium silicate.
- 5 2. The composition of claim 1 wherein the molecular weight of the polyethylene oxide is from 100,000 to 8,000,000 grams/mole.
3. The composition of claim 2 wherein the molecular weight of the polyethylene oxide is from 4,000,000 to 8,000,000 grams/mole.
- 10 4. The composition of claim 1 wherein the amount of said calcium silicate is in the range of 0.1 to 5% by weight with respect to the amount polyethylene oxide.
5. The composition of claim 4 wherein the amount of said calcium silicate is in the
15 range of 0.25 to 3% by weight with respect to the amount polyethylene oxide.
6. The composition of claim 4 wherein the amount of said calcium silicate is in the range of 0.5 to 2% by weight with respect to the amount polyethylene oxide.
- 20 7. The composition of claim 1 further comprising one or more of a binder, osmogen, glidant, disintegrant, lubricant, pigment, other filler and supplementary antioxidant.
8. An orally ingestible dosage form prepared with the composition of claim 1.
- 25 9. A polyethylene oxide-containing composition having improved shelf life when compared to polyethylene alone of the same molecular weight, comprising a blend of polyethylene oxide and a shelf-life prolonging amount of calcium silicate.

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10. The polyethylene oxide-containing composition of claim 9, wherein the amount of calcium silicate is an amount sufficient to reduce the viscosity loss of a 1% solution of polyethylene oxide by at least about 10% after 6 months of storage at either a) 30° C, 65% RH (relative humidity) or b) 40° C, 75% RH when compared to a 1% PEO solution
- 5 which does not contain calcium silicate.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/26643

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 9/16, 9/20, 9/22 (2016.01) CPC - A61K 9/16, 9/20 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) Classifications: A61K 9/16, 9/20, 9/22 (2016.01) CPC Classifications: A61K 9/16, 9/20 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; IP.com; EBSCO Discovery; polyethylene oxide, PEO, stabilizer, calcium silicate, Cal-Sil, shelf-life, high molecular weight, PEO, PEG, oxidative degradation, dry blend, oral		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2011/0250279 A1 (YOO, M-H et al.) 13 October 2011; paragraphs [0025]-[0026], claims 1, 4, 9	1 --- 1-10
Y	WO 2005/105036 A1 (NATCO PHARMA LIMITED) 10 November 2005; abstract; page 6, lines 28-30; page 8, lines 4-16; page 9, lines 14-15; page 11, lines 24-29; page 12, lines 1-9; page 12, lines 2-9	1-10
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
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Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774