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(71) Applicant: **EXXONMOBIL CHEMICAL PATENTS INC.** [US/US]; 5200 Bayway Drive, Baytown, TX 77520-2149 (US).

(72) Inventors: **LI, Lin**; 925 West Shangzhong Road, Shanghai 200237 (CN). **WONG, Waikeng**; Clos Stijn Streuvels No.2, Wezembeek Oppem (BE). **LU, Xuefeng**; 903 Room, 701 Shi Guang Road, Yangpu District, Shanghai 400438 (CN). **LU, Wenchang**; C8, 1800 Jin Ke Road, Pudong District, Shanghai 200129 (CN).

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(54) Title: AN ELASTOMERIC COMPOSITION, METHOD OF MAKING THE COMPOSITION, AND ARTICLES COMPRISING THE COMPOSITION

(57) Abstract: The present invention relates to a composition comprising rubber components, a cure package and fillers. The rubber component comprises 40 to 70 phr of a halogenated polymer and 30 to 60 phr of a polyisoprene. The halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the halogenated polymer. The cure package comprises a phenolic resin, and/or a metal oxide, and/or sulfur or sulfur compound. The elastomeric composition is useful in preparation of a stopper or seal for a parenteral drug packaging, in particular a soft parenteral drug packaging.



**AN ELASTOMERIC COMPOSITION, METHOD OF MAKING THE  
COMPOSITION, AND ARTICLES COMPRISING THE COMPOSITION**

**FIELD OF THE INVENTION**

5    **[0001]**     The present invention is directed to elastomeric compositions and pharmaceutical articles made therefrom. In particular, the disclosed compositions are compounded for reduced compression set.

**BACKGROUND OF THE INVENTION**

10   **[0002]**     Filled and vulcanized elastomers are widely adopted for pharmaceutical stopper and seal applications. Elastomers have the following desirable properties: sealing and re-sealing performance; ability to be penetrated by needles without resulting in significant fragmentation; and can be made into stoppers or seals which retain their physical dimensions upon high temperature sterilization. Other semi-crystalline materials, such as plastics and thermoplastic elastomers, are not able to match the elasticity, needle penetrability and  
15   dimension stability performance of elastomers. The most widely adopted elastomers for parenteral drug packaging today are halobutyl polymers due to their high gas and moisture barrier as well as low level of additives and impurities. The transition to elastomers or elastomeric compositions used for the pharmaceutical applications has been driven by many factors, including the need for high cleanliness stoppers that are compatible with modern  
20   sensitive drugs, the use of high purity ingredients to minimize any chemical species that migrate out of the stopper and interact with medicine (drug compatibility/turbidity), use of low amounts of clean curatives to assure drug stability/compatibility, a tight control on visible and non-visible particle contamination, and the need for low extractables and/or leachables.

25   **[0003]**     U.S. Patent Application Publication No. 2013/0072605 A1 discloses elastomer polymers and compounded elastomers having a reduced amount of leachables. The compound comprises a polymer and 50 to 100 phr of filler. The polymer is prepared by reacting a mixture of i) a C<sub>4</sub> to C<sub>7</sub> isomonoolefin monomer, ii) a styrene based monomer, and optionally iii) a C<sub>4</sub> to C<sub>14</sub> multiolefin monomer wherein the polymer contains 5 to 15 wt% of  
30   styrene derived units. At least 5% of the filler is precipitated silica. In one aspect of the disclosed article, the elastomeric pharmaceutical articles are vial stoppers or vial seals.

**[0004]**     Soft parenteral drug packaging, such as soft infusion bags, has been widely used in the recent years. For example, in China, the ratio between glass bottle, plastic bottle, and

soft packaging infusion bag has shifted from about 7:2:1 to about 1:1:1 in less than ten years. One type of stopper or seals commonly used for a soft parenteral drug packaging is made of an elastomer or an elastomeric composition fitted directly to a connector tubing of the soft packaging. Another type of stopper that is becoming widely used for soft parenteral drug packaging comprises an inner body made of an elastomer or an elastomeric composition and an outer cover containing the inner body. The outer cover can be made of a non-elastomeric polymer, such as polyolefin. By doing this, the stopper may prevent the inner body from being directly contacted with the drug in a soft packaging.

[0005] Including the above discussed properties, it is preferable that the elastomer or elastomeric composition for making such an inner body or a stopper fitted to the connector tubing have a low compression set value. As a packaging seal is manufactured with certain pressure, the inner body or stopper fitted within the connector tubing with a poor compression set can result in leakage of drug when the packaging is placed upside down during use. This leakage can occur particularly when the infusion packaging is stored for a period prior to use. In many cases, stoppers made of 100% halobutyl polymer based compositions developed for glass bottle infusion fluid do not have the low compression set performance required for this particular use.

[0006] Therefore, there is a need for an elastomeric composition that can provide balanced air impermeability, cleanliness, aging properties and mechanical properties, including a reduced compression set, and a need for a method of making such composition. There is also a need for a pharmaceutical article that can provide a balance of desirable air impermeability property, cleanliness, aging property, and mechanical properties including reduced compression set.

## **SUMMARY OF THE INVENTION**

[0007] The present disclosure is directed to an elastomeric composition having a balance of desirable properties, such as air impermeability property, cleanliness, and mechanical strength including a reduced compression set.

[0008] Disclosed herein is an elastomeric composition. The composition comprises: (i) a rubber component comprising 40 to 70 phr of a halogenated polymer and 60 to 30 phr of polyisoprene by weight of the polymer component; (ii) 50 to 100 phr of a filler; and (iii) 0.1 to 10 phr of a cure package, wherein the halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units

by weight of the halogenated polymer; and wherein the cure package comprises a phenolic resin.

[0009] In another aspect of the present disclosure, the elastomeric composition comprises a chlorinated or brominated copolymer.

5 [0010] In another aspect of the present disclosure, the elastomeric composition comprises a curing package that comprises 0.5 to 8 phr of a phenolic resin, and/or 0.1 to 2 phr of sulfur or a sulfur compound, and/or 0.1 to 5 phr of a metal oxide.

[0011] Also disclosed is a method of making an composition, comprising the steps of: (a) forming a blend of (i) a rubber component comprising 40 to 70 phr of a halogenated polymer and 60 to 30 phr of a polyisoprene by weight of the rubber component, and (ii) 10 to 100 phr  
10 of a filler; and (b) adding to the blend 0.5 to 10 phr of a cure package comprising a phenolic resin; wherein the halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the halogenated polymer.

15 [0012] Also disclosed is an article that comprises an elastomeric composition, the composition comprises: (i) a rubber component comprising 40 to 70 phr of a halogenated polymer and 60 to 30 phr of polyisoprene by weight of the polymer component; (ii) 50 to 100 phr of a filler; and (iii) 0.1 to 10 phr of a cure package comprising a phenolic resin, wherein the halogenated polymer comprises 70 to 99.5 wt% of a C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of a C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the polymer.  
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[0013] In one aspect of the disclosed article, the elastomeric pharmaceutical articles are soft packaging stoppers or seals comprising an inner body made of the elastomeric composition of the present disclosure and an outer cover containing the inner body. In another aspect, the elastomeric stoppers are fitted directly into the connector tubing of soft  
25 packaging bags and separate from the infusion fluid by a plastic membrane.

#### **DETAILED DESCRIPTION OF THE INVENTION**

[0014] Applicants have determined by compounding different rubber components at certain proportions and curing with a particular cure package, the resulting composition may have balanced air impermeability, aging properties, and mechanical properties including an  
30 improved compression set performance. Such compositions are particularly suitable for pharmaceutical stopper and seal applications. In addition, as the amount of curing agent is used in a limited percentage, the resulting elastomeric composition can enable pharmaceutical

product manufacturers to obtain stoppers that exhibit lower than conventional levels of potential extractables.

[0015] Various specific embodiments, versions and examples of the invention will now be described, including preferred embodiments and definitions that are adopted herein for purposes of understanding the claimed invention.

[0016] "Polymer" may be used to refer to homopolymers, copolymers, interpolymers, terpolymers, etc. "Copolymer" may refer to a polymer comprising at least two monomers, optionally with other monomers. When a polymer is referred to as comprising a monomer, the monomer is present in the polymer in the polymerized form of the monomer or in the derivative form of the monomer. However, for ease of reference, the phrase comprising the (respective) monomer or the like is used as shorthand. Likewise, when catalyst components are described as comprising neutral stable forms of the components, it is well understood by one skilled in the art, that the ionic form of the component is the form that reacts with the monomers to produce polymers.

[0017] Rubber refers to any polymer or composition of polymers consistent with the ASTM D1566 definition: "a material that is outer coverable of recovering from large deformations, and can be, or already is, modified to a state in which it is essentially insoluble (but can swell) in boiling solvent . . . ". Elastomer is a term that may be used interchangeably with the term rubber.

[0018] Elastomeric composition refers to any composition comprising at least one elastomer as defined above.

[0019] A vulcanized rubber compound by ASTM D1566 definition refers to "a crosslinked elastic material compounded from an elastomer, susceptible to large deformations by a small force outer coverable of rapid, forceful recovery to approximately its original dimensions and shape upon removal of the deforming force." A cured elastomeric composition refers to any elastomeric composition that has undergone a curing process and/or comprises or is produced using an effective amount of a curative or cure package, and is a term used interchangeably with the term vulcanized rubber compound.

[0020] The term "phr" is parts per hundred rubber component or "parts", and is a measure common in the art wherein components of a composition are measured relative to a total of all of the rubber components. The total phr or parts for all rubber components, whether one, two, three, or more different rubber components present in a given recipe is always defined as 100 phr. All other non-rubber components are ratioed against the 100 parts

of rubber and are expressed in phr. This way one can easily compare, for example, the levels of curatives or filler loadings, etc., between different compositions based on the same relative proportion of rubber without the need to recalculate percentages for every component after adjusting levels of only one, or more, component(s).

5 [0021] Isomonoolefin refers to any olefin monomer having at least one carbon having two substitutions on that carbon. Isomonoolefin refers to any isomonoolefin monomer having one double bond.

[0022] Multiolefin refers to any monomer having two or more double bonds. In a preferred embodiment, the multiolefin is any monomer comprising two conjugated double  
10 bonds such as a conjugated diene like isoprene.

[0023] Isobutylene-based elastomer or polymer refers to elastomers or polymers comprising at least 70 mol % repeat units from isobutylene.

[0024] Alkyl refers to a paraffinic hydrocarbon group which may be derived from an alkane by dropping one or more hydrogens from the formula, such as, for example, a methyl  
15 group ( $\text{CH}_3$ ), or an ethyl group ( $\text{CH}_3\text{CH}_2$ ), etc.

[0025] Substituted refers to at least one hydrogen group being replaced by at least one substituent selected from, for example, halogen (chlorine, bromine, fluorine, or iodine); alkyl: straight or branched chain having 1 to 20 carbon atoms which includes methyl, ethyl, propyl, isopropyl, normal butyl, isobutyl, secondary butyl, tertiary butyl, etc.; haloalkyl, which means  
20 straight or branched chain alkyl having 1 to 20 carbon atoms which is substituted by at least one halogen, and includes, for example, chloromethyl, bromomethyl, fluoromethyl, iodomethyl, 2-chloroethyl, 2-bromoethyl, 2-fluoroethyl, 3-chloropropyl, 3-bromopropyl, 3-fluoropropyl, 4-chlorobutyl, 4-fluorobutyl, dichloromethyl, dibromomethyl, difluoromethyl, diiodomethyl, 2,2-dichloroethyl, 2,2-dibromoethyl, 2,2-difluoroethyl, 3,3-dichloropropyl,  
25 3,3-difluoropropyl, 4,4-dichlorobutyl, 4,4-dibromobutyl, 4,4-difluorobutyl, trichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,3,3-trifluoropropyl, 1,1,2,2-tetrafluoroethyl, and 2,2,3,3-tetrafluoropropyl. Thus, for example, a substituted styrenic unit includes p-methylstyrene, p-ethylstyrene, etc.

[0026] The elastomeric composition of the present disclosure comprises a halogenated  
30 polymer and a polyisoprene. The amount of halogenated polymer can be in a range from 40 to 70 phr in one embodiment, from 45 to 65 phr in another embodiment, from 47 to 63 phr in yet another embodiment, and from 50 to 60 phr in still yet another embodiment, by weight of the total weight of the rubber component in the elastomeric composition. The amount of

polyisoprene can be in a range from 30 to 60 phr in one embodiment, from 35 to 55 phr in another embodiment, from 37 to 53 phr in yet another embodiment, and from 40 to 50 phr in still yet another embodiment, by weight of the total weight of rubber components in the elastomeric composition.

5 Halogenated Polymer

[0027] Halogenated polymers useful in this invention comprise at least one isoolefin based polymer. These polymers can comprise 70 to 99.5 wt% of a C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of a C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the polymer. Preferably, the isomonoolefin derived units can be in a range from 85 to 99.5 wt%  
10 in one embodiment, and from 92 to 99.5 wt% in another embodiment. The multiolefin derived units can be in a range from 15 to 0.5 wt% in one embodiment, and from 8 to 0.5 wt% in another embodiment.

[0028] Non-limiting examples of the C<sub>4</sub> to C<sub>7</sub> isomonoolefin monomer include isobutylene (also referred to as isobutene), 2-methyl-1-butene, 3-methyl-1-butene, 2-methyl-  
15 2-butene, 1-butene, 2-butene, hexene, and 4-methyl-1-pentene. One preferred isomonoolefin monomer is isobutylene. Non-limiting examples of the C<sub>4</sub> to C<sub>14</sub> multiolefin monomer include isoprene, butadiene, 2,3-dimethyl-1,3-butadiene, myrcene, 6,6-dimethyl-fulvene, hexadiene, cyclopentadiene, and piperylene. One preferred multiolefin monomer is isoprene.

[0029] The halogenated polymers can be prepared by reacting a mixture of a C<sub>4</sub> to C<sub>7</sub>  
20 isomonoolefin monomer and a C<sub>4</sub> to C<sub>14</sub> multiolefin monomer, followed by halogenation. Halogenation typically occurs as a separate step after polymerization of the polymer. Halogenation can be carried out by any means, and the invention is not herein limited by the halogenation process. One method used to prepare halogenated polymer is by halogenating the polymer in a solution (cement) containing between about 1% to about 60 % by weight of  
25 the polymer in a substantially inert C<sub>5</sub>–C<sub>8</sub> hydrocarbon solvent, such as, pentane, hexane, heptane, and mixtures thereof, and contacting the polymer cement with a halogen for a period of up to about 30 minutes.

[0030] The halogen wt% is from 0.1 to 10 wt% based on the weight of the halogenated polymer in one embodiment, and from 0.5 to 5 wt% in another embodiment. In yet another  
30 embodiment, the halogen wt% of the halogenated butyl rubber is from 1 to 2.5 wt%.

[0031] Preferred halogenated polymers useful in the practice of this invention include halogenated isobutylene-based polymers. These polymers can be described as random

copolymer of a C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived unit, such as isobutylene derived unit, and at least one other multiolefin unit.

[0032] The halogenated polymer according to the present invention is preferably a halogenated butyl rubber, such as bromobutyl rubber, chlorobutyl rubber and halogenated branched ("star-branched") butyl rubbers. One embodiment of the butyl rubber polymer of the invention can be obtained by reacting 95 to 99.5 wt% of isobutylene with 0.5 to 8 wt% isoprene, or from 0.5 wt% to 5.0 wt% isoprene in yet another embodiment. Butyl rubbers and methods of their production are described in detail in, for example, U.S. Pat. Nos. 4,474,924, 4,068,051 and 5,532,312, and PCT Publication Nos. WO 2004/058828 and WO 2004/058829.

[0033] A commercial embodiment of a suitable halogenated butyl rubber of the present invention is Bromobutyl 2255 (BB2255; ExxonMobil Chemical Company, Houston, Tex.). Its Mooney viscosity is from 41 to 51 (ML 1+8 at 125 °C., ASTM D1646, modified), and the bromine content is from 0.93 to 1.13 wt% relative to the Bromobutyl 2255. Further, cure characteristics of Bromobutyl 2255 are as follows: MH is from 37 to 51 dN.m, ML is from 14.5 to 23.5 dN.m (ASTM D2084). Another commercial bromobutyl is Bromobutyl 2222 (BB2222; ExxonMobil Chemical Company, Houston, Tex.), which has a Mooney viscosity in the range of 29-35 (ML 1+8 at 125 °C., ASTM D1646, modified), with a bromine content of 0.93 to 1.13 wt% relative to the total weight of the bromobutyl.

[0034] Another commercial embodiment of a suitable halogenated butyl rubber of the present invention is Chlorobutyl 1066 (CB 1066; ExxonMobil Chemical Company, Houston, Tex.). Its Mooney viscosity is from 33 to 43 (ML 1+8 at 125 °C., ASTM D1646, modified), and the chlorine content is from 1.18 to 1.34 wt% relative to the Chlorobutyl 1066. Further, cure characteristics of Chlorobutyl 1066 are as follows: MH is from 34 to 48 dN.m, ML is from 9.5 to 18.5 dN.m (ASTM D2084).

[0035] A commercial embodiment of the halogenated star branched butyl rubber of the present invention is Bromobutyl 6222 (ExxonMobil Chemical Company, Houston, Tex.), having a Mooney viscosity (ML 1+8 at 125 °C., ASTM D1646, modified) of from 27 to 37, and a bromine content of from 2.2 to 2.6 wt% relative to the halogenated star branched butyl rubber. Further, cure characteristics of Bromobutyl 6222 are as follows: MH is from 24 to 38 dN.m, ML is from 6 to 16 dN.m (ASTM D2084).

#### Polyisoprene

[0036] As used herein, "polyisoprene" refers to a polymer of isoprene (i.e., 2-methyl-1,3-butadiene). In certain embodiments, the microstructure of the polyisoprene comprises a

mixture of one or more polymerized isoprene residues (isoprene units) along the backbone of the polyisoprene chain selected from 1,4-polyisoprene, 3,4-polyisoprene, and 1,2-polyisoprene units. As used herein, the percentage of a particular geometry of the polymerized isoprene residues (units) refers to the relative amount (w/w) of that geometry provided in the polyisoprene (e.g., as determined by NMR). As used herein, "1,4-polyisoprene" refers to 1,4-cis-polyisoprene, 1,4-trans-polyisoprene, or a mixture thereof. In certain embodiments, the polyisoprene comprises a mixture of one or more polymerized isoprene residues (units) along the backbone of the polyisoprene chain selected from 1,4-cis-polyisoprene, 1,4-trans-polyisoprene, 3,4-polyisoprene and 1,2-polyisoprene. Likewise, the percentage of a particular geometry of any polymer as described herein refers to the relative amount (w/w) of that geometry of polymerized residues (units) along the backbone of the polymer chain, e.g., selected from any one of "1,4", "1,2", or "3,4", or a mixture thereof.

[0037] A commercial embodiment of a suitable polyisoprene rubber of the present invention is Cariflex<sup>TM</sup> IR0307 (Kraton Performance Polymer, Inc., Houston, Tex.).

#### 15 Filler

[0038] The elastomeric compositions, e.g., compounded for pharmaceutical applications, are typically provided with one or more filler components. Calcined clay is widely used by the pharmaceutical industry as "clean" filler, i.e., a filler that exhibits a low level of extractables and/or leachables. Non-limiting examples of other fillers include talc, titanium oxide powder, and precipitated silica.

[0039] Each filler is typically present in the elastomeric composition in an amount of from 10 to 100 phr in one embodiment, more preferably from 30 to 80 phr in another embodiment, and from 50 to 80 phr in yet another embodiment. Preferably the total amount of filler in the composition is in a range from 50 to 100 phr.

25 [0040] Calcined clay and precipitated silica are distinct from nanoclay and layered silicates. Calcined clay is a layered clay that has been heat treated to remove all volatiles from the clay layers, rendering the clay inert. A nanoclay is a broad category of layered clays that have thin layers and spacing between the layers in the nanoscale range. The layers of the nanoclay are held together by ionic forces due to naturally occurring sodium charges on the layer surfaces. Layered silicates are generally a type of layered material wherein the layers contain a silicon bearing ion, i.e., silicate materials. Precipitated silica is a material comprising silicon dioxides and is prepared by reacting an alkaline silicate solution with a mineral acid; typically sulfuric acid and sodium silicate solution are agitated in water and,

under alkaline conditions, silica is precipitated from the solution. The properties of the precipitated silica may vary depending on the different process conditions such as temperature, pH, and addition rate of reactants.

#### Cure Package

5 [0041] A cure package including one or more crosslinking agents is used to vulcanize the elastomeric compositions of the present invention. In one embodiment of the invention, the cure package is present from 0.1 to 10 phr, and from 0.5 to 8 phr in another embodiment, and from 1 phr to 5 phr in yet another embodiment.

[0042] A resin cure system is useful in the present invention, with or without accelerators and/or activators. Preferably the resin used to cure the elastomeric composition is a phenolic resin, for example, a alkyl and/or halogenated phenolic resin. An amount of the phenolic resin included in the cure package can be in a range from a minimum of 0.1, 0.5, or 1.0 phr to a maximum of 5, 8, or 10 wherein the resin may be within a range defined by any one of the minimum values and the maximum values; such ranges include 0.1 phr to 10 phr, 0.5 to 10  
15 phr, 0.5 phr to 8 phr, and 1.0 to 8 phr.

[0043] Halogen-containing elastomers such as halogenated poly(isobutylene-co-isoprene) may be crosslinked by reacting with metal oxides. The metal oxide is believed to react with halogen groups in the polymer to produce an active intermediate which then reacts further to produce carbon-carbon bonds. Zinc halide is liberated as a by-product and it serves as an autocatalyst for this reaction. In particular, the following metal oxides are common curatives  
20 that can function in the present invention: ZnO, CaO, MgO, Al<sub>2</sub>O<sub>3</sub>, CrO<sub>3</sub>, FeO, Fe<sub>2</sub>O<sub>3</sub>, and NiO. These metal oxides can be used alone or in conjunction with the corresponding metal fatty acid complex (e.g., zinc stearate, calcium stearate, etc.), or with the organic and fatty acids added alone, such as stearic acid or salicylic acid, an alkylperoxide compound, diamines or derivatives thereof. When a metal oxide is included in the cure package, an  
25 amount of the metal oxide can be in a range from 0.1 phr to 5 phr in one embodiment, or from 0.5 phr to 3 phr in another embodiment.

[0044] Sulfur or a sulfur compound is another chemical curing agent for diene-containing elastomers used in amounts of 0.5 phr to 10 phr. Sulfur compounds useful as cure agents  
30 include those having a rhombic 8-member ring structure or are in an amorphous polymeric form. The sulfur vulcanization system may also include an accelerator to activate the sulfur, an activator, and optionally a retarder to help control the rate of vulcanization. When a sulfur or sulfur compound is included in the cure package, the amount of the metal oxide can be in a

range from 0.1 phr to 2 phr in one embodiment, or from 0.5 phr to 1.5 phr in another embodiment.

[0045] Accelerators serve to control the onset of and rate of vulcanization, and the number and type of crosslinks that are formed. Activators are chemicals that increase the rate of vulcanization. General classes of accelerators include amines, diamines, guanidines, thioureas, thiazoles, thiurams, sulfenamides, sulfenimides, thiocarbamates, xanthates, and the like. The cure package useful in the invention can also include an accelerator present in an amount of from 0.1 to 2.5 phr in one embodiment, and from 0.1 to 2.0 phr in another embodiment, and from 0.3 to 1.5 phr in yet another embodiment.

#### Processing Oils and Aids

[0046] Due to the requirement of a clean elastomer and the need to restrict potential leachables in the composition, the amount of additional conventional processing oils and aids, such as plastomers and plasticizers, is usually limited. At most, if present, a processing oil or aid is used in an amount of not more than 10 phr. Preferably, paraffinic, naphthenic and/or aromatic oils, as well as plastomers and other processing oils, are substantially absent from the composition; meaning, they have not been deliberately added to the compositions, or, in the alternative, if present, are present up to 0.2 wt% of the compositions.

#### Processing and properties

[0047] Elastomeric compositions are typically melt mix blends wherein mixing of the components is carried out by combining the rubber component, filler and other additives in any suitable mixing device such as a two-roll open mill, Brabender™ internal mixer, Banbury™ internal mixer with tangential rotors, Krupp internal mixer with intermeshing rotors, or preferably a mixer/extruder, by techniques known in the art. Typically, the rubber component is first mixed for 20 to 90 seconds, or until the temperature reaches from 40 °C. to 75 °C. Then, from 1/2 to 3/4 of the filler is typically added to the mixer, and mixing continues until the temperature reaches from 90 °C. to 150 °C. Next, the remaining filler is added, as well as the processing oil, if any, and mixing continues until the temperature reaches from 120 °C. to 160 °C. The masterbatch mixture is then finished by sheeting on an open mill or through a second stage mixing and allowed to cool, for example, to from 50 °C. to 110 °C. when the curatives are added.

[0048] The vulcanized elastomeric composition of the present disclosure has a compression set, as determined by ASTM-D395, of less than 20 %, or from 10 to 16 % in one embodiment.

Application

[0049] The elastomeric composition of the present disclosure may be useful in preparation of a pharmaceutical article, such as a stopper or seal for parenteral drug packaging, in particular a soft parenteral drug packaging.

5 [0050] In one embodiment of the invention, the stopper or seal can be formed of the elastomeric composition. In another embodiment of the invention, the stopper or seal can comprise an inner body formed of the elastomeric composition and an outer cover containing the inner body. In the latter embodiment, the outer cover may have a direct contact with the infusion drugs and can be formed of other polymers, such as polypropylene, polyethylene, etc.

10 Examples

[0051] Without wishing to be bound by this theory, it is believed that a cure package comprising phenolic resin can co-vulcanize halogenated polymer and polyisoprene, resulting in balanced mechanical properties, air impermeability and aging performance of the cured composition. In addition, because the cure packages have a low content of sulfur and  
15 accelerator in the composition, a cleaner final product and a reduction of potential extractables and leachables can be obtained compared to the use of polyisoprene only.

[0052] Elastomeric compositions were prepared in accordance with the process described herein, wherein the amount and types of rubber components and cure package were varied. Comparative compositions have alphabetical identifiers; compositions within the scope of the  
20 present invention have numerical identifiers. The compositions are set forth in Table 1 below; all components are expressed in parts per hundred (phr).

**Table 1: Formulations**

| Examples                       | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   |
|--------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| CB 1066                        | 100 |     |     |     |     | 50  | 60  |     |     |
| BB 2222                        |     |     | 100 |     |     |     |     |     |     |
| BB 2255                        |     |     |     | 100 | 100 |     |     | 50  | 60  |
| IR0307                         |     | 100 |     |     |     | 50  | 40  | 50  | 40  |
| Clay, Translink 37             | 30  | 40  | 30  | 30  | 60  | 40  | 40  | 40  | 40  |
| Talc, Mistron Vapor            | 30  | 40  | 30  | 30  |     | 40  | 40  | 40  | 40  |
| TiO <sub>2</sub> , Kronos 1000 | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   | 4   |
| SP-1045 <sup>1</sup>           | 2   |     |     |     |     | 1   | 1   |     |     |
| ZnO, Kadox 911                 | 2   | 2   |     |     |     | 2   | 2   | 2   | 2   |
| Sulfur <sup>2</sup>            |     | 1.5 |     |     |     | 1   | 1   | 1.5 | 1.5 |
| Perkacit ZBEC <sup>3</sup>     |     | 0.5 |     |     |     | 0.5 | 0.5 | 0.5 | 0.5 |
| Diak No. 1 <sup>4</sup>        |     |     | 0.6 | 0.6 | 0.6 |     |     |     |     |

<sup>1</sup>: An octyl phenol resin available from SI Group India Ltd.

<sup>2</sup>: Sulfur available from the Standard Chemical Co Pvt. Ltd. India.

<sup>3</sup>: Perkacit ZBEC: Zinc dibenzylthiocarbamate available from AKZO Noble/Performance Additives Sdn-Bdn, Malaysia.

<sup>4</sup>: Diak No. 1: A curing agent containing hexamethylenediamine carbamate available from Dupont

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**[0053]** The physical properties of these compounds were tested. When possible, standard ASTM tests were used to determine the cured compound physical properties (see Table 2). Stress/strain properties (tensile strength, elongation at break, modulus values) were measured at room temperature using an Instron 4202 or an Instron Series IX Automated.

10 **[0054]** Tensile measurements were done at ambient temperature on specimens (dog-bone shaped) width of 0.25 inches (0.62 cm) and a length of 1.0 inches (2.5 cm) length (between two tabs) were used. The thickness of the specimens varied and was measured manually by a Mitutoyo Digimatic Indicator connected to the system computer.

**[0055]** The specimens were pulled at a crosshead speed of 20 inches/min. (51 cm/min.) and the stress/strain data was recorded. The average stress/strain value of at least three  
15 specimens is reported. The error (2 sigma) in Tensile measurements is +/-0.47 MPa units. The error (2 sigma) in measuring 100% Modulus is +/-0.11 MPa units; the error (2 sigma) in measuring Elongation is +/-13% units.

**Table 2: Test Methods**

| Parameter                                                   | Units                 | Test                |
|-------------------------------------------------------------|-----------------------|---------------------|
| Mooney Viscosity (composition)                              | ML 1 + 4, 100 °C., MU | ASTM D1646          |
| Moving Die Rheometer (MDR)<br>@160 °C., ±0.5 ° arc, 30 mins |                       |                     |
| ML                                                          | decinewton.meter      | ASTM D5289          |
| MH                                                          | decinewton.meter      |                     |
| ts2                                                         | Minutes               |                     |
| t90                                                         | Minutes               |                     |
| Physical Properties<br>Tc 90 +2 min @ 160 °C.               |                       |                     |
| Hardness                                                    | Shore A               | ASTM D2240          |
| Modulus 100%, 300%                                          | MPa                   | ASTM D412 die C     |
| Tensile Strength                                            | MPa                   |                     |
| Elongation at Break                                         | %                     |                     |
| Tear Resistance                                             | MPa                   | ASTM D624 die C     |
| Tc 90 +5 min @ 160 °C.                                      |                       |                     |
| Compression Set                                             | %                     | ASTM D395, Method B |

20

**[0056]** The results of the testing are set forth in Table 3 below.

**Table 3: Properties**

| Example                                                      | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    |
|--------------------------------------------------------------|------|------|------|------|------|------|------|------|------|
| ML                                                           | 2.1  | 0.6  | n/a  | 2.1  | 2.3  | 1.4  | 1.3  | 1.0  | 1.3  |
| MH                                                           | 6.1  | 1.9  | n/a  | 5.6  | 5.9  | 8.3  | 8.3  | 3.3  | 4.1  |
| MH-ML                                                        | 4    | 1.3  | n/a  | 3.5  | 3.6  | 7    | 7    | 2.3  | 2.8  |
| T2                                                           | 6.8  | n/a  | n/a  | 2.9  | 2.8  | 1.3  | 1.1  | 24.4 | 11.5 |
| t90                                                          | 29.4 | 12.0 | n/a  | 6.0  | 5.7  | 22.0 | 25.0 | 30.1 | 29.3 |
| Hardness Shore A                                             | 46   | n/a  | 40   | 44   | 42   | 48   | 51   | 36   | 42   |
| 100 Modulus [MPa]                                            | 2.1  | n/a  | 1.3  | 1.5  | 1.6  | 1.9  | 2.6  | 1.1  | 1.5  |
| 300 Modulus [MPa]                                            | 4.4  | n/a  | 2.4  | 3.2  | 3.7  | 4.3  | 5.1  | 1.9  | 2.9  |
| Stress at break [MPa]                                        | 4.6  | n/a  | 8.0  | 6.1  | 7.2  | 6.0  | 6.1  | 2.4  | 4.0  |
| Strain at break %                                            | 282  | n/a  | 781  | 642  | 616  | 488  | 420  | 517  | 542  |
| Compression Set %                                            | 33   | n/a  | 33   | 25   | 22   | 10   | 16   | 54   | 52   |
| Tear resistance [N/mm]                                       | 22.3 | n/a  | 21.1 | 25.8 | 20.9 | 22.9 | 23.0 | 16.7 | 19.4 |
| Permeability Coefficient<br>cc•mm/(m <sup>2</sup> •day•mmHg) | 0.13 | n/a  | 0.13 | 0.14 | 0.16 | 0.67 | 0.42 | 0.69 | 0.47 |

[0057] The samples were then aged in an oven at 120 °C for 2 hours and then the mechanical properties were tested again. The test results were show in Table 4. A changed value in percentage is obtained by comparing with samples tested before the aging treatment.

**Table 4: Aging performance**

| Example               | 1     | 2   | 3    | 4     | 5     | 6    | 7    | 8     | 9     |
|-----------------------|-------|-----|------|-------|-------|------|------|-------|-------|
| 100 Modulus [MPa]     | 1.8   | N/A | 1.3  | 1.7   | 1.4   | 1.8  | 2.5  | 1.4   | 1.5   |
| Changed value ±%      | -14.3 | N/A | 0    | +13.3 | -12.5 | -6.4 | -4.9 | +33.2 | -2.5  |
| 300 Modulus [MPa]     | 4.6   | N/A | 2.4  | 3.4   | 3.1   | 4.5  | 5.1  | 2.8   | 2.9   |
| Changed value ±%      | +4.5  | N/A | 0    | +6.3  | -16.2 | +4.7 | 0    | +47   | 0     |
| Stress at break [MPa] | 4.6   | N/A | 8.1  | 5.7   | 5.8   | 5.8  | 5.8  | 3.2   | 4.5   |
| Changed value ±%      | 0     | N/A | +1.3 | -6.6  | -19.4 | -2.1 | -4.9 | +29.3 | +13.9 |
| Strain at break %     | 281   | N/A | 795  | 620   | 651   | 440  | 405  | 416   | 594   |
| Changed value ±%      | 0     | N/A | +1.8 | -3.4  | +5.7  | -9.9 | -3.6 | -19.6 | +9.5  |

[0058] It can be seen from the above results that by curing chlorobutyl polymer and polyisoprene blends with a cure package comprising phenolic resin (examples 6 and 7), the compositions showed good cure performance with higher cure speed and cure state compared with that of phenolic resin cure of 100% chlorobutyl formulation (comparative example 1).

Furthermore, the composition containing chlorobutyl and polyisoprene also shows good aging performance comparable to that of 100% chlorobutyl formulation but with much better compression set as well as tensile performance.

[0059] Also observed from the above results is that without the addition of phenolic resin as curing agent, formulations containing high Mooney bromobutyl and polyisoprene (examples 8 and 9) exhibit slow cure rate and low cure state. The compression set of these blends are also high and the aging performance poor.

[0060] It was also observed when the rubber component contained only polyisoprene (comparative example 2) the cure package was not able to cure the polyisoprene effectively.

[0061] For compositions comprising the higher Mooney bromobutyl cured with a cure agent containing hexamethylenediamine carbamate (comparative examples 4 and 5), compression set values of 22 and 25% were obtained.

[0062] The use of both chlorinated isobutylene-isoprene copolymer and polyisoprene in the elastomeric composition achieved excellent compression set performance (examples 6 and 7) compared with the formulation where only halogenated polymer or only polyisoprene was used (comparative examples 1 to 5).

[0063] It can be seen from the above results that by curing halogenated polymer and polyisoprene blended compositions with a cure package comprising phenolic resin (examples 6 and 7), the cured composition showed a balanced performance for pharmaceutical stopper applications. This includes lower compression set, slightly higher air impermeability and improved physical / aging properties. In addition, because the addition amount of curatives used was very small in the elastomeric composition, it would not lead to excessive amount of extractable for the stopper.

[0064] Having described the various aspects of the compositions herein, further specific embodiments of the invention include those set forth in the following lettered paragraphs:

Paragraph A: An elastomeric composition comprising (i) a rubber component comprising 40 to 70 phr of a halogenated polymer, 60 to 30 phr of a polyisoprene by weight of the rubber component, (ii) 10 to 100 phr of a filler; and (iii) 0.5 to 10 phr of a cure package comprising a phenolic resin; wherein the halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the halogenated polymer;

Paragraph B: The elastomeric composition of Paragraph A, wherein the rubber component comprises 50 to 60 phr of a halogenated polymer and 60 to 50 phr of a polyisoprene by weight of the rubber component;

Paragraph C: The elastomeric composition of Paragraph A or B, wherein the  
5 halogenated polymer contains 92 to 99.5 wt% of isomonoolefin derived units and 8 to 0.5 wt% of multiolefin derived units by weight of the halogenated polymer;

Paragraph D: The elastomeric composition of any one of Paragraphs A to C, wherein the isomonoolefin is selected from the group consisting of isobutylene, 2-methyl-1-butene, 3-methyl-1-butene, 2-methyl-2-butylene, 1-butene, 2-butene, hexene, and 4-methyl-1-pentene;

10 Paragraph E: The elastomeric composition of any one or any combination of Paragraphs A to D, wherein the isomonoolefin is isobutylene;

Paragraph F: The elastomeric composition of any one or any combination of Paragraphs A to E, wherein the multiolefin is selected from the group consisting of isoprene, butadiene, 2,3-dimethyl-1,3-butadiene, myrcene, 6,6-dimethyl-fulvene, hexadiene,  
15 cyclopentadiene, and piperylene;

Paragraph G: The elastomeric composition of any one or any combination of Paragraphs A to F, wherein the multiolefin is isoprene;

Paragraph H: The elastomeric composition of any one or any combination of Paragraphs A to G, wherein the halogenated polymer contains 0.1 to 10 wt% of halogen by  
20 weight of the halogenated polymer;

Paragraph I: The elastomeric composition of any one or any combination of Paragraphs A to H, wherein the halogenated polymer contains 0.1 to 5 wt% of halogen by weight of the halogenated polymer;

Paragraph J: The elastomeric composition of any one or any combination of  
25 Paragraphs A to I, wherein the halogenated polymer contains sulfur or a sulfur compound;

Paragraph K: The elastomeric composition of any one or any combination of Paragraphs A to J comprising 2 to 6 phr of the cure package;

Paragraph L: The elastomeric composition of any one or any combination of Paragraphs A to K, wherein the cure package comprises 0.5 to 8 phr of the phenolic resin;

30 Paragraph M: The elastomeric composition of any one or any combination of Paragraphs A to L, wherein the cure package further comprises 0.1 to 2 phr of sulfur or sulfur compound;

Paragraph N: The elastomeric composition of any one or any combination of Paragraphs A to M, wherein the cure package further comprises 0.1 to 5 phr of a metal oxide;

Paragraph O: The elastomeric composition of any one or any combination of Paragraphs A to N having a compression set of less than 20 % as determined by ASTM-D395;

5 Paragraph P: An article comprising the elastomeric composition of one or any combination any of Paragraphs A to O;

Paragraph Q: The article of Paragraph P, wherein the article is a stopper;

Paragraph R: A stopper comprising an inner body and an outer cover containing the inner body, wherein the inner body comprises an elastomeric composition of any one or any  
10 combination of Paragraphs A to O;

Paragraph S: A method of making an elastomeric composition, comprising the steps of (a) forming a blend of (i) a rubber component comprising 40 to 70 phr of a halogenated polymer and 60 to 30 phr of a polyisoprene by weight of the rubber component, and (ii) 10 to 100 phr of a filler and (b) adding to the blend 0.5 to 10 phr of a cure package comprising a  
15 phenolic resin; wherein the halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the halogenated polymer;

Paragraph T: The method of Paragraph S, wherein 50 to 75 % of the amount of the total filler is added to the mixer when blend reaches a temperature in the range of 40 to 75 °C  
20 and then the remaining filler is added when the blend is at a temperature of 90 to 150° °C;

Paragraph U: The method of Paragraph S or T, wherein the halogenated polymer contains 92 to 99.5 wt% of isomonoolefin derived units and 8 to 0.5 wt% of multiolefin derived units by weight of the halogenated polymer;

Paragraph V: The method of any of Paragraphs S to U, wherein the isomonoolefin is  
25 isobutylene;

Paragraph W: The method of any one or any combination of Paragraphs S to V, wherein the multiolefin is isoprene;

Paragraph X: The method of any one or any combination of Paragraphs S to W, wherein the halogenated polymer contains 0.1 to 5 wt% of chlorine or bromine by weight of  
30 the halogenated polymer; and

Paragraph Y: The method of any one or any combination of Paragraphs S to X, wherein 2 to 6 phr of the cure package is added.

[0065] All patents and patent applications, test procedures (such as ASTM methods, UL methods, and the like), and other documents cited herein are fully incorporated by reference to the extent such disclosure is not inconsistent with this invention and for all jurisdictions in which such incorporation is permitted.

5 [0066] When numerical lower limits and numerical upper limits are listed herein, ranges from any lower limit to any upper limit are contemplated. While the illustrative embodiments of the invention have been described with particularity, it can be understood that various other modifications can be apparent to and can be readily made by those skilled in the art without departing from the spirit and scope of the invention. Accordingly, it is not intended  
10 that the scope of the claims appended hereto be limited to the examples and descriptions set forth herein but rather that the claims be construed as encompassing all the features of patentable novelty which reside in the present invention, including all features which would be treated as equivalents thereof by those skilled in the art to which the invention pertains.

[0067] The invention has been described above with reference to numerous embodiments  
15 and specific examples. Many variations can suggest themselves to those skilled in this art in light of the above detailed description. All such obvious variations are within the full intended scope of the appended claims.

**CLAIMS**

*What is claimed is:*

1. An elastomeric composition comprising:
  - (i) a rubber component comprising 40 to 70 phr of a halogenated polymer and 60 to 30 phr of a polyisoprene by weight of the rubber component;
  - (ii) 10 to 100 phr of a filler; and
  - (iii) 0.5 to 10 phr of a cure package comprising a phenolic resin,wherein the halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the halogenated polymer.
2. The elastomeric composition of claim 1, wherein the rubber component comprises 50 to 60 phr of a halogenated polymer and 60 to 50 phr of a polyisoprene by weight of the rubber component.
3. The elastomeric composition of claim 1, wherein the halogenated polymer contains 92 to 99.5 wt% of isomonoolefin derived units and 8 to 0.5 wt% of multiolefin derived units by weight of the halogenated polymer.
4. The elastomeric composition of claim 1, wherein the isomonoolefin is selected from the group consisting of isobutylene, 2-methyl-1-butene, 3-methyl-1-butene, 2-methyl-2-butylene, 1-butene, 2-butene, hexene, and 4-methyl-1-pentene.
5. The elastomeric composition of claim 1, wherein the isomonoolefin is isobutylene.
6. The elastomeric composition of claim 1, wherein the multiolefin is selected from the group consisting of isoprene, butadiene, 2,3-dimethyl-1,3-butadiene, myrcene, 6,6-dimethyl-fulvene, hexadiene, cyclopentadiene, and piperylene.
7. The elastomeric composition of claim 1, wherein the multiolefin is isoprene.
8. The elastomeric composition of claim 1, wherein the halogenated polymer contains 0.1 to 10 wt% of halogen by weight of the halogenated polymer.
9. The elastomeric composition of claim 1, wherein the halogenated polymer contains 0.1 to 5 wt% of halogen by weight of the halogenated polymer.
10. The elastomeric composition of claim 1, wherein the halogenated polymer contains sulfur or a sulfur compound.
11. The elastomeric composition of claim 1 comprising 2 to 6 phr of the cure package.
12. The elastomeric composition of claim 1, wherein the cure package comprises 0.5 to 8 phr of the phenolic resin.

13. The elastomeric composition of claim 1, wherein the cure package further comprises 0.1 to 2 phr of sulfur or sulfur compound.
14. The elastomeric composition of claim 1, wherein the cure package further comprises 0.1 to 5 phr of a metal oxide.
- 5 15. The elastomeric composition of claim 1 having a compression set of less than 20 % as determined by ASTM-D395.
16. An article comprising the elastomeric composition of any of claims 1 to 15.
17. The article of claim 16, wherein the article is a stopper.
18. A stopper comprising an inner body and an outer cover containing the inner body,  
10 wherein the inner body comprises an elastomeric composition of any of claims 1 to 15.
19. A method of making an elastomeric composition, comprising the steps of:
- (a) in a mixer forming a blend of
- (i) a rubber component comprising 40 to 70 phr of a halogenated polymer and 60 to 30 phr of a polyisoprene by weight of the rubber component and  
15 (ii) 10 to 100 phr of a filler; and
- (b) adding to the blend 0.5 to 10 phr of a cure package comprising a phenolic resin; wherein the halogenated polymer comprises 70 to 99.5 wt% of C<sub>4</sub> to C<sub>7</sub> isomonoolefin derived units and 30 to 0.5 wt% of C<sub>4</sub> to C<sub>14</sub> multiolefin derived units by weight of the halogenated polymer.
- 20 20. The method of claim 19, wherein 50 to 75 % of the amount of the total filler is added to the mixer when blend reaches a temperature in the range of 40 to 75 °C and then the remaining filler is added when the blend is at a temperature of 90 to 150° °C.
21. The method of claim 19, wherein the halogenated polymer contains 92 to 99.5 wt% of isomonoolefin derived units and 8 to 0.5 wt% of multiolefin derived units by weight of the  
25 halogenated polymer.
22. The method of claim 19, wherein the isomonoolefin is isobutylene.
23. The method of claim 19, wherein the multiolefin is isoprene.
24. The method of claim 19, wherein the halogenated polymer contains 0.1 to 5 wt% of chlorine or bromine by weight of the halogenated polymer.
- 30 25. The method of claim 19, wherein 2 to 6 phr of the cure package is added.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2013/001112

**A. CLASSIFICATION OF SUBJECT MATTER**

C08L 23/28(2006.01)i; C08L 9/00(2006.01)i; A61J 1/14(2006.01)i

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)

C08L; A61J

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)

CNPAT,CNKI,CA,WPLEPODOC,CNTEXT,DWPI,SIPOABS:polyisoprene,isoprene,isomonoolefin,multiolefin,STOPPER,SEAL,phenolic resin,parenteral,halogen+,exxon mobil

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                           | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | CN 101094890A (EXXONMOBIL CHEM PATENTS INC.) 26 December 2007 (2007-12-26)<br>description, example CX1                                                       | 1-25                  |
| X         | CN 1458181A (BAYER AG) 26 November 2003 (2003-11-26)<br>description, page 3, line 13 to page 9, line 10                                                      | 1-25                  |
| X         | CN 1474855A (EXXONMOBIL CHEM PATENTS INC.) 11 February 2004 (2004-02-11)<br>description, page 22, line 20 to page 23, line 10, table 9, table 10A, table 10B | 1-25                  |
| X         | CN 1602335A (EXXONMOBIL CHEM PATENTS INC.) 30 March 2005 (2005-03-30)<br>description, page 6, lines 12 to 18, table 4                                        | 1-25                  |

☐ 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                                                                | “T” | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |
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| “P” | document published prior to the international filing date but later than the priority date claimed                                                                  |     |                                                                                                                                                                                                                                              |

Date of the actual completion of the international search

03 June 2014

Date of mailing of the international search report

09 July 2014

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STATE INTELLECTUAL PROPERTY OFFICE OF THE  
P.R.CHINA(ISA/CN)  
6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing  
100088 China

Authorized officer

YAN,Yan

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

**PCT/CN2013/001112**

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