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(54) Elastomeric Bladders for Medical Infusers

(57) Elastomeric bladders having improved resistance to spontaneous rupture when inflated are made by vulcanizing a homogeneous mixture of synthetic polyisoprene having 90% to 98% cis-1,4 linkages, finely divided silicon dioxide or carbon black, and vulcanizing agent while simultaneously forming the mixture into hollow tubular bodies. After being formed the bodies are solvent extracted to remove unreacted vulcanizing agent and the degradation products of the vulcanizing agent. Following the solvent extraction a nontoxic, nonleachable antioxidant is imbibed into the bodies by contacting the bodies with a liquid solution of the antioxidant.

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SPECIFICATION

Elastomeric Bladders for Medical Infusers

Technical Field

The invention relates to synthetic polyisoprene bladders for medical infusers which have improved resistance to spontaneous rupture.

Background Art

Medical devices that infuse liquids into patients are called infusers. One type of infuser uses an elastomeric bladder as its power source. Such infusers and bladders are described in U.S. Patents Nos. 3,993,069 and 4,201,207. These infusers consist of a housing, an elastomeric bladder contained within the housing that is inflated with the liquid to be infused, and a conduit that leads from the bladder to the infusion site. The rate at which the liquid is infused from the infuser depends upon the pressure exerted on the liquid by the bladder, the viscosity of the liquid, and the flow restriction characteristics of the conduit. The above cited patents describe bladders that are capable of maintaining the pressure on the liquid substantially constant over the discharge of a large proportion of the liquid. The bladders described in these patents are made from vulcanized synthetic polyisoprene that has a low frequency hysteresis less than about 10% and a stress relaxation less than 10%. Such hysteresis and stress relaxation characteristics were considered as key factors in realizing substantially constant pressure performance.

In making large numbers of such bladders from synthetic polyisoprene it was found that a small but significant number of them ruptured when inflated particularly after prolonged storage in an inflated state. Even though only a small portion of the bladdes so ruptured it was desirable to decrease the incidence of rupture in order to provide a greater margin of safety against rupture in the marketplace. The above patents say nothing about reducing the incidence of bladder rupture.

A principal object of the present invention is to provide synthetic polyisoprene bladders that have a reduced incidence of rupture and acceptable pressure constancy performance.

Disclosure of the Invention

One aspect of the invention is an elastomeric bladder for use in a medical infuser that has improved resistance to rupture when inflated, the bladder being tubular body

(a) Made from a vulcanized homogeneous mixture of synthetic polyisoprene having about 90% to about 98% cis-1,4 linkages and particulate silicon dioxide or particulate carbon black which have a nominal average diameter in the range of about 1×10^{-5} to about 5×10^{-3} mm and

(b) into which a nontoxic substantially nonleachable antioxidant has been diffused, the amounts of silicon dioxide or carbon black and antioxidant being sufficient to make the half-life of a population of the bladders at least about ten times longer than the half-life of a comparable population of bladders made from said vulcanized synthetic polyisoprene that do not include the silicon dioxide or carbon black and the antioxidant.

Another aspect of the invention is a process for making an elastomeric bladder for use in a medical infuser and having an improved resistance to rupture when inflated comprising:

(a) mixing homogeneously a synthetic polyisoprene having about 90% to about 98% cis-1,4 linkages, about 3 to about 10 phr particulate silicon dioxide or particulate carbon black which have a nominal average diameter in the range of about 1×10^{-5} to about 5×10^{-3} mm, and an amount of vulcanizing agent sufficient to vulcanize the mixture;

(b) subjecting the mixture to vulcanizing conditions while simultaneously

(c) forming the mixture into a tubular body;

(d) solvent extracting the degradation products of the vulcanizing agent from the body; and

(e) diffusing about 0.2 to about 2 phr of a nontoxic substantially nonleachable antioxidant into the body by contacting the body with a liquid solution of the antioxidant.

As used herein the designation "phr" means parts per hundred parts of synthetic polyisoprene.

Best Mode of Invention

The synthetic polyisoprene that is used to make the bladders has about 90% to about 98% of its monomeric units joined in cis-1,4 orientation. It is preferably of the type made using Zeigler catalysts which is characterized by having about 96% to about 98% cis-1,4 linkages. This polyisoprene is mixed homogeneously with particulate silicon dioxide or particulate carbon black or mixtures thereof which have the above indicated particle size. Fumed silicon dioxide is preferred. Such silicon dioxide is produced by the hydrolysis of silicon tetrachloride vapor in a flame of hydrogen and oxygen at temperatures above the fusion temperature of silica (ca 1710 C). In this combustion process molten spheres of silica are formed that on cooling fuse with one another to form branched, three-dimensional, chain-like aggregates. The final product typically has a surface area in the range of about 150 to about 450 m^2/gram as measured by the BET method. Such fumed silicon dioxides are sold by Cabot Corporation, Boston, Mass. under the trademark Cab-O-sil®. The carbon black will typically have a surface area in the range of about 50 to about 250 m^2/gram as measured by the BET method. The amount of silicon dioxide or carbon black that is mixed with the polyisoprene should be sufficient to substantially inhibit spontaneous rupture of the bladder due to the stresses that occur in the bladder walls when the bladder is inflated with medical fluid. About 3 to about 10 phr, preferably 3 to 7 phr, of the silicon dioxide or carbon black will normally be mixed with the synthetic polyisoprene. Lesser amounts will not

give a significant increase in rupture resistance. More than 10 phr may be added, but such amounts do not produce correspondingly greater enhancement of rupture resistance and may affect the pressure constancy performance of the bladder adversely.

The polyisoprene-silicon dioxide/carbon black mixture is vulcanized to form carbon-to-carbon or monothio crosslinks at the 1 and 4 positions of the isoprene unit. To achieve such vulcanization a vulcanizing agent is added to the mixture and the mixture is subjected to vulcanization conditions. Vulcanizing agents and procedures that may be used are disclosed in U.S. Patent No. 4,201,207 at column 2, line 54 to column 3, line 13 and in U.S. Patent No. 3,993,069 at column 8, line 50 to column 10, line 25, which disclosures are incorporate herein by reference. Dicumyl peroxide added in amounts in the range of about 1 to 2 phr is a preferred vulcanizing agent. The vulcanization will typically be effected during the forming process that is used to make the tubular bodies from the mixture. One such process involves calendering the polyisoprene-silicon dioxide/carbon black-vulcanizing agent mixture into a sheet and placing a disc-shaped segment of the sheet into a transfer mold that forms the sheet into hollow cylindrical tubes of the desired geometry. Conventional injection molding techniques may also be used to form the body. The molding temperature, pressure, and time are such as to achieve the desired vulcanization (crosslinking) of the polyisoprene. The geometry of the tubular bodies is the same as that disclosed in U.S. Patent No. 3,993,069 at column 4, lines 26 to 41, which disclosure is incorporated herein by reference.

After the mixture is formed into tubular bodies, the bodies are extracted with a solvent that removes substantially all unreacted vulcanizing agent and the degradation products of the vulcanizing agent from the body. The solvent should have no lasting deleterious effects on the body and should not leave a toxic residue in or on the body. The particular solvent used and the extraction time and temperature will depend upon the vulcanizing agent that was used. The purpose of the extraction is to prevent contamination of the medical fluid that is ultimately charged to the bladder with the vulcanizing agent or its degradation products.

After the extraction, the antioxidant is imbibed into the bodies by placing them into contact with a solution of the antioxidant. The antioxidant enters the bodies, which are usually swollen several fold with solvent, by diffusion. The amount of antioxidant imbibed into a body will, accordingly, depend upon the diffusion coefficient of the body with respect to the antioxidant, the concentration of the antioxidant in the solution, the solubility of the antioxidant in the body, the thickness of the body, the equilibrium swelling volume that is characteristic of the elastomeric-solvent combination, and the conditions (time and temperature) under which the contact is made. Preferably the same pure solvent is used for the extraction and antioxidant imbibition. The amount of antioxidant imbibed into the body should be sufficient to inhibit oxidative degradation (and thus rupture) of the bladder, usually over a period of at least about one year. The quantity required to achieve such inhibition will depend on the particular antioxidant that is used. In the case of the hindered phenol antioxidants described below, about 0.2 to about 2 phr, preferably about 1 phr, will usually be imbibed. Antioxidants that are nontoxic, such as those approved and under the provisions of Title 21 of the Code of Federal Regulations for use in plastics that are used in association with drugs or food, and which are substantially nonleachable by the medical fluid with which the bladder is to be inflated may be used. The term "substantially nonleachable" means that the antioxidant is less than 0.1% by weight soluble in the medical fluid. Nontoxic hindered polyphenol antioxidants, such as tetrakis [methylene 3-(3',5'-di-t-butyl-4'-hydroxyphenyl) propionate] methane and 1,3,5-trimethyl-2,4,6-tris(3,5-di-t-butyl-4-4-hydroxybenzyl) benzene, are preferred antioxidants for use in the invention. After the desired amount of antioxidant has diffused into the body, the body is taken from the solution and the solvent is removed from the body, such as by drying at temperatures up to 50 C. At this stage, the bladder is ready for incorporation into the infuser.

The inclusion of the silicon dioxide or carbon black and the antioxidant in the bladder together substantially reduce the likelihood that the bladder will rupture spontaneously when it is inflated. This reduction (or increase in rupture resistance) may be quantified relative to synthetic polyisoprene bladders that do not contain silicon dioxide or carbon black and antioxidant by comparing the half-lives of populations of the respective bladders under the same inflation conditions. The half-life is the time period from inflation to rupture of 50% of the bladders in the population. A population of at least ten bladders is desired to ensure that the results are statistically significant. Such comparisons carried out at 40 C indicate that the half life of the invention bladders is at least 10 times, and typically more than 100 times, longer than the half-life of bladders that do not contain silicon dioxide or carbon black and antioxidant.

The following example illustrates one embodiment of the invention. This example is not intended to limit the invention and is offered only by way of exemplification.

Preparation of Mixture

One hundred parts of synthetic polyisoprene (Natsyn 2200, 96% to 98% cis-1,4 linkages) were added to a Farrell Laboratory Mill (6 in.×13 in. rolls) at 130±10 F and the gap between rolls was adjusted to 0.08—0.09 in. After about 3 minutes of milling, 5.0 phr fumed silicon dioxide (Cab-O-Sil® M5, 200±25 m^2/gram surface area, 1.4×10^{-5} mm nominal average diameter) were

added to the mill over a 5 min. period. One and one-half phr of dicumyl peroxide (Di Cup R) were then added to the polyisoprene-silicon dioxide mix in four equal portions. Milling was continued until at least 18 min. has elapsed from the time the polyisoprene was added to the mill.

Vulcanization and Molding

The above mixture was charged to a four-cavity transfer mold maintained at 325—330 F and having 25,000 kg of clamping force. The mold cavities and mandrels were designed to make hollow cylindrical bladders 75.6 mm long with a 6.63 mm outer diameter and 5.16 mm inner diameter having diameter and having an integral circular flange at each end 1.587 mm wide and 12.7 mm in diameter. The curing time was 20 min.

Extraction

Bladders formed and vulcanized as above were placed vertically in the extraction pot of a Soxhlet extraction apparatus fitted to a 1000 ml flask. Enough ethyl acetate was added to fill the Soxhlet apparatus and have 250 ml of ethyl acetate in the flask. the flask was heated and extraction of the bladders with the ethyl was carried out for four hours.

Inhibition of Antioxidant

A 1.1% by weight solution of 1,3,5-trimethyl-2,4,6-tris(3,4-di-t-butyl-4-hydroxybenzyl) benzene in ethyl acetate was placed in a flask. Freshly extracted bladders were placed into the solution and kept there at ambient temperature for four hours. Previous tests had shown that the relationship between the wt.% of this antioxidant imbibed into the bladders was linear with 0.45% imbibed at a 1% concentration, and 0.68% imbibed at 1.5% concentration (four hours imbibition time). Accordingly about 0.5 phr antioxidant was imbibed into the bladders.

Half-life Tests

Half-life tests were carried out on bladders prepared as above except that 1.2 phr of tetrakis [methylene 3-(3′,5′-di-t-butyl-4′-hydroxyphenyl)propionate] methane was imbibed into the bladders from an acetone/toluene solution instead of the above described antioxidant. A population of 24 of these bladders inflated with 60 ml water and kept in air at 40 C had a half-life of approximately 14 months. Similar tests on populations of synthetic polyisoprene bladders made in substantially the same manner but without silicon dioxide or antioxidant indicate such bladders have a half-life of about 1 to 2 days.

Modification of the above-described bladders that are obvious to those or ordinary skill in the arts related to the invention are intended to be within the scope of the following claims.

Claims

1. An elastomeric bladder for use in a medical infuser comprising a tubular body formed of a vulcanized homogeneous mixture of synthetic polyisoprene having about 90% to about 98% cis-1,4 linkages said bladder having improved resistance to rupture when inflated and being characterized by containing particulate silicon dioxide or particulate carbon black having a nominal average diameter in the range of about 1×10^{-5} to about 5×10^{-3} mm; and a nontoxic, substantially nonleachable antioxidant the amounts of silicon dioxide or carbon black and antioxidant being sufficient to make the half-life of a population of the bladders at 40°C at least about ten times longer than the half-life of a comparable population of bladders made from said vulcanized synthetic polyisoprene but without the silicon dioxide or carbon black and the antioxidant.

2. The elastomeric bladder of Claim 1 further characterized in the particulate silicon dioxide is fumed silicon dioxide and is present in amounts of from 3 to 10 phr.

3. The elastomeric bladder of Claim 1 or 2 further characterized by the synthetic polysoprene having about 96% to 98% cis-1,4 linkages.

4. The elastomeric bladder of Claim 1, 2 or 3 further characterized by the vulcanized synthetic polyisoprene having carbon-to-carbon crosslinks.

5. The elastomeric bladder of claims 1, 2, 3 or 4 further characterized by containing from about 0.2 to about 2 phr of the nontoxic, substantially nonleachable antioxidant.

6. The elastomeric bladder of Claims 1, 3, 4, or 5 being further characterized by containing about 3 to about 7 phr of fumed silicon dioxide having a surface area in the range of about 150 to about 450 m^2/gram.

7. The elastomeric bladder of Claim 6 by further characterizing by the surface area being 200 ± 20 m^2/gram.

8. The elastomeric bladder of Claim 1, 2, 3, 4, 5, 6 or 7 being further characterized by the antioxidant being a hindered polphenol.

9. The elastomeric bladder of Claim 8 being further characterized by the hindered polyphenol being tetrakis [methylene 3-(3′,5′,di-t-buty-4′-hydroxyphenynl)propionate] methane or 1,3,5-trimethyl-2,4,6-tris(3,5-di-t-butyl-4-hydroxybenzyl) benzene.

10. The elastomeric bladder of claim 9 being further characterized by being vulcanized with about 1.5 phr dicumyl peroxide; and containing about 1 phr of 1,3,5-trimethyl-2,4,6-tris (3,5-ei-t-butyl-4-hydroxybenzyl) benzene.

11. A process for making an elastomeric bladder for use in a medical infuser having improved resistance to rupture when inflated comprising mixing homogeneously a synthetic polyisoprene having about 90% to about 98% cis-1,4 linkages, a sufficient amount of particulate silicon dioxide or particulate carbon black which have a nomical average diameter in the rage of about 1×10^{-5} to about 5×10^{-3} mm to substantially inhibit spontaneous rupture of the bladder due to stress in the bladder wall caused

by inflation of the bladder and an amount of vulcanizing agent sufficient to vulcanize the mixture and vulcanizing said mixture said process being characterized by subjecting the mixture to vulcanizing conditions while simultaneously:

(a) forming the mixture into a tubular body;

(b) solvent extracting unreacted vulcanizing agent and the degradation products of the vulcanizing agent from the body and

(c) diffusing a nontoxic, substantially nonleachable antioxidant into the body by contacting the body with a liquid solution of the antioxidant, the amount of antioxidant diffused into the body being sufficient to substantially inhibit oxidative degradation of the body.

12. The process of Claim 11 being further characterized by synthetic polyisoprene being mixed with fumed silicon dioxide.

13. The process of Claim 12 being further characterized by the amount of fumed silicon dioxide being about 3 to about 10 phr, the antioxidant being a hindered polyphenol, and the amount of antioxidant being about 0.5 to 2 phr.

14. The process of Claim 13 being further characterized by the fumed silicon dioxide having a surface area of 200 ± 20 m^2/gram, the amount of fumed silicon dioxide being 5 phr, the vulcanizing agent being dicumul peroxide, the amount of vulcanizing agent being 1.5 phr, the antioxidant being tetrakis [methylene 3-(3′,5′,di-t-butyl-4′-hydroxyphenyl)propionate] methane or 1,3,5-trimethyl-2,4,6-tris (3,5-di-t-butyl-4-hydroxybenzyl) benzene, and the amount of antioxidant being about 0.2 to about 2 phr.

15. The process of Claim 14 being further characterized by antioxidant being 1,3,5-trimethyl-2,4,6-tris(3,5-di-t-butyl-4-hydroxybenzyl) benzene, the amount of antioxidant being 1 phr, the solvent being ethyl acetate, and the antioxidant being dissolved in ethyl acetate.

16. An elastomeric bladder as claimed in claim 1 and substantially as herein described.

17. A process as claimed in claim 11 and substantially as described in the specific embodiment hereinbefore set forth.

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