

## Description

### Liquid Container

### Technical Field

[0001]

The present invention relates to a liquid container suitable for storing an injection liquid containing a drug that can be adsorbed by resin or that can permeate resin such as nitroglycerin, a protein, hyaluronic acid, a vitamin, a trace element, or a radical scavenger.

### Background Art

[0002]

So-called soft bag pharmaceutical products, which have been developed in recent years, are employed as drip infusion products. Such a soft bag pharmaceutical product is produced by diluting a drug(s) for injection use in advance and charging with the drug(s) a flexible container made of a plastic resin or the like. Upon use, soft bag pharmaceutical products can be easily handled and set within a short time, and disposal thereof is easier than that of glass bottles and ampoules. Therefore, soft bag pharmaceutical products are advantageously used in the field. One promising application of a soft bag pharmaceutical product is a nitroglycerin injection liquid, which is in some cases used as a drip infusion for controlling the blood pressure of a patient during surgery and for treating acute cardiac failure

(including an acute increment stage of chronic cardiac failure) and unstable angina. Replacement of a glass container with a soft bag will also be encouraged for a drug such as a protein (human plasma-derived albumin or albumin produced through a recombination technique), a hormone, a vitamin, or hyaluronic acid, from the viewpoints of reduction of possible breakage and environmental concerns.

[0003]

Meanwhile, some drugs including nitroglycerin, proteins (e.g., albumin and a hormone), hyaluronic acid, vitamins, trace elements, and radical scavengers are known to be adsorbed by or to permeate a film produced by molding vinyl chloride resin or a polyolefin-based resin such as polyethylene or polypropylene, these resins being generally employed as material for drug containers and medical apparatus. This property is a problem to be solved in the development of soft bag pharmaceutical products. At present, some polycycloolefin-based resins are known to be a material exhibiting no drug-adsorbability or drug-permeability. For example, Patent Documents 1 and 2 disclose that a syringe having an outer pipe made of a polycycloolefin-based resin is useful for producing a pre-filled syringe pharmaceutical product containing a drug that can be adsorbed by resin.

[0004]

As compared with a polyolefin such as polyethylene, polycycloolefin-based resin forms a high-density, 3-dimensional structure. Therefore, polycycloolefin-based

resin film tends to have high hardness and fragility. For forming a soft bag, polycycloolefin-based resin film is generally laminated with a film such as polyethylene-based resin film or polypropylene-based resin, to thereby form a laminated film. Patent Document 3 discloses a wrapping bag formed of a laminated film having an outer layer of polyolefin-based resin and an inner layer of polycycloolefin-based resin. The disclosed laminated film is suitable for producing an injection liquid containing a drug that can be adsorbed by resin, since the film can receive high-pressure steam sterilization and prevents adsorption of drugs. Patent Document 4 discloses a soft bag formed of a laminated film including a layer of polycycloolefin-based resin or a resin mixture containing polycycloolefin-based resin and a layer made of polyester-based resin or polyolefin-based resin. In the aforementioned soft bags made from multilayer film, the innermost layer is preferably formed of polycycloolefin-based resin, from the viewpoint of prevention of drug adsorption. Such soft bags essentially have a port member for discharging a drug, and the port member is also formed of polycycloolefin-based resin from the viewpoint of compatibility and adhesion between two resins. However, a port member made of polycycloolefin-based resin is expensive and is readily broken in the case of falling, which is problematic. Therefore, preferred is use of a polyethylene or polypropylene port member, which is inexpensive and resistant to shock impact breakage in the case of, for

example, falling.

[0005]

When a port member made of polyethylene or polypropylene is employed in a laminated film, a polyethylene-based resin layer or a polypropylene-based resin layer is formed on the inner side of the polycycloolefin-based resin layer. In this case, the polyethylene-based resin layer or the polypropylene-based resin layer comes into direct contact with a drug liquid containing, for example, nitroglycerin, a protein (e.g., albumin or a hormone), hyaluronic acid, a vitamin, a trace element, or a radical scavenger, and the amount of drug component(s) would vary due to adsorption or permeation. Patent Document 5 discloses a drug container for solving the problem, the container being formed of a multilayer film including a barrier layer formed from a resin mixture of a polycycloolefin-based resin and a specific polyethylene-based resin. The multilayer film of the drug container includes a polyethylene-based resin serving as a seal layer which comes into contact with a drug liquid. When the thickness of the seal layer is controlled to a small thickness (5 to 80  $\mu\text{m}$ ), and a barrier layer is formed on the outer side of the seal layer, adsorption of the drug can be prevented. Patent Document 3 discloses a soft bag having a polyethylene port member and a tri-layer film in which a polycycloolefin-based resin is sandwiched by polyethylene layers. The disclosed soft bag has a polycycloolefin-based resin layer corresponding to the

aforementioned barrier layer on the outer side of a 50  $\mu$ m-thickness polyethylene layer corresponding to the aforementioned seal layer. After post-sterilization storage at 40°C for one month, the nitroglycerin content was found to decrease by 7.0%. When polycycloolefin is employed as a resin mixture with another resin, drug storage stability and other properties of the soft bag are impaired in some cases. In fact, the container disclosed in Patent Document 5 also exhibited a decrease of 3.0% to 7.0% in nitroglycerin after post-sterilization storage at 60°C for two weeks, indicating poor storage stability.

Patent Document 1: JP-A-2003-024415

Patent Document 2: JP-A-2004-298220

Patent Document 3: JP-A-2005-254508

Patent Document 4: JP-A-2006-081898

Patent Document 5: JP-A-2005-525952

Disclosure of the Invention

Problems to be Solved by the Invention

[0006]

An object of the present invention is to provide a liquid container, which exhibits excellent storage stability and impact resistance and which is applicable for producing a soft bag pharmaceutical product of an injection liquid containing nitroglycerin, a protein (e.g., albumin or a hormone), hyaluronic acid, a vitamin, a trace element, a radical scavenger, and the like.

Means for Solving the Problems

[0007]

The present inventors have carried out extensive studies on the element and composition of a laminate film for producing a soft bag and, quite surprisingly, have found that through provision of a barrier layer containing, as a predominant component, a polycycloolefin-based resin having a glass transition temperature ( $T_g$ ) higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization and preferably having a glass transition temperature of 130°C or higher, the barrier layer being adjacent to a seal layer, there can be produced a container for a soft bag pharmaceutical product which prevents adsorption and permeation of a drug such as nitroglycerin, a protein (e.g., albumin or a hormone), hyaluronic acid, a vitamin, a trace element, or a radical scavenger, even when the seal layer is formed of a polyethylene-based resin or a polypropylene-based resin; which has excellent drug storage stability; and which exhibits excellent impact resistance through combination with a port member made of polyethylene or polypropylene. The present invention has been accomplished on the basis of this finding.

[0008]

Accordingly, the present invention provides a liquid container formed of a multilayer film and/or multilayer sheet, characterized in that the multilayer film and/or multilayer sheet has a barrier layer containing, as a predominant

component, a polycycloolefin-based resin having a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization, and a seal layer containing, as a predominant component, a polyethylene-based resin or a polypropylene-based resin, and the barrier layer is provided adjacent to the seal layer.

The present invention also provides a pharmaceutical product containing a drug liquid that can be adsorbed by a resin, the drug liquid being contained in a liquid container formed of a multilayer film and/or multilayer sheet, characterized in that the multilayer film and/or multilayer sheet has a barrier layer containing, as a predominant component, a polycycloolefin-based resin having a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization, and a seal layer containing, as a predominant component, a polyethylene-based resin or a polypropylene-based resin, and the barrier layer is provided adjacent to the seal layer.

#### Effects of the Invention

[0009]

The liquid container according to the present invention can solve problems such as adsorption and permeation of a drug such as nitroglycerin, a protein (e.g., albumin or a hormone), hyaluronic acid, a vitamin, a trace element, or a radical scavenger, and exhibits excellent drug storage

stability and impact resistance. Even when the liquid container is subjected to thermal treatment including high-pressure steam sterilization, sticking does not occur. Thus, the liquid container of the invention is very useful in practice.

#### Detailed Description of the Invention

[0010]

In the present invention, the term "seal layer" refers to a component layer of the multilayer film and/or multilayer sheet for forming a liquid container, which component layer serves as the innermost layer of the container and comes into direct contact with a drug contained in the container.

[0011]

No particular limitation is imposed on the multilayer film and/or multilayer sheet of the present invention, so long as the film and/or sheet includes a barrier layer containing, as a predominant component, a polycycloolefin-based resin having a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization (preferably a glass transition temperature of 130°C or higher), and a seal layer containing, as a predominant component, a polyethylene-based resin or a polypropylene-based resin, the barrier layer being adjacent to the seal layer. An additional adhesive layer or an adhesive resin layer may also be disposed between the seal layer and the barrier layer. Such an adhesive is preferably

a two-liquid curing type polyester-urethane adhesive or polyether-urethane adhesive. The adhesive resin layer may employ a known resin, so long as the resin provides excellent adhesion with respect to a counter material of a different resin. Examples of the adhesive resin include Admer (product of Mitsui Chemicals, Inc.), Modic (product of Mitsubishi Chemical Co., Ltd.), DLZ (product of Tosoh Corporation), and metallocene-type linear low-density polyethylene having a density of 0.91 or lower. On the surface of the barrier layer opposite the seal layer, several component layers which modulate strength, softness, gas-barrier property, and vapor-barrier property required as a liquid container, may also be laminated. Examples of the method of laminating such additional layers on the barrier layer include known techniques such as dry lamination, extrusion coating, extrusion lamination, co-extrusion lamination (e.g., co-extrusion blowing or co-extrusion T-die method), co-extrusion water-cooled blowing, and heat lamination. These techniques may be employed singly or in combination. Examples of the material which imparts gas-barrier or vapor-barrier property to the liquid container and which may be employed in the invention include silica- or alumina-vapor-deposited PET film, silica- or alumina-vapor-deposited nylon film, aluminum-vapor-deposited PET, aluminum-vapor-deposited nylon, aluminum foil, EVOH, PVA, PVDC, and MXD nylon.

[0012]

In the present invention, no particular limitation is

imposed on the polycycloolefin employed in the barrier layer, so long as the polycycloolefin has a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization (preferably a glass transition temperature of 130°C or higher). The glass transition temperature is more preferably 130 to 170°C, most preferably 132 to 150°C. In the present invention, the term "glass transition temperature" refers to a temperature determined in accordance with JIS K7121 (DSC). Generally, glass transition temperature is a well-known physical parameter characterizing polycycloolefin-based resin. However, no relationship between glass transition temperature and drug adsorbability or drug permeability has ever been known. Specifically, Patent Document 3 discloses that the polycycloolefin-based resin employed in the sealant layer has a glass transition temperature of 100 to 170°C, preferably 120°C or higher, and that such a limitation in range of glass transition temperature is provided in order to prevent deformation or breakage of a bag during high-pressure steam sterilization at 110°C or higher. However, Patent Document 3 does not disclose relationships between the glass transition temperature of the polycycloolefin-based resin and adsorption and storage stability of a drug, thermal treatment, high-pressure steam sterilization, etc. Patent Document 5 discloses that the polycycloolefin-based resin employed in the seal layer and the barrier layer more preferably has a

glass transition temperature of 80 to 150°C. However, Patent Document 5 does not disclose that relationships between the glass transition temperature and adsorption and storage stability of a drug in the seal layer. Under such circumstances, the present inventors have found that when the polycycloolefin-based resin has a higher glass transition temperature, the effect of suppressing drug adsorption and the effect on drug storage stability are enhanced. The inventors have also found that when the barrier layer adjacent to the seal layer that is formed of polyethylene-based resin or polypropylene-based resin is formed from the polycycloolefin-based resin having a glass transition temperature 130°C or higher, storage stability of a drug is enhanced to a great extent. The inventors have found that the effect of enhancing drug storage stability can be attained to a great extent, especially when the drug is subjected to a thermal treatment at 60°C or higher or high-pressure steam sterilization at 105°C or higher in a pharmaceutical production step. The thermal treatment at 60°C or higher is carried out mainly for inactivating viruses, and high-pressure steam sterilization at 105°C or higher is carried out for sterilization.

The inventors have also found that incorporation of a resin other than polycycloolefin-based resin into the barrier layer reduces the effect of preventing adsorption or permeation of a drug, thereby lowering storage stability.

[0013]

Examples of the polycycloolefin-based resin include polymers produced from a variety of cycloolefin monomers, copolymers produced from a cycloolefin monomer and another monomer such as ethylene, and a hydrogenated product thereof. Examples of the cycloolefin monomer include bicyclic cycloolefins such as norbornene, norbornadiene, methylnorbornene, dimethylnorbornene, ethylnorbornene, chlorinated norbornene, chloromethylnorbornene, trimethylsilylnorbornene, phenylnorbornene, cyanonorbornene, dicyanonorbornene, methoxycarbonylnorbornene, pyridylnorbornene, nadic anhydride, and nadic acid imide; tricyclic cycloolefins such as dicyclopentadiene, dihydrodicyclopentadiene, and alkyl-, alkenyl-, alkylidene-, and aryl-substituted products thereof; tetracyclic cycloolefins such as dimethanohexahydronaphthalene, dimethanooctahydronaphthalene, and alkyl-, alkenyl-, alkylidene-, and aryl-substituted products thereof; pentacyclic cycloolefins such as tricyclopentadiene; and hexacyclic cycloolefins such as hexacycloheptadecene. Examples also include norbornene-ring-containing compounds such as dinorbornene, compounds in which two norbornene rings are linked via a linker such as a hydrocarbon chain or an ester group, and alkyl- and aryl-substituted products thereof. The polycycloolefin-based resin of the present invention is preferably a polynorbornene-based resin produced through polymerization of one or more nonbornene compound monomers having a norbornene moiety in the molecular skeleton thereof;

e.g., dicyclopentadiene, norbornene, and tetracyclododecene, a hydrogenated product of the polynorbornene-based resin, or a mixture of one or more species thereof, from the viewpoint of strength and softness of a liquid container molded from the resin.

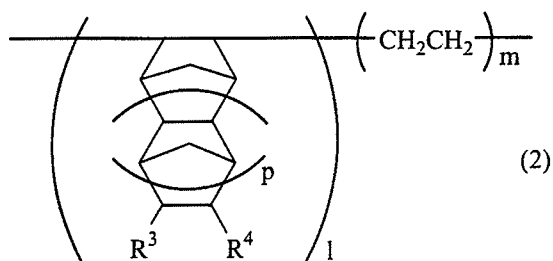
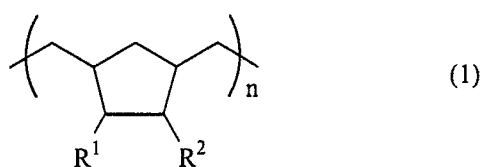
[0014]

The method and mechanism of polymerization of a cycloolefin monomer employed in the present invention may be ring-opening polymerization or additional polymerization. In the case where a plurality of monomers are used in combination, a known method and mechanism of polymerization may be employed. For example, a mixture of monomers may be copolymerized, or an additional monomer may be added to a polymer having a certain polymerization degree, to thereby form a block copolymer.

[0015]

Specific examples of the structure of the aforementioned polycycloolefin-based resin include those represented by the following structures (1) and (2):

[0016]



[0017]

(wherein  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$ , which may be identical to or different from one another, each represent a C1 to C20 organic group;  $R^1$  and  $R^2$  and/or  $R^3$  and  $R^4$  each may form a ring; each of  $m$  and  $p$  is an integer of 0 or  $\geq 1$ ; and each of  $l$  and  $n$  represents an integer of  $\geq 1$ ). The inventors have found that when the polycycloolefin-based resin is represented by formula (1) among these structures, the effect of enhancing drug storage stability is attained to a high degree.

[0018]

Specific examples of the C1 to C20 organic group, which are not limited to, include alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, i-pentyl, t-pentyl, n-hexyl, n-heptyl, n-octyl, t-octyl(1,1-dimethyl-3,3-dimethylbutyl), 2-ethylhexyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, and icosyl; cycloalkyl groups such as cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; alkylcycloalkyl groups such as

1-methylcyclopentyl, 1-methylcyclohexyl, and 1-methyl-4-i-propylcyclohexyl; alkenyl groups such as allyl, propenyl, butenyl, 2-butenyl, hexenyl, and cyclohexenyl; aryl groups such as phenyl, naphthyl, methylphenyl, methoxyphenyl, biphenyl, phenoxyphenyl, chlorophenyl, and sulfophenyl; and aralkyl groups such as benzyl, 2-phenylethyl (phenethyl),  $\alpha$ -methylbenzyl, and  $\alpha,\alpha$ -dimethylbenzyl. These organic groups may be employed singly or in combination of two or more species.

[0019]

The glass transition temperature of such polycycloolefins may be appropriately tuned through appropriately selecting the substituents and the values of l, m, n, and p in formula (1) and (2). The glass transition temperature of polycycloolefins other than the polycycloolefins represented by formula (1) and (2) may also be tuned to a desired value through appropriately selecting the species, ratio, and sequence of monomer(s), the type of substituents, etc.

[0020]

The polycycloolefin represented by formula (1) may be a commercial product. For example, Zeonex and Zeonoa (products of Nippon Zeon Co., Ltd.) are preferably used. The polycycloolefin represented by formula (2) also may be a commercial product. For example, Apel (product of Mitsui Chemicals Inc.) and TOPAS (product of TICONA) are preferably used.

[0021]

In the present invention, most preferably, a polycycloolefin represented by formula (1) is employed. The polycycloolefin of the invention is preferably formed solely of a resin represented by formula (1) and containing no other resins.

[0022]

In a drug container made of a polymer, an originally intended amount of the drug often fails to be maintained due to adsorption, permeation, or missing, since the drug contained in the container is captured by polymer chains of the polymer forming the container. Through molecule-level analysis, polymer chains of a polymer material are rotated via microbrownian motion. When the temperature of the polymer material is equal to or higher than the glass transition temperature, microbrownian motion of the molecular chains is promoted, thus, the polymer material becomes softer. As a result, a low-molecular-weight drug is readily captured by the polymer material, resulting in adsorption, permeation, or missing of the drug. Thus, the amount of effective component decreases. Particularly, glass transition temperature is a temperature at which microbrownian motion of polymer chains occurs, and therefore, reflects the ease of polymer chain motion. Studies conducted by the present inventors have shown that material design of a drug container based on the glass transition temperature is the best solution for preventing problematic adsorption of a drug on

the container and permeation or missing of the drug, which would otherwise cause a decrease in the amount of effective component. Since movement of polymer chains is determined by internal rotation of the chains and steric hindrance, the higher the internal rotation barrier, the higher the glass transition temperature. Such a polymer material can prevent mass transfer of a drug such as adsorption, permeation, or missing. By incorporating a large number of aromatic rings or heterocyclic rings, which has high internal rotation barrier, into backbones, a polymer material having high glass transition temperature can be obtained. An example of such polymer material is a polymer represented by formula (1). More preferably, in formula (1), each of  $R^1$  and  $R^2$  is a heterocyclic ring, and the "n" is adjusted to  $\geq 3$ , whereby the internal rotation barrier is considerably elevated, and a polycycloolefin having a glass transition temperature of 130°C or higher can be readily synthesized. The structure of formula (1) does not contain ethylene repeating units  $(-\text{CH}_2\text{CH}_2-)_m$ , which are contained in the structure of formula (2). Therefore, larger steric hindrance is realized, and a higher internal rotation barrier can be attained. Generally, polymers formed of ethylene repeating units such as polyethylene have a molecular structure having very small steric hindrance, and rotational motion of molecules is readily promoted at low temperature. When an element of a liquid container is produced solely from a polymer having such a molecular structure, a drug contained in the container

is readily adsorbed by the molecular chains, and permeation or missing of the drug occurs, thereby reducing the amount of effective component. In the structure of formula (2), ethylene repeating units are introduced between norbornene ring units, and the glass transition temperature is tuned by modifying the length of the ethylene unit sequence. Specifically, the glass transition temperature can be elevated by shortening the ethylene unit sequence. However, when ethylene repeating units are introduced into a backbone including norbornene rings or heterocyclic rings, steric hindrance decreases. Even though the glass transition temperature is equivalent, a drug is possibly captured by polymer chains of such a polymer. Therefore, the structure represented by formula (1) is more preferred.

[0023]

After introduction of a drug into the container, the container is preferably subjected to thermal treatment at 60°C or higher temperature or to high-pressure steam sterilization at 105°C or higher, more preferably at 121°C. Thus, another very important factor is that the molecular structure is designed so that microbrownian motion does not occur at the above temperatures, and the glass transition temperature is determined. The barrier layer of the liquid container is required to have a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization. If the glass transition temperature is

near the sterilization temperature or lower, the aforementioned microbrownian motion occurs during thermal treatment or high-pressure steam sterilization, and rotation of molecular chains occurs. Thus, adsorption of a drug contained in the container and permeation or missing of the drug cannot be prevented, thereby reducing the amount of effective component. The optimum glass transition temperature of polycycloolefin for preventing such phenomena must be higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization. The inventors' studies have shown that a preferable glass transition temperature of 130°C or higher is most effective.

[0024]

The barrier layer of the present invention contains a polycycloolefin-based resin having a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure steam sterilization, preferably having a glass transition temperature of 130°C or higher. The barrier layer may contain a resin other than the aforementioned polycycloolefin-based resin in such an amount that the effect of the invention is not impaired. However, the barrier layer preferably contain no such additional resin.

[0025]

In the present invention, the barrier layer preferably has a thickness of 5 to 40  $\mu\text{m}$ , more preferably 10 to 30  $\mu\text{m}$ ,

from the viewpoints of drug storage stability and softness of the container.

[0026]

In the present invention, the polyethylene-based resin or the polypropylene-based resin employed in the seal layer may be linear low-density polyethylene and/or high-density polyethylene, ethylene-propylene random copolymer or block copolymer, or polypropylene-based elastomer, which are generally employed for producing drug containers. The linear low-density polyethylene preferably has a melting point (melting peak temperature determined in accordance with JIS K7121 (DSC)) of 105 to 130°C, particularly preferably 110 to 130°C. The high-density polyethylene preferably has a melting point (melting peak temperature determined in accordance with JIS K7121 (DSC)) of 120 to 145°C, particularly preferably 130 to 140°C. Examples of preferably employed linear low-density polyethylenes and high-density polyethylenes include Petrothene and Nipolon (products of Tosoh Corporation), Moretec and Evolve (products of Prime Polymer), and Harmolex and Novatec HD (products of Japan Polyethylene Corporation). A polymer blend predominantly containing the aforementioned linear low-density polyethylene or high-density polyethylene may also be employed. To the aforementioned polyethylene-based resin, known additives such as an antioxidant, a photo-stabilizer, a neutralizing agent, an  $\alpha$ -nucleating agent, a  $\beta$ -nucleating agent, an anti-blocking agent, and a lubricant may be added, in such an amount that

the object of the invention is not impaired. In the present invention, the term "predominant component" refers to a component preferably having a content of 90 wt.% or more, particularly preferably 95 wt.% or more. The seal layer is subjected to a thermal treatment at 60°C or higher temperature or high-pressure steam sterilization at 105°C or higher temperature while it is in contact with a drug, and a so-called "sticking"; i.e., melting of an inner surface of the container, occurs in some cases. In order to prevent sticking, the polyethylene-based resin employed in the seal layer is preferably a linear low-density polyethylene having a melting point of 110 to 130°C and/or a high-density polyethylene having a melting point of 120 to 145°C.

[0027]

In the present invention, the seal layer preferably has a thickness of 20 to 120  $\mu\text{m}$ , more preferably 30 to 80  $\mu\text{m}$ , from the viewpoint of maintenance of the strength of the container.

[0028]

In the present invention, a base layer predominantly containing a polyolefin-based resin is preferably disposed on the surface of the barrier layer opposite to the seal layer, from the viewpoint of controlling strength and softness of the molded container. The polyolefin-based resin may be the same polyethylene-based resin as employed in the seal layer, or a polypropylene-based resin such as ethylene-propylene random or block copolymer or polypropylene-based elastomer.

Among them, the aforementioned polyethylene-based resin is particularly preferred. When the base layer is laminated on the barrier layer, an adhesive layer or an adhesive resin layer may be used. Such an adhesive is preferably a two-liquid curing type polyester-urethane adhesive or polyether-urethane adhesive. The adhesive resin layer may employ a known resin so long as the resin provides excellent adhesion with respect to a counter hetero-material. Examples of the adhesive resin include Admer (product of Mitsui Chemicals, Inc.), Modic (product of Mitsubishi Chemical Co., Ltd.), DLZ (product of Tosoh Corporation), and metallocene-type linear low-density polyethylene having a density of 0.91 or lower.

[0029]

When a base layer is provided in the present invention, the base layer preferably has a thickness of 30 to 200  $\mu\text{m}$ , more preferably 70 to 160  $\mu\text{m}$ , from the viewpoint of maintenance of the strength of the container.

[0030]

In the present invention, the total thickness of the multilayer film and/or multilayer sheet is preferably 100 to 400  $\mu\text{m}$ , since the liquid container is a medical-use container. When the total thickness is 100  $\mu\text{m}$  or less, the container may have a decreased strength, whereas when the total thickness is in excess of 400  $\mu\text{m}$ , the softness and handling performance of the container may be impaired.

[0031]

Most preferably, the multilayer film and/or multilayer

sheet of the present invention is a film and/or a sheet with three or more layers including a seal layer containing, as a predominant component, a linear low-density polyethylene having a melting point of 110 to 130°C and/or a high-density polyethylene having a melting point of 120 to 145°C; a barrier layer formed of a norbornene-based resin having a glass transition temperature of 130 to 170°C; and a base layer formed of a linear low-density polyethylene having a melting point of 110 to 130°C and/or a high-density polyethylene having a melting point of 120 to 145°C. In this embodiment, the barrier layer, seal layer, and base layer preferably have a thickness of 5 to 40  $\mu\text{m}$ , 20 to 120  $\mu\text{m}$ , and 30 to 200  $\mu\text{m}$ , respectively, particularly preferably 10 to 30  $\mu\text{m}$ , 30 to 80  $\mu\text{m}$ , and 70 to 160  $\mu\text{m}$ , respectively. In the case where the barrier layer is laminated with the seal layer and with the base layer by the mediation of an adhesive layer, the adhesive layer preferably has a thickness of 0.1 to 70  $\mu\text{m}$ , particularly preferably 0.5 to 30  $\mu\text{m}$ .

[0032]

The multilayer film and/or multilayer sheet of the present invention may be produced through a variety of known techniques such as dry lamination, extrusion coating, extrusion lamination, co-extrusion lamination (e.g., co-extrusion blowing or co-extrusion T-die method), co-extrusion water-cooled blowing, and heat lamination. These techniques may be employed singly or in combination.

[0033]

The liquid container of the present invention may be produced through, for example, a procedure which includes cutting two multilayer films through a customary method, stacking the two film pieces such that each seal layer is disposed inside, and heat-sealing the periphery of the stacked film pieces. Alternatively, the multilayer film is molded into a tube such that the seal layer is disposed inside, and the tube is heat-sealed for closure. The multilayer film is heat-sealed at 150 to 230°C. [0034]

In order to smoothly discharge the content of the liquid container, the liquid container of the present invention is preferably provided with a port member. No particular limitation is imposed on the material for the port member, so long as the material does not have such a problem that the material is readily broken by impact in the case of, for example, falling, and exhibits an excellent melt-adhesion property with respect to the aforementioned multilayer film and/or multilayer sheet. For example, a port member made of a polyethylene-based resin or a polypropylene-based material may be employed. The polyethylene-based resin is preferably a high-density polyethylene having a melting point of 120 to 145°C. Notably, when a port member made of polyethylene-based resin or polypropylene-based resin is employed, storage stability of a drug (e.g., nitroglycerin, a protein, hyaluronic acid, a vitamin, a trace element, or a radical scavenger) is not affected by adsorption and other phenomena. This unaffected storage stability may conceivably be provided

due to the difference in inner surface area between the container main body and the port member. When the port member is formed from a high-density polyethylene having a melting point of 120 to 145°C, melt bonding is performed through the following procedure. A port member is preliminarily heated for several seconds and then heated once or several times at 180 to 250°C for about 2 to about 6 seconds for sealing, and the sealed product is cooled at 5 to 30°C for 1 to 5 seconds. When the port member is formed from polypropylene having a melting point 120 to 165°C, melt bonding is performed through the following procedure. A port member is preliminarily heated for several seconds and then heated once or several times at 180 to 250°C for about 2 to about 6 seconds for sealing, and the sealed product is cooled at 5 to 30°C for 1 to 5 seconds.

[0035]

The liquid container of the present invention, which does not cause problems such as adsorption of a drug and exhibits excellent storage stability, can be employed for receiving a variety of liquid drugs that are adsorbed by resin. Particularly, the liquid container of the invention is suitable for producing pharmaceutical products each containing a drug such as a nitroglycerin-containing drug, a protein-containing drug, a hyaluronic acid-containing drug, a vitamin-containing drug, a trace element-containing drug, or a radical scavenger-containing drug, in the liquid container. More specifically, the liquid container is preferably

employed for producing a soft bag pharmaceutical product containing a drip infusion. For producing such pharmaceutical products, the liquid container is generally subjected to a thermal treatment or high-pressure steam sterilization. In the liquid container of the present invention, no sticking (i.e., melt adhesion or adhesion of an inner surface of the container) occurs after the thermal treatment or high-pressure steam sterilization. Preferably, the thermal treatment is performed at 60°C for 10 hours, and high-pressure steam sterilization is performed at 105°C or higher for 30 minutes or longer. More preferably, high-pressure steam sterilization at 110°C for 40 minutes is performed.

[0036]

When the liquid container of the present invention is employed for producing a pharmaceutical product of a nitroglycerin injection liquid, a raw drug (nitroglycerin) for producing pharmaceutical products generally employed in the art may be used. An example of the raw drug is powdered nitroglycerin-D-glucose. For producing a nitroglycerin injection liquid, the raw nitroglycerin is processed through a customary method. Specifically, the powdered nitroglycerin-D-glucose is dissolved in distilled water for injection liquid (Pharmacopoeia of Japan), and if required, a tonicity agent such as D-glucose or sodium chloride and a pH-regulator such as sodium hydroxide and hydrochloric acid are added, to thereby prepare a pharmaceutical product. No

particular limitation is imposed on the nitroglycerin concentration of the pharmaceutical product of the present invention, and the concentration is preferably 0.001 to 0.1 w/v%, more preferably 0.005 to 0.05 w/v%.

#### Examples

[0037]

The present invention will next be described in detail by way of Examples and Comparative Examples, which should not be construed as limiting the invention thereto.

[0038]

#### Examples and Comparative Examples

Multilayer (3 or more layers) film samples each including a base layer, a barrier layer, and a seal layer, formed of materials shown in Table 1, were produced through co-extrusion and dry lamination in combination. Port members were produced from materials shown in Table 1 through injection molding. Liquid containers (capacity: 100 mL) were produced from the film samples having three or more layers and port members.

[0039]

The following resins a to l and I to VI were employed for producing the film samples.

a: A 80:20 mixture of a linear low-density polyethylene (melting point: 120°C) (Moretec, products of Prime Polymer) and a linear low-density polyethylene (melting point: 105°C) (Harmolex, product of Japan Polyethylene Corporation)

b: A 85:15 mixture of a linear low-density polyethylene

(melting point: 120°C) (Moretec, product of Prime Polymer)  
and a linear low-density polyethylene (melting point: 105°C)  
(Harmolex, product of Japan Polyethylene Corporation)

c: Linear low-density polyethylene (melting point:  
120°C) (Petrothene, product of Tosoh Corporation)

d: Linear low-density polyethylene (melting point:  
120°C) (Moretec, product of Prime Polymer)

e: High-density polyethylene (melting point: 135°C)  
(product of Japan Polyethylene Corporation)

f: Alumina-vapor-deposited PET film (GL, product of  
Toppan Printing Co., Ltd.)

g: A 80:20 mixture of a high-density polyethylene  
(melting point: 136°C) (Nipolon Hard, product of Tosoh  
Corporation) and a linear low-density polyethylene (melting  
point: 120°C) (Moretec, product of Prime Polymer)

h: Linear low-density polyethylene (melting point:  
111°C) (Umerit, product of Ube-Maruzen polyethylene)

i: Linear low-density polyethylene (melting point:  
108°C) (Harmolex, product of Japan Polyethylene Corporation)

j: Polypropylene-based elastomer (melting point: 165°C)  
(Zelas, product of Mitsubishi Chemical Co., Ltd.)

k: Adhesive resin (Modic, product of Mitsubishi  
Chemical Co., Ltd.)

l: Polypropylene (melting point: 160°C) (Novatec,  
product of Japan Polyethylene Corporation)

[0040]

I: Polycycloolefin (glass transition temperature: 136°C)

(Zeonex 690R, product of Nippon Zeon Co., Ltd.)

II: Polycycloolefin (glass transition temperature: 163°C) (1600R, product of Nippon Zeon Co., Ltd.)

III: Polycycloolefin (glass transition temperature: 135°C) (Apel APL5014DP, product of Mitsui Chemicals Inc.)

IV: Polycycloolefin (glass transition temperature: 105°C) (Zeonox 1020R, product of Nippon Zeon Co., Ltd.)

V: Polycycloolefin (glass transition temperature: 75°C) (Zeonox 750R, product of Nippon Zeon Co., Ltd.)

VI: A 8:2 mixture of a polycycloolefin (glass transition temperature: 145°C) (Apel APL6015T, product of Mitsui Chemicals Inc.) and a linear low-density polyethylene (Evolue, product of Prime Polymer)

[0041]

[Table 1]

|                   |                      | Examples |     |     |     |     |     |     |     |     | Comparative Examples |     |     |     |     |
|-------------------|----------------------|----------|-----|-----|-----|-----|-----|-----|-----|-----|----------------------|-----|-----|-----|-----|
|                   |                      | 1        | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 1                    | 2   | 3   | 4   | 5   |
| Base layer        | Resin Thickness (μm) | a        | a   | a   | d   | a   | g   | j   | e   | a   | d                    | d   | d   | a   | h   |
|                   |                      | 155      | 160 | 155 | 170 | 155 | 150 | 155 | 155 | 155 | 170                  | 170 | 171 | 200 | 170 |
| Gas barrier layer | Resin Thickness (μm) | -        | -   | -   | -   | f   | -   | -   | -   | -   | -                    | -   | -   | -   | -   |
|                   |                      | -        | -   | -   | -   | 12  | -   | -   | -   | -   | -                    | -   | -   | -   | -   |
| Adhesive layer    | Type Thickness (μm)  | -        | -   | -   | -   | -   | -   | k   | a   | -   | -                    | -   | -   | -   | -   |
|                   |                      | -        | -   | -   | -   | -   | -   | 10  | 10  | -   | -                    | -   | -   | -   | -   |
| Barrier layer     | Resin Thickness (μm) | I        | I   | II  | III | I   | I   | I   | I   | V   | IV                   | V   | VI  | -   | IV  |
|                   |                      | 25       | 15  | 20  | 25  | 25  | 30  | 25  | 25  | 25  | 30                   | 25  | 25  | -   | 30  |
| Adhesive layer    | Type Thickness (μm)  | -        | -   | -   | -   | -   | -   | k   | a   | -   | -                    | -   | -   | -   | -   |
|                   |                      | -        | -   | -   | -   | -   | -   | 10  | 10  | -   | -                    | -   | -   | -   | -   |
| Seal layer        | Resin Thickness (μm) | b        | c   | b   | d   | b   | g   | j   | e   | b   | d                    | c   | c   | I   | i   |
|                   |                      | 70       | 75  | 70  | 50  | 70  | 70  | 50  | 50  | 70  | 50                   | 50  | 70  | 50  | 50  |
| Port member       | Resin                | e        | e   | e   | e   | e   | e   | l   | e   | e   | d                    | e   | e   | I   | d   |

[0042]

#### Test Example 1: Storage test

In each of the liquid container produced in the Examples and Comparative Examples, 0.05% nitroglycerin injection liquid (100 mL) was packed. The container was subjected to high-pressure steam sterilization at 110°C and 0.106 MPa for 40 minutes. After sterilization, the appearance of the container was observed to evaluate occurrence of sticking. Thereafter, a storage test was performed at 40°C. The nitroglycerin concentration of each pharmaceutical product was determined one month and three months after the start of the storage test, through high-performance liquid chromatography (HPLC). The ratio of the measured concentration to the initial concentration was employed as a percent maintenance of nitroglycerin. Table 2 shows the results.

[0043]

#### Test Example 2: Falling test

The impact resistance of the liquid container of the present invention was evaluated through a falling test. Similar to Test Example 1, a drug was packed in each of the liquid containers of the Examples and Comparative Examples, and the container was subjected to high-pressure steam sterilization. The treated container was stored at 5°C for 48 hours. Thereafter, the container was allowed to fall from a height of 1.80 m to the ground. Fallings were repeated for ten times, and the appearance of the container was observed.

Then, the container was placed on an iron plate having no foreign objects on a surface thereof and pushed by hand. The presence of breakage (cracking) of the container and leakage were checked. In each Example, 100 containers were tested. Table 2 shows the results.

[0044]

[Table 2]

|                                     |         | Examples |      |      |      | Comparative Examples |      |      |      |
|-------------------------------------|---------|----------|------|------|------|----------------------|------|------|------|
|                                     |         | 1        | 2    | 3    | 7    | 1                    | 2    | 3    | 4    |
| Storage test                        |         |          |      |      |      |                      |      |      |      |
| Sticking                            |         | no       | no   | no   | no   | no                   | no   | no   | no   |
| Effective component maintenance (%) | Month 1 | 99.6     | 99.0 | 99.9 | 99.3 | 93.0                 | 90.0 | 91.0 | 99.3 |
|                                     | Month 3 | 98.0     | 98.6 | 99.9 | 98.1 | -                    | -    | -    | -    |
| Falling test (breakage/leakage)     |         | no       | no   | no   | no   | no                   | no   | no   | yes  |

[0045]

As shown in Table 2, liquid containers falling within the scope of the present invention exhibited no substantial change in nitroglycerin content after storage at 40°C for three months. In contrast, a container including a barrier layer formed of a polycycloolefin-based resin having a glass transition temperature of 105°C (Comparative Example 1), a container including a barrier layer formed of a polycycloolefin-based resin having a glass transition temperature of 75°C (Comparative Example 2), and a container including a barrier layer formed of a resin mixture of a polycycloolefin-based resin having a glass transition temperature of 145°C and a linear low-density polyethylene

(Comparative Example 3) exhibited large decreases in nitroglycerin content after storage at 40°C for one month; specifically, 7%, 10%, and 9%, respectively.

[0046]

None of the liquid containers falling within the scope of the present invention exhibited breakage or leakage after the falling test, indicating that the liquid containers of the invention have been found to have high resistance to impact by falling. In contrast, in Comparative Example 4, wherein a bag was produced from a seal layer formed of a polycycloolefin-based resin having a glass transition temperature of 136°C and a port member formed of a polycycloolefin-based resin having a glass transition temperature of 136°C, leakage through the port member was confirmed after the falling test, although satisfactory storage stability was attained.

[0047]

#### Test Example 3

The procedure of Test Examples 1 and 2 was repeated, except that 20% albumin injection liquid was used as a drug, and a thermal treatment at 60°C for 10 hours was performed instead of high-pressure steam sterilization. Table 3 shows the results. Human plasma-derived albumin was packed in the container of Example 1, and albumin produced through a recombination technique was packed in the containers of the other Examples and Comparative Examples.

[0048]

[Table 3]

|                                     |         | Examples |      |      |      | Comp. Exs. |      |
|-------------------------------------|---------|----------|------|------|------|------------|------|
|                                     |         | 1        | 2    | 5    | 9    | 2          | 3    |
| Storage test                        |         |          |      |      |      |            |      |
| Sticking                            |         | no       | no   | no   | no   | no         | no   |
| Effective component maintenance (%) | Month 1 | 98.1     | 98   | 98.4 | 98.1 | 94.0       | 93.0 |
|                                     | Month 3 | 97.0     | 97.5 | 97.9 | 97.2 | -          | -    |
| Falling test (breakage/leakage)     |         | no       | no   | no   | no   | no         | no   |

[0049]

As shown in Table 3, similar to the case of nitroglycerin, liquid containers falling within the scope of the present invention exhibited no substantial change in albumin content after storage at 40°C for three months. In contrast, a container including a barrier layer formed of a polycycloolefin-based resin having a glass transition temperature of 75°C (Comparative Example 2) and a container including a barrier layer formed of a resin mixture of a polycycloolefin-based resin having a glass transition temperature of 145°C and a linear low-density polyethylene (Comparative Example 3) exhibited large decreases in albumin content after storage at 40°C for one month; specifically, 6% and 7%, respectively.

[0050]

None of the liquid containers falling within the scope of the present invention exhibited breakage or leakage even after the thermal treatment at 60°C for 10 hours, indicating that the liquid containers of the invention have been found

to have high resistance to impact by falling.

[0051]

#### Test Example 4

The procedure of Test Examples 1 and 2 was repeated, except that the drug was changed to a vitamin D3-containing pharmaceutical product, and high-pressure steam sterilization was performed at 105°C and 0.106 MPa for 30 minutes. Table 4 shows the results.

[0052]

[Table 4]

|                                     |         | Examples |      |      | Comp. Exs. |      |      |
|-------------------------------------|---------|----------|------|------|------------|------|------|
|                                     |         | 1        | 2    | 7    | 1          | 2    | 3    |
| Storage test                        |         |          |      |      |            |      |      |
| Sticking                            |         | no       | no   | no   | no         | no   | no   |
| Effective component maintenance (%) | Month 1 | 97.0     | 97.1 | 97.1 | 90.3       | 90.0 | 89.0 |
|                                     | Month 3 | 96.5     | 96.3 | 97.2 | -          | -    | -    |
| Falling test (breakage/leakage)     |         | no       | no   | no   | no         | no   | no   |

[0053]

As shown in Table 4, similar to the cases of nitroglycerin and albumin, liquid containers falling within the scope of the present invention exhibited no substantial change in vitamin D3 content after storage at 40°C for three months. In contrast, a container including a barrier layer formed of a polycycloolefin-based resin having a glass transition temperature of 105°C (Comparative Example 1), a container including a barrier layer formed of a polycycloolefin-based resin having a glass transition

temperature of 75°C (Comparative Example 2), and a container including a barrier layer formed of a resin mixture of a polycycloolefin-based resin having a glass transition temperature of 145°C and a linear low-density polyethylene (Comparative Example 3) exhibited large decreases in vitamin D3 content after storage at 40°C for one month; specifically, 6.7%, 7%, and 9%, respectively.

[0054]

None of the liquid containers falling within the scope of the present invention exhibited breakage or leakage when the content was vitamin D3, indicating that the liquid containers of the invention have been found to have high resistance to impact by falling.

[0055]

#### Test Example 5

The procedure of Test Examples 1 and 2 was repeated, except that the drug was changed to a radical scavenger-containing pharmaceutical product (edaravone), and high-pressure steam sterilization was performed at 105°C and 0.106 MPa for 30 minutes. Table 5 shows the results.

[0056]

[Table 5]

|                     |         | Examples |      |      | Comp. Exs. |      |      |
|---------------------|---------|----------|------|------|------------|------|------|
|                     |         | 1        | 2    | 8    | 2          | 3    | 5    |
| Storing test        |         |          |      |      |            |      |      |
| Sticking            |         | no       | no   | no   | no         | no   | yes  |
| Effective component | Month 1 | 98.0     | 98.1 | 98.1 | 89.3       | 88.9 | 88.7 |
| maintenance (%)     | Month 3 | 97.5     | 97.3 | 97.3 | -          | -    | -    |
| Falling test        |         |          |      |      |            |      |      |
| (breakage/leakage)  |         | no       | no   | no   | no         | no   | no   |

[0057]

As shown in Table 5, similar to the cases of nitroglycerin and albumin, liquid containers falling within the scope of the present invention exhibited no substantial change in edaravone (radical scavenger) content after storage at 40°C for three months. In contrast, a container including a barrier layer formed of a polycycloolefin-based resin having a glass transition temperature of 75°C (Comparative Example 2) and a container including a barrier layer formed of a resin mixture of a polycycloolefin-based resin having a glass transition temperature of 145°C and a linear low-density polyethylene (Comparative Example 3) exhibited large decreases in edaravone content after storage at 40°C for one month; specifically, 11% and 11.1%, respectively.

In the liquid container of Comparative Example 5, having a base layer and a seal layer formed of polyethylene having a melting point of 120°C or lower temperature, sticking occurred in portions inside thereof. The outside of the container was very sticky after sterilization, and one container was stuck to another container, which was

problematic.

[0058]

None of the liquid containers falling within the scope of the present invention exhibited breakage or leakage when the content was edaravone, indicating that the liquid containers of the invention have been found to have high resistance to impact by falling.

## Claims

[1] A liquid container formed of a multilayer film and/or multilayer sheet and a port member formed of a polyethylene-based resin or a polypropylene-based resin,

characterized in that the multilayer film and/or multilayer sheet has a barrier layer comprising, as a predominant component, a polycycloolefin-based resin having a glass transition temperature higher by 5°C or more than the temperature at which the container is subjected to thermal treatment or high-pressure stream sterilization,

a seal layer comprising, as a predominant component, a polyethylene-based resin or a polypropylene-based resin, and

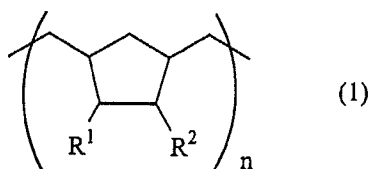
the barrier layer being provided adjacent to the seal layer.

[2] The liquid container according to claim 1, wherein the polycycloolefin-based resin is a polycycloolefin-based resin having a glass transition temperature of 130°C or higher.

[3] The liquid container according to claim 1 or 2, wherein the polyelthylene-based resin is a linear low-density polyethylene having a melting point of 110 to 130°C and/or a high-density polyethylene having a melting point of 120 to 145°C.

[4] The liquid container according to any one of claims 1 to 3, wherein the multilayer film and/or multiplayer sheet has, on the surface of the barrier layer opposite to the seal layer, a base layer predominantly comprising linear low-density polyethylene having a melting point of 110 to 130°C and/or high-density polyethylene having a melting point of 120 to 145°C.

[5] The liquid container according to any one of claims 1 to 4, wherein the polycycloolefin-based resin is represented by formula (1):



wherein R<sup>1</sup> and R<sup>2</sup>, which are identical to or different from each other, each represent a C1 to C20 organic group, and R<sup>1</sup> and R<sup>2</sup> may be linked to form a ring.

[6] The liquid container according to claim 5, wherein the barrier layer is formed solely of a polycycloolefin-based resin.

[7] The liquid container according to any one of claims 1 to 6, which is subjected to a thermal treatment at 60°C or higher or high-pressure stream sterilization at 105°C or higher.

[8] A pharmaceutical product for injection liquid, the pharmaceutical product comprising the liquid container according to any one of claim 1 to 7, filled by a solution of a drug that can be adsorbed by a resin and/or that can permeate a resin.

[9] The pharmaceutical product according to claim 8, wherein the drug which can be adsorbed by a resin and/or which can permeate a resin is a nitroglycerin-containing drug.

[10] The pharmaceutical product according to claim 8, wherein the drug which can be adsorbed by a resin and/or which can permeate a resin is a protein-containing drug, a hyaluronic acid-containing drug, a vitamin-containing drug, a trace element-containing drug, or a radical scavenger-containing drug.

[11] The pharmaceutical product according to claim 10, wherein the protein-containing drug is a drug containing human plasma-derived albumin, albumin produced through a recombination technique, or a hormone.