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Sommermeyer et al.

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[54] **PACKAGE UNITS FOR MEDICAL PURPOSES**

[75] Inventors: **Klaus Sommermeyer**, Rosbach; **Jürgen Koenig**, Wiesbaden; **Franz Cech**, Rosbach; **Reinhold Herbert**, Neu-Anspach, all of Fed. Rep. of Germany

[73] Assignee: **Fresenius AG**, Bad Homburg, Fed. Rep. of Germany

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[58] **Field of Search** ..... 604/408, 409, 410, 403

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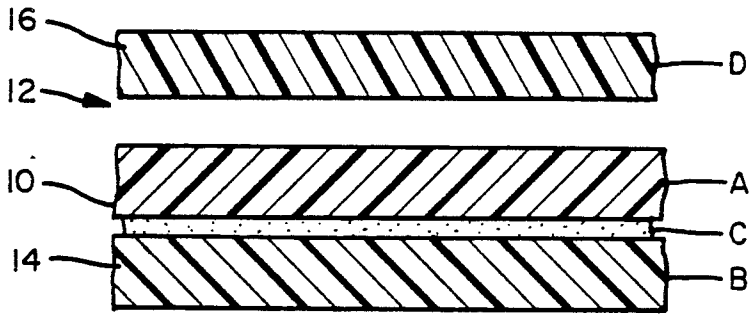
*Primary Examiner*—Robert A. Hafer
*Assistant Examiner*—Kerry Owens
*Attorney, Agent, or Firm*—Pravel, Gambrell, Hewitt, Kimball & Krieger

[57] **ABSTRACT**

The present invention describes package units for medical purposes, in particular for receiving and/or storing sterilizable preparations for parenteral uses or dialysis solutions, comprising a container having at least one discharge spout and consisting of polyamide **66** or a laminate of polyamide **66** sheet and polyolefin sheet, the polyolefin sheet being disposed on the side facing the liquid to be stored and the sheet of polyamide **66** being disposed on the outside and the two sheets being bonded together in usual manner by means of an adhesive. The package units may further comprise an inner container or an outer container. The package unit is made in that a container having at least one discharge spout is made from polyamide **66** or the aforementioned laminate, said container filled with the liquid to be stored, then sealed and sterilized and possibly subsequently surrounded after cooling and drying with an outer container of polymeric material. Package units according to the invention may also be made in that from a polymeric material an inner container having at least one discharge spout is made, said container filled with the liquid to be stored, sealed, then surrounded with an outer container of polyamide **66** or a laminate of polyamide **66** sheet and polyolefin sheet, the polyolefin sheet being disposed at the side of the laminate facing the inner container and the sheet of polyamide **66** of the laminate representing the outer sheet, and thereafter sterilized.

**20 Claims, 1 Drawing Sheet**



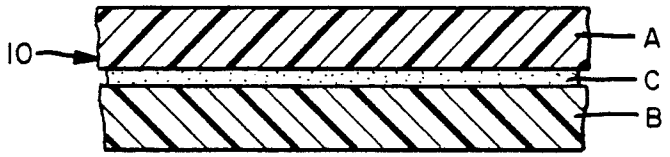



fig. 1

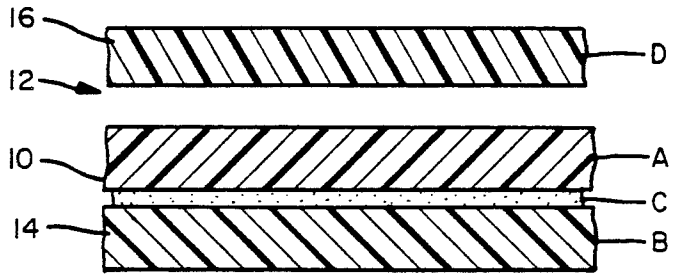



fig. 2

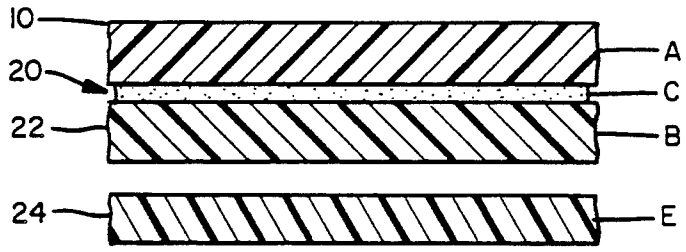



fig. 3

# PACKAGE UNITS FOR MEDICAL PURPOSES

The subject of the present invention is package units for medical purposes, in particular for receiving and/or storing sterilizable preparations for parenteral use of dialysis solutions, including a container having at least one discharge spout and consisting of a polymeric material including polyamide, which possibly have also an inner container or an outer container, and method for the production thereof.

It has been known for a long time to employ package units, for example bags, in particular for medical purposes for storing preparations for parenteral use or dialysis solutions, instead of glass bottles, for receiving and sterile storing of infusion solutions to be administered parenterally or of dialysis solutions. For this purpose these bags must be completely sterile and this is usually achieved by heating to at least 100° C., in particular to about 120° C.

This leads directly to the requirement made of the thermoplastic polymeric material that the latter be stable at least up to the heating temperature. In addition, such a storage bag must be easy to make in economical manner in an automatic production process and disposable after use because of its low value. It should also be flexible, foldable and in the processed state transparent so that changes of the liquid contained in the bag can be immediately noticed.

As material for filling these requirements preferably soft PVC containing plasticizer to improve its elastic properties was employed. These plasticizers, for example diisoctylphthalate, are however the cause of worrying phenomena, said plasticizers of softeners are not completely enclosed in the voids between the polymeric chains and can therefore be dissolved out of the polymer by the water or aqueous solution introduced into the bag so that contamination of the liquid contained in the bag occurs. Estimates have shown that a patent treated for a relatively long time using such PVC bags will have absorbed a few g plasticizer and this in itself is extremely worrying physiologically and can lead to permanent damage in the patient. Moreover, such a bag consisting of soft PVC easily be attacked by microorganisms which in particular dissolve out the plasticizers and thus regularly destroy the bag. To prevent this, after filling such a PVC bag had to be protected from harmful organisms by a special surrounding package.

These facts led to such PVC bags not being able to supersede to an appreciable extent the glass bottles used normally as storage containers for medical solutions and even not being allowed at all in the field of medicine in some industrial countries.

Attempts have therefore been made to replace the soft PVC by other materials. However, such attempts failed because these materials were either too expensive or had mechanical and physiological disadvantages. For example, their water permeability was too high and this led to an undesirable increase of the concentration of the substances contained in the solution. In addition, lixiviatable substances were liberated from them or they were easily damaged under excessive mechanical stress. CH-PS 444,382 describes such a plastic bag which can be used for therapeutical solutions to be employed parenterally. In this plastic bag the wall consists of a plastic laminate which comprises on the outside, i.e. the side remote from the liquid, a PVC layer and on the inside a polyhalogen hydrogen synthetic resin layer. The latter layer does not have any pharmacologically inadmissible constituents which by dissolving might pass into the solution contained in the bag. However, the polyhalogen hydrocarbon substances employed have the disadvantage that they are very expensive to produce and process and do not fuse adequately at the welds so that there is still a direct contact with the PVC. This contact also exists moreover at the discharge opening which is usually completely made of PVC and with which further PVC compound flexible tubes can be connected. Moreover, as disposable bag these plastic bags represent an environmental hazard because burning of said bags leads to highly aggressive hydrocarbons.

Polyolefins, e.g. polyethylene, have also already been proposed as materials for the storage package. Polyolefins are free from plasticizer and are thus not attacked by microorganisms. In addition, they have a good water vapour barrier and are sterilizable. Bags of polyolefins are described for example in DE-PS 3,200,264 and DE-PS 3,305,365.

These bags of polyolefins unfortunately however have the disadvantage that they have a relatively high oxygen permeability and this is problematical in the storage of solutions which must be kept for relatively long times in so far as due to the oxygen permeability oxidation of the dissolved constituents can occur. This is in particular extremely critical with amino acid solutions and must therefore be avoided. To overcome this problem it has been proposed according to DE-PS 3,200,264 and DE-PS 3,305,365 to coat the bag sheet of polyolefin on its outside with one or more layer(s) reducing this oxygen permeability, for example of a metal foil or a further polymer. Such a coating is also used for safety reasons because even on extremely careful production the bag sheet can have pinholes which cannot be seen and which can impair the sterility of the solution introduced. In addition, such a covering or coating can also considerably improve the mechanical loadability of such a bag so that such a bag even when dropped from a height of several metres does not burst. The sheet or layer used is one having a higher melting point than the polymer facing the solution, i.e. which at the melting temperature of the inner sheet does not itself melt and consequently will not stick to a sealing tool either. Such an outer sheet can thus also serve as parting agent in the sealing of the inner sheet. Named as preferred polymers for coating the polyolefin sheet are polymers having a low water vapour permeability and a low oxygen permeability, such as polyamides, and as polyamide polycaprolactam (PA 6) is preferred, containing no stabilizing additives and thus complying in its composition with the requirements for use in the foodstuff sector.

As however recent investigations on bags of such polyolefin/polyamide laminates have shown the laminates of polyolefin and polyamide, such as laminates of polyethylene and polycaprolactam, have disadvantages in that undesirable toxic foreign constituents are released into the liquids to be stored in the sterilization and render the solution unemployable for its intended use, for example the injection. As it has been possible to show, these foreign constituents reach the liquid to be stored by migration from the outer sheet of the laminate through the inner sheet of the laminate facing the liquid.

Bags of such laminates are therefore extremely dubious from the medical point of view.

Accordingly, the problem underlying the present invention is to provide package units of the aforemen-

tioned type which do not have the disadvantages of the known package units or bags, are unobjectionable from the medical point of view and in which no migration of foreign constituents into the solution to be stored takes place, and which furthermore are mechanically stable, transparent and heat-sterilizable and have low water vapour permeability and low oxygen permeability and in addition cannot be attacked by microorganisms.

According to the invention this problem is solved in that as polyamide polyamide **66** is employed.

Under the term "polymeric material including polyamide" herein polyamide or polyamide-containing laminate of polymeric material is meant. Thus, according to the invention the container of the package unit according to the invention may consist both only of polyamide **66** and of a laminate of polymeric material including polyamide **66**.

Polyamide **66** (PA **66**) means the polycondensate obtained by polycondensation of hexamethylene diamine and adipic acid.

It has surprisingly been found according to the invention that when using polyamide **66**, in contrast to the other polyamides, for example polyamide **6**, polyamide **11**, polyamide **12** or polyamide **13**, as polymeric material for the container for the package unit after the sterilization no foreign constituents or no ponderable amounts of foreign constituents are to be found in the liquid to be stored. The same is true when as polymeric material for the containers of the package unit polyamide **66** is employed in the laminate with polyolefin sheets, the polyolefin sheet being disposed on the side facing the liquid to be stored and on the outside the sheet of polyamide **66**, the two sheets being bonded together in usual manner by means of an adhesive. Whereas for example in using bags of a laminate of polyethylene and polyamide **6**, the polyethylene sheet being used as inner sheet and the polyamide **6** sheet as outer sheet, after sterilization in the liquid to be stored foreign constituents were found in an amount of 5 to 15 ppm, the respect to the product, under the same conditions for bags made from a laminate of polyethylene and polyamide **66**, the polyethylene sheet being disposed on the side facing the liquid and the polyamide **66** sheet on the outside, no or no ponderable amounts (weighing accuracy $<1$ mg) of foreign constituents could be found in the liquid to be stored.

According to a preferred embodiment as material for the container of the package unit according to the invention the polyamide **66** is used in a laminate with a polyolefin, the polyolefin sheet being disposed on the side facing the liquid to be stored and the polyamide **66** sheet on the outside and the two sheets being bonded together in usual manner by means of an adhesive.

As polyolefins which for making the package unit according to the invention can be used as polymer for the inner sheet, according to the invention polymers of olefins are suitable, such as ethylene, propylene, butylene and the like, which are possibly substituted. As substituents for example the methyl or ethyl group, the vinyl group and halogen atoms, in particular fluorene or chlorine atoms, may be present. Preferably employed as starting olefin are ethylene and propylene, in particular ethylene polymerized to polyethylene being employed.

Specific examples for polyolefins are: polyethylene, polypropylene, poly-n-butylene, polyisobutylene, poly-4-methylpentene-1, chlorosulfonated polyethylene, polystyrene, halogenated polyethylene, such as polyvinyl fluoride, polyvinylidene fluoride and polyvinylidene chloride, polymethylmethacrylate and the like. The olefins employed for making the above polyolefins may also be used as copolymers and mixed polymers with other vinyl compounds, for example ethylene/propylene plastics, poly (ethylene/vinyl acetate), acrylonitrile/butadiene/styrene polymers, ethylene-propylene block copolymers, styrene copolymers, copolymers containing vinylidene fluoride and copolymers containing styrene.

According to the invention polyolefins are products which are made by the vinyl polymerization of possibly substituted olefin, preferably ethylene. These products may also have slight additives of other polymers which do not essentially destroy or change the structure of said polyolefins. Thus, for example, small amounts of styrene-substituted or polyacrylonitrile-substituted ethylene compounds may be added. The resulting polyolefin products are considered as belonging to the polyolefins specified above.

According to the invention, as polyolefin preferably polyethylene is used as material for the inner sheet, possibly with slight additions of vinyl acetate in the form of the copolymer of ethylene and vinyl acetate.

In such a case for example the vinyl acetate content may be up to 10% by weight.

In particular a polyethylene is used of medium or high density (MDPE and HDPE) which is usually made by low-pressure polymerization. The density lies within a range of 0.91 to 0.94 g/cm$^3$, in particular about 0.935 g/cm$^3$.

Furthermore, the polyethylene preferably used according to the invention has a high molecular weight and a narrow molecular weight distribution.

It is however to be ensured in every case that such polyolefins do not have a melting point below the sterilization temperature of about 110°–120° C. Preferably, the melting range should be above 110° C.

For making the sheets suitable for the laminates the usual extruding method of making sheets or hose sheets can be employed and do not present the expert with any appreciable problems. The polymeric inner sheet and the polymeric outer sheet are bonded together in a manner known per se. Any known method suitable for making the laminates according to the invention can be employed. Preferably, the inner and outer sheets are adhered together by means of a laminating adhesive such as polyvinylidene chloride or a polyurethane. Such a polyurethane adhesive can advantageously be a two-component adhesive, the first component consisting of a laminated adhesive and the second component of an additive lacquer.

In the production technique the polyolefin used as inner sheet can be extruded in the form of a hose-like sheet and thereafter adhered to the laminated sheet of polyamide **66** using the laminating adhesive mentioned above, polyurethane being preferred.

FIG. **1** is a side view in cross-section of a polymeric laminate material according to the present invention.

FIG. **2** is a partial side view in cross-section of a package unit according to the present invention.

FIG. **3** is a partial side view in cross-section of a package unit according to the present invention.

Preferred laminates have at a temperature of about 23° C. and a relative air humidity of 85% as a rule a water vapour permeability according to DIN 53122 of $<1$. Such values apply to standard laminates which are advantageously up to 0.2 mm thick, with a thickness of 50 to 150 μm, in particular about 100 μm, for the poly-

olefin sheet and 20 to 100 μm, in particular 30 to 80 μm, for the polymeric laminating sheet of polyamide **66**. For example, a particularly suitable laminate consists of a 130 μm thick polyethylene sheet and a 50 μm thick sheet of polyamide **66**.

In the laminates according to the invention, particularly in the preferred laminates, the oxygen permeability is reduced, this value lying below 15 $cm^3/m^2 \times$ day $\times$ bar pressure difference.

The sheets used according to the invention for making the laminate have been approved both by the Federal Health Office in Berlin and by the FDA (Federal Drug Administration) in the U.S.A. as physiologically harmless for use in the foodstuff sector and in the medical sector.

The laminates of polyolefin and polyamide **66** used for the package units according to the invention are free from plasticizers and additives or constituents which might possibly be physiologically objectionable and in particular could diffuse or migrate into the aqueous solution. The laminates used according to the invention are heat-sterilizable, clear and transparent and also have these properties after the sterilization.

Furthermore, they are mechanically stable and have low vapour permeability and a high oxygen barrier effect.

The package units according to the invention or the containers of said package units according to the invention may have any suitable shape or form. Expediently, they are made in the form of bags.

The package units or containers or bags according to the invention have at least one discharge spout or outlet nozzle which is formed in hose manner or includes a tube piece or insert piece. The latter may consist of respectively suitable material and can be formed in any desired manner and secured in the container or bag. For example, they may be formed in the manner described in DE-PS 3,305,365 and DE-PS 3,200,264, to which reference is made hereby, and consist of the materials specified therein.

The production and processing of the materials for the package units or containers according to the invention is carried out by the methods usual in plastics technology, as already explained above. Thus, for example, the containers may be made by an extrusion of hose-like sheets, corresponding cutting to size of the sheets and lamination and subsequent edge welding thereof. The containers, in which the edge provided for the discharge spout remains unwelded, are subsequently fused to a tube piece possibly comprising a bonding layer or an insert piece comprising the discharge opening(s) and possibly surrounded by a bonding layer. When using a bonding layer as described for example in DE-PS 3,305,365 the tube or insert piece is provided with such a bonding layer in accordance with the usual techniques, as can be done for example by simply drawing on or pushing over the elastic material of the bonding layer in hose form onto the tube piece or insert piece and introducing it into the opened container. Thereafter the heat sealing of the entire still not welded edge to the hose connection piece or to the tube piece or insert piece provided with the bonding layer is carried out. If several tube pieces are provided this processing step is carried out simultaneously, corresponding sealing tools being of course employed. The heat sealing is carried out by the usual methods.

The sterilization of the containers thus made is by the usual methods in an autoclave and of course to avoid bursting of the containers in the autoclave an excess pressure must be applied to balance the pressure obtaining in the container interior. For safety reasons and, if a bonding layer is employed, to fix the bonding layer, however, a higher excess pressure is used than would be necessary to balance the pressure obtaining in the container interior. The excess of this pressure over the pressure obtaining in the container is not critical but for example it should be at least 0.5 bar greater than the pressure obtaining in the container. It may be 2 to 3 bar, for example 2.2 bar.

If this is necessary due to the materials employed, the laminates according to the invention can further be subjected to a crosslinking after the sealing of the containers, before the liquid to be stored is introduced and before the sterilization.

In the cases where a crosslinking of the welded container material comprising discharge spouts with hose connection pieces or tube or insert pieces is intended, said crosslinking is carried out before the sterilization, if a sterilization is then still necessary, by methods known per se as described for example in DE-PS 3,200,264 and EP-PS 0 068 271.

In accordance with a further embodiment, in particular in cases where a particularly high protection against mechanical damage is to be obtained and/or for long-time storing of the package units, the container of the package unit according to the invention may be surrounded by a further container, an outer container.

Suitable materials for such a further container or outer container are materials which are able to protect the container according to the invention, which when using an outer container represents the inner container, from mechanical damage, avoid any water vapour losses, prevent access of microorganisms (no fungus formation or sporulation), represent a gas barrier, i.e. oxygen barrier, are preferably substantially transparent and permit a long-time storage of the package units.

Examples of such materials are metal or plastic foils or laminates which fulfil the aforementioned conditions. Preferred are foils or laminates of plastic.

Examples for metal foils or laminates are:
aluminium foils,
laminates of polyethylene sheets and aluminium foils,
laminates of polypropylene sheets and aluminium foils.

Suitable as plastics are essentially the polyolefins as names above in conjunction with the containers according to the invention, which when using outer containers represent the inner containers. Said plastics may be used in the form of individual sheets or in the form of laminates of two or more sheets. Preferred are laminates of two sheets: inner sheet, i.e. the sheet facing the inner container, and outer sheet, i.e. the outer foil or sheet coming into contact with the environment.

Particularly suitable according to the invention for the outer container are laminates of polyolefins as named above for the inner container, polyethylene being particularly preferred as polyolefin, and polyesters, copolymers of ethylene and vinyl alcohol, copolymers of ethylene and vinyl acetate. Examples of suitable laminates are laminates of polyethylene sheet and polyester sheet, as polyester polyethylene terephthalate and polybutylene terephthalate being particularly suitable, laminates of polyethylene sheet and a sheet of copolymers of ethylene and vinyl alcohol, laminates of polyethylene sheet and a sheet of copolymers of ethylene and vinyl acetate.

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