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(54) Molded PVC medical device
Geformte medizinische Vorrichtung aus PVC
Dispositif médical moulé à base de polychlore de vinyle

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(56) References cited:
EP-A- 0 165 579
FR-A- 2 542 320
GB-A- 834 235

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BACKGROUND OF THE INVENTION

[0001] This invention relates to a medical device, and more particularly, to a highly safe medical device. More illustratively, this invention is directed to a highly safe blood bag system having an excellent blood- or blood component-storability.

[0002] Soft bags fabricated from polyvinyl chloride are recently used to store blood for transfusion instead of rigid glass containers mainly in view of the reduced damage of erythrocytes during the storage. Use of such polyvinyl chloride soft bags has increased also for their superior workability, flexibility, transparency, resistance to vapor permeation, heat resistance, and the like. Conventional polyvinyl chloride resins which has been used for fabricating such blood storage bags contain from about 30 to 60 parts by weight of a phthalate for plasticizing purpose. Such phthalate elutes into blood during the blood storage, and it has been found out that the phthalate in blood protects membrane of various cells of the blood, in particular, erythrocytes. Despite such positive effects, the phthalate eluted into the blood may induce safety problems upon its introduction into the body by blood transfusion.

SUMMARY OF THE INVENTION

[0003] In view of the above-described situation, an object of the present invention is to provide a medical device molded from a highly safe, flexible polyvinyl chloride resin composition which has blood storability equivalent to or higher than conventional materials. Such an object is attained by the selection of a plasticizing agent which has a plasticizing efficiency equivalent to or higher than the phthalate, the plasticizer that has been used for medical flexible polyvinyl chloride resins, and which has an erythrocyte membrane-protecting action equivalent to or higher than the phthalate, and which is safer than the phthalate.

[0004] According to the present invention, there is provided a medical device comprising a molded article of a resin composition prepared by blending 100 parts by weight of a vinyl chloride-based resin; 5 to 100 parts by weight of a dialkyl malate represented by the general formula:

\[
\text{RO-CH} \quad \text{CH}_2 \quad \text{COO(CH}_2\text{)}_a\text{H} \\
\text{CH}_2 \\
\text{COO(CH}_2\text{)}_b\text{H}
\]

wherein a and b independently represent an integer of from 2 to 12, and R represent a member selected from the group consisting of hydrogen atom, acetyl group, propionyl group, and butyryl group; and 1 to 20 parts by weight of a stabilizer.

[0005] In the formula (I), a and b may most preferably be from 4 to 8, and the dialkyl malate may preferably be dihexyl malate, diocetyl malate, monohexyl monoocetyl malate, dihexyl acetylmalate, diocetyl acetylmalate, monohexyl monoocetyl acetylmalate, dihexyl butyrylmalate, diocetyl butyrylmalate, or monohexyl monoocetyl butyrylmalate.

[0006] The stabilizer may mainly comprise an epoxidized vegetable oil, and/or a Ba-Zn or a Ca-Zn-based stabilizer.

[0007] The medical device of the invention may preferably be a flexible medical device that is brought into contact with a body fluid or a medicament fluid, and most preferably, a blood bag system comprising blood bags and tubes.

BRIEF DESCRIPTION OF THE DRAWING

[0008] FIG. 1 is a plan view of a blood bag system according to an embodiment of the invention. FIG. 2 diagrammatically shows decomposition of various plasticizers in relation to incubation period.

DETAILED DESCRIPTION OF THE INVENTION

[0009] As mentioned above, the medical device of the present invention comprises an article molded from a resin composition prepared by blending 100 parts by weight of a vinyl chloride-based resin; 5 to 100 parts by weight of a
dialkyl malate represented by the general formula (I); and 1 to 20 parts by weight of a stabilizer.

[0010] The vinyl chloride-based resins which may be used in the present invention include vinyl chloride homopolymers and vinyl chloride copolymers containing at least 70% by weight, and preferably, at least 85% by weight of vinyl chloride. The vinyl chloride homopolymers and copolymers may have an average degree of polymerization of from 700 to 3,000, and preferably, from 1,000 to 2,400. The comonomers which may be copolymerized with the vinyl chloride include vinylidene chloride; ethylene; propylene; vinyl acetate; vinyl bromide; vinyl fluoride; styrene; vinyltoluene; vinyl pyridine; acrylic acid; allyl acrylate such as methyl acrylate, ethyl acrylate, isopropyl acrylate, n-butyl acrylate, and 2-ethylhexyl acrylate; methacrylic acid; allyl methacrylate such as methyl methacrylate, ethyl methacrylate, and 2-ethylhexyl methacrylate; acrylonitrile, and methacrylonitrile. The vinyl chloride-based resins may optionally have blended therewith a resin such as a styrene-acrylonitrile copolymer or a styrene-methacrylonitrile copolymer.

[0011] The dialkyl malates blended in the present resin composition as a plasticizing agent include those represented by the general formula:

\[
\begin{align*}
\text{COO(CH}_2\text{)}_a\text{H} \\
| \\
\text{RO-CH} \\
| \\
\text{CH}_2 \\
| \\
\text{COO(CH}_2\text{)}_b\text{H}
\end{align*}
\]

wherein a and b may independently represent an integer of from 2 to 12; and preferably, from 4 to 8; and R may represent hydrogen atom or an acyl group represented by the formula: R'CO, which may preferably be acetyl group, propionyl group, or butyryl group.

[0012] When a or b is 1 or less, an excessive amount of the plasticizing agent would elute from the resulting resin composition. On the other hand, when a or b is 13 or more, the dialkyl malate would have an insufficient plasticizing efficiency, and as a result, an excessive amount of dialkyl malate would be required to achieve a sufficient plasticizing effect to induce the problem of an insufficient compatibility with the vinyl chloride-based resin.

[0013] Preferable dialkyl malates include dihexyl malate, dioctyl malate, monoheptyl monoctyl malate, dihexyl acetylmalate, dioctyl acetylmalate, monohexyl monoctyl acetylmalate, dihexyl butyrylmalate, dioctyl butyrylmalate, and monoheptyl monooctyl butyrylmalate.

[0014] It should be noted that the alkyl group represented by the formula: \((\text{CH}_2\text{)}_a\text{H}\) or \((\text{CH}_3\text{)}_b\text{H}\) in the general formula (I) may be either a straight chain or a branched alkyl group. Exemplary branched alkyl groups include ethyl hexyl group.

[0015] The dialkyl malates as described above may be synthesized by any desired conventional process. For example, the dialkyl malate may be produced by heating malic acid and more than two molar amounts of an aliphatic alcohol in the presence of an acid such as sulfuric acid to allow a reaction to take place; neutralizing the reaction product with a base such as caustic soda; washing the product with water; and distilling the product for purification. When it is desired to react the hydroxyl group in the malate, an aliphatic acid anhydride may be further reacted with the malate in the presence of an acid such as sulfuric acid, followed by neutralization with a base such as caustic soda, washing with water, and purification by distillation.

[0016] The dialkyl malate may be used in an amount of from 5 to 100 parts by weight, preferably, from 40 to 80 parts by weight, and most preferably, from 50 to 70 parts by weight per 100 parts by weight of the vinyl chloride-based resin.

[0017] The stabilizer which may be used in the present resin composition include epoxy compounds such as epoxidized vegetable oils, for example, epoxidized soybean oil and epoxidized linseed oil; cycloclohexene oxide derivatives such as di-2-ethylhexyl epoxy hexahydropthalate, vinylcyclohexane dioxide, 3,4-epoxy-6-methylcyclohexylyl-3,4-epoxy-6-methylcyclohexene carbonate, and dicyclopentadiene dioxide; metallic salts such as salts between calcium, zinc, barium, magnesium or tin and stearic acid, lauric acid, ricinoleic acid, naphthenic acid or 2-ethylhexoic acid, for example calcium stearate, zinc stearate, calcium laurate, zinc laurate, barium stearate, magnesium stearate, and tin stearate; phosphorous esters such as didecylphenyl phosphite; organic stabilizers such as a mixture of stearoylbenzoylmethane and palmitoylbenzoylmethane; and mixtures thereof.

[0018] The stabilizer may be used generally in an amount of from 1 to 20 parts by weight, and preferably, from 1 to 15 parts by weight per 100 parts by weight of the vinyl chloride-based resin. Although the above-mentioned stabilizers can be used alone, use of the epoxy compound in combination with the metallic salt, the phosphorous ester, or the organic stabilizer is preferred. When the epoxy compound is used as the stabilizer, it may be used generally in an amount of from 1 to 15 parts by weight, and preferably, from 5 to 10 parts by weight per 100 parts by weight of the vinyl chloride-based resin, and use of epoxidized soybean oil is the most preferred. When the metallic salt, the phosphorous
ester, or the organic stabilizer is used in combination with the epoxy compound, it may be used in an amount of from 0.01 to 8 parts by weight, and preferably, from 0.05 to 5 parts by weight per 100 parts by weight of the vinyl chloride-based resin, and use of a Ca-Zn-based or Ba-Zn-based metallic salt is the most preferred.

[0019] The resin composition of the present invention may optionally contain a conventional additive such as an inorganic or an organic filler or a pigment. Exemplary fillers include talc, calcium carbonate, silica, carbon, tar and asphalt.

[0020] In producing the resin composition of the present invention, components may be blended in a ribbon blender, tumbling mixer or Henschel mixer. The resulting blend may be directly molded into the product, or alternatively, further melt milled in an extruder, Banbury mixer or two-roll mill before molding. Alternatively, the components may be dissolved in a suitable solvent such as a hydrocarbon or an aromatic solvent to form a polymeric solution. The molten mixture or the mixed solution may then be molded into the product of desired shape by means of a suitable molding machine, for example, a single-screw extruder, vented extruder, twin-screw extruder, co-kneader, plasticator, mixtruder, twin conical screw extruder, planetary screw extruder, gear extruder, and screwless extruder.

[0021] No in vivo data is available for the case of the dialkyl malate administered into blood by such means as blood transfusion. However, malic acid is a substance which is naturally present in the human body, and it is readily estimated that a malate should be less toxic than a phthalate having phthalic acid structure which does not naturally exist in the human body. In an in vitro experiment, which will be described later, malates showed a decomposition rate in a solution containing plasma significantly higher than that of phthalate. Surprisingly, decomposition of the malates were even faster than citrates. The results of the experiment are also shown in FIG. 2.

[0022] Next, production of a blood bag system, which is an example of the medical device according to the present invention, is described in detail by referring to the drawing. In the drawing, there is depicted an exemplary blood bag system comprising a main blood bag 3 and auxiliary blood bags 13 and 22. The blood bag 3 is fabricated from the resin composition of the present invention, and is sealed in its periphery 4 by such means as high frequency heating to define an interior space 5. The blood bag 3 is formed with a plurality of outlets 1 each provided with a peel-tab, and an outlet 2. A blood-collecting tube 6 which also comprises the resin composition of the present invention is connected to the blood bag 3 such that the interior of the tube 6 is in communication with the interior space 5 of the blood bag 3. In the interior space 5 of the blood bag 3 is accommodated an anticoagulant such as citrate-phosphate-dextrose (CPD) solution. To the distal end of the blood collecting tube 6 is attached a blood collecting needle 7.

[0023] The auxiliary blood bag 13 is also fabricated from the resin composition of the present invention, and is sealed in its periphery 10 by such means as high frequency heating to define an interior space 11. The blood bag 13 is formed with a plurality of outlets 9 each provided with a peel-tab. A connection tube 12 which also comprises the resin composition of the present invention is connected to the blood bag 13 such that the interior of the tube 12 is in communication with the interior space 11 of the blood bag 13. For connecting the auxiliary blood bag 13 to the main blood bag 3, the connection tube 12 is connected to a connection tube 16 via a branch pipe 14, and the connection tube 16 is connected to the outlet 2 which is provided for such connection purpose at its connecting site 15.

[0024] The auxiliary blood bag 22 is also fabricated from the resin composition of the present invention, and is sealed in its periphery 18 by such means as high frequency heating to define an interior space 19. The blood bag 22 is formed with a plurality of outlets 17 each provided with a peel-tab. A connection tube 21 which also comprises the resin composition of the present invention is connected to the blood bag 22 such that the interior of the tube 21 is in communication with the interior space 19 of the blood bag 22. The connection tube 21 is connected to the connection tubes 12 and 16 via the branch pipe 14. The main blood bag 3 is thereby connected to the auxiliary blood bag 22 as well as the auxiliary blood bag 13.

[0025] In the above description, the medical device according to the present invention has been described by referring to the embodiment of a blood bag system. The resin composition of the present invention can also be used in such medical devices as blood storage containers, containers for a blood transfusion system, containers for a blood circuit, infusion bags, catheters, dialysis tubes and various other medical tubes; artificial kidneys, artificial lungs, artificial livers, and other artificial organs; and tubes and other devices used for a respiratory circuit.

[0026] The present invention is hereinafter described in further detail by referring to the following Examples and Comparative Example.

EXAMPLES

Examples 1 to 7 and Comparative Example 1

[0027] To 100 parts by weight of a polyvinyl chloride having an average degree of polymerization of 1,300 (S-1003, manufactured by Kanegafuchi Chemical Industry Co., Ltd.) were mixed the plasticizing agent and the stabilizers shown in Table 1, below. The amount of the plasticizing agent and the stabilizers are also shown in Table 1. The mixture was fabricated into a sheet of about 0.4 mm thick by a conventional method, namely, extrusion molding.
**Tensile Properties**

[0028] The resulting sheet was evaluated for its tensile properties using Strograph manufactured by Toyo Precision Machines K.K. in accordance with Japanese Industrial Standards (JIS) K-6301 by using rubber #3 dumbbell at a tensile speed of 200 mm/min and at a temperature of 23°C.

**Elution**

[0029] The resulting sheet was also evaluated for its elution properties in accordance with "Standards for Blood Sets Fabricated from Polyvinyl Chloride" noticed by Ministry of Health and Welfare of Japan.

**Cytotoxicity Test**

[0030] The sheet was also evaluated for its safety with regard to its cytotoxicity.

[0031] A test sheet having a surface area of 18 cm² and 3 ml of MEM medium (manufactured by Nihon Pharmaceutical K.K.) were placed in a vial with threaded top, and subjected a treatment in an autoclave at 121°C for 60 minutes to obtain an extract. The liquid extract was administered to Hela-S3 cells, and the cells were incubated at 37°C for another 2 days. The cells were then microscopically observed by comparing with the blank cell culture wherein the cells had been incubated with no administration of such an extract. The cell culture which showed no difference with the blank cell culture was determined to be negative, and the cell culture wherein the cell growth had been hindered or wherein the cells had died was determined to be positive.

**Resistance to Sterilization after its fabrication into bag**

[0032] The sheet was cut into a predetermined shape, and two pieces of the thus cut sheets were stuck one on another and high-frequency sealed to produce a blood bag having an interior surface area of about 50 cm². The thus produced blood bag was heat sealed, and sterilized in an autoclave. No significant deformation was noted for both the bags of the Examples and the Comparative Example to indicate that the bags could endure the sterilization under practical conditions.

**Evaluation for Hemolysis**

[0033] A test piece having a surface area of 6 cm² (total of the front and back surfaces) was cut out of the sheet. The test piece was placed in a glass test tube, and sterilized in an autoclave at 121°C for 20 minutes. To the test tube was aseptically poured 5 ml of whole blood having added thereto citrate-phosphate-dextrose (CPD). The test tube was then sealed and stored at 4°C for 28 days. After the storage, the blood was centrifuged at 1,500 rpm for 10 minutes at room temperature. Concentration of hemoglobin in the supernatant plasma was measured by cyanmethemoglobin method to use it for the index of hemolysis during the storage.

[0034] The results are shown in Table 1.
<table>
<thead>
<tr>
<th>Resin Composition</th>
<th>Ex. 1</th>
<th>Ex. 2</th>
<th>Ex. 3</th>
<th>Ex. 4</th>
<th>Ex. 5</th>
<th>Ex. 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVC (S-1003)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Plasticizing agent</td>
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<td>100</td>
<td>100</td>
<td>100</td>
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<td>Plasticizer</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Amount</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Epoxylated oil</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
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<td>Amount</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>Ba-Zn-based stabilizer</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
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<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tensile properties</th>
<th>Ex. 1</th>
<th>Ex. 2</th>
<th>Ex. 3</th>
<th>Ex. 4</th>
<th>Ex. 5</th>
<th>Ex. 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tensile strength, kg/cm²</td>
<td>180</td>
<td>160</td>
<td>180</td>
<td>180</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>Elongation, g</td>
<td>530</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
<td>560</td>
</tr>
<tr>
<td>Modulus, kg/cm²</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytotoxicity Test</th>
<th>Hemoglobin concentration of the plasma after storage, mg/dl</th>
<th>Ex. 1</th>
<th>Ex. 2</th>
<th>Ex. 3</th>
<th>Ex. 4</th>
<th>Ex. 5</th>
<th>Ex. 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elution Test</td>
<td>Negative positive</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>negative positive</td>
<td>107</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>Di-n-butyl malate</td>
<td>Negative positive</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Di-n-hexyl malate</td>
<td>Negative positive</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
</tr>
<tr>
<td>Di-n-octyl malate</td>
<td>Negative positive</td>
<td>40</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Di-n-octyl-acetil malate</td>
<td>Negative positive</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Di-n-propyl phthalate</td>
<td>Negative positive</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity Test</th>
<th>Hemoglobin concentration of the plasma after storage, mg/dl</th>
<th>Ex. 1</th>
<th>Ex. 2</th>
<th>Ex. 3</th>
<th>Ex. 4</th>
<th>Ex. 5</th>
<th>Ex. 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity Test</td>
<td>Negative positive</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>negative positive</td>
<td>107</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>Di-n-butyl malate</td>
<td>Negative positive</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Di-n-hexyl malate</td>
<td>Negative positive</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
</tr>
<tr>
<td>Di-n-octyl malate</td>
<td>Negative positive</td>
<td>40</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Di-n-octyl-acetil malate</td>
<td>Negative positive</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Di-n-propyl phthalate</td>
<td>Negative positive</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
</tbody>
</table>
Experiment

[0035] Plasticizers as shown in Table 2 were evaluated for their decomposition in a solution containing plasma by such an enzyme as esterase. Of the plasticizers evaluated, di-n-butyl acetyl malate, di-n-hexyl acetyl malate, and di-n-octyl acetyl malate are the ones used in the resins according to the present invention, and phthalate (di-n-decyl-phthalate) tri-n-butyl acetyl citrate, and tri-n-hexyl acetyl citrate are the ones evaluated for the purpose of comparison.

[0036] The plasticizers were respectively dissolved in ethanol to 50,000 ppm.

[0037] Two glass test tubes were used for the evaluation of each plasticizer. The test tubes were filled with 4.90 ml of 10 mM phosphate buffered saline (PBS), pH 7.4, and then, with 50 μl of the plasticizer solution in ethanol to a final concentration of 500 ppm. The mixture was stirred. To one test tube was added 50 μl of human plasma having CPD added thereto, and to the other test tube was added 50 μl of PBS as a control. The test tubes were incubated at 37°C.

[0038] After 0, 15, 30, 60, 120 and 240 minutes, 500 μl samples were removed from each test tube. To the sample was sequentially added 5 ml isopropanol and 5 ml diethylether, and the mixture was stirred after each addition. The mixture was subjected to centrifugation at 2,500 rpm for 10 min. The upper layer was collected and the solvent was removed under nitrogen atmosphere at 30°C. The residue was dissolved in 500 μl ethyl acetate, and evaluated for its content of the plasticizer by gas chromatography under the following conditions.

Conditions of Gas chromatography

[0039]

Column: Silicone SE-30, Chromosorb WAW DMCS 5%, 1.1m
Helium gas flow rate: 60 ml/min
Detector: FID
Volume of sample added: 5μl
Column temperature: 200°C

[0040] The results are shown in Table 2.

<table>
<thead>
<tr>
<th>Type of the plasticizer</th>
<th>Residual percentage Incubation in plasma, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>phthalate (di-n-decyl-phthalate)</td>
<td>100 96.6 93.7 97.8 96.2 96.2</td>
</tr>
<tr>
<td>tri-n-butyl acetyl citrate</td>
<td>100 97.5 94.5 97.1 97.6 97.0</td>
</tr>
<tr>
<td>tri-n-hexyl acetyl citrate</td>
<td>100 98.8 99.9 98.8 92.4 92.4</td>
</tr>
<tr>
<td>di-n-butyl acetyl malate</td>
<td>100 91.9 79.6 60.8 45.0 37.9</td>
</tr>
<tr>
<td>di-n-hexyl acetyl malate</td>
<td>100 94.4 90.9 80.9 55.5 48.2</td>
</tr>
<tr>
<td>di-n-octyl acetyl malate</td>
<td>100 96.8 93.2 89.6 77.3 64.9</td>
</tr>
</tbody>
</table>

[0041] In the cases of the plasma-free controls, substantially no plasticizer was decomposed after the 4 hour incubation at 37°C irrespective of the type of the plasticizer employed. In contrast, in the cases of the incubation in the plasma-containing solution, the malates underwent 30-60% decomposition after the 4 hour incubation at 37°C, while little phthalate and citrates were decomposed after such an incubation, as shown in Table 2 and FIG. 2. The results indicate that the malates are highly susceptible to decomposition by the enzymes in the plasma. Although the experiments have only been carried out in vitro, the results indicate that the malates would be readily decomposed in vivo into malic acid and an alcohol. It is likely that use of a malate is significantly safer than a phthalate or a citrate.

[0042] As described above, the medical device of the present invention molded from a resin composition prepared by blending 100 parts by weight of a vinyl chloride-based resin; 5 to 100 parts by weight of a dialkyl malate; and 1 to 20 parts by weight of a stabilizer is equivalent to the conventional medical device molded from a resin composition having blended therein a phthalate as the plasticizing agent in its physical properties (tensile properties), workability (susceptibility for high-frequency sealing, and adhesion), as well as sterilization resistance. In addition, the medical device of the present invention is highly safe, and exhibits an erythrocyte retention properties superior to such a conventional
medical device when it is kept in contact with blood.

Claims

1. A blood bag made from a resin composition prepared by blending 100 parts by weight of a vinyl chloride-based resin; 5 to 100 parts by weight of a dialkyl maleate represented by the general formula:

\[
\text{COO}(\text{CH}_2)_a \text{H} \\
\text{RO} \text{CH} \hspace{2cm} \text{(I)} \\
\text{CH}_2 \\
\text{COO}(\text{CH}_2)_b \text{H}
\]

wherein \(a\) and \(b\) independently represent an integer of from 1 to 12, and \(R\) represent a member selected from the group consisting of hydrogen atom, acetyl group, propionyl group, and butyryl group; and 1 to 20 parts by weight of a stabilizer.

2. The blood bag according to claim 1 wherein said vinyl chloride-based resin is at least one member selected from the group consisting of a vinyl chloride homopolymer and a vinyl chloride copolymer containing at least 70% by weight of vinyl chloride, said vinyl chloride homopolymer and copolymer having optionally added thereto at least one member selected from the group consisting of a styrene-acrylonitrile copolymer and a styrene-methacrylonitrile copolymer.

3. The blood bag according to claim 1 or 2 wherein said vinyl chloride-based resin has an average degree of polymerization in the range of from 700 to 3,000.

4. The blood bag according to one of claims 1 to 3 wherein said dialkyl maleate is at least one member selected from the group consisting of dihexyl maleate, dioctyl maleate, monohexyl monoocetyl maleate, dihexyl acetylmalate, dioctyl acetylmalate, monohexyl monoocetyl acetylmalate, dihexyl butyrylmaleate, dioctyl butyrylmaleate, and monohexyl monoocetyl butyrylmaleate.

5. The blood bag according to one of claims 1 to 3 wherein said dialkyl maleate is dibutyl acetylmalate.

6. The blood bag according to one of claims 1 to 5 wherein said stabilizer mainly comprises at least one member selected from the group consisting of an epoxidized vegetable oil, a cyclohexene oxide derivative, a metallic salt, a mixture of an epoxidized oil and a metallic salt, a phosphorous ester, and a mixture of stearoylbenzoylmethane and palmitoylbenzoylmethane.

7. The blood bag according to one of claims 1 to 6 which comprises at least one tube connected thereto.

Patentansprüche

1. Blutbeutel, hergestellt aus einer Harzzusammensetzung, die durch Mischen von 100 Gewichtsteilen eines Harzes auf Vinylchloridbasis; 5 bis 100 Gewichtsteilen eines Dialkylmalats, das durch die allgemeine Formel
dargestellt ist, in der a und b unabhängig voneinander eine ganze Zahl von 1 bis 12 darstellen, und R einen Rest, ausgewählt aus der Gruppe, bestehend aus einem Wasserstoffatom, einer Acetylgruppe, einer Propionylgruppe und einer Butyrylgruppe, darstellt; und 1 bis 20 Gewichtsteilen eines Stabilisators hergestellt worden ist.

2. Blutbeutel nach Anspruch 1, wobei das Harz auf Vinylchloridbasis mindestens ein Stoff ist, der aus der Gruppe, bestehend aus einem Vinylchloridhomopolymer und einem mindestens 70 Gewichtsprozent Vinylchlorid enthaltenden Vinylchloridcopolymer ausgewählt wurde, wobei gegebenenfalls mindestens ein Stoff, ausgewählt aus der Gruppe, bestehend aus einem Styrol/Acrylnitril-Copolymer und einem Styrol/Methacrylnitril-Copolymer zu dem Vinylchloridhomopolymer bzw. dem Vinylchloridcopolymer zugegeben worden ist.

3. Blutbeutel nach Anspruch 1 oder 2, wobei das Harz auf Vinylchloridbasis einen durchschnittlichen Polymerisationsgrad im Bereich von 700 bis 3000 besitzt.

4. Blutbeutel nach einem der Ansprüche 1 bis 3, wobei das Dialkyllmalat mindestens eine Verbindung ist, die aus der Gruppe, bestehend aus Diheptylmalat, Diocylmalat, Monohexylooctylmalat, Dihexylacetylmalat, Dioctylacetylemalat, Monohexylooctylacetylemalat, Diheptylbutyrilmalat, Dioctylbutyrilmalat und Monohexylooctylbutyrylmalat ausgewählt wurde.

5. Blutbeutel nach einem der Ansprüche 1 bis 3, wobei das Dialkyllmalat Dibutylyacetylemalat ist.


7. Blutbeutel nach einem der Ansprüche 1 bis 6, der mindestens einen mit ihm verbundenen Schlauch umfaßt.

Reviendications

1. Poche à sang constituée par une composition de résine préparée par mélange de 100 parties en poids d'une résine à base de chlorure de vinyle, 5 à 100 parties en poids d'un malate de dialkyle représenté par la formule générale :
où a et b représentent indépendamment un entier de 1 à 12, et R représente un élément choisi dans le groupe consistant en un atome d'hydrogène, un groupe acétylé, un groupe propionyle et un groupe butyryle, et 1 à 20 parties en poids d'un stabilisant.

2. Poche à sang selon la revendication 1, dans laquelle ladite résine à base de chlorure de vinyle est au moins un élément choisi dans le groupe consistant en un homopolymère de chlorure de vinyle et un copolymère de chlorure de vinyle contenant au moins 70 % en poids de chlorure de vinyle, au moins un élément choisi dans le groupe consistant en un copolymère styène-acrylonitrile et un copolymère styène-méthacrylonitrile étant éventuellement ajouté audit homopolymère de chlorure de vinyle et audit copolymère de chlorure de vinyle.

3. Poche à sang selon la revendication 1 ou 2, dans laquelle ladite résine à base de chlorure de vinyle a un degré moyen de polymérisation dans le domaine de 700 à 3 000.

4. Poche à sang selon l'une des revendications 1 à 3, dans laquelle ledit malate de dialkyle est au moins un élément choisi dans le groupe consistant en le malate de dihexyle, le malate de dioctyle, le malate de monoxyde et de monoocyle, l'acétylmalate de dihexyle, l'acétylmalate de dioctyle, l'acétylmalate de monoxyde et de monoocyle le butyrylmalate de dihexyle, le butyrylmalate de dioctyle et le butyrylmalate de monoxyde et de monoocyle.

5. Poche à sang selon l'une des revendications 1 à 3, dans laquelle ledit malate de dialkyle est l'acétylmalate de dibutyle.

6. Poche à sang selon l'une des revendications 1 à 5, dans laquelle ledit stabilisant comprend principalement au moins un élément choisi dans le groupe consistant en une huile végétale époxydée, un dérivé d'oxyde de cyclohexène, un sel métallique, un mélange d'une huile époxidée et d'un sel métallique, un ester phosphoren et un mélange de stéaroylbenzoylméthane et de palmitylbenzoylméthane.

7. Poche à sang selon l'une des revendications 1 à 6 qui comprend au moins un tube relié à elle.