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A CONTAINER CONTAINING DIAGNOSTIC CONTRAST COMPOSITIONS

BEHÄLTER MIT DIAGNOSE-KONTRASTZUSAMMENSETZUNG

CONTENANT AVEC COMPOSITIONS DE CONTRASTE DIAGNOSTIQUES

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References cited:
EP-A- 0 510 388
WO-A-87/02893
WO-A-91/18612
US-A- 3 177 871
US-A- 4 363 841

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This invention refers to a packaging comprising in combination a container and degassed aqueous compositions contained therein for the oral air-free administration of the same.

Examination of the gastro-intestinal tract is often made difficult by the presence of gases which prevent the homogeneous distribution of the contrastographic compositions inside the digestive tract. This is particularly true when ultrasonic echography of the stomach is to be performed.

Large gas volumes act as a reflecting surface for the ultrasonic waves thus darkening the nearby walls. Gas bubbles act similarly, reducing the visualization of the walls of stomach, duodenum and nearby structures. The use of water has been proposed to replace the gases in the stomach in order to improve the echographic visualization of the stomach and the other nearby organs, such as the pancreas (Crade M. et al., Am. J. Radiol. 131, 348, 1978; Fleischer et al., Am. J. Radiol. 136, 887, 1981).

For the same purpose, water containing D-sorbitol has been proposed (Hirok et al., J. Clin. Ultrasound 17, 585, 1989). In this case, water has been previously heated to become gas-free.

WO 91/18612, published on December 12, 1991, proposes the use of aqueous solutions containing biocompatible polymers which can be mixed to a compound containing silica. Unfortunately the results could not be fully reproduced since the liquid ingestion from an open container, such as a glass, also brings about the ingestion of air. The quantity of ingested air varies according to people. The ingested air can partly destroy the effect of enhanced echographic transparency deriving from water administration. In addition, tap water and the water left in an opened container become saturated with air. Water is heated in the stomach, causing the development of air which produces bubbles. These bubbles can mar some of the positive effects on echographic images generated by water ingestion.

This invention overcomes the above mentioned drawbacks, by supplying a packaging ready to be used comprising an air-tight, collapsible container, equipped with an erogating bead sealed with relative detachable cap, containing a degassed aqueous diagnostic solution or suspension.

This invention is also useful for the packaging of air sensitive diagnostic contrast media, such as for instance, solutions containing salts and/or oxidizable paramagnetic metal ion complexes, in particular Mn²⁺, Fe²⁺, Co²⁺, Eu²⁺ and Y³⁺.

Moreover the invention is also applicable to the packaging of diagnostic formulations for the examination of the digestive tract by using X-ray and MRI techniques. Said compositions can for example be solutions or suspensions of iodinated compounds, paramagnetic chelate complexes, ferromagnetic and or superparamagnetic metal derivatives or opacifying compounds like for instances, BaSO₄. Obviously said compositions can also be formulated with the addition of suitable additives and excipients (i.e. viscosity enhancers, sweeteners and so on) usually employed for the formulation of gastro-intestinal preparations.

The packaging of this invention allows the administration of degassed diagnostic compositions without the simultaneous ingestion of air since the patient drinks from the container which is squeezed directly into the oral cavity, avoiding contact between the latter and the environment.

The container has to be filled with said solution or suspension. The container can be constituted of any material but preferably of materials compatible with heat sterilization conditions, preferably by using vapour at 121°C or with gamma-ray sterilization. Suitable materials include for instance polyethylene, polyesters and in some cases aluminium.

Preferably the container is made of rolled plastic characterized by an inner layer compatible with water and other possible ingredients, preferably of polyethylene, a metallic layer, preferably aluminium, protecting the internal part from light, a second layer of polyethylene followed by an external plastic layer providing mechanical resistance, preferably polyester. The collapsible container can be prepared by soldering the rolled plastic sheets in a folded shape which is flat when the container is empty and swellable when filled with the diagnostic solution or suspension. The container will be able to contain from 50 ml to 2 l, preferably between 250 ml and 1 l of diagnostic solution or suspension. Such containers are known and available on the market, as for EP 510388 published on October 28, 1992.

The containers described in the above mentioned patent application EP 510388, which can be usefully used in this invention, include a beak connected to the container consisting of a tubular structure with a internal diameter between 2 and 14 mm, preferably between 4 and 10 mm. Said tubular structure crosses the container walls and the junction of the wall to said beak is air-tight sealed. This air-tight junction can be equipped with fins, in correspondence with the external side of the junction. At the external tip of the beak there is a air-tight detachable locking device, preferably a screw cap, which can be sealed. The tubular structure of the beak has some openings near its upper tip, which are inside the container wall, these openings being from 0.3 to 5 times, preferably from 1 to 1.2 times, bigger than the cross section of the tube calibre and are extended up to the junction between the tube and the wall of the container. The tubular structure of the beak penetrates the inside of the container up to a length equivalent to 5-75%, preferably 30-60% of the total depth of the container.

As various changes could be made in materials, shape and size without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.
EXAMPLE 1

Under air-tight conditions, a degassed aqueous solution of D-sorbitol 0.3 M is prepared. The solution passes from the dissolver to the filling machine through the tubes without any air contact. The machine prepares Guala-Pack® packages of 500 ml, hermetically sealed, totally filled with liquid. The product is sterilized in autoclave at 121°C for 20 minutes.

EXAMPLE 2

Following the same procedure of Example 1 packages of 250, 500 and 1000 ml of degassed pure water are produced.

EXAMPLE 3

The formulations of a contrast medium for echography described in WO 91/18612 (E. Unger) are prepared under vacuum as described in Example 1 with Guala-Pack® packages of 200 and 500 ml. The sealed product is sterilized with gamma rays of 1-5 Mrad according to the bacterial charge of the solution.

EXAMPLE 4

Gastromiro® is a contrast medium designed for X-ray examination of the digestive tract either by the oral or by the rectal route (enema) and in Computed Tomography (CT) as an oral agent for the outlining of the digestive tract in the diagnosis of the abdomen.

Gastromiro® composition contains (for 100 ml of solution):

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iopamidol (active iodinated component)</td>
<td>61.24 g</td>
</tr>
<tr>
<td>Orange flavour</td>
<td>220 mg</td>
</tr>
<tr>
<td>Sodium cyclamate</td>
<td>150 mg</td>
</tr>
<tr>
<td>Red curacao flavour</td>
<td>110 mg</td>
</tr>
<tr>
<td>Disodium edetate dihydrate</td>
<td>30 mg</td>
</tr>
<tr>
<td>Saccharin</td>
<td>13.4 mg</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td>5.5 mg</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>2.93 mg</td>
</tr>
<tr>
<td>Water for injections</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

A solution according to this composition was prepared and transferred in Guala-Pack® packages of 100 and 200 ml following the procedure of Example 1.

For CT scanning 200 ml of the preceding solution were diluted to 5000 ml with water for injections. The resulting solution was transferred in Guala-Pack® packages of 500 ml following the procedure of Example 1.

EXAMPLE 5

Magnevist® enteral is a contrast medium for gastro-intestinal MRI examinations.

Composition (for 10 ml of solution):
A solution according to this composition was prepared and transferred in Guala-Pack® packages of 500 ml following the procedure of Example 1.

**EXAMPLE 6**

A solution 0.1 mM of Prohance (Gadolinium(III) (1,4,7-tris(carboxy methyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazacyclododecane: EP 292689) was prepared and transferred in Guala-Pack® packages of 100, 250 and 500 ml, following the procedure of Example 1.

**EXAMPLE 7** A solution 0.1 mM of di-Natrium Gd-BOPTA

(Gadolinate(2-),(4R,S)-4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazaidecan-13-oate (5)] di-sodium(2+) salt: EP 230936) was prepared and transferred into Guala-Pack® packages of 100, 250 and 500 ml, following the procedure of Example 1.

**EXAMPLE 8**

Ferric Ammonium Citrate formulations

2.4 g of ferric ammonium citrate were dissolved in 1500 ml of water with the addition of 180 mg of aspartame and 12 mg of grape flavour. The resulting solution was transferred in Guala-Pack® packages of 500 ml, following the procedure of Example 1. This formulation is particularly useful for MR examinations of the upper abdomen.

**EXAMPLE 9**

Suspensions of paramagnetic/superparamagnetic oral contrast media for magnetic resonance tomography.

- Magnetite nanoparticles suspensions analogous to those obtained with the Abdoscan® (Nycomed) speciality were prepared containing 94 mg Fe, viscosity enhancing agents till 24 g, aspartame as sweetener in 1000 ml of water and transferred into 500 ml Guala-Pack® packages following the procedure of Example 1.
- Magnetite particles suspensions according to the Lumiren® speciality (Guerbet), i.e. containing: 0.175 mg Fe: 29.25 mg sorbitol (70%), color (pararange), preservatives (methyl-, ethyl-, propyl- para-oxibenzoate), NaCl, NaOH q.s., purified water up to 1 ml, were prepared.

5000 ml of a suspension according to the above composition were transferred in 500 ml Guala-Pack® packages following the procedure of Example 1.

**EXAMPLE 10**

Suspensions of Barium sulphate (BaSO₄)

Prontobario® 60% (Bracco) suspensions were prepared according to the following composition:
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barium sulphate</td>
<td>60 g</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>0.26 g</td>
</tr>
<tr>
<td>Strawberry flavouring</td>
<td>0.15 g</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>0.12 g</td>
</tr>
<tr>
<td>Dimethylpolysiloxane</td>
<td>0.10 g</td>
</tr>
<tr>
<td>Vanilla and cream flavouring</td>
<td>0.03 g</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td>0.02 g</td>
</tr>
<tr>
<td>Sodium saccharine dihydrate</td>
<td>0.01 g</td>
</tr>
<tr>
<td>Sulphuric acid 15%</td>
<td>q.s. to pH 4.5</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s. to 100 ml</td>
</tr>
</tbody>
</table>

Packages of Guala-Pack from 250 to 500 ml were prepared following the procedure of Example 1.

**Claims**

1. A packaging ready for the use for the oral administration of air-free diagnostic contrast solutions or suspensions comprising in combination an air-tight collapsable container, equipped with a distributing beak with relative sealing detachable cap, and a diagnostic degassed aqueous composition contained in said collapsable container.

2. A packaging according to claim 1, in which the container is made of rolled plastic characterized by:
   a) an internal layer compatible with water and the other ingredients of the diagnostic composition,
   b) a metal layer, which protects the inside from light,
   c) a second layer formed by a material of the same type as a),
   d) an external plastic layer, which supplies the mechanical resistance.

3. A packaging according to claim 2, in which the constituent materials are preferably selected from:
   a) polyethylene,
   b) aluminium,
   c) polyethylene,
   d) polyester.

4. A packaging according to claim 1 containing from 50 ml to 2 l of diagnostic composition.

5. A packaging according to claim 4, in which the diagnostic composition contains, as contrast agents, an iodinated X-ray opacifying compound or BaSO₄.

6. A packaging according to claim 4, in which the diagnostic composition contains, as contrast agents, a paramagnetic chelate complex for magnetic resonance imaging or superparamagnetic particles.

7. A packaging according to claim 4, in which the diagnostic composition contains, as contrast agents, an echographic reflecting agent.

8. A packaging according to claim 4, in which the diagnostic liquid is degassed pure water.

9. A packaging according to claims 2 and 3 in which the materials are compatible with vapour sterilization at 121°C or gamma rays sterilization.
EP 0 740 559 B1

Patentansprüche

1. Verpackung, fertig für die Verwendung zum oralen Verabreichen luftfreier diagnostischer Kontrastlösungen oder Suspensionen, die in Kombination einen luftdichten Behälter, der zusammenfallen kann, versehen mit einem Vertheilerhahn und dazu passender lösbarer Dichtkappe, und einer diagnostischen, gasfreien, wässrigen Zusammensetzung, die in dem Behälter, der zusammenfallen kann, enthalten ist, aufweist.

2. Verpackung nach Anspruch 1, bei der der Behälter aus gewalztem Kunststoff hergestellt ist, gekennzeichnet durch:
   a) eine innere Schicht, die mit Wasser und den anderen Bestandteilen der diagnostischen Zusammensetzung kompatibel ist,
   b) eine metallische Schicht, die das Innere vor Licht schützt,
   c) eine zweite Schicht, gebildet aus einem Material desselben Typs wie bei a),
   d) eine äußere Kunststoffschicht, die den mechanischen Widerstand gibt.

3. Verpackung nach Anspruch 2, bei der die Materialien der Bestandteile bevorzugt ausgewählt sind aus:
   a) Polyethylen,
   b) Aluminium,
   c) Polyethylen,
   d) Polyester.

4. Verpackung nach Anspruch 1, die zwischen 50 ml und 2 l diagnostischer Zusammensetzung enthält.

5. Verpackung nach Anspruch 4, bei der die diagnostische Zusammensetzung als Kontrastmittel eine jodierte, Röntgenstrahlen trübende Verbindung oder BaSO₄ enthält.

6. Verpackung nach Anspruch 4, bei der die diagnostische Zusammensetzung als Kontrastmittel einen paramagnetischen Chelat-Komplex für die Magnetresonanzabbildung oder superparamagnetische Teilchen enthält.


8. Verpackung nach Anspruch 4, bei der die diagnostische Flüssigkeit gasfreies reines Wasser ist.


Revendications

1. Emballage prêt à l’emploi pour l’utilisation pour l’administration orale de solutions ou de suspensions diagnostiques de contraste sans air comprenant, en combinaison, un récipient écrasable étanche à l’air, équipé d’un bec de distribution avec un bouchon détachable relativement étanche, et une composition aqueuse diagnostique dégazée, contene dans ledit récipient écrasable.

2. Emballage conforme à la revendication 1, ce récipient étant constitué de plastique stratifié caractérisé par:
   a) une couche interne compatible avec l’eau et les autres ingrédients de la composition diagnostique,
   b) une couche de métal, qui protège l’intérieur de la lumière,
   c) une seconde couche formée d’un matériau du même type que celui de a),
   d) une couche externe de matière plastique, qui confère la résistance mécanique.

3. Emballage conforme à la revendication 2, dans lequel les matériaux constitutants sont de préférence choisis parmi :
   a) le polyéthylène,
   b) l’aluminium,
   c) le polyéthylène,
   d) le polyester.
4. Emballage conforme à la revendication 1, contenant de 50 ml à 2 l de composition diagnostique.

5. Emballage conforme à la revendication 4, dans lequel la composition diagnostique contient, comme agents de contraste, un composé opacifiant aux rayons X iodé ou du BaSO₄.

6. Emballage conforme à la revendication 4, dans lequel la composition diagnostique contient, comme agents de contraste, un complexe chélate paramagnétique pour l'imagerie par résonance magnétique ou des particules superparamagnétiques.

7. Emballage conforme à la revendication 4, dans lequel la composition diagnostique contient, comme agents de contraste, un agent réfléchissant échographique.

8. Emballage conforme à la revendication 4, dans lequel le liquide diagnostique est de l'eau pure dégazée.

9. Emballage conforme aux revendications 2 et 3, dans lequel les matériaux sont compatibles avec la stérilisation à la vapeur à 121°C ou la stérilisation aux rayons gamma.