Multi-layered plastic polymeric container useful for the storage and conservation of pharmaceutical compositions, sterile or non-sterile, which comprises an inner layer and an outer layer, a gas barrier layer, and adhesive layers.

Order of the five or six layers
1: outer polymer layer in direct contact with environment
2: intermediate adhesive layer
3: central gas barrier layer
4: intermediate adhesive layer
5: inner polymer layer in direct contact with the composition
6: second polymer layer
Figure 2

- Channel A: adhesive agent
- Channel B: gas barrier agent
- Channel C: polymer
- Channel D: polymer

Layer 1
Layer 2
Layer 3
Layer 4
Layer 5 (second polymer layer)
Layer 6
Figure 4

Drop test

Non-irradiated bottles
15 kGray
25 kGray
50 kGray

Number of unbroken bottles

1 m
1.2 m
1.4 m

Heights
The present invention relates to a multi-layered plastic polymeric container for storing compositions, particularly pharmaceutical compositions, which may be sterilized by irradiation with or without the composition and allows for a stable conservation of said composition for a long period of time in sterile conditions. Also, the container of the present invention fulfills the strict regulations and requirements for storing pharmaceutical compositions.

Some pharmaceutical compositions, such as injectable compositions, require to be sterilized before administration. These pharmaceutical compositions are thus in general manufactured and stored in sterile conditions. The container may be sterilized either empty or filled with a composition. Alternatively, the container and the composition may be sterilized separately, and the container may then be filled in sterile conditions according to well known methods in the art.

The container, and particularly its inner layer which is in direct contact with the pharmaceutical composition, generally have a definite structure as required by European Pharmacopeia regulations. The container also must maintain properties of resistance after sterilization, as well as stability, mechanical resistance, transparency, and impermeability towards environmental factors, chemical products or various treatments; the reference being the glass material.

The material for the packaging or container must be pharmaceutically acceptable and should therefore not alter the quality of the pharmaceutical compositions. Also, pharmaceutical compositions must not alter the nature and composition of the container or packaging in contact therewith. Such alterations may result in the migration of chemicals from and to the packaging or container and the pharmaceutical composition. Such chemicals may be impurities, degradation products that appear over time under the action of oxygen, light and temperature, or due to processing of the container or packaging, such as sterilization process by irradiation. These interactions may alter over time the chemical properties of the pharmaceutical composition, such as the stability of the active ingredient and/or of the container or packaging, transparency or/in colour of the composition or flask, thereby reducing the lifetime of the container or packaging. Furthermore, such interactions may modify the stability, safety and efficacy of the pharmaceutical composition.

Containers or packagings that are made of plastic materials have been broadly developed as containers of pharmaceutical compositions. Materials such as polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), poly(vinyl chloride) (PVC), poly(ethylene-vinyl acetate) have been used for manufacturing monolayer containers such as pockets of perfusion, syringes, pipes. These materials are also used for syringes containers, tablets containers, or sterile aqueous solutions containers, particularly physiological serum and orthopaedic compositions. However, the use of these materials in the manufacture of monolayer containers for compositions that are sensitive to environmental factors are not generally satisfying, since the monolayer is not sufficient as a barrier to store in stable conditions the pharmaceutical composition over time, and the composition is sensitive to treatments of the container such as sterilization or solvent actions.

Complex multi-layered containers have also been developed for use inter alia for packaging of foods and cosmetics. Such packagings or containers are in general formed by the association of several material layers (sheets), thereby improving the properties of the packagings, which is then particularly less rigid, less breakable, and more resistant to heat, to light, to gas and chemical treatments.

These multi-layered containers are made of materials such as polyamides, polyolefin (PO) (polypropylene (PP), polyethylene (PE)), polyethylene terephthalate (PET), polyvinyl chloride (PVC), poly(ethylenevinyl acetate) which are associated with gas barrier layer made of ethylene vinyl acetate copolymer (copolymer EVOH), ethyl vinyl acetate (EVA), and polyamides, in order to yield an increased barrier protection against oxygen and water vapor and limit any possible alterations of the pharmaceutical composition.

For example, the European application EP0288595 describes multi-layered layer containers having from the inside to the outside, a thick layer of polypropylene, a gas barrier layer formed of copolymer EVOH, bound to a layer of polypropylene by an adhesive, and an external layer made of polyamide.

Other multi-layered containers are described in U.S. Pat. No. 4,919,984 and comprise a central gas barrier layer formed of copolymer EVOH, inner and outer layers that are made of a thermoplastic resin which is capable of resisting to humidity, and intermediary resin layers in between the outer and inner layers, made of polyacrylic polymers, cellulose, and divinylbenzene that are marketed under AQUAKEEP® or SUMIKAGEL®, and present high capacity of water absorption.

Furthermore, U.S. Pat. No. 5,164,258 describes a multi-layered container comprising a central gas barrier layer formed of EVOH, outer and inner layers made of a mixture of polyolefins and agents capable of increasing water vapour transmission rate, thereby avoiding altering of the properties of the central gas barrier layer.

These various multi-layered containers are thus restricted to moist heat sterilisation (autoclaving), but may not be used when sterilization of the container, empty or filled, is conducted using beta or gamma irradiation; these methods of sterilization by irradiation being preferred for sterilizing non aqueous compositions. Also, gamma irradiation is particularly preferred since gamma rays penetrate more deeply in the structures than beta rays, thereby allowing sterilizing of a greater number of containers or bottles at the same time, the bottles being filled or empty. Given this step of sterilization may however induce modifications of the containers properties, which may become more breakable. Gamma rays generally alter the polyolefins, and for example break the polypropylene chains. Further, gamma rays sterilization is subject to regulations ISO11137 which require consideration of several parameters, such as size of the product to sterilize or the use of additives. Also, the regulations ISO11137 require the use of maximal irradiation dose. Particularly, in the case of polyolefins containers, such as polyolefins containers, the irradiation dose must be lesser than 60 Kgy (Kilo Gray).

Containers that have been developed so far are not adapted to the constraints of sterilization by irradiation and present many alterations of the polymers of the containers after irradiation. Also, such containers are not useful for long term storage of sterile compositions which are found to be altered by environmental factors. In addition, compatibility of these containers with pharmaceutical compositions is usually poor.
The present invention provides multi-layered containers that overcome defects of the above-described containers. The containers of the present invention allows for the storage of liquid or non-liquid, sterile pharmaceutical compositions comprising solvents aqueous or non-aqueous.

The present invention thus relates to a plastic multi-layered polymeric container for the storage of sterile compositions, comprising at least three layers of different types, i.e., a polymer layer, a gas barrier layer and an adhesive layer. Preferably, the container comprises five or six layers, including inner and outer layers of polyolefin polymer or polyester in direct contact with the composition and in contact with the environment, respectively, a central gas barrier layer and two intermediate adhesive layers, each of which provides adhesion of the polymer layer with the central gas barrier layer.

Advantageously, the invention relates to a plastic multi-layered stable container which may be sterilized by irradiation when filled with a pharmaceutical composition or empty. Also, the present invention relates to a plastic multi-layered stable container being sterile. Finally, the present invention relates to a plastic multi-layered polymeric stable container which can be sterilized by irradiation, either empty or filled with a sterile or non-sterile composition. Plastic multi-layered polymeric stable containers of the present invention are preferably sterilized by gamma irradiation.

It has been found that association of at least two outer and inner layers comprising particular polymers, with at least one gas barrier central layer results in a significant reduction of the alteration and degradation of the polymers after sterilization by irradiation. Such association is thus useful for conditioning pharmaceutical composition, for example sterile compositions, that may then be stored with optimal stability, and stay chemically inert over time, as well as optimal resistance of the container.

Containers of the present invention may contain aqueous or non-aqueous compositions, or solid compositions, such as powders, tablets, pills, capsules, granules, pellets, pastes, or gels.

Liquid non-aqueous compositions generally contain, in addition to the active ingredients, vegetal oils, and aggressive organic solvents, e.g., heterocyclic organic solvents, such as acetonitrides and pyrrolidone, oil solvents, such as glycol ester or propylene glycol diester, or glycerides, such as triglycerides. Vegetal oils usually migrate within the polyolefin layers, causing the layer to swell. This reaction is due to the high affinity of polyolefins for the vegetal oils of the composition. Similarly to the vegetal oils, but to a lesser extend, the organic solvents also react with the polyolefins chains. However, according to the present invention, migration of the components of the non-aqueous solvents within the polyolefin compositions has not been observed.

The polymer layer is preferably made of polyolefins and polyesters. Preferred polymers are polyolefins, such as propylene, ethylene, or copolymers of propylene and ethylene. Polyolefins are formed of unsaturated hydrocarbonated monomers having the following general formula $R_1=CR_2R_3$ (wherein $R_1$ and $R_2$ are $-H$, $-CH_3$, or $-CH_2-CH_2-CH_3$). Most preferably, outer and inner layers comprise polyethylene copolymer. Polyethylene (PE) has the following chemical formula: $-\left(-CH_2-\right)_n$ and is obtained by polymerization of propylene monomers ($CH_2-CH_2-CH_3$) in presence of catalysts according to the Ziegler-Natta reaction. Polypropylene is a statistical copolymer of propylene/ethylene with a Melt Flow Rate (MFR) ranging from 1 to 15 g/10 min, and preferably about 2 g/10 min (ISO 1133), a fusion temperature ranging from 130 to 170°C, and a density from 0.9 to 1.0 g/cm³. Polypropylene is initially under the form of beads which are extruded for the manufacture of the layer.

According to the present invention, the inner layer of the container preferably comprises polypropylene while the outer layer comprises a mixture of polyolefin and at least one branched polyolefin. Branched polyolefins present a base linear structure on which are coupled or bound a plurality of polyolefinic polymeric arms. Branched polyolefins as used in the present invention comprise arms or ramifications of polymers comprising 1-alkene having 3 to 10 carbon atoms, preferably between 5 and 15 carbon atoms, and most preferably 8 carbon atoms, such as polyoxetanes. They are used in a proportion comprised between 5 and 25%, between 10 and 25%, and preferably between 15 and 25%, and most preferably in proportion of about 20% within the outer layer. Preferably, the outer layer comprises a combination of polypropylene and 20% polyoxetane.

Also, according to the present invention, outer and inner layers comprise at least one and preferably up to three conventional additives within combination with basic polymers. The conventional additives may be chosen among antioxidants, plasticizers, stabilizers, lubricants, colorants, mechanical strengtheners.

Preferably, the outer and inner layers comprise anti-oxidants as authorized by the European Pharmacopeia, such as butylhydroxytoluene; ethylene bis(3,3-bis(1,1-dimethylbutyl)-4-hydroxy-phenyl)butanoate; pentane-thiiryl tet-rakis(3,5-di-tert-butyl-4-hydroxyphenyl)-propionate) or IRGANOX 1010®; 4,4'-bis(2,6-di-tert-butyl-4-methylphenyl)-azo-terephthalic acid or IRGANOX 1330; octodecyl 3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-propionate or IRGANOX 1076®; phosphite tris(2,4-bis(1,1-dimethyl-n)-phenyl) or IRGAPHOS 168®; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1H,3H,5H)-trione or IRGANOX 3114®; 2,2’-bis(4-tert-octyl cyloxy)-5,5’-di-spiro(1,3,2-dioxa phosphorane); dioctadeyl disulfide, didodecyl 3,3’-thiodipropionate; dioctadeyl 3,3’-thiodipropionate, or a mixture of seven components that are obtained from the reaction of di-tert-buty1 phosphite with trichloride biphosthene, with biphenyl and 2,4-bis(1,1-dimethyl-phenyl)phenol; copolymer of dimethyl succinate and of (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-y)ethanol, or a mixture of at least two of these additives.

Preferably, the outer and inner layers of polymeric according to the present invention comprise a combination of up to three additives which may be either primary phenol additives or secondary phenol antioxidants. Most preferred secondary phenol antioxidant is IRGAPHOS 168® and preferred primary phenol antioxidants are chosen among IRGANOX 1010®, IRGANOX 1330® and/or IRGANOX 3114®. Also, inner and outer layers comprise a combination of up to three additives chosen among the four that are described above. Phenol antioxidants such as IRGAPHOS 168®, IRGANOX 1010® and IRGANOX 3114® are present in proportions from about 0.001% to 0.01%. Maximal amount of antioxidant additives within the outer and inner layers is generally less than 0.3%, except for the butylhydroxytoluene and the mixture of the seven components which correspond to the reaction products of di-tert-butyl phosphite with trichloride biphosthene, and with biphenyl and 2,4-bis(1,1-dim-
ethylethyl)phenol, which may be present within the maximal amount of 0.125 and 0.1%, respectively.

[0024] Compounds such as ethylene vinyl alcohol (EVOH) or polyamide (PA) are preferred as gas barrier agent of the central layer. Most preferably, the gas barrier agent is EVOH. The EVOH contains from 20% to 60% of ethylene, preferably from 27% to 47%, more preferably of about 32%. The EVOH has a fluid index of 1 to 5 g/cm/min, preferably of about 1.6 g/cm/10 min, a melt temperature of 185°C - 200°C, a temperature of vitreous transition of 60°C - 70°C, a OTR (Oxygen Transmission Rate), also called QO, for <<Oxygen Gas Permeation>> or PO for <<Oxygen Permeability>> of 0.4 ml/m²/24 h for a 20 μm thick film at 20°C , 85% HR (relative humidity).

[0025] The adhesive agent layer may be formed of modified polyolefins grafted with variable functional groups depending on the composition of the outer and inner layers. The functional groups may be polyolefins, polyamides, or poly-carbonates, and allow binding between the polyolefins and EVOH. Preferably, polyolefins are modified by functional groups such as homopolymers with propylene. The functional groups may be adapted to the various polymers ranging from polyolefins to PET and polyethylene. Most preferably, the adhesive agent used belongs to the ADMER® compounds, which is marketed by company Mitsui Chemical, such as for example ADMER QB 501 E®.

[0026] Incorporation of an adhesive agent ensures perfect adhesion between both layers of polyolefin and copolymer EVOH. Absence of adhesive may alter the multi-layered structure, and polyolefin layers may lose their transparency. The structure of adhesive agents being close to polyolefins or copolymers, maintains characteristics of each of these polymers.

[0027] Outer and inner layers based on polymer polypropylene are devoid of agents which act by increasing the water vapour transmission rate.

[0028] Multi-layered polymeric plastic containers according to the present invention are sterilized, with or without their content, by beta or gamma irradiation. According to a preferred embodiment, gamma irradiation is used, and containers so sterilized maintain a stable structure even after gamma irradiation as demonstrated by drop test and tensile strength studies in the Examples below. When antioxidant additives are incorporated in the outer and inner layers of the containers according to the present invention, these antioxidants are not detected after irradiation.

[0029] Therefore, according to a preferred embodiment, the multi-layered plastic polymeric container is sterilized by irradiation and contains inner and outer layers in direct contact with the composition and the environment, respectively, the outer layer comprising a mixture of polyolefins or polyesters and at least one branched polyolefin, which is present in the range from about 5 to 25%, or from 10 to 25%, from about 15 to 25%, and preferably in a proportion of about 20%, the inner layer comprising a mixture of polyethylene or polyesters, a gas barrier layer, and two intermediary adhesive layers in between the central layer and the inner and outer polymeric layers.

[0030] Outer and inner layers may be made of polyolefins, such as for example, polypropylene and/or polyethylene under the form of homopolymers or copolymers. The outer layer comprises polypropylene and/or polyethylene in a proportion ranging from 5-25%, 10-25%, or 15-25% and preferably of about 20%, at least a branched polyolefin such as polyacrylate having 3 to 30 carbons, preferably 5 to 15 carbons. Preferably, branched polyolefins used in the outer layer are chosen among polyoctene, polybutene, or polyhexene in a proportion of about 20%. Most preferably, polyoctene is used in a proportion of about 20%. Polyoctenes are marketed under EXACT 0201®, EXACT 0202®, EXACT 0203®, EXACT 801® by Dex-Plastomer or Exxon. The polybutenes and polyhexenes are marketed under EXACT305® and EXACT9106® by Dex-Plastomer or Exxon. The gas barrier layer comprises compounds such as ethylene vinyl alcohol (EVOH) or polyamide (PA). Preferably EVOH comprises from 20% to 60% of ethylene arms, or from 27% to 47%, and most preferably a proportion of 32% of ethylene arms. Also, adhesive layer comprises compounds of the polyolefin family such as polyolefin are grafted with functional groups chosen among polyolefin, polyamide, or polycarbonate.

[0031] The outer and inner layers also comprise up to three additives, such as antioxidants, plasticizers, stabilizers, lubricants, colorants, and mechanical strengtheners. The antioxidants are as described above and are present in proportion of less than 0.3% within outer and inner layers. More preferably, these include IRGANOX 1010®, IRGAPHOS 168®, and IRGANOS 3114®.

[0032] The outer layers may also comprise additives allowing softening the outer layer of polypropylene of the multi-layered plastic polymeric containers. Alternatively, the additives may render the outer layers more resistant to the sterilization by irradiation. Such additives may be inter alia polymers SEBS, i.e., polypropylene polymers marketed under the name of CATALON PR 3704® by the company Wittenburg, or polypropylene marketed under the name PURELL® by Basell, or polyolefins marketed under the name MELIFLEX® by the company Melitex.

[0033] Therefore, according to a preferred embodiment, non-sterile multi-layered containers before irradiation comprise:

[0034] an outer layer 1 comprising a mixture of polypropylene and polyoctene in a proportion ranging from 5 and 25%, 10 and 25%, or 15 and 25%, and preferably equal to about 20%;

[0035] a first intermediate outer layer 2 comprising an adhesive agent of the type ADMER® in a sufficient amount;

[0036] a central layer 3 comprising EVOH in a sufficient amount;

[0037] a second intermediate inner layer 4 comprising an adhesive agent of the type ADMER® in a sufficient amount; and

[0038] an inner layer 5 comprising polypropylene.

[0039] According to a preferred embodiment, the multi-layered plastic polymeric container is non-sterile before irradiation and comprises:

[0040] an outer layer 1 comprising polypropylene, about 20% of polyoctene, and up to three additives chosen among antioxidants, plasticizers, stabilizers, lubricants, colorants, and mechanical strengtheners;

[0041] a first intermediate outer layer 2 comprising an adhesive agent of the type ADMER® in a sufficient amount;

[0042] a central layer 3 comprising EVOH in a sufficient amount;
[0043] a second intermediate inner layer 4 comprising an adhesive agent of the type ADMER® in a sufficient amount; and

[0044] an inner layer 5 comprising polypropylene, and up to three additives chosen among antioxidants, plasticizers, stabilizers, lubricants, colorants, and mechanical strengtheners.

[0045] According to another preferred embodiment, the multi-layered plastic polymeric container is non sterile before irradiation and comprises:

[0046] an inner layer 1 comprising polypropylene, about 20% of polyoctene, and up to three antioxidants chosen among IRGANOX 1010®, IRGAPHOS 168®, and IRGANOX 3114®;

[0047] a first intermediate layer 2 comprising an adhesive agent of the type ADMER® in a sufficient amount;

[0048] a central layer 3 comprising EVOH in a sufficient amount;

[0049] a second intermediate layer 4 comprising an adhesive agent of the type ADMER® in a sufficient amount; and

[0050] an inner layer 5 comprising polypropylene and up to three antioxidants chosen among IRGANOX 1010®, IRGAPHOS 168®, and IRGANOX 3114®.

[0051] According to this embodiment, the container comprises five layers and presents an average total thickness ranging from 380 to 1320 µm:

[0052] an outer layer 1 which is in contact with the environment, is made of polymers polyolefins and/or polyesters, and has an average thickness ranging from 150 to 400 µm, preferably from 150 to 300 µm, and most preferably of about 250 µm;

[0053] an intermediate outer layer 2 of adhesive agent, which presents an average thickness from 5 to 75 µm, preferably from 5 to 50 µm, and most preferably of about 10 µm;

[0054] a central layer 3 of gas barrier copolymers, which presents an average thickness from 20 to 170 µm, preferably 20 to 100 µm, and most preferably of about 30 µm;

[0055] an intermediate inner layer 4 of adhesive agent, which presents an average thickness ranging from 5 to 75 µm, preferably 5 and 50 µm, and most preferably of about 10 µm;

[0056] an inner layer 5, in contact with the composition, made of polyolefins or polyesters, which presents an average thickness ranging from 200 to 600 µm, preferably 450 to 600 µm, and most preferably of about 500 µm.

[0057] According to this embodiment, the multi-layered plastic polymeric sterile containers after irradiation are similar to the non-irradiated containers, with the exception of antioxidants which are not detectable within the outer and inner layers of the containers after irradiation.

[0058] The sterile plastic multi-layered polymeric containers after irradiation thus preferably comprise:

[0059] an outer layer 1 comprising a mixture of polypropylene and polyoctene in a proportion from 5-25%, 10-25%, or 15-25% and about 20%;

[0060] a first intermediate outer layer 2 comprising an adhesive agent such as ADMER® in a sufficient amount;

[0061] a central layer 3 comprising EVOH in a sufficient amount;

[0062] an inner layer 4 comprising an adhesive agent such as ADMER® in a sufficient amount; and

[0063] an inner layer 5 comprising polypropylene.

[0064] The average thickness of sterile containers is similar to that of the containers before irradiation.

[0065] According to another embodiment, the multi-layered plastic polymeric container of the present invention may comprise six layers. The container has the same structure as that of a five-layer container with an inner polymeric layer in direct contact with the composition and the outer polymeric layer in direct contact with the environment, and presents an additional polymeric layer. Such additional polymeric layer is useful when additional compounds, such as colorants are used so as to provide visual characteristics to the container. These additional compounds may thus be introduced within the additional polymeric layer which has no direct contact with the composition and environment. This absence of direct contact between the additional polymeric layer and the composition or the environment is necessary to prevent any interaction between the composition and said additional compounds, and to prevent degradation of said additional compounds under the action of the environment (air, humidity, etc.).

[0066] According to another object, the present invention relates to the multi-layered plastic polymeric container comprising a liquid aqueous or non aqueous composition or alternatively comprising a solid composition such as powders, tablets, pills, capsules, granules, pellets, pastes, or gels.

[0067] The container is useful for storage of compositions in sterile conditions. The container may be first filled with the composition and sterilized by irradiation together with the composition, and particularly by gamma or beta irradiation. Alternatively, the composition and the container may be sterilized separately, and the container is then filled with the sterile composition under sterile conditions. Sterilization of the composition may be conducted by conventional methods, such as filtration, by moist or dry heat or by irradiation, whereas container is sterilized by gamma or beta irradiation.

[0068] The multi-layered plastic polymeric container, according to the present invention, is sterilized by irradiation at dose rates ranging from 10 kGy to 25 kGy, and is then filled with the composition under sterile conditions, the compositions being filtered for example on a filter 0.22 µm, prior to the filling.

[0069] Preferably, containers that are either empty or filled with the compositions are sterilized with gamma irradiation and maintain a good stability over time as demonstrated by the Examples herein below. Gamma rays have a high penetration into the structures, thereby allowing to sterilization of a greater number of containers empty and/or filled in a very efficient manner.

[0070] Thus, multi-layered plastic polymeric containers according to the present invention allow for an efficient storage of sterile compositions as that of glass containers. As demonstrated in the Examples, said multi-layered containers allow the conservation of physical and chemical properties of the containers and compositions over time after sterilization by irradiation.

[0071] When sterile compositions are stored in the containers of the present invention, organoleptic characteristics as well as the physical and chemical properties are maintained over time similar to that of the glass container. Conservation of the composition in plastic containers is said to be relative to
the glass container, when evolution of the properties in plastic containers is compared to the evolution of the same parameters for an identical composition in a glass container. Storage of the composition in the multi-layered plastic polymeric container may also be appreciated in an absolute manner. Parameters are then measured and are not compared to those of a composition in a glass container. The evaluation of the conservation of the composition in an absolute manner is required in the case of pharmaceutical or veterinary compositions. Regulations and Pharmacopoeias (European Pharmacopeia) define parameters that have to be taken into consideration and in what extend these parameters may vary in an acceptable manner. The evolution over time of these parameters allows assessing chemical and physical stability of the pharmaceutical compositions over time.

[0072] In order to assess conservation of the pharmaceutical composition, several qualitative and quantitative parameters may be taken into account. Qualitative parameters include color, transparency, and smell of the composition. Quantitative parameters of stability of the composition over time include concentration of the active ingredient in the composition, and relative percentage of degradation products in comparison with the active ingredient, pH, and viscosity.

[0073] Variations of these parameters are function of the composition, i.e., solution, suspension, or emulsion, of the nature of the active ingredient, of the route of administration of the composition, i.e., injectable, oral, or topical. Visual evaluation of the composition and determination of the concentration of the active ingredient in the composition, percentage of the degradation products relative to the active ingredient and eventually the pH for the multi-layered plastic polymeric container filled with the composition may be compared to same parameters for the glass container filled with the same composition.

[0074] A pharmaceutical composition is said to be stable when the concentration of active ingredient in the composition, the percentage relative of degradation products, and optionally the pH, vary within proportions such that efficacy and safety of the composition are not modified. These proportions are also function of the nature of the active ingredient, the form of the composition, and the mode of administration. For example, appearance of degradation products should be as low as possible for injectable compositions contrary to topical compositions. These various parameters are generally provided in the pharmaceutical regulations, particularly European Pharmacopeia, and such parameters are measured according to pre-defined methods. The measures are conducted at various times, i.e., 3 months, 6 months, 12 months, 18 months, and 24 months, at various temperatures, i.e., 40, 25°C, or 40°C, and under defined humidity conditions.

[0075] For example, the pharmaceutical composition is considered to be stable when the above parameters, after 6 months storage at a temperature of 400 and under relative humidity of 75%, vary in specified proportions as detailed below. Said composition does not present any significant changes of aspect, i.e., color, transparency and odour. Acceptable variations of the concentration of the active ingredient in the composition are generally less than 0%, and preferably less than 5%. Acceptable variations of the relative percentage of degradation products as compared to the active ingredient are generally less than 10%, and preferably less than 5%. Acceptable pH variations are generally not more than 0.5.

[0076] Duration of the storage may last as long as stability of composition during storage is maintained and as long as the variations of the concentration of the active ingredient and apparition of degradation products are low over time.

[0077] Active ingredients of these compositions generally comprise therapeutic and pharmaceutical agents, prophylactic agents, diagnostic agents, and any other agents that are capable of treating, preventing or diagnosing a pathology, an infection, or any other diseases of human or animal non human subjects, such as mammals, fishes, birds, insects and any other organisms, and even plants. Active ingredients may be for example antibiotics, such as amoxicillins, cefotiofur, oxytetracyclines, trimethoprimes, clarithromycines, in solution or suspension, anti-infective agents, vaccines, vitamins, non-steroid anti-inflammatory agents such as meloxicam, indomethacin and zileuton, anti-depressive agents, such as imipramine, anthelmintic agents such as praziquantel, pyrantel and ivermectine, anti-viral agents, cardiotic agents such as digoxin, antihypertensive agents, diuretic agents such as furosemide, therapeutic agents for the treatment of CHF (cardiac heart failure), enzymes, antagonists inhibitors, diagnostic agents for the diagnosis of croro-vascular diseases, metabolism dysregulation or of atherosclerosis, G protein coupled receptors (GPCR), kinases and proteases, or agents for the diagnosis of infectious diseases. Also, diagnostic agents may be polypeptides, nucleic acids, polysaccharides, lipids, glycoproteins, glycolipids, carbohydrates, or small molecules. According to one aspect, diagnostic agents are markers of active ingredients and may be radiotopes and radioactive agents, or may be magnetic markers, fluorescent or chromoluminescent markers, or enzymatic markers, such as peroxidase, luciferase, beta-galactosidase, alkaline phosphatase, glucose oxidase or catalase. These diagnostic agents may also be antibodies, antibody fragments, peptides or proteins of a pathogenic organism, such as a cholera protein, hepatitis virus protein, influenza virus protein, interferons, interleukins, cytokine, human growth hormone (hGH), anti-sense oligonucleotides, RNAi, siRNA, or shRNA.

[0078] According to a preferred embodiment, pharmaceutical compositions are anti-inflammatory compositions and comprise a suspension of micronised powder of meloxicam, dispersed in a physiological vehicle, and comprising 0.01 to 1% by weight of xanthan gum, 0.1 to 2% by weight of silicon oxide and 50 to 70% of polyols mixture.

[0079] According to another preferred embodiment, pharmaceutical compositions comprise a suspension of Cefitiofur HCl 5% as a veterinary treatment.

[0080] According to another aspect, the present invention relates to a kit which comprises multi-layered plastic polymeric containers and the pharmaceutical compositions as previously described, as well as instructions on the mode of administration of the composition to a subject. Such pharmaceutical compositions may be present under liquid, aqueous or non-aqueous form, or under solid form, such as for example powders, tablets, pills, capsules, granules, pellets, pastes, or gels.

[0081] This composition may be administered via multiple routes such as oral, nasal or by injections for the treatment and prevention of pathologies of human or non-human animal, i.e., dogs, cats, horses, and rodents.

[0082] According to a preferred embodiment, kits according to the present invention are useful for the vaccination of human or non-human animal, i.e., mammals and/or birds. Kits
according to this embodiment comprise one or more antigenic agents that are capable to increase the immune response against a pathogenic agent.

[0083] Also, anti-inflammatory and/or analgesic kits according to the present invention comprise a multi-layered polymeric plastic container as previously described and a micorized powder of meloxicam, dispersed in a physiologic medium, and 0.01 to 1% by weight of xanthan gum, 0.1 to 2% by weight of silicon oxide, and 50 to 70% of a polysols mixture, as well as instructions for the administration and use of the diagnostic kit for the diagnosis of a specific disease in a patient.

[0084] In addition, kits according to the present invention are useful for the diagnosis of pathology in a subject or patient comprising a multi-layered plastic polymeric container as previously described one or more diagnostic agents, as well as instructions for the administration and use of the diagnostic kit for the diagnosis of a specific disease in a patient.

[0085] According to another object, the present invention relates to a process of manufacture of the multi-layered plastic polymeric container. Manufacture of the container according to the invention is realized by methods that are well known in the art, and preferably by extrusion-blow molding.

[0086] For example, a container with five layers may be obtained by using a conventional device with four concentric channels to manufacture a preform which is then blow-molded. By way of example, manufacture of such container with four channels is summarized in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Layers</strong></td>
</tr>
<tr>
<td><strong>Intermediate 2</strong> Adhesive (channel A)</td>
</tr>
<tr>
<td><strong>Central 3</strong> Gas barrier agent (channel B)</td>
</tr>
<tr>
<td><strong>Intermediate 4</strong> Adhesive (channel A)</td>
</tr>
<tr>
<td><strong>Inner 5</strong> Polyolefin (channel D + C)</td>
</tr>
<tr>
<td><strong>Inner 6</strong> —</td>
</tr>
</tbody>
</table>

[0087] The present invention will be better understood from the Examples herein below referring to the following Figures.

**BRIEF DESCRIPTION OF THE FIGURES**

[0088] FIG. 1 displays a schematic transversal view of the wall of a container having five layers and of two containers having six layers. The layers are numbered as follows: 1/outer layer of polymer in direct contact with the environment; 2/intermediate adhesive layer; 3/central gas barrier layer; 4/intermediate adhesive layer; 5/inner layer of polymer in direct contact with the composition; and 6/a second polymer layer.

[0089] FIG. 2 shows a schematic view of the channels for the manufacture of the container according to the invention;

[0090] FIG. 3 displays an elevated view of a container according to the present invention;

[0091] FIG. 4 shows the results of the drop test study of the container before and after irradiation at dose rates of 15, 25, 25, and 50 kGy;

[0092] FIG. 5 shows the results of a stability study of a suspension containing 15% of an antibiotic sensitive to humidity;

[0093] FIG. 6 shows the results of a stability study of a solution containing 10% of an antibiotic sensitive to oxidation;

[0094] FIG. 7 shows the results of a drop test study of the container wherein the outer layer comprise 0%, 10%, or 20% of polymer ExactO203®;

[0095] FIG. 8 displays views of container of 100 ml, 250 ml, and 500 ml according to the present invention.

**EXAMPLES**

**Example 1**

Preparation of a 5-Layer Container

[0096] A container according to the invention, as obtained by extrusion-blow molding was manufactured and comprised 5 layers, as listed in the Table 2, under references 1 to 5, and with different channels (A to D) corresponding to the coextrusion of a preform that was expanded by blown molding for the manufacture of the bottle, as displayed in FIGS. 1 and 2.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Layers</strong></td>
</tr>
<tr>
<td>Outer 1</td>
</tr>
<tr>
<td>Intermediate 2</td>
</tr>
<tr>
<td>Central 3</td>
</tr>
<tr>
<td>Intermediate 4</td>
</tr>
<tr>
<td>Inner 5</td>
</tr>
</tbody>
</table>

[0097] The container is sterilized using gamma irradiation of 25 kGy or 10 kGy and then filled under sterile conditions with a non aqueous composition that are beforehand filtered using a 0.22 μm filter.

**Example 2**

Characteristics of the Container and Resistance to Gamma Irradiation

[0098] Polypropylenes having a fluidity index of less than 8 associated with primary antioxidants such as Irganox® were used. A comparative study of the polypropylene primary material based container before and after irradiation at 25 kGy was conducted. This study was done (2A) to assess the physico-chemical properties by analysis of differential enthalpy (DSC) to study the structure of the materials, and (2B) to control the mechanical properties of the containers.

**Example 2A**

Evaluation of the Physico-Chemical Properties by Analysis of Differential Enthalpy (DSC)

[0099] Thermodynamic characterization of the materials was provided by the differential enthalpy analysis, fusion temperature (Tf (°C)) and enthalpy of fusion (ΔHf (kJ/g)). Crystalline regions of the materials were characterized by the fusion enthalpy parameters associated to the fusion temperature. Amorphous regions of the materials were characterized by the vitreous transition when the temperature was increased.

[0100] Variations of the thermodynamic parameters for materials that were sterilized by irradiation were usually observed for polyolefins. In effect, ionizing rays induced a
modification of the temperature of fusion and enthalpy of fusion, indicating a modification of the semi-crystalline structure of polyolefins.

**Example 3** Compatibility Study of the Multi-Layered Plastic Polymeric Container

**[0107]** Interactions between composition and container have been assessed and showed that conservation of the composition in said containers is optimal over time and that there is no diffusion or migration of compounds of the composition towards materials of the container and that the integrity of the container and pharmaceutical composition is maintained.

**[0108]** At first, compatibility of the irradiated mono-, bi- and multi-layered irradiated bottles containing a sterile composition, such as non aqueous solution oxytetacyclin in a dimethylacetamide solvent was studied for a period of one month at 40°C, in comparison with a glass bottle. Aspects of the composition and of the container were observed.

**[0109]** Table 5 provides the results on the aspect of the composition and bottle prior to the storage (T₀) and after 1 month of storage at 40°C, under 75% relative humidity (RH).

**[0110]** Before storage, the composition was limpid with a light yellow color, and there was no modification of the aspect of the composition after a 1 month storage at 40°C under 75% RH, thereby showing optimal conservation of the composition. In effect, interactions between the environment and the composition would have been evidenced by a composition turning to brown, also indicating the weakness of the bottle material as gas barrier, penetration of the oxygen and degradation of the active ingredient.

**[0111]** Similarly prior to storage bottles presented a transparent aspect, which was maintained after 1 month storage at 40°C under 75% RH, and thus showed optimal stability of the bottles. On the contrary, migration of the elements of the composition or of the solvent within the bottle’s material would have yielded an opaque aspect of the bottle. In effect, this migration would have induced a degradation of the polymeric structure, thereby modifying the properties of the bottle.

**[0112]** These experiments showed that mono- and bi-layered bottles could not be used for storing compositions, whereas multi-layered polymeric bottles according to the present invention provide for optimal conservation.

**Example 2B Evaluation of the Mechanical Properties of the Bottles**

**[0103]** Extrusion-blow molding was used for manufacturing bottles having regular and layers having regular and homogeneous aspects. The irradiation step did not modify the structure of the layers.

**[0104]** A drop test was performed before and after irradiation in order to control the mechanical properties. The bottles filled with water were dropped vertically onto a solid base. A tensile strength test or axial strength test was also performed, wherein a vertical pressure of at least 55 kg is applied to the bottle. Finally, a cracking test was conducted and consisted in soaking the bottles for 70 h in a solution of tension-active at 50°C and washing with water before controlling leakage thereof. Results of these experiments are provided in Table 4.

**[0105]** The mechanical properties of these bottles before and after irradiation at 10 kGy or 25 kGy were maintained. No cracking was observed, contrary to what was observed in the case of bottles made of polypropylene only.

**[0106]** The yellow coloration was very weak, the bottle remains mostly transparent, and the composition could be clearly seen through the bottles as it was usually required for injectable pharmaceutical compositions.

**TABLE 5**

<table>
<thead>
<tr>
<th>Tested materials</th>
<th>Aspect of the material</th>
<th>Aspect of the composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>Transparent</td>
<td>Light yellow</td>
</tr>
<tr>
<td>PET*</td>
<td>Opake</td>
<td>Light yellow</td>
</tr>
<tr>
<td>PET/PEN**</td>
<td>Opake</td>
<td>Light yellow</td>
</tr>
<tr>
<td>COC***</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>PP</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>PE</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>PP/polyamide</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>PE/polyamide</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>Polyamide/PE</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>PP/EVOH</td>
<td>Transparent</td>
<td>Dark brown</td>
</tr>
<tr>
<td>PP/EVOH/PET</td>
<td>Transparent</td>
<td>Light yellow</td>
</tr>
</tbody>
</table>

* (Polyethylene terephthalate)  
** (Polystyrene)  
*** (Cyclohexane Copolymer)

**[0113]** Also, as listed below are some parameters showing stability of the pharmaceutical compositions for a time period of 6 months at 40°C, with reference of the glass material which was neutral and was optimal in terms of gas barrier protection:

**TABLE 4**

<table>
<thead>
<tr>
<th>Test</th>
<th>Non irradiated bottles</th>
<th>Irradiated bottles at 10 kGy</th>
<th>Irradiated bottles at 25 kGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drop test</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Axial strength</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Cracking test</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
</tbody>
</table>
Table 6

Stability of a non aqueous sterile solution
Non aqueous solutions containing oxetrecyclin in dimethylacetamide as solvent have been tested for stability.

<table>
<thead>
<tr>
<th>Solutions</th>
<th>T0 (glass and plastic)</th>
<th>6 months at 40°C (glass)</th>
<th>6 months at 40°C (Plastic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of active ingredient (%)</td>
<td>19.4%</td>
<td>18.70</td>
<td>18.66%</td>
</tr>
<tr>
<td>Concentration of degradation products (%)</td>
<td>1.2%</td>
<td>2.6%</td>
<td>3%</td>
</tr>
<tr>
<td>Color of the composition</td>
<td>Light yellow</td>
<td>Light yellow</td>
<td>Light yellow</td>
</tr>
<tr>
<td>pH</td>
<td>8.70</td>
<td>8.90</td>
<td>8.80</td>
</tr>
</tbody>
</table>

Table 7

Stability of a non aqueous sterile suspension
Non aqueous suspensions containing amoxicillin and propylene glycol have been tested for stability.

<table>
<thead>
<tr>
<th>Suspensions</th>
<th>T0 (glass and plastic)</th>
<th>6 months at 40°C (glass)</th>
<th>6 months at 40°C (Plastic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration of the active ingredient (%)</td>
<td>14.28%</td>
<td>13.59%</td>
<td>14.04%</td>
</tr>
<tr>
<td>Concentration of the degradation products (%)</td>
<td>0.9%</td>
<td>2.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Color of the composition</td>
<td>White suspension</td>
<td>White suspension</td>
<td>White suspension</td>
</tr>
</tbody>
</table>

Example 5

Characterization of Interactions Between the Multi-Layered Plastic Polymeric Container and the Active Ingredients of the Composition

[0121] Analysis of differential enthalpy indicated the fusion temperature (T<sub>f</sub>°C) and enthalpy of fusion (ΔH<sub>f</sub> J/g), thereby allowing to thermodynamically characterize the materials. The enthalpy of fusion and fusion temperature characterized the crystalline regions of the materials. Vitreous transition characterized amorphous regions of the material.

[0122] Variations of the thermodynamic parameters for the radio-sterilized materials were generally evidenced for polyolefins. In effect, ionizing radiations induced a modification of the fusion temperature and fusion enthalpy, as well as a modification of the semi-crystalline structure of the polyolefins.

[0123] A physico-chemical study of the outer layers made of polypropylene before and after irradiation at 25 kGy was performed. Results were provided in the following Tables 9-11.

[0124] A very low variation of the two parameters was observed. This small variation showed that the crystalline structure of polypropylene was preserved. The DSC thus did not evidence any substantial difference between irradiated and non irradiated bottles. Surprisingly, these containers were not subject to any substantial modifications of their spectral and thermodynamic characteristics due to the irradiation treatment. Conservation of the compositions was thus optimal.

Table 9

Analysis of additives in the multi-layered plastic container before and after the sterilization by irradiation

<table>
<thead>
<tr>
<th>Quantity of additives in polypropylene (ppm)</th>
<th>Before irradiation</th>
<th>After irradiation - dose of 25 kGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRGANOX 1010 (ppm)</td>
<td>10 to 100</td>
<td>Not detected</td>
</tr>
<tr>
<td>IRGAPHOS 168 (ppm)</td>
<td>10 to 100</td>
<td>Not detected</td>
</tr>
<tr>
<td>IRGANOX 3114 (ppm)</td>
<td>10 to 100</td>
<td>Not detected</td>
</tr>
</tbody>
</table>
TABLE 10

Analysis of differential enthalpy of the outer layers of polypropylene of the bottle before and after irradiation at 25 kGy

<table>
<thead>
<tr>
<th></th>
<th>Before irradiation</th>
<th>After irradiation - dose at 25 kGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion temperature</td>
<td>160.7 ± 1.53</td>
<td>159.81 ± 0.58</td>
</tr>
<tr>
<td>(Tf °C.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion enthalpy</td>
<td>49.27 ± 1.90</td>
<td>49.66 ± 0.29</td>
</tr>
<tr>
<td>(AHf J/g)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 11

Analysis of the stability of the layers by analysis of differential enthalpy of polypropylene before and after 6 months of storage at 40°C.

<table>
<thead>
<tr>
<th></th>
<th>Product A: SUSPENSION</th>
<th>Product B: SOLUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months of storage</td>
<td>AMOXICILLIN</td>
<td>OXYTETRACYCLINE</td>
</tr>
<tr>
<td>Fusion temperature</td>
<td>176.37 ± 0.22</td>
<td>177.16 ± 0.65</td>
</tr>
<tr>
<td>(Tf °C.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion enthalpy</td>
<td>54.09 ± 0.94</td>
<td>50.78 ± 0.37</td>
</tr>
<tr>
<td>(AHf J/g)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[0125] The results showed that the multi-layered plastic containers according to the present invention were not altered after sterilization by irradiation. Besides, the containers according to the present invention ensured an excellent conservation of compositions, since no interaction between the components of the layers of the container and the composition was observed after 6 months of storage at 40°C.

Example 6

Study of the Mechanical Properties of the Container

[0126] Physico-chemical properties of the multi-layered plastic bottles of 500 ml having a structure as described in the Example 4 were tested before and after sterilization by irradiation at doses of 15 kGy, 25 kGy, and 50 kGy.

[0127] The drop test study consisted in dropping from a predefined height on a firm base a bottle filled with water. Presence of leakage evidenced brittleness or cracking of the bottle. Results as provided in FIG. 4 showed that bottles irradiated at 15 kGy stayed intact even when dropped from 1.4 m and even after irradiation.

[0128] The elasticity of the bottle was also experimented. The measure of elasticity was done using a tensile testing machine MTS Alliance RF 100. A tensile force was applied on a test tube made of plastic material (size of 50x15 mm). Mechanical properties were determined using a crosshead speed of 50 mm/min and a grip distance of 50 mm. The Young modulus was defined as a ratio of the applied force and the deformation of the test tube. Results were provided in Table 12.

TABLE 12

Calculation of the elasticity modulus or Young modulus

<table>
<thead>
<tr>
<th></th>
<th>Non irradiated bottle</th>
<th>Bottle irradiated with 15 kGy</th>
<th>Bottle irradiated with 25 kGy</th>
<th>Bottle irradiated with 50 kGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young modulus (Gpa)</td>
<td>1.19</td>
<td>1.23</td>
<td>1.35</td>
<td>1.29</td>
</tr>
</tbody>
</table>

[0129] The Young modulus showed no statistically significant change after irradiation at doses up to 50 kGy, indicating that the rigidity of the material was not impacted by the different doses of irradiation.

Example 7

Study of the Mechanical Properties of the Container

[0130] A container (100 ml) according to the invention, as obtained by extrusion-blown molding was manufactured and comprised 5 layers, as listed in the following Table 13. The outer layer of the container contained a variable proportion of the polyoctene exact0203®: 0%, 10%, or 20%.

TABLE 13

Layers 5-layer bottle before irradiation

| Outer layer | Polypropylene with IRGANOX 1010® + IRGAPHOS 168® + IRGANOX 3114® + EXACT0203® (0%, 10% or 20%) |
| Central layer | EVOH |
| Intermediate layer | Adhesive |
| Inner layer | Polypropylene with IRGANOX 1010® + IRGAPHOS 168® + IRGANOX 3114® |

[0131] A drop test was performed to test the resistance of the multi-layers plastic polymeric containers function of percentage of exact0203® incorporated within the outer layer. The bottles filled with water were dropped vertically onto a metallic plaque at various heights. Results were presented in FIG. 7 showing the effect of the incorporation of polyoctene exact0203® on the resistance. A percentage of at least 20% of polyoctene allowed obtaining a very high resistance of the containers, even when dropped at a height of 2 m.

Example 8

Stability of the Active Substances

[0132] A stability study was conducted on an antibiotic suspension of amoxicillin containing 15% of active ingredient very sensitive to humidity. Results were presented in FIG. 5 and evidenced that multi-layered polymeric plastic bottles guaranteed an excellent protection against humidity of the active ingredient at least for 6 months at 40°C.

[0133] Also, a stability study was conducted on antibiotic solution containing 10% tetracycline which is very sensitive against the oxidation. Results as presented in FIG. 6 evidenced that multi-layered plastic bottles guaranteed an excellent protection against the oxidation reactions of the active product at least for 6 months at 40°C.
Example 9

Stability of Composition of Ceftiofur as Stored in the Multi-Layered Plastic Polymeric Containers

A stability of the oily suspension of Ceftiofur HCI 5% in the multi-layered plastic polymeric containers according to the present invention was tested. Multi-layered plastic polymeric containers were first filled with the suspensions of Ceftiofur HCI 5%, and then sterilized by irradiation. Results of the stability are provided in the following Table 14.

<table>
<thead>
<tr>
<th>Concentration of active: CEFTIOFUR HCI</th>
<th>Total Concentration of Degradation Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before irradiation</td>
<td></td>
</tr>
<tr>
<td>5.03%</td>
<td>0.3%</td>
</tr>
<tr>
<td>After 15 kGy Irradiation</td>
<td></td>
</tr>
<tr>
<td>5.04%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Appearance of suspension</td>
<td></td>
</tr>
<tr>
<td>Oily white suspension</td>
<td>Oily white suspension</td>
</tr>
</tbody>
</table>

Example 10

Plastic Multi-Layered Containers

Plastic multi-layered containers of various volumes for example from 50 ml to 500 ml were prepared as shown in FIGS. 3 and 8. Advantageously, the containers were shaped with a depression at the upper part allowing gripping thereof by the users. Gripping means were shown in FIG. 8 for example for the containers of 100 ml, 250 ml and 500 ml without any limitations.

1. Multi-layered plastic polymeric container for the storage of a composition comprising an inner layer and an outer layer in direct contact with the composition and the environment, respectively, a central gas barrier layer and two intermediate adhesive layers in between the central layer and the outer and inner polymeric layers, wherein the outer and inner layers comprise a mixture of polymers.
2. Container of claim 1, wherein polymers of outer and inner layers are polyolefins or polyesters.
3. Container of any one of the claims 1 and 2, wherein polymers of outer and inner layers are polyolefins and polyolefins are chosen among polypropylene and/or polyethylene in the form of homopolymers or copolymers.
4. Container of any one of claims 1-3, wherein the outer layer comprises a mixture of polymers and at least one branched polyolefin.
5. Container of any one of claims 1-4, wherein the outer layer comprises a mixture of polymers and at least one branched polyolefin, wherein the branched polyolefin in range of 5 to 25%.
6. Container of any one of claims 1-5, wherein the outer layer comprises a mixture of polymers and at least one branched polyolefin, wherein the branched polyolefin is present in a proportion of 20%.
7. Container of any one of claims 1-6, wherein the outer layer comprises a mixture of polymers and at least one branched polyolefin, and wherein the branched polyolefin is a polyolefin having 5 to 30 carbons, preferably between 5 to 15 carbons.
8. Container of any one of claims 1-7, wherein the outer layer comprises a mixture of polymers and at least one branched polyolefin, and wherein the branched polyolefin is a polyolefin which is present in a proportion of about 20%.
9. Container of any one of claims 1-8, wherein the central gas barrier layer comprises ethylene vinyl alcohol (EVOH) or polyamide (PA).
10. Container of claim 9, wherein the EVOH is present in a range of 20 to 60% of ethylene arms, preferably in a range of 27% to 47%, and preferably in an amount of 32%.
11. Container of any one of claims 1-10, wherein the adhesive layer comprises polyolefins compounds, said polyolefins being grafted with various functional groups chosen among polyolefin, polyamide, and polycarbonate.
12. Container of any one of claims 1-11, wherein the outer and inner layers further comprise up to three conventional additives.
13. Container of claim 12, wherein the conventional additives are chosen among antioxidants, plasticizers, stabilizers, hueants, dyes, or mechanical strengtheners.
14. Container of claim 12, wherein the conventional additives are conventional antioxidants.
15. Container of claim 14, wherein the conventional antioxidants are present within the range of up to 0.3% in the outer and inner layers.
16. Container of claim 15, wherein the antioxidants are chosen among butylhydroxytoluene, ethylene bis(3,3-bis(1,1-dimethyl-ethyl)-4-hydroxy-phenoxy)butanate; pentanehexyl tetraakis(3,5-di-tert-butyl-4-hydroxy phenyl-propionate) or IRGANOX 1010®; 4,4',4"-(2,4,6 trimehtylbenzene-1,3,5-tri-yltrimethylethylene)-tris(2,6-bis(1,1-dimethyl-ethyl)phenol) or IRGANOX 1330®; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate or IRGANOX 1076®; tris(2,4-bis(1,1-dimethyl-ethyl)phenyl)phosphite; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1H,3H,5H)-trione; 2,2'-bis(octadeoxyloxy)-5,5'-spirobi(1,3,2-dioxaphosphinan); dioctadecyl disulfide; diiododecyl 3,3'-thiodipropionate; dioctadecyl 3,3'-thiodipropionate; or a mixture of seven components corresponding to the reaction products of di-tert-butyl phosphite with trichloride biphosphors, with biphenyl and 2,4-bis(1,1-dimethyl-ethyl)phenol; copolymer of dimethyl succinate and of (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol.
17. Container of any one of claims 14 and 15, wherein the outer and inner layers comprise a combination of two additives, one being a primary antioxidant additive and a secondary antioxidant additive.
18. Container of claim 17, wherein outer and inner layers comprise IRGAPHOS 168® as a primary antioxidant additive, and IRGANOX 1010®, IRGANOX 1330® or IRGANOX 1076® as secondary antioxidant additive.
19. Container of any one of claims 1-18, wherein the outer layer comprises a mixture of polypropylene, polystyrene, and a sufficient amount of up to three antioxidant additives, wherein the inner layer comprises a mixture of polypropylene and a sufficient amount of up to three antioxidant additives.
20. Container of any one of claims 1-19, wherein the outer layer comprises a mixture of polypropylene, polystyrene, and up to three antioxidant additives, wherein the inner layer comprises a mixture of polypropylene and up to three antioxidant additives, and wherein the polyolefin polymers, the polystyrene and the antioxidants are present in sufficient amounts to allow sterilization of the container at dose rates from 15 kGy to 25 kGy without inducing any modification of physical and chemical properties of the container.
21. Container of any one of claims 1-20, wherein the outer layer comprises a mixture of polypropylene, polyoctene, and up to three antioxidant additives, wherein the outer layer comprises a mixture of polypropylene and up to three antioxidant additives, and wherein the polypropylene polymers, the polyoctene and the antioxidants are present in sufficient amounts to allow sterilization of the container at dose rate of 15 kGy, without any modification of the elasticity modulus of the container as measured by the Young modulus.

22. Container of any one of claims 1-21, wherein the outer layer comprises a mixture of polypropylene, polyoctene, and up to three antioxidant additives, wherein the outer layer comprises a mixture of polypropylene and up to three antioxidant additives, and wherein the polypropylene polymers, the polyoctene polymers and the antioxidants are present in sufficient amounts to allow the stable storage of a sterile non-aqueous composition for at least 6 months at about 40°C.

23. Container of any one of claims 1-22, wherein the container comprises:
an outer layer 1 comprising polypropylene, about 20% of polyoctene, and up to three additives chosen among IRGANOX 1010®, IRGAMATS® 168®, and IRGANOX 3114®;
a first intermediate layer 2 comprising a sufficient proportion of an adhesive agent ADMER®;
a central layer 3 comprising a sufficient proportion of EVOH;
a second intermediate layer 4 comprising a sufficient proportion of an adhesive agent ADMER®; and
an inner layer 5 comprising polypropylene, and up to three antioxidant additives chosen among IRGANOX 1010®, IRGAMATS® 168®, and IRGANOX 3114®.

24. Container of any one of claims 1-23 comprising the five following layers:
an outer layer 1 in direct contact with the environment, comprising polyolefins, and having an average thickness ranging from 150 to 400 µm, preferably from 150 to 300 µm;
an intermediate outer layer 2 comprising adhesive agent and having an average thickness ranging from 5 to 75 µm, preferably from 5 to 50 µm;
a central layer 3 comprising a gas barrier copolymer agent and having an average thickness ranging from 20 to 170 µm, preferably from 20 to 100 µm;
an intermediate inner layer 4 comprising adhesive agent and having an average thickness ranging from 5 to 75 µm, preferably from 5 to 50 µm; and
an outer layer 5 in direct contact with the composition, comprising polyolefins and having an average thickness ranging from 200 to 600 µm, preferably from 450 to 600 µm.

25. Container of any one of claims 1-24 comprising the five following layers:
an outer layer 1 in direct contact with the environment, comprising polyolefins and having an average thickness of about 250 µm;
an intermediate outer layer 2 comprising adhesive agent and having an average thickness of 10 µm;
a central layer 3 comprising a gas barrier copolymer agent and having an average thickness of about 30 µm;
an intermediate inner layer 4 comprising adhesive agent and having an average thickness ranging of about 10 µm; and
an outer layer 5 in direct contact with the composition comprising polyolefins and having an average thickness of about 500 µm.

26. Container of any one of claims 1-25, wherein said container is sterilized by irradiation.

27. Container of any one of claims 1-26, wherein said container is sterilized by gamma irradiation.

28. Container of any one of claims 26 and 27, wherein the outer and inner layers contain no antioxidant additives after irradiation.

29. Multi-layered plastic polymeric container which is sterilized by irradiation, comprising an inner layer and an outer layer respectively in direct contact with the composition and the environment, a central gas barrier layer, and two intermediate adhesive layers in between the central layer and the polymeric inner and outer layers, said outer and inner layers comprising a mixture of polymers of polyolefins and/or polyesters.

30. Container of claim 29, wherein the outer and inner layers comprise a mixture of polyolefins.

31. Container of any one of claims 29 and 30, wherein the outer layer comprises a mixture of polymers of polyolefins and/or polyesters and at least one branched polyolefin in a proportion ranging from 5 to 25% and the inner layer comprises a mixture of polymers of polyolefins and/or polyesters.

32. Container of claim 31, wherein the branched polyolefin is present in a proportion of about 20% within the outer layer.

33. Container of any one of claims 31 and 32, wherein the branched polyolefin is a polyalcohol having 3 to 30 carbons, and preferably 5 to 15 carbons.

34. Container of any one of claims 31-33, wherein the branched of the outer layer is a polyoctene.

35. Container of any one of claims 31-34, wherein the polyoctene is present in a proportion of about 20%.

36. Container of any one of claims 29-35, wherein the polyolefins of the outer and inner layers are chosen among polypropylene and/or polyethylene under the form of homopolymers or copolymers.

37. Container of any one of claims 29-36, wherein the gas barrier layer comprises a gas barrier agent such as ethylene vinyl alcohol (EVOH) or polyamide (PA).

38. Container of claim 37, wherein the EVOH is present in a range from 20% to 60% of ethylene, preferably from 27% to 47%, or preferably about 32%.

39. Container of any one of claims 29-38, wherein the adhesive central layer comprises compounds of the polyolefin family, said polyolefin being grafted with variable functional groups chosen among polyolefin, polyamide, and polycarbonate.

40. Container of any one of claims 29-39 comprising:
an outer layer 1 comprising polypropylene and about 20% of polyoctene;
a first intermediate inner layer 2 comprising a sufficient proportion of an adhesive agent ADMER®;
a central layer 3 comprising a sufficient proportion of EVOH;
a second intermediate outer layer 4 comprising a sufficient proportion of an adhesive agent ADMER®; and
an outer layer 5 comprising polypropylene.

41. Container of any one of claims 1-40, for the storage of a sterile composition.

42. Container of any one of claims 1-41, wherein the container is first sterilized by irradiation and then filled with the composition.
43. Container of any one of claims 1-42, wherein the composition is first sterilized by any conventional methods of sterilization and then introduced in the container which is sterilized beforehand by gamma irradiation, the filling of the sterile container with the sterile composition is performed under sterile conditions.

44. Container of any one of claims 1-43, wherein the container is first filled with the composition and the container/composition is then sterilized by irradiation.

45. Container of claim 44, wherein the sterilization is done by gamma irradiation.

46. Container of any one of claims 1-45, wherein the composition is a pharmaceutical composition.

47. Container of claim 46, wherein the composition is a pharmaceutical non-aqueous composition and comprises one or more active ingredients, a carrier comprising vegetal oils, organic solvents, heterocyclic organic solvents such as acetamides and pyrrolidone, glycol ester of oil solvents such as propylene glycol diester, or glycerides, such as triglycerides.

48. Container of claim 46 or 47, wherein said composition comprises amoxicillin or oxytetracycline as active ingredient.

49. Container of claim 46 or 47, wherein said composition is a suspension of Ceftriaxone HCl 5%.

50. Container of claim 46, wherein said composition comprises a suspension of micronized powder of meloxicam, dispersed within a physiological medium, and 0.01 to 1% in weight of xanthan gum, 0.1 to 2% in weight of silicon oxide, and 50 to 70% of a mixture of polyols.

51. Container of any one of claims 1-50, wherein the pharmaceutical composition is present under liquid form, aqueous or non-aqueous, or under solid form, such as powders, tablets, pills, capsules, granules, pellets, pastes, or gels.

52. Kit for the treatment and/or the prevention of a pathology, comprising a multi-layered plastic polymeric container as defined in any one of the claims 1-45, a pharmaceutical composition, and instructions for the treatment and/or prevention of said pathologies.

53. Kit for the vaccination of a subject, comprising a multi-layered plastic polymeric container as defined in any one of the claims 1-45, a pharmaceutical composition comprising an antigenic substance capable of activating immune response of said subject against a pathogenic agent, and instructions for the vaccination of said subject.

54. Kit for the diagnosis of a pathology in a patient comprising a multi-layered plastic polymeric container as defined in any one of the claims 1-45, a pharmaceutical composition comprising a diagnostic agent, and instructions for the diagnosis of said pathology in the patient.

55. Method of manufacture of the multi-layered plastic polymeric container as defined in any one of the claims 1-45, wherein the various layers are obtained by extrusion-blown molding.