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SIMULTANEOUSLY MAINTAINING LOW
MOISTURE AND LOW OXYGEN LEVELS**(75) Inventors: **Dwayne T. Friesen**, Bend, OR (US);
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GROTON, CT 06340 (US)(73) Assignee: **PFIZER INC.**(21) Appl. No.: **11/572,150**(22) PCT Filed: **Jul. 4, 2005**(86) PCT No.: **PCT/IB05/02446**§ 371(c)(1),
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16, 2004.**Publication Classification**(51) **Int. Cl.**
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(52) **U.S. Cl.** **206/528**(57) **ABSTRACT**

The present invention relates to a device for reducing the oxygen content of the air surrounding pharmaceutical dosage forms contained within an oxygen-permeable bottle, while also maintaining a relatively low moisture level in said air during the shelf-life of the product. Accordingly, a pharmaceutical package contains a dessicant in a first sub-container and a self-activated oxygen-absorber in a second sub-container.

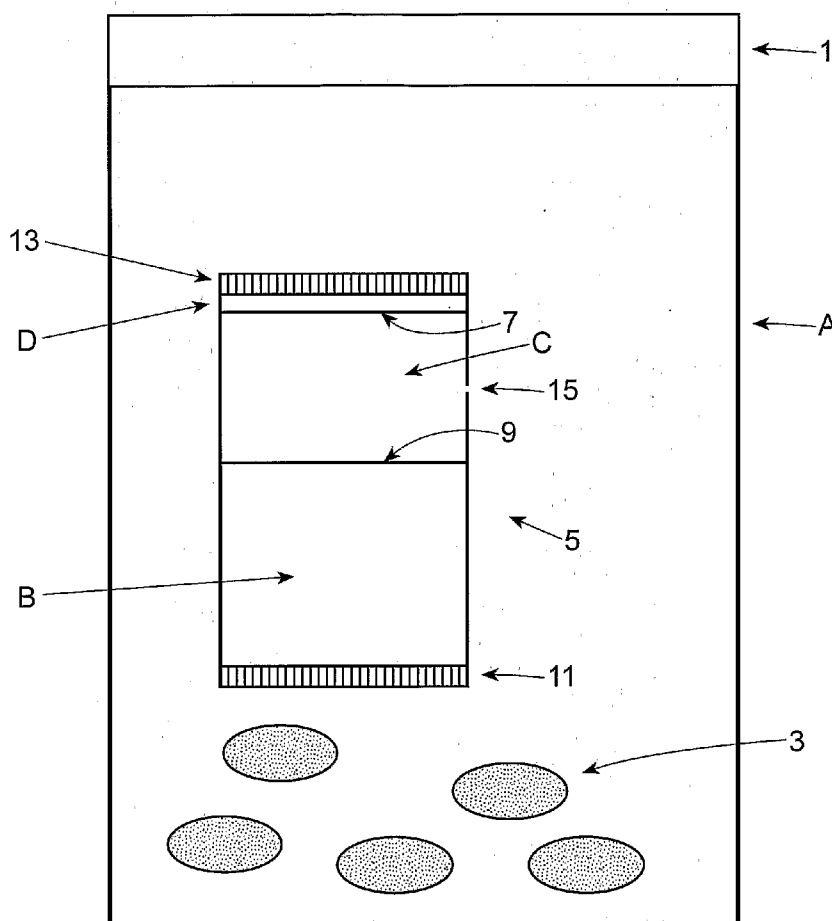


FIG. 2

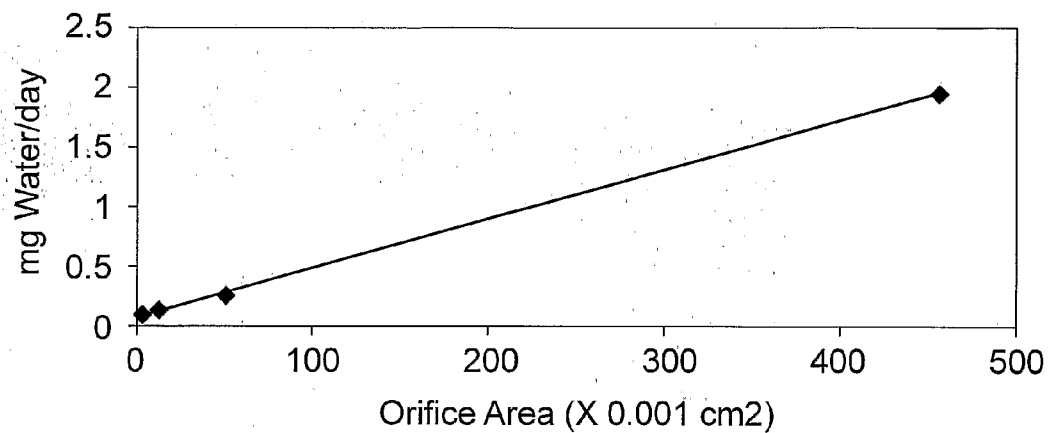
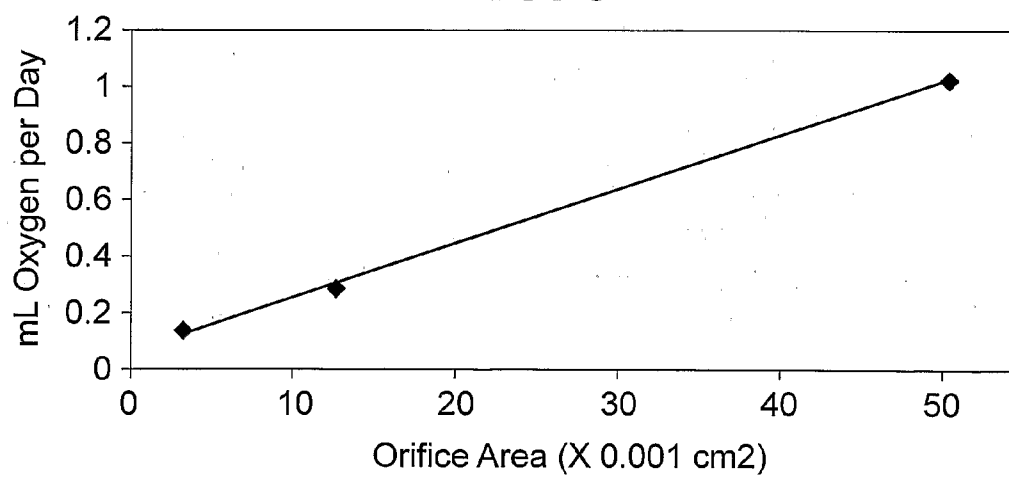


FIG. 3



PACKAGE AND DEVICE FOR SIMULTANEOUSLY MAINTAINING LOW MOISTURE AND LOW OXYGEN LEVELS

FIELD OF THE INVENTION

[0001] The present invention relates to a device for reducing the oxygen content of the air surrounding pharmaceutical dosage forms contained within an oxygen-permeable bottle, while also maintaining a relatively low moisture level in said air during the shelf-life of the product.

BACKGROUND OF THE INVENTION

[0002] Oxygen induced drug degradation is a factor that can limit the shelf life, usually as indicated by the expiration date, of a drug product. In the case of drugs that are highly oxygen-sensitive, such degradation may render a drug unmarketable or cause a candidate to be excluded from development.

[0003] In some cases, oxygen sensitivity occurs only in the presence of certain excipients. Since oxidation is often not accelerated by standard Arrhenius-based increased temperature studies (known in the art as "accelerated aging studies"), instances can occur in which the oxygen sensitivity of the drug is not recognized until drug development has progressed into late stages of development. At such later stages of development, reformulation and addition of standard antioxidants can require considerably more time and money. In addition, more clinical data may be necessary with a new formulation. Thus, a need for reducing or eliminating oxygen-based drug instability, without requiring a formulation change, has existed in the art.

[0004] Often in drug development, a need may arise to reduce or prevent oxygen-induced degradation of a drug candidate or to provide adequate stability for initial studies without investing a lot of resources prior to proof of concept. Once a candidate has been selected for further development, oxygen-sensitivity can then be addressed by more traditional strategies.

[0005] In addition to oxygen sensitivity of a pharmaceutically active ingredient in a dosage form, the dosage form itself can be sensitive to moisture. This sensitivity can be due to direct reaction (e.g., hydrolysis), or to physical effects such as plasticization of drug or excipients, sticking of dosage forms together ("twinning"), or to deliquescence (absorption of atmospheric moisture). For these reasons, many pharmaceutical dosage forms are packaged with added desiccants. The most common pharmaceutically acceptable desiccant is silica, which controls the relative humidity (RH) to below 20%.

[0006] The use of metal-based oxygen absorbers in the food industry for preservation of foods is well known. In such systems a metal in a reduced oxidation state reacts with oxygen in the presence of water to form a metal oxide. For example, Mitsubishi Gas Corporation introduced iron-plus-carbonate salt sachets under the trade name Ageless™ for use in stabilizing packaged foods by preventing oxidation. Other iron and metal-based oxygen absorbers combined with various salts and other incremental improvements quickly followed suit, usually with the metal in the form of a powder or other subdivided form, and with all components of the absorber being contained within an oxygen permeable

sachet. In a metal oxidation reaction, water provides the activation mechanism used in most such oxygen-scavenging applications. Oxygen-absorbing sachets are generally stored dry where they can be handled without consuming oxygen. In the presence of moist foods, the oxygen-absorber is activated and begins removing oxygen.

[0007] Recently, companies in the food industry have introduced self-activated oxygen absorbers to provide oxygen absorption with dry food products. These have involved combining moisture-holding additives with the metals (usually iron) in sachets (See, e.g., Japanese Publications SHO56-50618 and SHO57-31449; and U.S. Pat. No. **5,725,795**). European Patent Application Nos. 864630A1 and 964046A1 describe the use of iron iodide and bromide to allow oxygen absorption in a low humidity environment without the need to bring in water; however, commercial application of this technology has not been realized.

[0008] In the pharmaceutical industry, there have been some limited reports of using oxygen absorbers to stabilize drugs. For example, in 1984, tablets of an anti-inflammatory drug were stabilized in large glass (i.e., oxygen-impermeable) jars with oxygen absorbing sachets for six months at 50° C. (Japanese Patent No. SHO59-176247). The source of the oxygen being removed was primarily from the headspace and not from ingress, i.e., due to permeation of oxygen through the walls of the jar. Similarly, Japanese Patent No. SHO96-253638 describes cold remedy powders stabilized in impermeable bottles by either nitrogen purging or with oxygen absorbers in the bottle. In a 1990 publication, L-cysteine in an ophthalmic ointment was stored with an oxygen absorber. (See, i.e., *Kyushu Yakugakkai Kaiho*, "L-Cysteine Ophthalmic Solution Stabilized with Oxygen Absorber," 44, 37-41 (1990).) In 1995, tonic solutions of vitamin C were stabilized using a bottle cap having an oxygen absorber covered with a polyolefin (Japanese Patent No. SHO94-17056). U.S. Pat. No. 5,839,593 describes the incorporation of an oxygen-absorber into the liner of a bottle cap. More recently, U.S. Pat. Nos. 6,093,572; 6,007,529; and 5,881,534; and PCT publication WO 9737628 describe the use of oxygen absorbers with parenterals and their particular benefit for sterilization. Placement of oxygen-absorbing sachets between an intravenous (IV) bag or blood bag and its outer packaging is commonly used in commercial applications. Pre-filled syringes with absorbers between the syringes and outer packaging are also known. EP 0 837 069 A1 discloses the use of oxygen absorbers to stabilize acarbose in gas-impermeable bottles.

[0009] U.S. Pat. No. 6,688,468B2 and EP 1 243 524 A2 disclose the use of oxygen absorbers with pharmaceutical dosage forms in permeable packaging. The oxygen absorbers used in these patent applications are largely iron based with added moisture controlled by salt slurries. Although these systems perform well for many pharmaceutical applications, they cause the humidity in the bottle environment to be at 55 to 75% relative humidity, since the oxygen consumption reaction requires humidity to operate. Although it is possible to dry the bottle environment somewhat using a desiccant, the oxygen absorber will, in general, also be dried by the desiccant and be less effective at removing the oxygen permeating through the bottle walls. The result is that the oxygen level in the bottle will not remain low enough to provide for beneficial stabilization of the pharmaceutically active ingredient over its entire shelf life.

[0010] In all of the aforementioned documents, there is no disclosure or guidance relating to the issue of how to use a self-activated oxygen absorber to absorb oxygen in an oxygen-permeable pharmaceutical container while simultaneously maintaining the environment in the container low in moisture, for example through the use of a dessicant. Doing so would require the combination of a self-activated oxygen absorber, which requires water to function, with a dessicant which absorbs the water.

[0011] Non-iron based oxygen absorbers that do not increase the relative humidity near the absorbing unit have been marketed for use with pharmaceuticals under the registered trademark PharmaKeep® by Mitsubishi Gas Corporation and Süd-Chemie Corporation. These absorbers, however, provide only a limited absorption capacity (typically less than about 40-cc of oxygen), which is not adequate to provide for protection of pharmaceuticals in permeable packages for a typical shelf life of at least two years. Although it is possible, in theory, to use a number of such units to provide for adequate oxygen absorption on an ongoing basis, for common bottle sizes of 30-250 cc, the sheer number needed to maintain a low oxygen level during the shelf life of the pharmaceutical would generally preclude filling with dosage forms.

[0012] For all of the reasons noted above, there remains a need for an oxygen absorber that is capable of providing, in a convenient and cost effective manner, adequate oxygen absorption capacity to be usable with oxygen permeable pharmaceutical packaging for at least two years of shelf life, but which also allows the relative humidity inside the packaging to be maintained below 50%, preferably less than 40%, more preferably less than 30%.

SUMMARY OF THE INVENTION

[0013] The present invention provides a pharmaceutical package comprising an oxygen permeable bottle containing therein at least one sub-container containing a self-activated oxygen absorber and at least one sub-container containing a desiccant. The sub-containers can be separate units or unitary, i.e., fabricated together as separate compartments within a single unit, termed herein a "cartridge", containing the self-activated oxygen absorber in one compartment and the desiccant in a separate compartment. The invention solves a problem, namely that the interior of the bottle is maintained at a low oxygen level to protect oxygen-sensitive pharmaceuticals and also at a low moisture level to protect moisture-sensitive pharmaceuticals and/or dosage forms. This dual protection occurs even though the self-activated oxygen absorber requires moisture to function and the sub-container or compartment in which it resides is exposed to the interior of the bottle.

[0014] In one aspect the invention provides a method of maintaining the oxygen content of the air inside a pharmaceutical bottle at a reduced level relative to the oxygen content of the air outside the bottle, said bottle being fabricated at least in part of a pharmaceutically acceptable oxygen-permeable material, while simultaneously maintaining said inside air at a relative humidity of less than 50%, comprising the steps of:

[0015] disposing, within said bottle, a first and second sub-container,

[0016] said first sub-container containing a desiccant and being adapted to expose said desiccant to the interior of said bottle,

[0017] said second sub-container containing a self-activated metal-based oxygen-absorber,

[0018] said absorber having sufficient oxygen-reducing capacity to reduce and to maintain the oxygen content of said inside air at a level that is less than the oxygen level of the ambient (i.e., outside the bottle) air,

[0019] said second sub-container having an orifice that exposes said absorber to the interior of said bottle, said orifice having dimensions that allow oxygen scavenging by said absorber inside said bottle while simultaneously limiting the diffusion rate of water from said second sub-container such that the interior of said bottle is maintained below 50% RH, preferably below 40% RH, more preferably below 30% RH.

[0020] In a second aspect the invention provides a pharmaceutical package comprising a bottle that maintains the oxygen content of the air within its interior volume at a reduced level relative to the oxygen content of the ambient air, comprising:

[0021] A) said bottle, which is fabricated at least in part of an oxygen permeable material,

[0022] B) a desiccant disposed within a first sub-container disposed inside said bottle, said first sub-container being adapted to expose said dessicant to the interior of said bottle,

[0023] C) a self-activated metal-based oxygen-absorber disposed within a second sub-container disposed inside said bottle,

[0024] said absorber having sufficient oxygen-scavenging capacity to reduce and to maintain the interior of said bottle at an oxygen level less than the oxygen level of the ambient air,

[0025] said second sub-container having an orifice that exposes said absorber to the interior of said bottle, said orifice having dimensions that allow oxygen scavenging while limiting the diffusion rate of water from said second sub-container such that the interior of said bottle is maintained below 50% RH, preferably below 40% RH, more preferably below 30% RH.

[0026] In most embodiments the bottle is closed, and preferably sealed, although it is possible to implement the invention in the absence of a seal.

[0027] The term "bottle" is intended to be general, and to include any type or shape of pharmaceutical container that is fabricated at least in part from an oxygen-permeable material. A "pharmaceutical bottle" is one wherein the oxygen-permeable material from which it is fabricated is pharmaceutically acceptable. Thus "bottle" includes traditional square or round plastic bottles, jars, bags, pouches, or other pharmaceutically-acceptable containers.

[0028] "Relative humidity", sometimes abbreviated herein as "RH", has its usual meaning, i.e., the ratio of the actual humidity over the saturated humidity at the same temperature.

[0029] The “package” disclosed herein refers to the combination of a pharmaceutical bottle having disposed therein a self-activated oxygen absorber and a desiccant, each contained in its own sub-container, the bottle being intended to be filled by a (usually pre-determined) number of solid pharmaceutical dosage forms, typically tablets or capsules. The “inside” or “interior” of the bottle refers to the free, i.e., unoccupied volume of the bottle once filled and containing the first and second sub-containers described in (B) and (C) above, or additional sub-containers or cartridges, as described below. The free volume, also referred to in the art as “headspace”, of such filled bottles is generally between 10 and 100 cc. The amount of headspace is not critical since more than one oxygen-absorbing sub-container can be added to the bottle. Generally, given the typical size of a pharmaceutical bottle and the rate at which oxygen permeates known oxygen-permeable plastics used to fabricate pharmaceutical bottles, the oxygen-absorbing sub-container is implemented to have a hole (uncovered) that is 100-700 microns in diameter, preferably 200-600 microns. The hole will generally be round since it can be implemented with a drill, although shape is not critical and other shapes having an equivalent area can also be used. In an alternate embodiment a larger hole can be implemented and covered with a microporous material having a porosity generally between 0.05 and 0.2, and a thickness between 0.5 and 2.5 mm. Suitable membranes are widely commercially available, for example from General Electric Osmonics (a division of GE Water Technologies, Trevose, Pa.) and from Millipore Corporation, (Billerica, Mass.). The total amount of pore area, defined as the porosity times the area, should be equivalent to the area of a hole having dimensions as described above.

[0030] An oxygen-permeable bottle generally refers to one made of a material that, when sealed or closed, will admit sufficient oxygen to cause oxidative degradation of the contained active pharmaceutical ingredient over a reasonable shelf life, a “reasonable shelf life” usually being between six months and three years, typically two years. Such materials include any of the pharmaceutically acceptable available plastics commonly used in the industry and further discussed and identified below. As stated above, the bottle is one that, as part of the manufacturing operation, is closed and preferably sealed once it has been filled with pharmaceutical dosage forms and the at least two sub-containers (B) and (C) described above. Any oxygen-permeable bottle that allows for oxidative degradation of more than 0.2% of the contained active pharmaceutical ingredient or compound during its reasonable shelf life can benefit from this invention. Bottle shape is not critical.

[0031] The term “self-activated oxygen absorber” refers to a metal-based substance that removes oxygen by reacting with it to chemically bind it, generally by forming a metal oxide. The term “activated” means that the metal-based substance requires the presence of water (i.e., as a reactant) to drive the metallic oxide-forming reaction. The oxygen absorbers useful in the present invention are “self-activated”, meaning that they are sold as a unit that contains the water needed to enable the oxide-formation, the water usually being present in the form of a humidity controlling substance, typically an aqueous slurry of a salt or a sugar, such compositions being designed to maintain a specific humidity in a closed environment. The preferred metal is

elemental iron, powdered to increase its surface area. Other metals that are useful, although less preferred, include nickel, tin, copper and zinc.

[0032] The oxygen absorber reduces the oxygen content of the air within the bottle, once the bottle has been closed or sealed, to a level that is below the oxygen level of the surrounding air outside the bottle, for example the ambient air in a warehouse or shipping hold, or other storage environment or transportation means. Thereafter, the absorber maintains the oxygen in the headspace air at a level preferably below 10.0% (i.e., by volume, based on the headspace volume) preferably below 3.0%, more preferably below 1.0%, most preferably below 0.5%.

[0033] Sub-containers (B) and (C) can be implemented as physically separate containers that are added to the bottle separately in the manufacturing process. In a preferred embodiment, and as disclosed further below, sub-containers (B) and (C) are formed as physically separate compartments of a single unit, referred to herein as a “cartridge”. When discussing such a cartridge, the compartments therein are designated as (B), (C), etc to have a meaning corresponding to the letter designations given above for sub-containers (B), (C), and so forth. The cartridge can advantageously be fabricated out of a plastic (including the oxygen-permeable ones disclosed herein) by a suitable molding operation.

[0034] A further preferred embodiment, illustrated below, relates to the inclusion, in said bottle, of a third sub-container or cartridge compartment (D) adapted to contain a separate quantity of self-activated metal-based oxygen absorber from that in sub-container or canister compartment (C). This third sub-container or compartment functions to rapidly reduce or remove the oxygen initially contained in the bottle headspace once the bottle has been closed or sealed for storage, transport, and/or sale. Preferably, (D) is engineered as a third compartment in a cartridge also containing, as individual compartments therein, (B) and (C). Because this third sub-container or compartment is designed to remove the oxygen initially present in the headspace, it preferably contains only enough metal and water to react approximately stoichiometrically with the oxygen initially present in the headspace once the bottle has been closed or sealed. To facilitate oxygen removal from the headspace, the third sub-container or compartment has an orifice, preferably in the form of a porous membrane having a permeability such that the flux of oxygen allows the entire head space to be scavenged to below 3% (VN) of oxygen in less than 3 days, preferably to below 2% in 3 days relative to the orifice provided in the sub-container or compartment (C) that contains the self-activated oxygen-absorber. Providing a much larger pore area in sub-container or compartment (D) enables it to effect oxygen removal rapidly and, therefore, to quickly implement a relatively oxygen-free environment once the bottle has been closed or sealed. Thereafter, sub-container or compartment (C) maintains the oxygen at a relatively low level.

[0035] Hereinafter the invention will be described by reference to cartridges and the compartments therein, it being understood that this is for convenience and ease of description, and that the cartridges and compartments described hereinafter can also be implemented equivalently as separate sub-containers.

[0036] The access opening to compartment (B) which contains the desiccant is also relatively much larger, hence

more open to the bottle interior, than the access to the bottle interior provided by the orifice in compartment (C). The opening that exposes the desiccant in compartment (B) to the headspace is preferably in the form of a membrane, having a large pore area, to avoid spillage of the desiccant from compartment (B). Alternatively, a plurality of small orifices, such as drilled holes, can be separately implemented in lieu of a membrane. By making the total orifice surface area in compartment (B) relatively much larger than the orifice in canister compartment (C), the interior of the bottle is maintained relatively dry, much drier than the interior of the (water-containing) oxygen-absorbing compartment (C). This area, however, may be restricted to provide a relative humidity in bottle A at a somewhat higher value than is typically maintained with desiccants. This serves to minimize moisture loss from compartment (C). The total area of the orifice area in sub-container (B), whether the area is in the form of holes or a porous membrane, is typically at least 0.3 cm^2 , preferably between 0.3 cm^2 and 0.4 cm^2 .

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] FIG. 1 is a front view of a bottle having a cartridge disposed therein in a preferred embodiment according to the invention.

[0038] FIG. 2 is a graph illustrating the rate of water removal by the desiccant as a function of orifice size in compartment (B).

[0039] FIG. 3 is a graph illustrating the rate of oxygen consumption by an iron-based self-activated oxygen absorber in compartment (C) as a function of orifice size.

DETAILED DESCRIPTION

[0040] FIG. 1 illustrates a preferred embodiment of the present invention designed to provide oxygen absorption with low moisture for an extended period in a packaged product. In FIG. 1, "A" represents a pharmaceutical bottle, which is generally fabricated, in whole or in part, of an oxygen-permeable plastic. Bottle A is preferably sealed, most preferably with a heat induction seal (HIS) 1 made of a metal foil and an adhesive that effects bonding of the bottle to the foil. Disposed within pharmaceutical bottle A are pharmaceutical dosage forms 3, preferably tablets, capsules or the like. Also disposed within pharmaceutical bottle A is a cartridge, designated generally as 5 and comprised, for the sake of illustration only, of three separate compartments B, C, and D, separated from each other by dividers 7 and 9, which are walls preferably fabricated from the same material as the rest of canister 5 and manufactured integrally therewith, for example as part of a molding process. Compartment B contains a desiccant (not shown) such as silica gel and is exposed to the bottle interior by means of porous membrane 11, thereby allowing relatively free exchange between compartment (B) and the bottle headspace, whereby moist air inside bottle A enters and dry air leaves the compartment. A second compartment D contains a self-activated oxygen absorber present in sufficient quantity to remove the initial head-space oxygen in bottle A. Compartment D contains porous membrane 13 which allows for relatively free access by compartment D to the oxygen-containing air in the headspace of bottle A, thereby effecting oxygen scavenging. A third compartment C contains suffi-

cient self-activated iron absorber (i.e., metal and moisture) to scavenge oxygen permeating through the bottle walls during the shelf-life of the product. Compartment C contains an orifice 15 that can be implemented in the form of a hole, tube or microporous filter. The cross sectional area of the orifice is such that it effects a rate of oxygen scavenging sufficient to match the ingress rate of oxygen into bottle A, yet the area is such that the orifice limits the rate of moisture loss from compartment C so that there is adequate moisture in the compartment (i.e., to enable metallic oxide formation) during the entire shelf-life of the pharmaceutically active ingredient. Some moisture does escape from compartment (C), but the rate is small relative to the moisture-absorbing capacity of the desiccant in subunit "D". This is a critical feature of the invention, i.e., the cross-sectional area of the orifice (or orifices) in compartment (C). On one hand, the area is large enough to effect efficient oxygen scavenging from the interior of the bottle during the shelf life of the product, thereby eliminating or reducing oxidative degradation of the pharmaceutical product. On the other hand, the area is small enough to limit the amount of moisture that escapes compartment (C) to no more than that that can be removed by the desiccant during the shelf life.

[0041] As stated previously, if the orifice is implemented as a circular hole, it should have a diameter of from 100 to 700 microns, corresponding to a cross sectional area of from about 0.8×10^{-4} to about $38 \times 10^{-4} \text{ cm}^2$. Orifice shape is not critical, and other shapes having equivalent cross-sectional areas can be implemented equally effectively.

[0042] FIG. 2 shows the (experimentally-determined) variation in the rate of moisture scavenging by the desiccant silica gel as a function of orifice diameter (e.g., in compartment (C)) through a barrier having a single tube therein of varying diameter. The data points in the graph were measured while maintaining the external environment at 40° C . and 75% relative humidity (RH). The graph demonstrates that the rate of moisture transfer out of a cartridge with a high humidity compartment (C) can be controlled in a predictable manner by picking a suitable size for the orifice.

[0043] FIG. 3 shows the rate of oxygen scavenging by iron through a barrier having a single tube implemented therein, as a function of orifice (i.e., tube) cross sectional area. The data demonstrate that the rate of oxygen scavenging, i.e. by compartment (C) can be controlled in a predictable manner depending on orifice size.

[0044] In FIG. 1, pharmaceutical container A is a bottle or other container for dispensing pharmaceutical dosage forms. The bottle is designed to protect a dosage form from mechanical harm and to limit exposure of the dosage forms contained therein to light and contaminants in the environment. Glass bottles can in some cases function effectively due to the low (essentially no) permeability of glass to oxygen and moisture, and are within the scope of the present invention. However, due to the risk of breakage and the added expense of working with glass, bottles are preferably made, usually entirely, of plastic, essentially all of such plastics being oxygen-permeable in varying degrees. Suitable plastics for use in fabricating pharmaceutical bottles generally involve such plastics as low density polyethylene (LDPE), high density polyethylene (HDPE), polypropylene (PP), polystyrene (PS) and polycarbonate (PC). The oxygen permeability of these materials ranges from 3500 cc mil/

(m²day atm) for PS to 9500 cc mil/(m²day atm) for LDPE. Other suitable packaging materials include polyesters (PET, PEN), nylon, polyvinyl chloride (PVC), poly(vinylidene chloride) (PVDC), poly(tetrafluoroethylene), etc., and laminates containing layers of one or more such materials. The present invention provides, in a preferred embodiment, for a cartridge that can be added to a pharmaceutical bottle and that provides for a significant reduction in the oxygen and moisture levels, including such a reduction at the permeation rates disclosed above.

[0045] Once an oxygen permeable bottle is filled with a pre-determined amount of dosage forms containing an oxygen-sensitive drug and a cartridge according to the invention, the bottle is then closed, as by capping with a twist-on cap, or stoppering, or sealing. If the bottle is sealed, a preferred seal is a heat-induction seal (HIS). Other useful seals include adhesives such as pressure sensitive adhesives, thermal adhesives, photocured adhesives, and binary mixture adhesives such as epoxy resins. Adhesion can also be effected by such techniques as ultrasonic welding which do not require adhesives. A packing material (e.g., cotton) may be optionally added to the bottle prior to sealing to prevent any damage to the contents such as chipping or cracking of the unit dosage forms. HIS is commonly used in the pharmaceutical industry to seal plastic bottle tops, both as a means of protecting the dosage form from the environment and as a means of preventing (and making obvious) any tampering. The induction seal and the bottle are preferably matched to achieve an acceptable seal. Procedures for induction sealing are well known to those skilled in the art. For a detailed description see "Induction Sealing Guidelines", R. M. Cain (Kerr Group, Inc.), 1995 and W. F. Zito "Unraveling the Myths and Mysteries of Induction Sealing", *J. Packaging Tech.*, 1990.

[0046] Any pharmaceutical dosage form 3 containing an oxygen-sensitive pharmaceutical compound susceptible to degradation as a result of exposure to oxygen may be disposed within pharmaceutical bottle A. Examples of oxygen-sensitive materials that are subject to degradation due to oxygen exposure include materials such as amines either as salts or as free bases, sulfides, allylic alcohols, phenols, alcohols, aldehydes and the like. In addition, some basic pharmaceutically active materials or compounds, especially amines, with pK_a values in the range from about 1 to about 10, more particularly in the range from about 5 to about 9, are often subject to oxygen degradation and may accordingly benefit from the present invention, as well as some pharmaceutically active materials or compounds having redox potentials less than or equal to about 1300 mV vs. Ag/Ag⁺, more preferably less than or equal to about 1000 mV vs. Ag/Ag⁺. Suitable pharmaceutically active compounds include compounds such as atorvastatin (especially when used in an amorphous form), pseudoephedrine, tiagabine, acitretin, rescinnamine, lovastatin, tretinoin, isotretinoin, simvastatin, ivermectin, verapamil, oxybutynin, hydroxyurea, selegiline, esterified estrogens, tranlycypromine, carbamazepine, ticlopidine, methyl dopahydro, chlorothiazide, methyl dopa, naproxen, acetaminophen, erythromycin, bupropion, rifapentine, penicillamine, mexiletine, verapamil, diltiazem, ibuprofen, cyclosporine, saquinavir, morphine, sertraline, cetirizine, N-[[2-methoxy-5-(1-methyl)phenyl]methyl]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine and the like. The invention is particularly suitable for stabilizing high-energy drug forms to oxidation.

Examples of high-energy drug forms include amorphous forms and small particle sized drug forms. A preferred example of a high-energy form of a drug is prepared by spray-drying a drug as a dispersion in combination with an enteric polymer as described in EP 1027886A2 and EP 901786A2, each incorporated herein by reference. Suitable enteric polymers include those described in Patent application Nos. WO 0147495 A1, EP 1027886 A2, EP 1027885 A2, and U.S. Pub. No. 2002/0009494 A1, incorporated herein by reference.

[0047] The present invention can additionally stabilize excipients in the dosage form to oxidative degradation. For example, degradation that leads to discoloration, harmful reactivity with the active component of the drug or changes in the dosage form performance, such as dissolution or disintegration rates. Nonexclusive examples of excipients commonly used in pharmaceutical formulations that could be stabilized by application of the present invention include poly(ethylene oxides), poly(ethylene glycols) and poly(oxyethylene) alkyl ethers.

[0048] The present invention provides a reduction in the degree of oxidative degradation or discoloration where such degradation or discoloration can be measured by light absorption or reflection spectroscopy and/or chromatographic analysis, in particular, HPLC analysis. The invention need not totally eliminate such degradation; however, practice of the present invention preferably reduces the degradation by at least about 20%, more preferably by about 50% and most preferably by about 75% when compared to samples stored in the absence of the cartridge/oxygen absorber as disclosed herein.

[0049] Although the shape of the cartridge is not critical, the cartridges described herein can be generally tubular in shape to facilitate high speed bottle insertion. The cartridge can be in the form of a canister, i.e., a tubular container with the desired number of compartments and having either or both end compartments openable to facilitate filling. The ends of the tube can be flat or circular, convex or concave, as desired. The cartridge can be fabricated as known in the art by using a suitable mold and molding process, typically injection molding with a thermoformable polymer.

[0050] The desiccant (sub-container or compartment B) provides for a low relative humidity in the pharmaceutical package. The desiccant for use in the practice of the invention can be any available desiccant. Preferred desiccants include those commonly used in the pharmaceutical industry that have adequate capacity to handle the combination of moisture ingress into the bottle and moisture given off by the self-activated oxygen absorber. Suitable desiccants are discussed in R. L. Dobson, *J. Packaging Technol.*, 1, 127-131 (1987). A preferred desiccant is silica gel. The desiccant can be supplied in the form of a sachet, cartridge or canister.

[0051] It is desirable to maintain the relative humidity in the bottle A at a level that, while still providing protection of the dosage forms from the adverse effects of humidity, minimizes the loss of moisture from compartment C. To this effect, the barrier 11 can be made to limit the moisture transfer rate. This rate limitation can be effected using a membrane of somewhat limited moisture permeation (by virtue of material or thickness) or by suitable choice of a material having an appropriate permeability. This material and surface area selection can be made based on experi-

ments and depends on the particular moisture sensitivity of the dosage form used. In general, it is desirable that the permeability of barrier 11 to moisture be such that the relative humidity in the bottle A is maintained at or below 40% RH, more preferably, below 30% RH, under, as a reference, storage conditions of 30° C., and 75% RH).

[0052] The amount of desiccant used is preferably sufficient to handle moisture ingress through the pharmaceutical bottle walls during the storage duration, which depends on the humidity of the external environment. For conditions of 30° C. and 60% RH, the rate of water permeation into a 60-cc HDPE bottle with an internal humidity kept below 40% RH can be estimated at about 0.25 mg/day (91 mg/yr). In addition, there is preferably enough desiccant to handle moisture loss from the oxygen absorber (estimated at about 146 mg/yr, as discussed below). Silica gel has an approximate capacity to maintain a relative humidity below 40% at about 0.5 mg H₂O/mg silica. Thus an amount of silica gel to place in sub-container or compartment B is between 475 and 1100 mg, an amount that will absorb both moisture from external permeation and moisture escaping internally from absorber compartment (C), based on the orifice size in the compartment, during a reasonable shelf life. It will be recognized by those skilled in the art that similar calculations can be made for different bottle materials having different rates of water permeation, headspace volumes, and different conditions of temperature and relative humidity. The cartridge compartment is constructed such that it physically separates the desiccant from direct contact with the pharmaceutical ingredients, yet allows the moisture from inside the pharmaceutical package to be scavenged.

[0053] Compartment D of the cartridge contains a self-activated oxygen absorber capable of rapidly removing oxygen from the headspace in pharmaceutical bottle A. This absorber is preferably an iron-based absorber and can be the same material used as the self-activated oxygen absorber disposed within absorber compartment (C). To enable the metal to scavenge oxygen, a moisture source must be provided. In the present invention, and as commercially available, this moisture source is preferably provided in the form of a salt or sugar slurry. Because compartment D is designed to rapidly remove the oxygen from the headspace inside bottle A, it only needs to function for a few days, and thus requires only a relatively small amount of absorber. The absorber in compartment (D) can therefore be at a high relative humidity, though it will rapidly deplete its moisture as the desiccant in compartment B competes for the moisture. Preferably, the humidity source in compartment B maintains a relative humidity (RH) above about 50%; more preferably above 60%; still more preferably, above 65%. Preferred moisture sources are salts or salt mixtures. Particularly preferred salts are sodium chloride, potassium chloride and potassium sulfate. Compartment D is constructed such that it physically separates the self-activated oxygen absorber from direct contact with the pharmaceutical dosage forms, yet allows oxygen from inside the pharmaceutical package to be scavenged. Preferred compartments (D) contain sachets wherein the containment sack is fabricated of porous (e.g., woven) material. Alternatively the cartridge compartment (D) can itself be porous, as by having an open section covered with a porous fabric or membrane.

[0054] The amount of headspace oxygen in bottle A can be determined by measuring the volume of the bottle, subtract-

ing the volume of the dosage forms and dividing the remaining volume by five (to account for the oxygen abundance). For example, in an approximately 60-cc bottle that is half filled with dosage forms, the headspace volume will be about 6-cc of oxygen. The amount of iron used to remove the oxygen, and excluding any oxygen due to ingress, should be at least stoichiometrically sufficient. Since the oxygen-absorbing capacity of the iron is about 300-cc/g, the minimum amount of iron needed for removal of the headspace oxygen of a 60-cc bottle is 20 mg. Therefore, the amount of iron for this subunit is preferably between 20 and 100 mg.

[0055] Compartment C contains sufficient oxygen absorber to enable the oxygen level in the pharmaceutical bottle to remain low during the product's reasonable shelf life by balancing the oxygen ingress rate into the bottle with a comparable rate of oxygen scavenging. At the same time, the rate of loss of moisture from compartment C is sufficiently low that the overall moisture level in bottle A remains low due to the desiccant and there remains enough water in the subunit to provide for the needed relative humidity in the subunit for iron activity during the duration of the shelf-life. It has been determined that these contradictory and opposing goals can be met with an oxygen absorber and a moisture controlling element encased in a low permeability cartridge compartment in combination with a rate-controlling port (15 in FIG. 1). Preferentially, the cartridge is made from a plastic or metal material considered safe for contact with pharmaceutical ingredients. Examples of preferred materials include plastics such as polyethylene (PE), polystyrene (PS) and polyvinylchloride (PVC). Although the cartridge can be made out of permeable plastics, the actual amount of oxygen and moisture that transfers through these materials (as opposed to the holes or membranes) is a low due to the low surface area and does not significantly impact the oxygen and moisture levels in bottle A. The rate-controlling port has the property of restricting moisture transfer while allowing sufficient oxygen transfer.

[0056] FIG. 2 shows the rate of moisture transfer from a test environment controlled to be at 40° C. and 75% RH into a sub-container having a fixed amount of silica gel, the sub-container having a single orifice, implemented therein as a tube, as the only entrance for moisture from the environment. The amount of water entering through the tube was monitored as a function of time and the diameter of the tube. These data provide the basis for calculating the moisture transfer rate from the self-activated oxygen absorber compartment (C) to the bottle A headspace. Once this transfer rate has been calculated, it can in turn be used to calculate the amount of desiccant needed for compartment (B).

[0057] As an example, to function effectively in pharmaceutical applications, the relative humidity in bottle A is preferably maintained at below about 50% RH, more preferably below 30% RH, while the RH in compartment (C) is preferably 40-70%, more preferably 50-60%. Therefore, the rate of moisture transfer from the test system (75% RH to 10% RH) can be corrected to take into account the relative humidities in the product as envisioned (60% RH to 30% RH) by dividing the value by

$$(75-15)/(60-30)=2$$

wherein

[0058] 75 is the RH (in %) of the test environment

[0059] 15 is the RH maintained by the desiccant

[0060] 60 is the minimum desired RH for the oxygen absorber to function

[0061] 30 is the desired RH of the headspace.

[0062] FIG. 3 shows the rate of oxygen transfer through similar tubes into an iron oxygen absorber. In this case, the oxygen depletion of a fixed oxygen volume was used for the measurement. Again the oxygen transfer rate was monitored as a function of the size of the tube. The desired rate of oxygen scavenging and, therefore, the diameter of a hole or tube needs to take into account the fact that the oxygen scavenger will need to handle the oxygen permeation into the pharmaceutical package and to maintain a low oxygen level (e.g., 1%). The tube (or other orifice) must accordingly have a hole large enough to compensate for the incremental difference in the rate of oxygen diffusion as the difference in pressure is increased from that used in the test. Since this latter rate should be proportional to the difference in pressure, on going from 0 to 20.8% oxygen of the test to 0 to 1% oxygen in the final product, the corresponding oxygen rate found from the graph in FIG. 3 should be multiplied by 20.8.

[0063] To determine the amount of oxygen entering the pharmaceutical package, a round bottle made of high-density polyethylene (HDPE) with a labeled capacity of 60 cm³ and a wall thickness of 37 mils (0.94 mm) can be used as a representative sample. If the bottle is 4 cm in diameter and 7.3 cm in height (in reality the bottle will taper to give less surface area than this approximation), then the surface area will be approximately 100 cm². If one uses HDPE as the bottle material and assumes the inside of the pharmaceutical package to be maintained at 1% oxygen, then the rate of oxygen permeation into the bottle can be calculated as follows:

$$\frac{4000 \text{ cm}^3 \text{ mil}/(\text{m}^2 \text{ d atm}) \times (0.18 - 0.009) \text{ atm} \times 0.01 \text{ m}^2/37 \text{ mil}}{= 0.18 \text{ cm}^3 \text{ of O}_2/\text{day}}$$

Using this value and the factor of 20.8 discussed above, it can be determined that the hole size to meet the oxygen demand for a 60-cm³ HDPE bottle (to bring the oxygen to 1%) is about 500 µm in diameter.

[0064] At this diameter, the amount of water loss can be estimated from the graph of FIG. 2 at 0.87 mg/day. Correcting this for the envisioned system as described above brings this value to 0.43 mg/day.

[0065] Thus the use of data such as that exemplified in FIGS. 2 and 3 will be appreciated by those skilled in the art. Using FIG. 3, one can calculate the size of the orifice in (oxygen absorber) compartment (C) to effectively scavenge oxygen. FIG. 2 can be used to determine the corresponding moisture loss from the compartment and the amount of desiccant needed.

[0066] The orifice in compartment (C) that controls the rate of moisture and oxygen transfer ("I5" in FIG. 1) can be produced in the following manners:

[0067] (1) A single hole can be used as the orifice. The hole preferably has a diameter of between 100 and 700 µm; more preferably, between 200 and 600 µm. The hole can be cylindrical (round with parallel sides),

conical (round with sloping sides) or rectangular. The hole can be made by any technique known in the art. Particularly preferred methods of forming the hole include drilling through the cartridge wall using a mechanical, ultrasonic or laser drill, or forming the compartment hole in place by, for example, injection molding. A high porosity material or mesh can be used in conjunction with this hole to prevent powder from escaping from the cartridge of canister. The diameter of a mesh should be smaller than the fine particles in the subunit, preferably smaller than about 15 µm.

[0068] (2) A tube is placed through the port area. The tube preferably has an internal diameter of between 100 and 700 µm; more preferably, between 200 and 600 µm. The tube is preferably sealed into the cartridge in the port area using an adhesive or by melting the adjacent wall. The tube length can range from 1 to 25 mm. A high porosity material or mesh can be used in conjunction with this tube to prevent powder from escaping from the cartridge of canister. The diameter of a mesh should be smaller than the fine particles in the subunit, preferably smaller than about 15 µm.

[0069] (3) A microporous membrane is placed in the port area. This filter restricts the moisture and oxygen diffusion. Preferably, the microporous membrane has a porosity of between 0.05 and 0.20 and a thickness of 0.5 to 2.5 mm. The preferred diameter of the membrane is between 100 and 1000 µm.

[0070] The active oxygen absorber in compartment (C) is preferably iron. The iron is preferably in its reduced form (that is, Fe⁰). The iron can be atomized, milled, pulverized, electrolyzed or otherwise treated to form a fine powder as is known in the art. The amount of iron used in the present invention can be optimized based on the permeability of the pharmaceutical packaging "A" and the storage duration. Using the round HDPE bottle described above as a representative example, the amount of oxygen that needs to be scavenged is about 66 cm³/yr. Based on an oxygen-absorption capacity for iron of about 300 cm³/g, the amount of iron needed in compartment (C) (FIG. 1) is about 220 mg. To build in for losses, the subunit therefore preferably contains between about 225 and 500 mg of iron.

[0071] To enable the iron to scavenge oxygen, a moisture source must be provided. In the present invention, this moisture source is preferably provided in the form of a salt or sugar slurry. The moisture controlling material should be able to control the moisture in the compartment of the oxygen absorber. Since the rate of loss of moisture from compartment (C) is proportional to the difference in relative humidity between that in compartment (C) and in the pharmaceutical bottle headspace itself, it is desirable to make the relative humidity in compartment (C) as low as possible while still providing adequate moisture to enable oxygen-scavenging activity. It is therefore preferred to control the humidity in compartment (C) to between 40 and 70% RH; more preferably, between 50 and 60% RH. The humidity-controlling salt or sugar slurry can be an inorganic or organic salt or salt mixture, a sugar or sugar mixture, or a mixture of salts and sugars, provided such materials can control the relative humidity to the desired range. Particularly preferred materials for controlling said relative humidity include sodium chloride, calcium nitrate, sodium bisul-

fate, sodium chlorate, potassium iodide, sodium bromide, magnesium acetate, sodium nitrate, ammonium chloride, potassium nitrate, potassium bromide and magnesium nitrate. The amount of salt or sugar used needs to be sufficient to provide for the desired control of the relative humidity even as some of the water is removed in the use of the present invention.

[0072] For the slurry to control the relative humidity in compartment (C) during the shelf life of the product, there must be sufficient water to handle the anticipated water loss. Based on the size of the rate-controlling port "I" (FIG. 1), this rate can be kept to about 157 mg per year. In the practice of the present invention, the amount of water in the cartridge is therefore preferably between 150 and 400 mg; more preferably, between 180 and 360 mg.

[0073] To control the relative humidity with this much water, the amount of the salt or sugar used must be sufficient that at least some of the solid remains undissolved. As such, one can determine the amount of salt or sugar by multiplying the amount of water added by the water solubility of the salt or sugar. As an example, for the humidity controlling additive magnesium nitrate, this leads to a preferred amount of this additive of between 225 and 450 mg, based on a solubility of 1250 mg/mL.

[0074] The present invention provides for the removal of oxygen not only from the entrapped air within the pharmaceutical bottle (FIG. 1) but also oxygen that enters the bottle via ingress. It will be appreciated that in the use of the oxygen-absorbing cartridge, one can engineer a unit having the appropriate absorption capacity for the given bottle and desired shelf-life. It is also possible to engineer an oxygen-absorbing unit that is standard, but for which the number of such units actually applied will depend on the bottle design and shelf-life.

[0075] The oxygen-absorber need not remove 100% of the oxygen from the interior air in the bottle; however, it is preferred that the absorber be present in an amount such that it is capable of maintaining a level of oxygen less than or equal to about 10.0% preferably less than or equal to about 3.0%, more preferably less than or equal to about 1.0%, most preferably less than or equal to about 0.5%, for about 2 years inside the oxygen permeable bottle.

EXAMPLES

Example 1

[0076] A 20 mm Flurotec® Teflon stopper (West Pharmaceutical Services, Jersey Shore, Pa.) was drilled through the center with a 1.0 mm drill bit. HPLC tubing (Upchurch Scientific, Oak Harbor, Wash.) was cut to 2 cm in length and forced through the drilled hole in the stopper. The tubing used included model 1520 (762 μ m inner diameter), model 1532 (508 μ m inner diameter), model 1531B (254 μ m inner diameter), model 1535 (127 μ m inner diameter) and model 1560 (64 μ m inner diameter), all from Upchurch Scientific (a division of Scivex Inc., Oak Harbor, Wash.).

[0077] For the measurement of water vapor uptake, a 1 gram Sorb-It® canister (Süd-Chemie, Belen, N. Mex.) was cut open and the silica gel contents poured into a 10-cc tubular flint Type I glass vial (Wheaton Science Products, Syracuse, Nebr.). The stopper with tubing was crimp-sealed

to the vial and the initial weight recorded. The test units were then placed in a 40° C./75% RH stability chamber and periodically weighed over two weeks.

[0078] For the measurement of oxygen consumption, the contents of an oxygen scavenger (DSR#4062B, 200-cc oxygen absorber from Multisorb Corp., Buffalo, N.Y.) was cut open and the contents poured into a vial (same as above), and the stopper with tubing was crimp-sealed to the vial within 3 minutes. Each test unit was placed in a 250-cc HDPE bottle, which was then heat induction sealed under ambient air conditions. Thus each system initially contained approximately 21% oxygen. The bottles were stored at ambient temperature and RH (approximately 20° C. and 30% RH). At the end of two weeks, the oxygen level inside the HDPE bottle was measured using a Mocon PAC Check 450 (Mocon Inc., Minneapolis, Minn.), which was standardized with ambient air (21% oxygen) and a 0.5% oxygen standard from Mocon Inc.

Example 2

[0079] A cartridge is made by injection molding polyethylene into two compartments with cylindrical shape of diameter 0.5 inches (1.3 cm) and wall diameters of approximately 1 mm. The top compartment has a single 600 μ m diameter hole with a lattice (diameter of openings of 25 μ m) on the side as part of the mold. The bottom compartment is 0.25 inches in height (0.63 cm). The top compartment is 0.5 inches in height (1.3 cm). Into the bottom compartment is filled 0.5 g of silica gel. A cap of sintered polyethylene (porosity of 0.1) is adhered to the bottom compartment to seal in the powder. Magnesium nitrate (1.0 kg) is slurried with 800 g of water to give a 44% (w:w) slurry. The top compartment is filled with a combination of 300 mg of fine iron powder (as described in U.S. Pat. No. 5,725,795) and 450 mg of the magnesium nitrate slurry. A cap is formed by injection molding polyethylene into a cylinder with a wall and a top having a high porosity (0.4). The cap is 0.55 inches in diameter (1.4 cm) and 0.2 inches in height (0.5 cm). The cap compartment is filled with 50 mg of self-activated iron oxygen absorber (available from Multisorb Corp., Buffalo, N.Y.), then the porous top is adhered to it. This entire cap is then adhered to the top compartment of the above cylinder. A 60 cm³ polyethylene bottle is loaded with pharmaceutically active tablets and one of the above cartridges. The bottle is sealed using a heat induction seal.

What is claimed is:

1. A pharmaceutical package comprising a bottle that maintains the oxygen content of the air within its interior volume at a reduced level relative to the oxygen content of the ambient air, comprising:

A) said bottle,

B) a desiccant disposed within a first sub-container disposed inside said bottle,

said first sub-container being adapted to expose said desiccant to the interior of said bottle,

C) a self-activated metal-based oxygen-absorber disposed within a second sub-container disposed inside said bottle,

said absorber having sufficient oxygen-reducing capacity to reduce and to maintain the interior of said container at an oxygen level less than the oxygen level of the ambient air,

said second sub-container having an orifice that exposes said absorber to the interior of said bottle, said orifice having dimensions that allow oxygen scavenging while limiting the diffusion rate of water from said second sub-container such that the interior of said container is maintained at a relative humidity less than 50%.

2. A package as defined in claim 1, wherein the metal used in said oxygen absorber is selected from iron, tin, nickel, copper and zinc

3. A package as defined in claim 1 or 2, wherein the cross sectional area of said orifice is between 0.8 and $38 \times 10^{-4} \text{ cm}^2$.

4. A package as defined in any one of claims 1-3, wherein said orifice is a hole having a diameter between 100 and 700 μM .

5. A package as defined in any one of claims 1-4, wherein said bottle is fabricated from a polymeric plastic having a thickness such that the oxygen permeability of said bottle is from 3500 cc mil/(m²day atm) to 9500 cc mil/(m²day atm).

6. A package as defined in any one of claims 1-5, wherein said sub-containers are physically separate.

7. A package as defined in any one of claims 1-6, wherein said sub-containers are formed as physically separate compartments of a unitary cartridge.

8. A package as defined in any one of claims 1-7, further comprising, within said bottle, a third sub-container (D) adapted to contain a quantity of self-activated metal-based oxygen absorber separate from the absorber contained in sub-container (C).

9. A package as defined in claim 8, wherein said sub-container (D) is physically separate from sub-containers (B) and (C).

10. A package as defined in claim 8 or 9, wherein said sub-container (D) is engineered as a compartment in a cartridge also containing, as individual compartments, sub-containers (B) and (C).

11. A package as defined in any one of claims 1-10, wherein said bottle is fabricated at least in part of a pharmaceutically acceptable polymer.

12. A package as defined in any one of claims 1-11, wherein said desiccant is silica gel.

13. A package as defined in any one of claims 1-12, wherein the metal used in said oxygen absorber is iron.

14. A package as defined in any one of claims 1-13, wherein the orifice of the second sub-container is a hole having a diameter between 200 and 600 μM .

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