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(54) Title: CONTROLLED-RELEASE DOSAGE FORMS FOR VARENICLINE

(57) Abstract: A controlled release pharmaceutical composition of varenicline or a pharmaceutically acceptable salt thereof wherein said controlled release pharmaceutical composition comprises a coating and an antioxidant wherein said antioxidant is present in an amount equal to a weight percent greater than about 0.1 % but less than 5% of the coating layer.

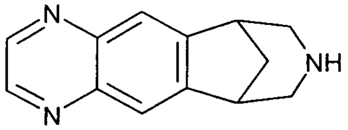
CONTROLLED-RELEASE DOSAGE FORMS FOR VARENICLINE

FIELD OF THE INVENTION

The present invention is directed to novel, oral controlled-release compositions of varenicline or its pharmaceutically acceptable salts wherein cores containing the drug are surrounded by a coating layer that comprises an antioxidant that protects the varenicline active from undergoing a reductive alkylation degradation pathway. The present invention is also directed at a kit for said cores surrounded by a coating layer wherein said kit comprises an oxygen absorber.

BACKGROUND OF THE INVENTION

Varenicline, which has the following structure, is useful in the treatment of nicotine addiction:

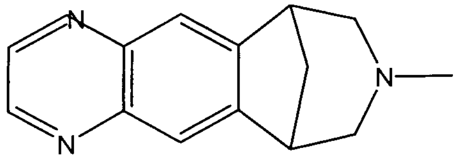


The drug may also be used in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and other addictions (e.g., dependencies on, or addictions to alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

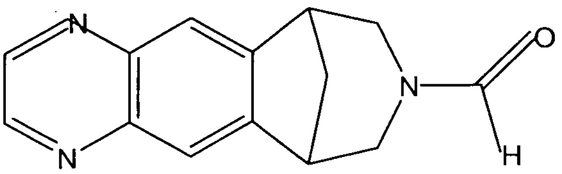
Varenicline and pharmaceutically acceptable acid addition salts thereof are referred to in International Patent Publication WO99/35131, published July 15, 1999, the contents of which are incorporated herein by reference.

Whereas immediate release (IR) dosage forms of the aforementioned compound, that is, dosage forms designed to provide the drug in a dissolved form upon swallowing in less than about 30 minutes, provide therapeutically useful levels of drug in the blood and brain, it has been observed that there is a significant level of nausea in patients, especially at doses sufficiently high to be therapeutically useful for some patients. Since nausea can lead to poor patient compliance with a dosing regimen, there is a need to provide varenicline or its pharmaceutically acceptable salts in a form that reduces the incidence of nausea. Accordingly, the present invention provides varenicline controlled release (CR) dosage forms that reduce or eliminate nausea while maintaining a therapeutic level of the drug in the blood and central nervous system (CNS).

The high potency of varenicline and its pharmaceutically acceptable salts as a nicotinic receptor ligand allows for administration of low dosage strengths. For ease of handling, manufacturing and patient convenience, low dosage strength drugs are often formulated at high dilution with excipients. In the preparation and storage of such dilute formulations, however, unique challenges are introduced. First, the high dilution can enable excipients or even excipient impurities to cause significant drug degradation during storage. Examples of excipient properties that may impact drug degradation include moisture content and mobility of moisture (see J.T. Carstensen, *Drug Stability: Principles and Practices,* 2nd Ed, Marcel Dekker, NY, 1995, 449-452), and excipient acidity affecting local pH microenvironments (see K. Waterman et al., *Pharm Dev. Tech.*, **2002**, 7(2), 113-146). Examples of excipient impurities that affect drug degradation include trace metals, peroxides, and formic acid (see K. Waterman, *et al., Pharm. Dev. Tech.*, **2002**, 7(1), 1-32). Although consideration of the chemical structure and identification of reactive moieties therein can be used to theorize potential degradation pathways, it remains impossible to predict *a priori* whether a particular excipient will form an acceptably stable formulation with a given drug. Moreover, varenicline and its pharmaceutically acceptable salts have been observed to react with many common excipients and excipient impurities. Varenicline, as a secondary amine, is subject to electrophilic attack. Although common excipients (outside of reducing carbohydrates, as disclosed in co-pending application WO03/045437) will not react with the drug, especially in the solid state, it was found that only certain excipients were able to provide adequate storage stability when used with varenicline. As disclosed in co-pending patent application, US 2004/0235850, two particular chemical degradants have been observed to form in coated, solid varenicline dosage forms on storage. The degradants are primarily the N-methyl adduct **1,** and to a lesser extent, the N-formyl adduct **2**. The formation of the primary degradant **1** reflects a formal reductive alkylation that is unlikely to occur directly with any of the formulation excipients examined (for reductive alkylations see J. March, Advanced Organic Chemistry, 4th ed., 1992 pp.898-900), yet significant levels of this degradant was observed upon aging with certain coated tablets.



Adduct 1



Adduct 2

Addition of the antioxidant, butylated hydroxytoluene (BHT), to an asymmetric membrane, osmotic coating surrounding tablets containing a core of a sulfide-containing drug was disclosed to prevent oxidation to a sulfoxide form of the drug (see *"Pharmaceutical Development and Technology"* 2005, 1, 115-125). While this disclosure teaches that adding an antioxidant to a coating can be used to prevent oxidation of a drug in a core, there is no similar teaching on how to prevent reductive methylation.

There remains a need to provide excipient and excipient combinations which can produce acceptable CR dosage forms while providing suitable stability for varenicline or its pharmaceutically acceptable salts. In the present invention, it has been surprisingly and unexpectedly found that the formation of the reductive alkylation adduct **1**, as well as the formyl adduct **2**, both degradants that are not formal oxidations, can be substantially reduced by the addition of an antioxidant to a coating layer of oral CR dosage forms comprising varenicline or its pharmaceutically acceptable salts, even when such coating contain PEG, PVP or PEO. The inventors have discovered specific preferred ways of formulating an antioxidant into the CR formulation of varenicline or its pharmaceutically acceptable salts to achieve the desired stability. More specifically for oral dosage forms which comprise a core of varenicline and at least one excipient surrounded by a coating layer comprising an antioxidant, the inventors have discovered specific formulations and processes to achieve the desired stability. Therefore, the present invention addresses a need in the art to provide suitable CR dosage forms of varenicline or its pharmaceutically acceptable salts which are storage-stable for a sufficient time that the dosage can be provided in a relatively pure form over a commercially viable term.

SUMMARY OF THE INVENTION

Accordingly, this invention relates to varenicline CR dosage forms comprising a coating wherein said coating contains an antioxidant, wherein said CR dosage forms have improved storage stability compared to similar formulations without added antioxidants. In particular, the present invention relates to oral CR formulations of varenicline or its pharmaceutically acceptable salts and at least one pharmaceutically acceptable excipient in a pharmaceutical core surrounded by a semi-permeable coating comprising an antioxidant. The antioxidant is present in an amount equal to a weight percentage greater than about 0.1% but less than 5% relative to the coating layer. The coated CR dosage form can have an enteric or osmotic coating. A particularly preferred dosage form is an asymmetric membrane technology (AMT) system (as described in U.S. Patent Nos. 5,612,059 and 5,698,220, the contents of which are incorporated herein by reference). Another preferred coating is an enteric coating wherein said coating contains antioxidant present in an amount equal to a weight percentage greater than about 0.1% but less than 5% relative to the coating layer. These enteric coatings become permeable as the pH increases when a dosage form exits the stomach. Preferred examples of such coatings include Eudragits™, cellulose acetate hydrogen phthalate and hydroxypropylmethylcellulose acetate succinate and and hydroxypropylmethylcellulose phthalate.

Yet another embodiment of the present invention teaches that a pharmaceutical kit comprising a coated CR composition of varenicline or its pharmaceutically acceptable salts and at least one oxygen absorber can provide adequate drug stability.

DEFINITIONS

The term "core" refers to a tablet core containing pharmaceutically acceptable excipients, diluents and/or carriers formed into a single uniform solid (i.e., single layer), or a multi-layered solid (e.g., compressed multi-layer construction, coated compressed core, or combination thereof). The additional coatings or layers may be present for a variety of functions (e.g., CR, enteric release, delayed release, adhesion enhancement of adjacent coatings or layers, identification (e. g., trademark), taste masking, to add drug combinations and for protection from environmental elements such as light, moisture and/or oxygen.

The term "controlled release" (CR) refers to dosage forms which slowly release or deliver the drug to the patient at a rate such that at least some of the drug is unavailable in the first hour. A CR system can provide the drug at a constant rate (zero order), at a steadily decreasing rate (first order) or an uneven or pulsatile rate. The drug delivery can also involve a lag time in initial drug release. This lag can be temporal or be related to the position of the drug in the body. For example, a CR dosage form may be prepared by exploiting an enteric coating where drug is released upon reaching the pH of the intestine after oral administration. The term "osmotic controlled release" refers to a controlled release dosage form where the means for metering the drug is controlled by osmotically driven ingress of water through a membrane.

The term "delayed release" refers to a dosage form designed to release drug rapidly or in a controlled release fashion where the delivery of the drug does not begin until either a predetermined time has passed or the dosage form reaches a certain environment during its transit through the GI tract.

The term "enteric release" refers to drug delivery systems designed to deliver drug in the intestine with little or no delivery of the drug in the stomach.

A "permeable coating" CR system refers to various coatings on tablets or particulates that act as barriers to drug leaving a tablet or to water reaching the drug. These coatings include enteric coatings which become permeable as the pH increases when a dosage form exits the stomach. Examples of such coatings include Eudragits™ sold by Rohm GmbH Pharma Polymers (Darmstadt, Germany) and cellulose acetate hydrogen phthalate (CAP) sold by Eastman Chemical (Kingsport, TN). One group of such coated CR systems includes osmotic systems. Such CR dosage forms involve a semi-permeable membrane surrounding a drug core containing sufficient osmotic pressure to drive water across the membrane in the GI system. The osmotic pressure can then force drug out of the core through preformed or *in situ* produced holes or pores in the coating. Such systems often involve the addition of agents (osmagents) designed to increase the osmotic pressure in the core. A review describing such systems is found in G. Santus and R. W. Baker, *J. Control. Rel.*, **1995**, *35*, 1-21.

The term “oxygen absorber” refers to substances provided in packaging to scavenge oxygen from within the package. Such oxygen absorbers are discussed in US Patent No. 6,688,468B2.

The drug, varenicline, for the purposes of the present invention refers to the parent drug and all pharmaceutically acceptable salts and prodrugs thereof. The term "pharmaceutically acceptable salt" refers to non-toxic acid addition salts derived from inorganic and organic acids. Suitable salt derivatives include halides, thiocyanates, sulfates, bisulfates, sulfites, bisulfites, arylsulfonates, alkylsulfates, phosphonates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphonates, alkanoates, cycloalkylalkanoates, arylalkonates, adipates, alginates, aspartates, benzoates, fumarates, glucoheptanoates, glycerophosphates, lactates, maleates, nicotinates, oxalates, palmitates, pectinates, picrates, pivalates, succinates, tartrates, citrates, camphorates, camphorsulfonates, digluconates, trifluoroacetates, and the like.

The term "mgA" refers to the number of milligrams of active drug based on the free base form of the drug.

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically, physically, and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The term "appropriate period of time" or "suitable period of time" refers to the period of time necessary to achieve a desired effect or result. For example, a mixture may be blended until a potency distribution is reached that is within an acceptable qualitative range for a given application or use of the blended mixture.

As used herein, the term "unit dose" or "unit dosage" refers to a physically discrete unit that contains a predetermined quantity of active ingredient calculated to produce a desired therapeutic effect. The unit dose or unit dosage may be in the form of a tablet, capsule, sachet, etc. referred to herein as a "unit dosage form."

DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the inventors have surprisingly and unexpectedly found that in coated solid CR dosage forms comprising varenicline, the formation of the reductive alkylation degradant **1**, as well as the formyl adduct **2**, can be substantially reduced by the addition of an antioxidant to the coating layer of the dosage form. While not wishing to be bound by theory or mechanism, the inventors postulate that in a solid state dosage form, the addition of an antioxidant to a coating inhibits the formation of migrating reactants from the coating, thereby preventing said reactants from degrading the drug in the core. The present inventors have also discovered specific preferred methods of formulating an antioxidant into the CR formulation of varenicline or its pharmaceutically acceptable salts to achieve the desired stability. More specifically, for oral dosage forms which comprise a core of varenicline and at least one excipient surrounded by a coating layer comprising an antioxidant, the inventors have discovered specific formulations and processes to achieve the desired stability. Therefore, a need in the art has been addressed to provide suitable CR dosage forms of varenicline or its pharmaceutically acceptable salts having formulations which are storage-stable for a sufficient time that the dosage can be provided in a relatively pure form over a commercially viable term.

Procedures for making varenicline are described in U.S. Patent No. 6,410,550, the contents of which are hereby incorporated herein by reference, and the resolution of racemic mixtures thereof is described in WO01/62736. In accordance with the present invention, the CR pharmaceutical compositions of varenicline can be desirably administered in doses ranging from about 0.1 mgA up to about 6 mgA per day, more preferably from about 0.5 to 4 mgA/day, and most preferably from about 1 to 4 mgA per day in single or divided doses, although variations will necessarily occur depending upon the weight and condition of the subject being treated. Depending on individual responses, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects.

Although any pharmaceutically acceptable form of varenicline may be used in connection with the present invention, it is preferable to use a salt form of the drug. A particularly preferred salt form of the drug is the L-tartrate salt.

Varenicline or its pharmaceutically acceptable salts can also be used, for the purposes of the present invention, in combination with one or more other pharmaceutically active ingredients. These combination dosage forms can provide for improved treatment of nicotine addiction or for the treatment of other medical conditions.

The active blend of a pharmaceutical core of a dosage form generally includes one or more pharmaceutically acceptable excipients, carriers or diluents. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the active ingredient is being applied. In particular, the inventors have found that preferred formulations contain less than about 20% w:w reducing carbohydrates. Reducing carbohydrates are sugars and their derivatives that contain a free aldehyde or ketone group capable of acting as a reducing agent through the donation of electrons. Examples of reducing carbohydrates include monosaccharides and disaccharides and more specifically include lactose, glucose, fructose, maltose and other similar sugars. The inventors have further found that formulations containing dicalcium phosphate are particularly stable. More specifically, stable formulations are produced with more than about 20% w:w dicalcium phosphate. Other acceptable excipients include starch, mannitol, kaolin, calcium sulfate, inorganic salts (e.g., sodium chloride), powdered cellulose derivatives, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers such as polyethylene oxide and hydroxypropyl methylcellulose. To ensure content uniformity of the blend, a volume mean diameter drug substance particle size of less than or equal to about 30 microns is preferably utilized. Preferred diluents are microcrystalline cellulose (e.g., Avicel® PH200, PH102 or PH101 available from FMC Pharmaceutical, Philadelphia, PA) and calcium phosphate dibasic, or dicalcium phosphate, (e.g. A-Tab® available from Rhodia, Chicago Heights, IL). The mean particle size for the microcrystalline cellulose generally ranges from about 90 μm to about 200 μm. Suitable grades of dicalcium phosphate include anhydrous (about 135 to 180 μm mean, available from PenWest Pharmaceuticals Co., Patterson, NY or Rhodia, Cranbury, NJ), and dihydrate (about 180 μm, available from PenWest Pharmaceuticals Co., Patterson, NY or Rhodia, Cranbury, NJ). Generally, the microcrystalline cellulose is present in an amount from about 10 wt% to about 70 wt% and the dicalcium phosphate is present in an amount from about 10 wt% to about 50 wt%, more preferably, microcrystalline cellulose is present in an amount of about 30-70 wt% and the dicalcium phosphate is present in an amount of about 20-40 wt%.

If desired, a binder may be added. Suitable binders include substances such as celluloses (e.g., cellulose, methylcellulose, ethylcellulose, hydroxypropyl cellulose and hydroxymethylcellulose), polypropylpyrrolidone, polyvinylprrolidone, gelatin, gum arabic, polyethylene glycol, starch, natural and synthetic gums (e.g., acacia, alginates, and gum arabic) and waxes.

A lubricant is typically used in a tablet formulation to prevent the tablet and punches from sticking in the die. Suitable lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate. A preferred lubricant is magnesium stearate. The magnesium stearate is generally present in an amount from about 0.25 wt% to about 4.0% wt%.

The pharmaceutical composition can be used to produce unit dosage forms containing about 0.1 mg to about 10.0 mg active ingredient per unit dosage, preferably, about 0.2 mg to about 5.0 mg active ingredient per unit dosage. The tablet size (i.e., unit dosage form) is typically between about 100 mg and 600 mg.

The inventors have found that preferred formulations consist of pharmaceutical cores made from the L-tartrate salt of the drug, mannitol, microcrystalline cellulose, dicalcium phosphate and magnesium stearate. These cores can be prepared by direct compression, wet granulation (with a high or low shear wet granulator or fluid bed granulator), extrusion granulation, rotogranulation or dry granulation including roller compaction. Roller compaction is especially preferred due to its ability to prevent drug segregation, while maintaining drug stability (in contrast to aqueous wet granulations which can lead to drug hydrate formation). The tablets can be prepared on standard rotary tablet presses. The tablet cores are then coated using a pan coater.

With CR dosage forms of varenicline, the drug is preferably delivered at a rate of between about 0.06 and 3 mgA/hr; and more preferably between 0.1 and 1 mgA/hr. Suitability for the present invention can be determined either by *in vivo* or *in vitro* testing. In particular, it is preferred that the average initial C_{max} be reduced to achieve a value of 10 to 80% of that achieved with an average initial IR bolus administration; more preferred is between 30 and 70%. For T_{max}, an increase in the average initial T_{max} for a CR dosage form compared to an average initial IR bolus is preferred to be at least 50%. Preferred dosage forms for the present invention provide 50% w:w of the total dose into solution between about 1 and 15 hours; more preferably between 2 and 10 hours.

While a number of means have been found to produce such a CR system to achieve the desired rate of drug administration (e.g., those set forth in International Patent Publications WO02/17918 and WO99/01121, both of which are hereby incorporated by reference), coated systems have particular advantages. Among such coated CR systems are osmotic dosage forms and enteric dosage forms. One example of an osmotic dosage form involves two-compartment systems (also known as “push-pull” systems) as described, for example, in U.S. Patent No. 4,111,202. In a push-pull system, the drug or drug formulation is present in one compartment of the core and water-soluble or water-swellable auxiliaries (e.g., salts, sugars, swellable polymers and hydrogels) for producing an osmotic pressure are present in a second compartment, the entire system surrounded by a semipermeable coating.

Fluids entering the second compartment cause an increase in volume of the lower compartment, which in turn expels the contents of the drug compartment from the system. A commercial embodiment of the push-pull system is known as GITS (gastro-intestinal therapeutic system) and is marketed in commercial products such as Procardia™ XL and Glucotrol™ XL (both available from Pfizer, Inc., New York, NY).

Another method of delivering drugs osmotically involves the use of single layer osmotic tablets. Such tablets are described in G. Santus and R. W. Baker, *J. Control. Rel.*, **1995**, *35*, 1-21, incorporated herein by reference. Other single-layer osmotic tablets are described in copending application PC11850 (need publication number), incorporated herein by reference. A preferred osmotic dosage form for varenicline utilizes an asymmetric membrane technology, AMT. In this CR system, the coating is made porous by a phase separation between a water-soluble and water-insoluble polymer during the coating operation as described in U.S. Patent Nos 5,612,059 and 5,698,220 (See, also, S.M. Herbig, *J. Control. Rel.*, **1995**, *35*, 127-136) the contents of which are hereby incorporated herein by reference. The use of AMT to provide CR for varenicline is described in US Patent Application Publication 2004/0235850A1 and International Patent Publication WO03/045437A1.

In the preparation of the asymmetric membrane coatings of the present invention, the water-insoluble component of the asymmetric membrane coating preferentially is formed from cellulose derivatives. In particular, these derivatives include cellulose esters and ethers, namely the mono-, di- and triacyl esters wherein the acyl group consists of two to four carbon atoms and lower alkyl ethers of cellulose wherein the alkyl group is one of four carbon atoms. The cellulose esters can also be mixed esters, such as cellulose acetate butyrate, or a blend of cellulose esters. The same variations can be found in ethers of cellulose and include blends of cellulose esters and cellulose ethers. Other cellulose derivatives which can be used in making asymmetric membranes of the present invention include cellulose nitrate, acetaldehyde dimethyl cellulose, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate dimethaminoacetate, cellulose aceate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose acetate p-toulene sulfonate, cellulose cyanoacetates, cellulose acetate trimellitate, cellulose methacrylates and hydroxypropylmethylcellulose acetate succinate. A particularly preferred water-insoluble component is cellulose acetate. Particularly preferred cellulose acetates include those having a substitution level of about 40% and a hydroxyl content of about 3.5%. Other materials also can be used in the fabrication of asymmetric membrane tablet coatings, provided such materials are substantially water-insoluble, film-forming and safe to use in pharmaceutical applications.

The water-soluble pore-forming component of the present invention comprises materials that have a water-solubility of greater than 0.5 mg/mL; more preferably, greater than 2 mg/mL; and still more preferably, greater than 5 mg/mL. Preferred water soluble materials include polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) derivatives, i.e., polymers that have ethylene glycol linkages.

CR systems for the present invention can involve a delay or lag period between when the dose is administered and when drug is available for absorption. Such delays can be temporal or related to the position in the gastrointestinal tract. A particularly preferred delayed release system is an enteric-coated tablet or multiparticulate. Preferred enteric systems can be prepared by coating tablets or multiparticulates. Preferred materials for such coatings include cellulose acetate phthalate (CAP), enteric polyacrylics (such as those marketed under the Eudragit brand name, available from Rohm Pharmaceuticals), hydroxypropylmethylcellulose acetate succinate and hydroxypropylmethylcellulose phthalate.

In the preparation of the asymmetric membrane coatings or enteric coatings of the present invention, the antioxidant preferentially is soluble in the solvents used to prepare the coating. The solvents used involve water, an organic solvent, or a combination of an organic solvent with water. These organic solvents include but are not limited to acetone, methanol, ethanol, propanol, ethyl acetate and methyl ethyl ketone. In particular, the antioxidants include acetyl cysteine, ascorbyl palmitate, cysteine, dithiothreitol, thioglycerol, thiourea, alpha tocopherol, propyl gallate, butylated hydroxyanisole (BHA) and alkyl hydroxytoluenes wherein the alkyl group consists of two to six carbon atoms. A particularly preferred antioxidant is butylated hydroxytoluene (BHT).

Preferred amounts of the antioxidant for use with the AMT coating range in an amount equal to a weight percent greater than about 0.1% but less than 5% relative to the coating layer. More preferred amounts of the antioxidant range in an amount equal to a weight percent greater than about 0.8% but less than 4% relative to the coating layer. Most preferred amounts of the antioxidant range in an amount equal to a weight percent greater than about 1.5% but less than 3% relative to the coating layer.

The pharmaceutical composition (or formulation) may be packaged in a variety of ways. Generally, an article for distribution includes a container that contains the pharmaceutical composition in an appropriate form. Suitable containers are well known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, blister packs, made from foil, PVC and Aclar and the like. The container may also include a tamper proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container typically has deposited thereon a label that describes the contents of the container and any appropriate warnings or instructions.

The preferred container of the present invention is described in US Patent No. 6,688,468, the contents of which are incorporated herein by reference. The preferred container provides for the removal of oxygen not only from the entrapped air within the container but also oxygen that enters the bottle via ingress. The amount of oxygen-absorber added will depend upon the volume of air surrounding the drug, the permeability of the container, the oxidation potential of the drug, and the means by which the oxygen-absorber is incorporated into the construction. The oxygen-absorber need not remove 100% of the oxygen from the air; however, the absorber should be 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 sealed oxygen permeable container. A water-initiated, a self- initiated or an ultraviolet (UV)-activated oxygen absorber can be incorporated into the construction. Alternatively, the combination of a self-activated absorber and a desiccant has been found to be effective. In particular, this system can be made more effective by use of a low water permeability container (e.g., sachet, cartridge, canister, or the like) for the self-activated, iron-based absorber with a desiccant either as a separate unit, or preferably as a single construction with the oxygen absorber. In the latter case, the material surrounding the desiccant is preferably moisture permeable either as a result of the materials chosen, or preferably due to holes (pores) that allow air exchange (moisture transport) with the air surrounding the solid dosage form.

The desiccant for use in the practice of the invention can be any available desiccants; however, preferred desiccants include those commonly used in the pharmaceutical industry, which have adequate capacity to handle the combination of moisture ingress through the bottle and moisture given off by the self-activating oxygen absorber. Suitable desiccant 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. A preferred form for the practice of the current invention is a canister of silica gel, such as that commercially supplied under the trade name, SorBit® (Süd-Chemie Corporation, Albuquerque, N.Mex.).

Suitable water-initiated, oxygen-absorbers include metal-based absorbers such as particulate-type iron (e.g., hydrogen reduced iron, electrolytically reduced iron, atomized iron, and milled pulverized iron powders), copper powder, and zinc powder. A preferred metal-based absorber is an iron powder. A moisture-holding material may be incorporated with the absorber to provide a self-activated system. Suitable moisture-holding materials include activated carbon, silicas, zeolites, molecular sieves, hydrogels, and diatomaceous earth. The particular moisture-holding materials used will depend upon the humidity level of the environment. For example, in a very low humidity environment, a moisture carrying material such as a hydrogel that partially binds water may be preferred. An accelerator may also be incorporated such as a metallic iodide or bromide as described in U.S. Patent No. 6,133,361, the contents of which are incorporated herein by reference. Useful commercially available sachets include D Series FreshPax® (available from Multisorb Technologies Inc., Buffalo, N.Y., USA), Ageless® and ZPTJ® sachets (both available from Mitsubishi Gas Corporation, Tokyo, JP), O-Buster® (available from Hsiao Sung Non-Oxygen Chemical Co., Ltd., Taiwan, R.O.C.), Bioka® Oxygen Absorber (available from Bioka Ltd., Kantvik, Finland) and the like.

Once the container is filled with a pre-determined amount of the varenicline dosage form and oxygen absorber, the container is then sealed, preferably with a heat-induction seal. 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 container prior to sealing to prevent any damage to the contents such as chipping or cracking of the unit dosage forms. Heat induction sealing 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.

For ease of manufacturing (packaging) and to assure there are no incidences of accidental ingestion of absorbers, a cartridge or canister rather than a sachet is preferred with solid dosage forms. Some challenges associated with the use of cartridges include the level of oxygen permeability of the cartridge or canister and the pharmaceutical acceptability of the cartridge plastic. Suitable materials include any materials known in the packaging industry to be moldable or extrudable either alone or in combination with other additives such as other polymers, plasticizers, stabilizers, etc. Additionally, the plastic materials should have sufficient oxygen permeability either directly or by addition of other additives (pore formers, plasticizers, etc.) or by the presence of holes or pores in the construction (see, e.g., U.S. Patent No. 4,093,105) such that the oxygen in the environment surrounding the dosage forms may come into contact with the oxygen absorber housed inside the cartridge or canister. Preferably, the plastics and additives have GRAS (generally regarded as safe) status. More preferably, the materials have been previously used in pharmaceutical packaging and have a proven record of pharmaceutical acceptability (e.g., minimal leaching of materials from the cartridge or canister to the dosage form) or acceptance by the appropriate governmental agency for use with pharmaceuticals. Examples of such polymers include polyethylenes, cellulosics, ethylene oxides and copolymers thereof. Suitable plasticizers include those commonly used in the food or pharmaceutical industry, such as triacetin, phthalate esters, PEG, dibutyl sebacate, glycerin, sorbitol, and citrate esters.

Cartridges, canisters, sachets or other containers which provide a means of physically separating the oxygen absorbing materials from direct contact with the dosage form may be used in the present invention. Cartridges are formed as a container with a lid (often one piece of plastic) which is sealed after addition of the powder to the cavity by standard powder fill techniques. The sealing can be effected using heat, ultrasonic welding or by use of an adhesive. Canisters are generally formed by crimping plastic tube ends after powder filling. As with cartridges, the filling is accomplished by common powder fill techniques. The crimping can be accomplished as part of a cutting operation by using heat, ultrasonics or other techniques well known in the field.

The pharmaceutical compositions containing varenicline described herein are useful in the treatment or prevention of nicotine addiction. In addition, this composition may be useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

Accordingly, the pharmaceutical formulations containing the compound varenicline and processes described herein may be used in the manufacture of a medicament for the therapeutic applications described above.

A therapeutically effective amount of the manufactured medicament may be administered to a human in need of such treatment or prevention. As used herein, the term "therapeutically effective amount" refers to an amount of active ingredient which is capable of inhibiting or preventing the various pathological conditions or symptoms thereof. The terms “inhibit" or “inhibiting” refers to prohibiting, treating, alleviating, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of a pathological condition or symptom related to or resultant from the respective condition being treated. As such, the pharmaceutical formulations may be used for both medical therapeutic (acute or chronic) and/or prophylactic (prevention) administration as appropriate. The dose, frequency and duration will vary depending on such factors as the nature and severity of the condition being treated, the age and general health of the host and the tolerance of the host to the active ingredient. The pharmaceutical composition or medicament may be given in a single daily dose, in multiple doses during the day or even in a weekly dose. The regimen may last from about 2-3 days to several weeks or longer. Typically, the composition is administered to a human patient once or twice a day with a unit dosage of about 0.25 mg to about 10.0 mg, but the above dosage may be properly varied depending on the age, body weight and medical condition of the patient and the type of administration.

The following examples are provided for illustrative purposes and should not be construed to limit the scope of the present invention.

Materials Used:

Varenicline (L-tartrate salt) was prepared by the methods described in patent applications WO9935131A1 or WO0162736A1, the contents of which are incorporated herein by reference.

Microcrystalline cellulose (Avicel^{TM} PH200) available from FMC Pharmaceutical (Philadelphia,PA)

Mannitol (granular 2080) available from SPI Polyols, Inc. (New Castle, DE).

Dicalcium phosphate, anhydrous, (A-tab^{TM}) available from Rhodia Inc. (Chicago Heights, IL).

Magnesium stearate, vegetable source, available from Mallinckrodt (St. Louis, MO).

Cellulose acetate (398-10 NF) available from Eastman Chemicals (Kingsport, TN).

Polyethyleneglycol (PEG3350) available from Union Carbide Corp. (subsidiary of Dow Chemical Co., Midland, MI).

Experimental:

Example 1

Preparation of AMT tablet cores of varenicline (1 mgA/tablet)

Varenicline formulation blending was carried out by geometric dilution to ensure drug content uniformity due to the low dose. Mannitol (7.875 kg, granular 2080 grade) was added to a 16-quart V-blender (Patterson-Kelley, East Stroudsburg, PA) and blended for 1 min. Varenicline (311.4 g, as the tartrate salt) was added to the mannitol in the 16-quart V-blender and blended for 30 min. The drug blend was discharged from the blender and kept for further processing. Additional mannitol (7.875 kg, granular 2080 grade) was added to the 16-quart V-blender, blended for 5 min, then discharged and held for further processing. Microcrystalline cellulose (6.75 kg, Avicel^{TM} PH200) and dibasic calcium phosphate (21.6 kg, A-tab^{TM}) were mixed in a 3 ft^3 V-blender for 20 min. Half of this blend was discharged and stored for further processing. The stored drug blend and mannitol wash were added to the 3 ft^3 V-blender and mixed for 10 min. The discharged half of the placebo blend was added to the polyethylene bag that held the drug blend and bag blended for one minute and then added to the 3 ft^3 V-blender, where the blend was mixed for 20 min. The blend was lubricated prior to roller compaction by adding 338 g of magnesium stearate and blending in the V-blender for 5 min. The blend was dry-granulated by roller compaction using a Freund TF-156 roller compactor (Vector Corporation, Marion, IA) using "S" type rolls, "B" auger screw feed and at a compaction pressure of 20 kg/cm^2 with a target ribbon thickness of 0.06-0.08". The ribbons were milled using a Fitzpartrick M5A mill (Elmhurst, IL) fitted with an 18-mesh conidur rasping screen bar head, with knives forward running at 300 rpm. The milled granulation was mixed in a 3 ft^3 V-blender for 10 min. The granules were lubricated by blending with 225 g of magnesium stearate in the V-blender for 5 min. Tablets were prepared using 9/32" standard round concave (SRC) tooling on a Kilian LX-21 (Kilian/IMA Gmbh & Co. Cologne, Germany) tablet press with Teflon® scrapers with a target hardness of 6.5±2 kp and a target weight of 250 mg/tablet.

Example 2

Coating of AMT tablets without antioxidant

A coating solutions of 3500 g containing 10% solids (w:w) was made in a 6 L Erlenmeyer flask by first adding 770 g of water followed by 70.0 g of PEG. A Heidolph (Germany) variable speed motorized overhead mixer with a glass rod and nylon mixing blade was used to stir the mixture for approximately 5 min. until the PEG dissolved in the water. The CA (280.0 g) was then added slowly with vigorous mixing to disperse it into the solution. Once dispersed, 2380 g of acetone was added to the flask and stirred for about an hour until the CA was dissolved. The coating process was performed using an HCT-30 Hicoater (Vector Inc., Marion, IA). The pan coater was charged with 1,100 g of tablet cores (from Example 1). The tablets were pre-heated to an inlet temperature of ~46°C. A two-part spray gun (Spraying Systems Co., Wheaton, IL) was mounted with the tip about 2.75" from the rotating tablet bed, with the atomizing air set at 20 psi. The coating pan rotation was 15 rpm. A peristaltic pump (Masterflex Digi-Staltic) was used to pump the coating solution from the flask to the spray gun at a rate of 20 g/min. The inlet air set temperature was ~50°C and the outlet temperature was maintained at 26-28°C. The pan airflow was 30-34 cfm. Tablets were removed from the bed when the weight gain reached the pre-27.3 weight percent. The tablets were tray-dried for 16 h at 40°C in a forced hot air oven (Gruenberg Oven Co, Williamsport, PA). Tablets for were sorted to ±3% of the target coating weight using a Mocon AB3 tablet weigher/sorter (Modern Controls Inc., Minneapolis, MN). Tablets were packaged with desiccant bags and stored at 5°C prior to stability set-up.

Example 3

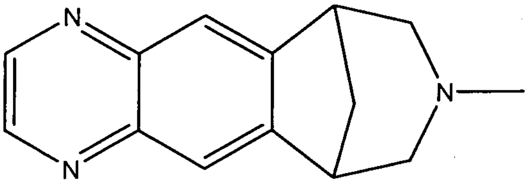
Coating of AMT tablets with antioxidant (BHT)

A coating solutions of 3500 g containing 10% solids (w:w) was made in a 6 L Erlenmeyer flask by first adding 770 g of water followed by 68.6 g of PEG. A Heidolph (Germany) variable speed motorized overhead mixer with a glass rod and nylon mixing blade was used to stir the mixture for approximately 5 min. until the PEG dissolved in the water. BHT (7.0 g) was added at this point and mixed for 5 min. The CA (274.4 g) was then added slowly with vigorous mixing to disperse it into the solution. Once dispersed, 2380 g of acetone was added to the flask and stirred for about an hour until the CA dissolved. The coating process was performed using an HCT-30 Hicoater (Vector Inc., Marion, IA). The pan coater was charged with 1,100 g of tablet cores prepared in Example 1. The tablets were pre-heated to an inlet temperature of ~46°C. A two-part spray gun (Spraying Systems Co., Wheaton, IL) was mounted with the tip about 2.75" from the rotating tablet bed, with the atomizing air set at 20 psi. The coating pan rotation was 15 rpm. A peristaltic pump (Masterflex Digi-Staltic) was used to pump the coating solution from the flask to the spray gun at a rate of 20 g/min. The inlet air set temperature was ~50°C and the outlet temperature was maintained at 26-28°C. The pan airflow was 30-34 cfm. Tablets were removed from the bed when the weight gain reached 27.9%. The tablets were tray-dried for 16 h at 40°C in a forced hot air oven (Gruenberg Oven Co, Williamsport, PA). Tablets were sorted to ±3% of the target coating weight using a Mocon AB3 tablet weigher/sorter (Modern Controls Inc., Minneapolis, MN). Tablets were packaged with desiccant bags and stored at 5°C prior to stability set-up.

Example 4

Analytical methods for determining stability of AMT tablets of varenicline

The degradation of varenicline in an osmotic CR dosage form predominantly yields two products. These products were determined by electrospray LC-MS to have masses of 225 and 239, which correspond to 14 and 28 mass units greater than the drug itself, respectively. MS-MS experiments showed the impurities to have similar spectra to that of the drug substance suggesting the mass gains are not affecting the main structure itself. Based on these mass spectral data, N-methylvarenicline (adduct **1**) and N-formylvarenicline (adduct **2**) were proposed as the major degradation products.



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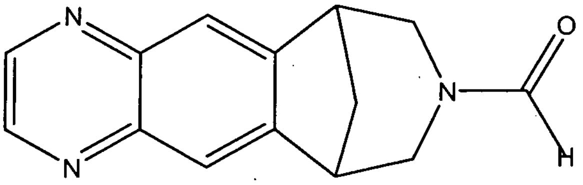

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To confirm the identification of the products, authentic samples were prepared by reaction of varenicline with methyl iodide for adduct **1** and with ethyl formate for adduct **2**. In each case, the products co-eluted with the impurities by HPLC and provided identical mass spectra supporting the identification of the products.

For the stability study, 20 tablets of each type were stored in 60-cc HDPE bottles (Drug Plastics, and Glass) inductively sealed with 33 mm child resistant closures (Kerr). A bottle of tablets was also set up containing an oxygen scavenger (Multisorb Corp., Buffalo, NY). Bottles were stored at 5°C and 40°C/75%RH and pulled at specified intervals for HPLC analysis.

Samples were prepared by first crushing a tablet and transferring to a 20 mL glass vial. Four milliliters of sample diluent (50/50, v/v, methanol/50 mM phosphate buffer, pH 6.5 with 0.1% triethylamine) were added to the vial and sonicated for 10 min with a Bransonic model 8510R-MT sonicator. Six milliliters of 50 mM phosphate buffer with 0.1% triethylamine were added to the flask and mixed well by swirling. The samples were transferred to glass centrifuge tubes and centrifuged for 30 min at 3000 rpm on a Jouann model C422 centrifuge.

Analyses were performed on an Agilent 1100 Series HPLC system with UV detection. The HPLC column was a 3 µm Atlantis (4.6 mm x 150 mm) from Waters. HPLC grade methanol (J.T. Baker), HPLC grade phosphoric acid (Fisher), HPLC grade ammonium hydroxide (J.T. Baker), and HPLC grade triethlyamine (Burdick and Jackson) were used. Milli-Q water was supplied from a Millipore gradient A10 water purification system installed in the laboratory. The HPLC method contained an isocratic hold with a gradient sweep to selectively quantitate adduct **1** and adduct **2**. The mobile phase components were methanol and 50 mM phosphate buffer (pH 6.5) with 0.1% triethylamine. The flow rate was 1.0 mL/min and the detection wavelength was 238 nm with an initial isocratic hold for 60 min at 18% methanol, followed by a gradient to 50% in 30 min. Percent recoveries of all degradation products were calculated against an external standard of adduct **2**.

Example 5

Stability of varenicline tablets with an oxygen absorber in the packaging

Control samples of varenicline tartrate tablets with an 8:2 ratio of CA to PEG were prepared according to Examples 1 and 2. Stability measurements were performed as described in Example 3. These tablets were stored six weeks at 40°C/75% RH and contained 16.9% adduct **1**, while with oxygen absorber in the package, identical tablets showed no detectable formation of adduct **1**. The results are shown in Table 1.

Example 6

Stability of varenicline AMT tablets with BHT in the tablet coating

Varenicline tartrate AMT tablets were produced with 2 weight percent BHT in the coating as described in Examples 1 and 2 above. Stability measurements were performed as described in Example 3 above. With the

BHT, the level of adduct **1** is reduced below the detection limit, as summarized in Table 1.

Table 1

Stability of varenicline AMT systems (14 mg PEG in coating) after six weeks.

Coating	Temperature	%RH	Adduct 1	Adduct 2
8:2 CA:PEG control	5°C	NA	<limit of detection	0.07%
	40°C	75%RH	16.90%	3.51%
7.84:1.96:0.2 CA:PEG:BHT	40°C	75%RH	<limit of detection	0.02%
8:2 CA:PEG	40°C	75%RH	<limit of detection	0.11%

What is Claimed is:

1. A controlled release pharmaceutical composition of varenicline or a pharmaceutically acceptable salt thereof which comprises a coating and an antioxidant wherein said antioxidant is present in an amount equal to a weight percent greater than about 0.1% but less than 5% of the coating layer.

2. The pharmaceutical composition of claim 1, wherein said coating layer constitutes between 5 and 30 weight/weight percent of the total composition.

3. The pharmaceutical composition of claim 2, wherein the release of varenicline or a pharmaceutically acceptable salt thereof is substantially controlled osmotically.

4. The pharmaceutical composition of claim 2, wherein the release of varenicline or a pharmaceutically acceptable salt thereof is substantially controlled by an enteric coating.

5. The pharmaceutical composition of claim 4, wherein said enteric coating comprises enteric cellulosics or polyacrylics.

6. The pharmaceutical composition of claim 1, wherein said coating layer is an asymmetric membrane.

7. The pharmaceutical composition of claim 6, wherein the asymmetric membrane comprises a water insoluble polymer, a water-soluble pore-former component and an antioxidant.

8. The pharmaceutical composition of claim 7, wherein said water insoluble polymer is cellulose acetate.

9. The pharmaceutical composition of claim 7, wherein said pore-former component is selected from polyethylene glycol or polyvinyl pyrrolidinone.

10. The pharmaceutical composition of claim 1, wherein the antioxidant is selected from acetyl cysteine, ascorbyl palmitate, cysteine, dithiothreitol, thioglycerol, thiourea, alpha tocopherol, propyl gallate, butylated hydroxyanisole (BHA) and alkyl hydroxytoluenes wherein the alkyl group consists of two to six carbon atoms.

11. The pharmaceutical composition of claim 1, wherein varenicline or a pharmaceutically acceptable salt thereof is present in an amount which releases from about 0.1 mgA to about 6 mgA per day.

12. The pharmaceutical composition of claim 1, where said antioxidant is butylated hydroxytoluene (BHT) in a weight percentage of about 0.5% to about 2% relative to the coating.

13. The pharmaceutical composition of claim 1, wherein the level of adducts **1** and **2** remains below 1 weight percent after 6 weeks of storage at 40°C and 75% relative humidity.

14. The pharmaceutical composition of any of claims 1 to 13, wherein varenicline or its pharmaceutically acceptable salt is present in a core.

15. The pharmaceutical composition of claim 14, wherein the core is a tablet.

16. The pharmaceutical composition of claim 14, wherein the core is a multiparticulate.

17. A pharmaceutical kit comprising a controlled release composition of varenicline or a pharmaceutically acceptable salt thereof and at least one oxygen absorber.

18. The pharmaceutical kit of claim 17, wherein the level of adducts **1** and **2** remains below 1 weight percent after 6 weeks of storage at 40°C and 75% relative humidity.

19. A method of treating nicotine addiction in a subject in need of such treatment, comprising administering to said subject an amount of a coated, controlled-release dosage form of varenicline or a pharmaceutically acceptable salt thereof wherein the coating of said dosage form comprises an antioxidant, said amount of varenicline or its pharmaceutically acceptable salt being effective to treat nicotine addiction.

20. The method of claim 19, wherein said dosage form is packaged in a kit comprising an oxygen absorber.