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(54) Title: STABLE TRANSDERMAL PHARMACEUTICAL DRUG DELIVERY SYSTEM COMPRISING RIVASTIGMINE

(57) Abstract: The present invention relates to a stable transdermal pharmaceutical drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, which is free from an antioxidant. In particularly, the present invention relates to a stable transdermal pharmaceutical drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, which provides an enhanced absorption of drug through skin, and remains stable during a longer storage period. In addition, the present invention relates to a method of treatment of mild to moderate dementia of alzheimer's type and mild to moderate dementia of parkinson's type diseases.

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STABLE TRANSDERMAL PHARMACEUTICAL DRUG DELIVERY SYSTEM COMPRISING RIVASTIGMINE

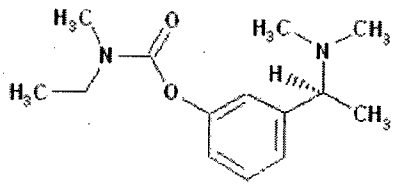
FIELD OF THE INVENTION

The present invention relates to a stable transdermal pharmaceutical drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, which is free from an antioxidant. In particularly, the present invention relates to a stable transdermal pharmaceutical drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, which provides an enhanced absorption of drug through skin, and remains stable during a longer storage period. In addition, the present invention relates to a method of treatment of mild to moderate dementia of alzheimer's type and mild to moderate dementia of parkinson's type diseases.

BACKGROUND OF THE INVENTION

Rivastigmine is a reversible cholinesterase inhibitor (parasympathomimetic or cholinergic agent) that has been approved for the treatment of mild to moderate dementia of the alzheimer's type, and mild to moderate dementia associated with parkinson's disease.

Chemically it is known as (S) -N-ethyl-3- [(1- dimethylamino) ethyl] -N-methyl phenyl carbamate and can be represented by following chemical structure -



Rivastigmine is known to be susceptible to degradation by oxygen from the environmental oxidation. Various pharmaceutical compositions comprising rivastigmine has been proposed in the prior art, claiming the use of antioxidants, particular carriers or excipients and packaging material containing oxygen scavengers to stabilize the formulation.

GB Patent Number 2203040 discloses transdermal composition of rivastigmine containing mixture of Eudragit E 100, DuroTak 280 - 2416 polymers and a plasticizer Brij 97. Such composition was found to degrade, possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around the rivastigmine and its storage in air tight packaging.

U.S. Patent Number 6,335,031 and 6,660,295 disclose a pharmaceutical composition comprising rivastigmine in free base or acid addition salt form and an antioxidant to prevent oxidative degradation of rivastigmine. Such formulations found to be stable for a longer period of time.

PCT Application Number WO 2012/012417 discloses a transdermal adhesive composition comprising a washed polymerization reaction products of at least two ethylenically unsaturated monomers, and at least one pharmaceutically active compound which are susceptible to oxidative degradations.

PCT Application Number WO 2012/087047 discloses a percutaneous absorption preparation comprising styrene-isoprene-styrene-block copolymer as an adhesive and rivastigmine, which provides an improved stability and potency of rivastigmine.

U.S. Patent Application Number 2010/0087768 discloses a monolithic device for transdermal administration of pharmaceutical active ingredients which are liquid at room temperature. The composition contains an acrylic polymer pressure-sensitive adhesive without cross-linking agent, and a non-volatile co-adjuvant selected from squalene and triethylcitrate. The composition provides a good adhesion property, and minimizes loss of drug during manufacture.

U.S. Patent Number 7,335,379 discloses a transdermal non-occlusive, semi-solid pharmaceutical formulation comprising rivastigmine and a solvent system containing a glycol, monoalkyl ether of diethylene glycol and a mixture of lower alcohols and water. The solvent system is present in an amount sufficient to solubilize rivastigmine and inhibit its crystallization when applied on the skin.

U.S. Patent Number 7,638,140 discloses a free base material which is suitable for use in an adhesive and or in a transdermal patch containing an acrylic polymeric adhesive which includes a C_4-C_{12} alkyl acrylate, a C_1-C_3 alkyl acrylate hardening monomer; a functionalizing monomer which facilitates crosslinking; and a highly plasticizing drug component.

U.S. Patent Application Number 2007/0128263 discloses a transdermal therapeutic system (TTS) comprising a backing layer, a reservoir layer comprising one or more pharmaceutically acceptable ingredients, antioxidant, polymers, and adhesive layer comprising a silicon polymer and a tackifier.

U.S. Patent Number 6,660,295 discloses a package for transdermal delivery device, which prevents oxidative degradation of active ingredient during storage. The package contains a transdermal drug delivery device comprising a drug reservoir layer positioned

between a release liner and a backing layer, at least one of said release liner and said backing layer being non-occlusive; and a degradation protectant.

Currently, marketed transdermal formulation of rivastigmine is available under trade name of Exelon® and contains antioxidant vitamin E to prevent oxidative degradation of rivastigmine.

Thus in order to achieve and maintain stable transdermal formulations of rivastigmine, the prior art references emphasize on use of antioxidants, use of special copolymers and use of specialized packaging system, which leads to increase in cost of final formulation. Moreover, in an attempt to render the desired stability, for example devising the transdermal formulation by proper selection of suitable polymers and excipients, resulting formulations may show less inter-individual variation with regard to plasma concentrations of rivastigmine required to produce a therapeutic benefit without unacceptable side effects.

Hence there still remains a need for alternative transdermal formulations of rivastigmine in order to achieve desired stability and also to improve compliance, adhesion, tolerability and/or safety.

SUMMARY OF THE INVENTION

In one general aspect, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system is free from an antioxidant.

In another general aspect, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof comprising a backing layer, an adhesive material, one or more pharmaceutically acceptable excipients and a release liner, wherein the drug delivery system is free from an antioxidant.

In another general aspect, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof comprising an adhesive material, wherein the drug delivery system is free from an antioxidant and the adhesive material is present in an amount from about 30 to about 90% by weight of the composition.

In another general aspect, there is provided a stable transdermal drug delivery system comprising a backing layer; an adhesive layer comprising rivastigmine or a pharmaceutically acceptable salt thereof, an adhesive material, one or more pharmaceutically acceptable excipients; and a release liner, wherein the adhesive layer

releasably fixes the transdermal drug delivery system to a patient skin and the drug delivery system is free from an antioxidant.

Embodiments of the stable transdermal drug delivery system may include one or more of the following features. For example, the stable transdermal drug delivery system may include one or more pharmaceutical excipients suitable for topical application selected from penetration enhancers, fillers, plasticizers, tackifiers, surfactants, humectants, or a combination thereof.

In another general aspect, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system is present in the form of matrix or reservoir.

In another general aspect, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system is free from an antioxidant and retains at least 90% of the potency of rivastigmine in the composition after storage for three months at accelerated storage condition (40°C ± 2°C/75%RH ± 5%RH).

In another general aspect, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system is free from an antioxidant and exhibits no significant difference in rate and extent of absorption of rivastigmine as compared to commercially available formulation of rivastigmine marketed under the trade name Exelon®.

In another general aspect, there is provided a process of preparing a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system is free from an antioxidant, the process comprises preparing a drug mass comprising rivastigmine or a pharmaceutically acceptable salts thereof and one or more pharmaceutically acceptable excipients, casting the drug mass onto a release liner film, drying the release liner to form an adhesive layer on release liner, and laminating a backing layer to the adhesive layer.

In another general aspect, there is provided a method of treating mild to moderate dementia of the alzheimer's type or mild to moderate dementia associated with parkinson's disease in a patient, comprising administering to the patient a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system is free from an antioxidant.

The details of one or more embodiments of the present invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description.

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found, in contrary to the teaching of the prior art that, it is possible to develop stable transdermal formulations of rivastigmine without using an antioxidant. Such formulations unexpectedly demonstrated a significant stability when subjected to storage for three months at accelerated storage condition (40°C ± 2°C/75%RH ± 5%RH). Such formulations may not require specialized packaging system to preclude the degradation of rivastigmine.

In the absence of teaching/suggestion in the art about how to develop stable transdermal formulations of rivastigmine without employing an antioxidant, the inventors have devised a pharmaceutical composition of rivastigmine by proper selection of pharmaceutical excipients. Such formulations may also demonstrate less inter-individual variation with regard to plasma concentrations of rivastigmine required to produce a therapeutic benefit without unacceptable side effects.

The term "free from an antioxidant" refers to a transdermal pharmaceutical composition, to which no antioxidant has been added for the purpose of preventing a pharmaceutical active compound susceptible to oxidative degradation from forming total impurities in excess of 1% during storage-stability period.

The transdermal drug delivery system of the present invention may show less than 1.0% degradation products as proposed by regulatory agency guidelines for stability testing at accelerated storage conditions (40°C ± 2°C/75%RH ± 5%RH) for three months.

The present invention relates to a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof comprising a backing layer, an adhesive material, one or more pharmaceutically acceptable excipients and a release liner, wherein the drug delivery system is free from an antioxidant.

The term "transdermal drug delivery system" refers to an administration of a drug to the skin surface of an individual, so that the drug passes through the skin tissue and into the individual's blood stream.

The term 'rivastigmine' is used in broad sense to include not only the rivastigmine *per se* but also its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers,

pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof, and also its various crystalline and amorphous forms.

The amount of rivastigmine or a pharmaceutically acceptable salt thereof in the compositions may range from about 1 to about 40% by weight of the composition, preferably from about 5 to about 20% by weight of the composition. The dosage amount of rivastigmine or a pharmaceutically acceptable salt thereof in the composition may present from about 2 mg to about 25 mg, preferably from about 4 mg to about 15 mg.

In another embodiment, the transdermal pharmaceutical drug delivery system comprising rivastigmine or a pharmaceutically acceptable salt thereof is present in the form of patch, film, or plaster.

The term "antioxidant" refers to a substance which lowers the level or prevents the formation of active radicals or active forms of oxygen. The transdermal drug delivery system free from antioxidants are selected from, but not limited to tocopherol and its esters such as tocopherol acetate, α-tocopherol, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, propyl gallate, polyphenolic antioxidants, sodium sulfite, sodium bisulfite, sodium metabisulfite, thioglycolic acid, monothioglycerol, L-cysteine or a combination thereof.

The term "adhesive material" refers to a viscoelastic material which adheres instantaneously to most substrates with the application of very slight pressure and remains permanently tacky. The term "adhesive" can be interchangeably used as "pressure-sensitive adhesive", if it has the properties of pressure-sensitive adhesive *per se* or function as a pressure-sensitive adhesive. An "adhesive" as used herein means any natural or synthetic material that is capable of sticking to the site of topical application. The adhesives must be biocompatible and non-irritating. It is also important that the adhesive should be selected such that it is compatible with the other components of the therapeutic adhesive formulation of the present invention.

Suitable adhesive materials are selected from, but not limited to one or more, polyisobutylene, acrylates, silicones, polyisoalkylenes, polyether block amide copolymers polybutadiene, styrene-butadiene (or isoprene)-styrene block copolymer rubber, vinyl-based high molecular weight materials such as polyvinyl alkyl ether, polyvinyl acetate, ethylenevinylacetate copolymers, a partially saponified product of polyvinyl acetate, polyvinyl alcohol and polyvinyl pyrrolidone, polyurethane or a combination thereof.

The polyisobutylene adhesives may contain blend of two different types of polyisobutylene having a different molecular weights. The high molecular weight polyisobutylene may range from about 450,000 to about 2,100,000 viscosity average molecular weight and a low molecular weight polyisobutylene may range from about 1,000 to about 450,000 viscosity average molecular weight The two polyisobutylenes with different molecular weight can be mixed with each other wherein the ratio of the polyisobutylene having the higher molecular weight to the polyisobutylene having the lower molecular weight is in the range from about 0.05:1 to about 20:1, preferably from about 0.5:1 to about 2:1, more preferably from about 1:1. Preferred polyisobutylenes are available commercially under the trade name of DuroTak® 87-617A, DuroTak® 87-608A, DuroTak® 87-6908A from National Starch and the others are under the trade name of Vistanex®.

The acrylic adhesives includes cross-linked and uncross-linked acrylic copolymers selected from polymethacrylate such as butyl acrylate, ethyl hexyl acrylate, vinyl acetate, (meth)acrylic acid such as butyl (meth)acrylate, pentyl (meth)acrylate, hexyl (meth)acrylate, heptyl (meth)acrylate, octyl (meth)acrylate, nonyl (meth)acrylate, decyl (meth)acrylate, undecyl (meth)acrylate, dodecyl (meth)acrylate, and tridecyl (meth)acrylate, and copolymers of at least one of the above esters and other monomers copolymerizable therewith. Preferred acrylate polymer are available commercially under the trade name Gelva® brand, e.g. Gelva® 3011 or DuroTak® brand available from National Starch and Chemical Company, Zutphen, Holland, e.g. DuroTak® 202A, DuroTak® 608, DuroTak® 4202, DuroTak® 4287, DuroTak® 2510, DuroTak® 617 A, DuroTak® 87-2353, DuroTak® 87-2852, DuroTak® 87-2287, DuroTak® 87-2353, DuroTak® 387-2051 or DuroTak®387-2052.

The silicon adhesive refers to a polydimethylsiloxane based polymers. Suitable silicone adhesives are commercially available under the trademarks BIO-PSA® X7-3027, BIO-PSA® X7-4503, BIO-PSA® X7-4603, BIO-PSA® X7-4301, BIO-PSA® X7-4303, BIO-PSA® X7-4919, BIO-PSA® X7-2685, and BIO-PSA® X7-3122 by Dow Corning Corporation, Medical Products, Midland, Mich.

The adhesive materials may present in an amount from about 30 to 90% by weight, preferably from about 50 to about 80% by weight, more preferably from about 65% to about 75% by weight. The ratio of the amount of adhesive material to rivastigmine or a pharmaceutically acceptable salt thereof in the composition may ranges from about 1:20 to about 20:1 in order to achieve the desire transdermal properties.

In another embodiment, there is provided a stable transdermal drug delivery system of rivastigmine or a pharmaceutically acceptable salt thereof comprising polyisobutylene, one or more pharmaceutically acceptable excipients and a release liner, wherein the drug delivery system is free from an antioxidant.

The transdermal drug delivery system comprises one or more pharmaceutical excipients suitable for topical application selected from penetration enhancers, fillers, plasticizers, tackifiers, surfactants, humectants, or a combination thereof.

Suitable penetration enhancers may be selected from, but not limited to 1-dodecylazacycloheptan-2-one(azone), N,N-diethyl-m-toluamide (DEET), mineral oil, polyhydric alcohols (for example propylene glycol, glycerol, dipropylene glycol), fatty acids and esters thereof (for example oleic acid, ethyl oleate, glyceryl monolaurate, ethyl palmitate), isopropyl myristate, lactic acid, lactic acid esters, monoglycerides, triacetin, methyl laurate, transcutanol, dibutylsebacate, lauramide diethanolamine, propylene glycoisostearate, triglycerides, AMIFAT (derived from glycerin, oleic acid and 2-pyrrolidone-5-carboxylic acid) or a combination thereof. The amount of penetration enhancers in the composition ranges from about 1 to about 40% by weight of the composition.

Suitable fillers are selected from, but not limited to metal oxides (such as zinc oxide and titanium oxide), metal salts (such as calcium carbonate, magnesium carbonate and zinc stearate), silicic acid compounds (such as kaolin, talc, bentonite, colloidal silicone dioxide, hydrous silica, aluminum silicate, magnesium silicate and magnesium aluminometasilicate), metal hydroxides (such as aluminum hydroxide) or a combination thereof. The fillers may present in an amount from about 1% to about 10% by weight.

The term "plasticizer" refers to compounds that provide flexibility to the pharmaceutical composition. Suitable plasticizers are selected from, but not limited to mineral oil, citric acid esters, triacetin, saturated triglycerides, triethyl citrate, acetyl tributyl citrate, low molecular weight hydrocarbons or a combination thereof, that act to plasticize adhesives and increase their permeability to the agent being delivered. The plasticizers may present in an amount from about 1% to about 20% by weight, preferably from about 5 to 15% about by weight.

The amount and type of plasticizers required may depend on a number of factors like drug content, and the amount of adhesive materials. The weight ratio of rivastigmine or a pharmaceutically acceptable salt thereof to plasticizer in the composition preferably ranges from about 1:0.25 to about 1:3.

Suitable surfactants are selected from, but not limited to polysorbates, their ether ethoxylates, produced by reaction of sorbitan esters with ethylene oxide, polyoxyethylene alkyl phenol, polyoxyethylene cetyl ether, polyoxyethylene alkyl-aryl ether, polyoxyethylene monolaurate, polyoxyethylene vegetable oil, polyoxyethylene sorbitan monolaurate, polyoxyethylene esters or mixed fatty and resin acids, polyoxyethylene sorbitol lanolin derivative, polyoxyethylene tridecylether, polyoxyethylene sorbitan esters of mixed fatty and resin acids, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, polyoxyethylene monostearate, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether, polyoxyethylene tridecyl ether, polyoxyethylene fatty alcohol, polyoxyethylene alkyl amine, polyoxyethylene glycol monopalmitate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene cetyl ether, polyoxyethylene oxypropylene stearate, polyoxyethylene lauryl ether, polyoxyethylene lanolin derivative, sodium oleate, quaternary ammonium derivative, potassium oleate, N-cetyl N-ethyl morpholinium ethosulfate, sodium lauryl sulfate or a combination thereof. The surfactants may present in an amount from about 1% to about 20% by weight, preferably from about 5 to 15% about by weight.

The term "tackifier" refers to an agent that improves the adhesive strength of the adhesive layer to the skin or mucosa. Suitable tackifiers are selected from, but not limited to aliphatic hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic hydrocarbons, substituted aromatic hydrocarbons, highly hydrogenated resin, terpene resin, petroleum resin, phenolic resin, xylene resin or a combination thereof. The plasticizers may present in an amount from about 1% to about 20% by weight, preferably from about 5 to 15% about by weight.

Suitable humectants are selected from, but not limited to glycerol, propylene glycol, polyethylene glycol, 1,3-butanediol and D-sorbitol solution or a combination thereof. The humectant may present in an amount from about 5% to about 70% by weight, preferably from about 10% to about 60% by weight, more preferably from about 30% to about 50% by weight.

The solvents used in the present invention for dissolving the substantial amount of drug substance are selected from aqueous or non-aqueous solvents. Non-aqueous solvents are selected from organic or inorganic solvents which include aromatic hydrocarbons such as toluene and xylene, aliphatic hydrocarbons such as acetone, heptane and hexane, alcohols such as methanol, ethanol, and isopropyl alcohol, aliphatic

esters such as ethyl acetate or a combination thereof. The amount of solvents used in the present invention may depend on the drug content.

In another embodiment, the transdermal drug delivery system of the present invention is in the form of matrix type or reservoir type system. Preferably, transdermal drug delivery system may be present of single-layer drug in adhesive matrix, multi-layer drug in adhesive matrix, matrix-dispersion system, matrix-diffusion system, multi-laminate system, membrane controlled reservoir system, micro-reservoir system, multi-reservoir system, and the like.

In another embodiment, the process of preparing the transdermal drug delivery system comprises the steps of preparing a drug mass comprising rivastigmine or a pharmaceutically acceptable salt thereof, adhesive materials and one or more pharmaceutically acceptable excipients; casting the drug mass onto a release liner film; drying the release liner and the drug mass to form a layer on release liner; laminating a backing layer to the adhesive layer; slitting and trimming the laminated coated layer; and die-cutting the laminate into dosage units using fixed size rotary dies.

In another embodiment, the process for preparing the transdermal drug delivery system comprises the steps of dissolving or dispersing rivastigmine or a pharmaceutically acceptable salt thereof with a one or more adhesive and one or more pharmaceutically acceptable excipients; applying the drug mass on the surface of release-controlling membrane made up from porous or non-porous materials and drying the drug mass; subsequently casting the drug mass onto the release liner; laminating the backing layer onto the upper surface of drug mass; slitting and trimming the laminated coated layer; and die-cutting the laminate into dosage units using fixed size rotary dies.

The transdermal drug delivery system of the present invention retains at least 90% of the potency of rivastigmine in the composition after storage for six months at accelerated storage conditions (40°C ± 2°C/75%RH ± 5%RH) and at long-term storage conditions (30°C ± 2°C/65%RH ± 5%RH). The drug content in the composition does not differ from the label claim range of 90%-110% as specified by regulatory agency guidelines during stability period. The transdermal composition exhibits less than 1% of total impurities during the storage period for at least three months, six months, and twelve months.

In another embodiment of the present invention, the transdermal drug delivery system is free from an antioxidant and exhibits no significant difference in rate and extent of absorption of rivastigmine or pharmaceutically acceptable salts thereof as compared to

commercially available formulation of rivastigmine marketed under the trade name Exelon®.

In another embodiment, the transdermal drug delivery system of the present invention comprising rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system exhibits an area under the curve (AUC_{0-t}) from about 80 ng.hr/ml to about 160 ng.hr/ml, preferably from about 100 ng.hr/ml to about 130 ng.hr/ml.

In another embodiment, the transdermal drug delivery system of the present invention comprising rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system exhibits a peak plasma concentration (C_{max}) from about 2 ng/ml to about 8 ng/ml, preferably from about 4 ng/ml to about 6 ng/ml.

In another embodiment, the transdermal drug delivery system of the present invention comprising rivastigmine or a pharmaceutically acceptable salt thereof, wherein the drug delivery system exhibits time to achieve maximum concentration time (T_{max}) from about 8 to about 24 hours, preferably from about 12 to about 16 hours.

In another embodiment, the transdermal drug delivery system minimizes skin irritation while maintaining high transdermal flux of rivastigmine. The transdermal drug delivery system of the present invention provides a flux rate of rivastigmine ranging from about 10 μg/cm².hr to about 50 μg/cm².hr, preferably from about 20 μg/cm².hr to about 30 μg/cm².hr. In the present invention, the transdermal drug delivery system provides a drug release for a period of 24 hours after application.

The transdermal drug delivery system of the present invention is intended to be applied once a day. The patch or film may be applied to upper or lower back, upper arm or chest.

The thickness of the transdermal drug delivery system of present invention is intended to be higher to dissolve the substantial amount of rivastigmine during application period. The thickness of the transdermal drug delivery system may range from about 500 μm to 1000 μm, preferably from about 700 μm to 900 μm.

In another embodiment of the present invention, the surface area of the transdermal drug delivery system is sufficient to maintain the effective contact with the skin during administration and also provides an intended drug delivery rate. The surface

area of the transdermal drug delivery system may range from about 2 cm^2 to 30 cm^2, preferably from about 5 cm^2 to 20 cm^2.

In another embodiment, the backing layer is selected from woven or non-woven fabric materials. The backing layer serves as the upper layer of the device during use and functions as the primary structural element of the device. The backing layer of the present invention is soft, flexible, and has the multi-directional stretchable properties. When the external tensile force is applied, the backing layer is capable of stretching and, when the tensile force is removed, it has the capacity to return in the original position. The backing film provides mechanical support to the drug-adhesive matrix formulation. It also provides physical integrity to the system, maintenance of the physical dimensions and shape of the formulation which prevents direct contact of patch formulation with the environment. Suitable materials for backing layer are selected from natural or synthetic polymeric. A suitable natural polymeric material is selected from, but not limited to cellulose, silk, cotton and a suitable synthetic polymeric material is selected from, but not limited to polyvinyl chloride, polyurethane, polyester, polyamide, polypropylene and the like. The thickness of backing layer may range from about 150μm to about 1000μm, preferably from about 300μm to 800μm.

Suitable backing layer are selected from, but not limited to Scotchpak® 9732, Scotchpak® 9727, Scotchpak® 1109, Scotchpak® 9730, Scotchpak® 9733, Scotchpak® 9735, Scotchpak® 9736, Scotchpak® 9738, Scotchpak® 9757, CoTran® 9700, CoTran® 9708, CoTran® 9718, CoTran® 9719, CoTran® 9720, and CoTran® 9722.

The backing layer may be coated with polymeric materials to maintain the adhesiveness of the patch on the skin. The polymeric materials used for coating are selected from, but not limited to acrylates, polyisobutylenes, silicones, ethylene vinyl acetate copolymers or a combination thereof. The backing layer may further be coated with foam coating to form modified backing layer. The foam coating materials used are selected from, but not limited to Volara Foam type coating, e.g. Volara Foam Type 6EO.

The adhesiveness property of the transdermal compositions may be evaluated by various methods, but not limited to a cold-flow method. In a cold-flow method, the adhesiveness result is evaluated at specific interval of time for a period of 24 hours with different scoring grades (score 0, 1, 2, 3, 4). The compositions of the present invention may have shown good adhesive property at the end of 24 hours period.

The skin irritancy effect of the transdermal composition may be evaluated by use of skin irritation study (primary skin irritation index - score 0, 1, 2, 3, and 4). The

composition of the present invention may not cause significant irritation during the 24 hours period after application. The result may be evaluated at different time intervals like at an interval of 30 minutes after application of the composition and after 24 hours of application.

The release liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release liner is produced from a material impermeable to drug, and adhesive. This release liner may be easily stripped away from the adhesive. A preferred release liner is made of fluoro polymer coated polyester, or polyethylene terephthalate (PET) foil. The thickness of release liner may range from about 25μm to 250μm, e.g. 50μm thickness PET film, may be applied over the pharmaceutical composition. Suitable release liner are selected from, but not limited to Scotchpak® and Loparex® grades like Scotchpak® 1022, Scotchpak® 9741, Scotchpak® 9742, Scotchpak® 9744, Scotchpak® 9748, Loparex® 48015, Loparex® 48011, and Loparex® 48036.

The release liner may be silicone-coated. Said coating is preferably formed of any fluorosilicone compound which is conventionally used in the art, e.g a polyfluoroalkylsiloxane. It is particularly preferred to employ such a fluorosilicone coating when the adhesive used to affix the pharmaceutical composition to the release liner is not itself a silicone adhesive.

In another embodiment, the transdermal patches or films are typically packaged in unit dose pouches where a single patch is present inside a sealed and printed pouch. Pouching materials of the present invention are multi-laminate films where the outermost layer is printable and inner-most layer is heat sealable layer with a protective foil layer in between to provide barrier function and may devoid of the oxygen scavengers, desiccants, or any other stabilizing materials. The selected pouching materials have characteristics of acceptable heat sealability, protected during stability and transportation.

The transdermal drug delivery system aforementioned may be conveniently formed in continuous sheets and may be cut into patches or films of any desirable size or configuration before use.

The method of delivering the pharmaceutically active compound to a mammal comprising the steps of: providing a transdermal adhesive composition according to any one of above composition; positioning the transdermal adhesive composition on the skin of the mammal; and allowing the composition to remain on the skin for a time sufficient

to permit systemic delivery of the pharmaceutically active compound and/or achieve the desired therapeutic result. The period of time for such treatment can be between about 6 hours and about 14 days, typically between about 1 day and about 7 days, and more typically between about 1 day and about 4 days.

In an embodiment, the invention provides a method of treating mild to moderate dementia of the alzheimer's type or mild to moderate dementia associated with parkinson's disease in a patient, comprising administering to said patient a stable pharmaceutical composition of rivastigmine or pharmaceutically acceptable salt thereof according to the present invention.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1

Table 1

• **Ingredients**	**Qty./ unit (mg)**	**Qty./ unit (%w/w)**
Rivastigmine	14.40	6.00
Polyisobutylene	169.20	70.50
Colloidal Silicon dioxide	25.20	10.50
Light mineral Oil	31.20	13.00
Heptane	0.00	0.00
Total	**240.00**	**100**
Modified Backing		
Volara Foam Type 6EO	121.6	16.000 cm^2
Polyisobutylene	24.0	
ScotchPak 9757	32.0	
Release Liner		
ScotchPak 1022 (Fluoropolymer coated Polyester Film)	263.42	25.135 cm^2
Paper Release Liner	--	25.135 cm^2

Procedure:

Preparation of drug blend

Heptane was taken into container and the rivastigmine was added into it and stirred for a few minutes. Then, light mineral oil, polyisobutylene and colloidal silicone dioxide were added in the resulting solution and again was stirred.

Preparation of Modified Backing layer

Polyisobutylene was coated on a paper release liner, dried using a coating and drying machine and then was laminated by scotchpak 9757 (PET) using laminator.

The drug blend was finally coated on a release liner (Scotchpak 1022) and dried in a coating and drying machine and then laminated by modified backing using laminator by de-laminating the paper release liner. The laminate is slit in 3 daughter rolls. The daughter rolls are placed into the die-cutting machine and converted into dosage unit of 16 cm^2 active area with 25.135 cm^2 release liner area. The resulting patches were finally packaged in a pouch or bag.

The stability study of this formulation was conducted at accelerated storage conditions (40°C ± 2°C/75% RH ± 5% RH) and at long-term storage conditions (30°C ± 2°C/65%RH ± 5%RH) over a period of 6 months.

Assay data of Example 1:

Table 2

	Initial	40±2°C/ 75 ±5% RH			30±2°C/ 65 ±5% RH		
		1 month	3 months	6 months	1 month	3 months	6 months
Mean	101.0	99.7	102.1	96.8	100.3	102.1	97.7
% RSD	2.4	1.3	2.8	1.6	1.2	2.2	1.0

Stability data of Example 1 for impurities (1 Month, 3 Months and 6 Months) at accelerated and long-term storage conditions:

Table 3

Impurities	40°C ± 2°C/75% RH ± 5%RH			30°C ± 2°C/65% RH ± 5%RH		
	1 Month	3 Months	6 Months	1 Month	3 Months	6 Months
Impurity A	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
N-Oxide Imp	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Impurity C	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
3-Vinylphenyl ethyl(methyl) carbamate	0.06	0.17	0.31	<0.05	0.05	0.13
Unknown	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Total	0.06	0.17	0.31	<0.05	0.05	0.13

The amount of the impurities measured in the formulation after the storage period indicates that the formulation of the invention is stable under stress conditions.

The pharmacokinetic study of transdermal patch containing rivastigmine of 16 cm^2 was carried out in total 39 subjects and the data (example 1) are summarized as in Table 4.

Table 4

Parameters	C_{max} (ng/ml)	AUC_{INF_obs} (hr*ng/ml)	AUC_{last} (hr*ng/ml)	T_{max} (hr)
Mean ± SD	5.87 ± 1.77	117.44 ± 37.45	116.82 ± 37.5	15.33 ± 4.00
CV %	30.10	31.89	32.10	25.97
Median	5.82	117.32	116.78	14.00
Min	2.42	51.87	51.33	8.00
Max	11.23	262.08	261.54	26.00

The *in-vitro* adhesion tests were also carried out for composition prepared as Example 1. The results of the tests are mentioned in Table 5 below.

Table 5

Properties	Limit	Actual value
Peel at 180°	NLT 10g/mm	48
Tack	NLT 10 g/mm^2	37
Shear	NLT 15 min	61
Release Force	NMT 100g/cm	6

WE CLAIM

1. A stable transdermal drug delivery system comprising a backing layer, rivastigmine or a pharmaceutically acceptable salt thereof, an adhesive material, one or more pharmaceutically acceptable excipients and a release liner, wherein the drug delivery system is free from an antioxidant.

2. The stable transdermal drug delivery system as claimed in claim 1, wherein rivastigmine or a pharmaceutically acceptable salt thereof is present in an amount from about 1 to about 40% by weight of the composition.

3. The stable transdermal drug delivery system as claimed in claim 1, wherein the adhesive material is selected from the group of polyisobutylene, acrylates, silicones, polyisoalkylenes, polyether block amide copolymers polybutadiene, styrene-butadiene (or isoprene)-styrene block copolymer rubber, vinyl-based high molecular weight materials such as polyvinyl alkyl ether, polyvinyl acetate, ethylenevinylacetate copolymers, a partially saponified product of polyvinyl acetate, polyvinyl alcohol and polyvinyl pyrrolidone, polyurethane or a combination thereof.

4. The stable transdermal drug delivery system as claimed in claim 1, wherein the adhesive material is present in an amount from about 30 to about 90% by weight of the composition.

5. The stable transdermal drug delivery system as claimed in claim 1, wherein the excipient is selected from the group of penetration enhancers, fillers, thickeners, plasticizers, tackifiers, surfactants, humectants, preservatives or a combination thereof.

6. The stable transdermal drug delivery system as claimed in claim 1, wherein the drug delivery system is present in the form of matrix or reservoir.

7. The stable transdermal drug delivery system as claimed in claim 1, wherein the drug delivery system exhibits no significant difference in rate and extent of

absorption of rivastigmine as compared to commercially available formulation of rivastigmine marketed under the trade name Exelon®.

8. The stable transdermal drug delivery system as claimed in claim 1, wherein the drug delivery system retains at least 90% of the potency of rivastigmine in the composition after storage for six months at 40°C ± 2°C/75% RH ± 5% RH.

9. The stable transdermal drug delivery system as claimed in claim 1, wherein the backing layer is coated with polymeric material to form a modified backing layer.

10. The stable transdermal drug delivery system as claimed in claim 1, wherein the drug delivery system is used in the treatment of mild to moderate dementia of alzheimer's type and mild to moderate dementia of parkinson's type diseases.