



The treatment of alzheimers disease by using donopezil loaded transdermal patch

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia, more than 100 years ago the alzheimer's disease was first identified, but research into its risk factors, causes, symptoms, and treatment has gained momentum only in the last 30 years. The cholinesterase inhibitors (ChEIs) were the first anti-Alzheimer drugs approved by the Food and Drug Administration (FDA), by inhibiting acetylcholinesterase these are capable of improving cholinergic neurotransmission. Rivastigmine, galantamine, and donepezil these are the most common ChEIs used to treat cognitive symptoms in mild to moderate AD. In particular, to treat AD patients worldwide the lattermost drug has been widely because it is significantly less hepatotoxic and superior tolerated than its predecessor, tetra hydro amino acridine. It also demonstrates high selectivity towards acetylcholinesterase inhibition and has a long duration of action. For the donepezil these are the formulations available like sustained release (23 mg), immediate release (5 or 10 mg), and orally disintegrating (5 or 10 mg) tablets, all of which are proposed for oral-route administration. Since the oral donepezil therapy is associated with adverse events in the gastrointestinal system and in fluctuations of plasma, an alternative route of administration, such as the transdermal one, has been recently attempted. The goal of this paper is to provide an important overview of AD therapy with donepezil, focusing particularly on the advantages of the transdermal over the oral route of administration.

Keywords: Alzheimer's disease, dementia, donepezil, transdermal patch.

INTRODUCTION

Alzheimer's disease (AD) is the most common type of senile dementia, affecting 30% of people older than 85 years and nearly 6–8% of people over the age of 65 years [1,2]. In fact, it has been confirmed that the number of people over 60 years old affected by AD doubles every 5 years.1,2 The common signs and symptoms of AD include apathy, agitation, irritability, disinhibition, delusions, mood disturbances, and aberrant motor behavior, as well as sleeping and eating abnormalities. Since this disease may progress in different ways, it has become difficult to make a precise diagnosis [3]. AD is associated with decreased levels of a number of cerebral neurotransmitters such as noradrenaline, somatostatin, serotonin, acetylcholine (ACh), and corticotrophin releasing factors, whereas the levels of glutamate raise [4].

However, the cognitive deficits seem to be mainly related to the degeneration of cholinergic neurons that originate in the basal-forebrain-cholinergic system and innervate the hippocampus, neocortex, and other brain areas [5]. Thus, AD treatment entails the restoration of cholinergic pathway neurotransmitters through several approaches such as exploitation of ACh precursor's examples like choline or lecithin, by using nicotinic or muscarinic agonists examples like arecoline, bethanacol, and milameline, as well as administering cholinesterase inhibitors (ChEIs) [6-8]. ChEIs, the first class of anti-AD drugs were approved by the United States Food and Drug Administration (FDA), decrease the hydrolysis of acetylcholine in the synaptic cleft by inhibiting cholinesterase. This inhibition increases the ACh levels and therefore improves neurotransmission [9]. Since AChE is found predominantly in the

brain, striated muscle, and erythrocytes, while BuChE is mainly found in the periphery (skin, plasma, and cardiac muscle), AD treatment strategies are mainly directed towards the inhibition of AChE [10, 11]. It is worth mentioning that these agents may not be effective in all patients because only 50% of AD patients have cholinergic deficits. Indeed, 30% of AD patients are also characterized by noradrenaline deficits [10].

In mild to moderate AD four ChEIs are commonly used to treat cognitive symptoms:

Donepezil hydrochloride, Galantamine hydrobromide, Rivastigmine tartrate, tacrine hydrochloride. The structures shown in figure 1.

The purpose of this paper is to provide an important overview of donepezil as an AD therapy, focusing particularly on the advantages of transdermal over the oral route of administration.

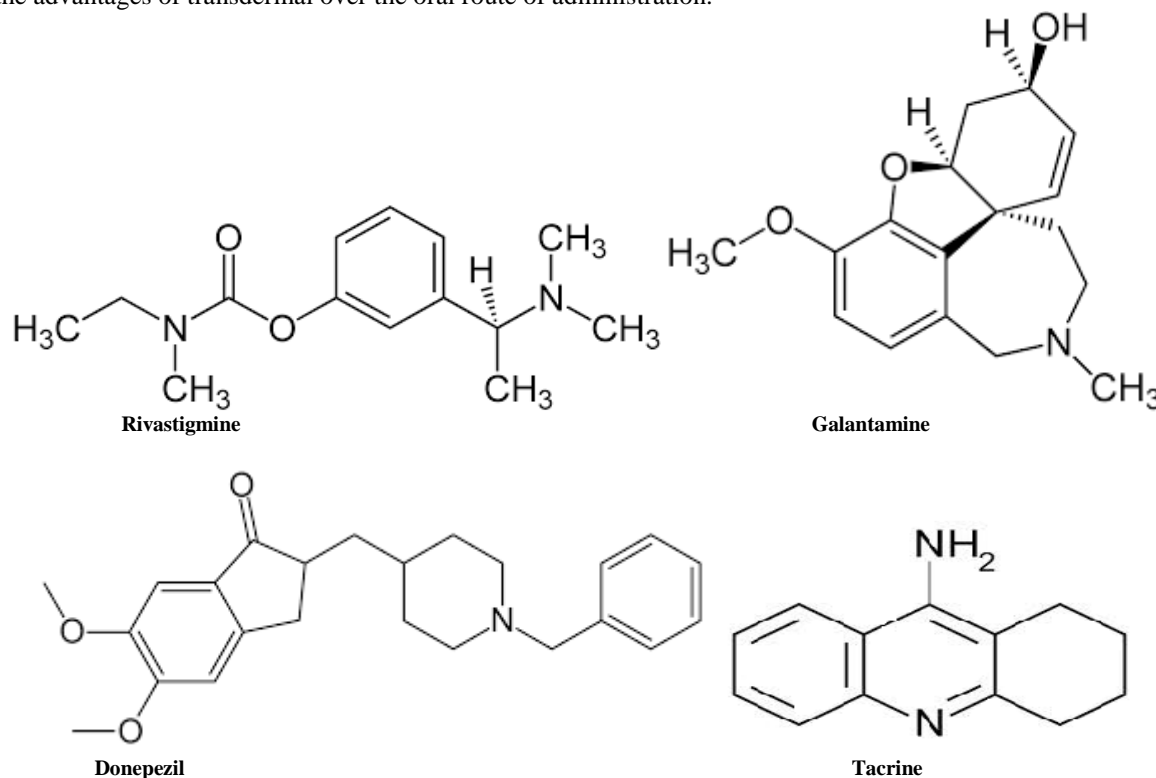


Figure 1: Structure of ChEIs (Cholinesterase inhibitors)

DISCUSSION

Oral donepezil therapy

Immediate-release tablets:

In November 1996 donepezil immediate-release (IR) tablets (5 or 10 mg) were approved for use in the US for the treatment of dementia of the Alzheimer's type [12]. Donepezil interacts with AChE via hydrogen bonds and is demonstrated to be a non-competitive, reversible, and selective ChEI that produces long-lasting inhibition of brain AChE without markedly affecting peripheral AChE activity [13]. Due to properties such as low hepatotoxicity, high selectivity towards AChE inhibition (IC₅₀ AChE/IC₅₀ BuChE = 6.7/7400 nM), and a duration of action (t_{1/2} = 90 h) that is sufficiently long enough to allow for convenient once-daily administration, to treat AD patients worldwide donepezil has been regularly used [14]. The long-term benefits and good safety profile of AChEIs shown by extended post-marketing studies allowed for the approval of donepezil for the treatment of the entire clinical spectra of the disease in 2007 [15,16].

The suggested dosage for donepezil IR for the first 4 weeks 5 mg/day and thereafter 10 mg/day [17]. Inactive ingredients in 5 and 10 mg tablets are hydroxypropyl cellulose, magnesium stearate lactose monohydrate, microcrystalline cellulose, and corn starch. The film coating contains talc, titanium dioxide, hypromellose, and polyethylene glycol [13]. The efficacy of donepezil was demonstrated both in 6 months, double-blind study and in a placebo-controlled trial (the AD2000 study) [18]. In a preliminary study, patients with mild to moderate AD were randomly treated with donepezil 5 mg/ day, 10 mg/day, or placebo. Patients cognition and clinicians global ratings)

were significantly improved in patients treated with the drug compared with placebo, whereas no development was noted on patient-related quality of life [19, 20].

In the latter study, 565 patients with mild to moderate AD were enrolled; in both the presence and absence of cerebrovascular disease, donepezil has been shown to improve cognition compared with placebo. In particular, the ratio of “enhanced” patients (as judged by the clinicians) across the presence of delusions, hallucinations, aggression, and wandering at last observation carried forward among patients receiving donepezil, and ranged between 59.6% and 65.6% [21]. For these reasons, donepezil may be a useful treatment not only for the behavioral and psychological symptoms of dementia (BPSD), but also for cognitive dysfunction.

Sustained-release tablets

The FDA approved in 2010 sustained-release (SR) tablets containing 23 mg of donepezil to give a higher daily dose in once while avoiding a sharp daily raise in peak concentration. Inactive ingredients in the 23 mg tablets are ethyl cellulose, magnesium stearate, hydroxyl propyl cellulose, lactose monohydrate, and methacrylic acid copolymer, type C. The film coating is composed of ferric oxide, hypromellose 2910, PEG 8000, talc, and titanium dioxide. These film coated tablets were compared with the marketed formulation of 10 mg IR tablets in patients with moderate to severe AD who were on a stable dose of 10 mg/day Aricept™ for at least 3 months before screening [22]. The 1500 enrolled patients received either 10 mg donepezil IR in combination with the placebo related to the 23 mg donepezil SR formulation, or 23 mg donepezil SR in combination with the placebo corresponding to 10 mg of the donepezil IR formulation. The 23 mg donepezil SR ensured significant cognitive and global functioning benefits, but safety and efficacy of long-term administration are still under study [23, 24].

Orally disintegrating tablets:

Orally disintegrating tablet (ODT) is also available like Aricept™, approved for use in the US in 2004. For patients who have difficulties to swallowing tablets, this formulation is particularly helpful. Moreover, the tablets allow for administration once in day. These tablets contain 5 or 10 mg of donepezil hydrochloride, mannitol, polyvinyl alcohol, carrageenan, and colloidal silicon dioxide, The 10 mg tablets are also contain ferric oxide (yellow) as a coloring agent [25].

Adverse events associated with oral donepezil therapy:

The most frequent adverse events (AEs) of donepezil, as well as other ChEIs, are cholinergic effects related to the gastrointestinal system like nausea, vomiting, and diarrhea, and sleep disturbances, the frequency and severity of which depends on the chosen dose [26, 27]. Less common adverse effects are vagotonia (eg, bradycardia, syncope), and central nervous system (eg, aggression, sleep disturbance) and para sympathetically mediated (e.g. urinary incontinence) AEs [28].

Due to the large and frequent plasma fluctuations, the incidence of AEs increases with oral administration. In fact, when donepezil is administered orally, it is rapidly absorbed through the gastrointestinal wall thus reaching its peak plasma level (C_{max}). The drug levels then decrease until the next dose is administered [9]. In order to decrease both the C_{max} level and the rate of C_{max} achievement so as to attenuate the AEs, the alternative route of transdermal administration was attempted.

Transdermal route versus oral route

Compared to the parenteral and oral routes of administration, transdermal drug delivery route has several advantages, particularly in the elderly [29]. Indeed, when a chronic neurological disorder is present this type of administration is particularly helpful because, this route is allows for the circumvention of the patient's unwillingness (or inability) to swallow, and the patient can be treated with intravenous infusions or intramuscular injections. Moreover, it provides stable drug blood levels over an extended period of time and improves patient compliance, because sometimes a patient does have to forget to take his/her medication or take pills for further administrations presently in the day [30].

The main disadvantages of transdermal delivery route include potential skin irritation or skin sensitization, discomfort caused by adhesives, imperfect adhesion to the skin, and its high cost. Moreover, since the skin is resistant to drug penetration, only drugs that do not require high blood concentrations can be administered by means of the transdermal route [31-34].

Human skin

- The human skin is planned to protect an organism from the outside environment and is effective as a barrier to chemical transport.

- It is a complex multilayer organ with a total thickness of 2–3 mm, formed by panniculus adiposus, dermis, epidermis, and stratum corneum.

Panniculus Adiposus: The panniculus adiposus a variably thick fatty layer is located below the dermis.

Dermis: The dermis is a layer of dense connective tissue that supports the epidermis.

Epidermis: The epidermis (about 100 μm thick) comprises a layer of epithelial cells and is composed of different layers, the outermost being the stratum corneum.

Stratum corneum: The stratum corneum (15–20 μm thick) comprises highly dense and keratinized tissue and is the skin's main source of penetration and permeation resistance [35, 36].

The capability of a drug to penetrate the skin is a main issue for clinical relevance of transdermal delivery systems. Indeed, only approximately 1 mg of a drug is delivered across a 1 cm area of skin in 24 hours [37, 38].

- The rate of absorption and efficiency of a drug through the skin depends on many physiochemical and biological factors.
- Lipophilic agents may pass rapidly across the stratum corneum through the lipid-rich intercellular space, whereas hydrophilic agents must dissolve and diffuse in cellular bound water molecules [39].
- The molecular size of the agent is also an significant factor in determining the suitability for transdermal delivery; smaller molecules tend to be absorbed faster than larger ones, with very large molecules such as insulin (5808 Da) being too large to pass through the skin.
- It has been recommended that any compound with a molecular weight above 500 Da is unlikely to be suitable for transdermal delivery [40].

Transdermal Patches [41, 42].

The transdermal route of drug delivery becoming the most popular route. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and directly into the bloodstream. Skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol because alcohol increases their ability to penetrate the skin in order to be used in a skin patch. Various drugs which are administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), lidocaine to relieve the pain of shingles and many more drugs. Transdermal drug delivery system has been in existence for a long time. In the past, the most commonly applied systems were topically applied creams and ointments for dermatological disorders. The occurrence of systemic side-effects with some of these formulations is indicative of absorption through the skin. A number of drugs have been applied to the skin for systemic treatment. Currently, transdermal patches are used in several therapeutic areas like pain management, smoking cessation, and treatment of heart disease, hormone replacement and management of motion sickness.

a) Single layer drug in adhesive: In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and this type of layer is responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing. A typical single layer drug in adhesive system is depicted in the following figure 2.

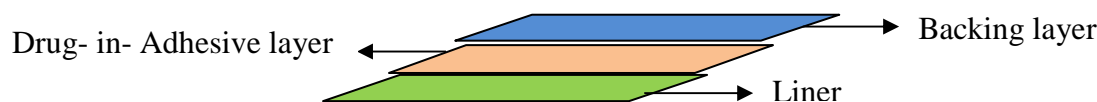


Figure 2: Single layer drug in adhesive

b) Multi -layer drug in adhesive: This type is also similar to the single layer but it contains an immediate drug release layer which is different from other layer which will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing. A typical Multi -layer drug in adhesive system is depicted in the following figure 3.

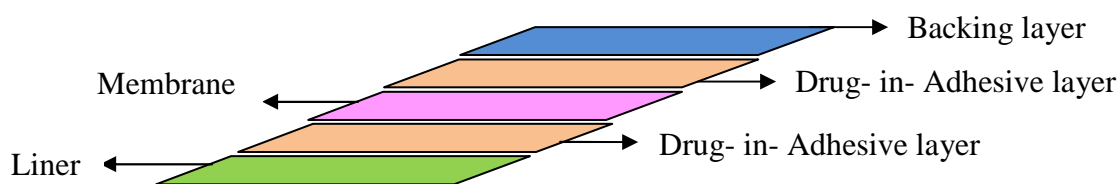


Figure 3: Multi - layer drug in adhesive

c) **Vapour patch:** In this type of patch the role of adhesive layer not only serves to adhere the various layers together but also serves market, commonly used for releasing of essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) **Reservoir system:** In this system the drug reservoir is embedded between the two layers; an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug. A typical Reservoir system is depicted in the following figure 4.

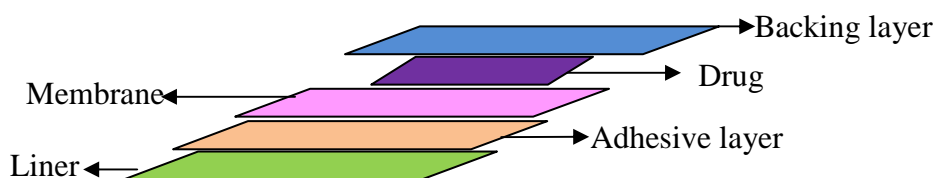


Figure 4: Reservoir system

e) Matrix system

i. **Drug-in-adhesive system:** In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose. A Drug matrix in adhesive system is depicted in the following figure 5.

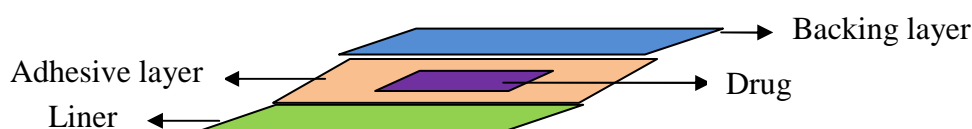


Figure 5: Drug matrix in adhesive system

ii. **Matrix-dispersion system:** In this type the drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) **Micro reservoir system:** In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachable, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

The various components of transdermal patches are discussed in Table 1.

Table 1: Various components of Transdermal Patch

S. NO	Component	Function
1	Backing	Protects the patch from the outer environment, is impermeable to the transdermal patch components, and provides the patch with its flexibility. It is made of elastomers (polyolefin oils, polyester, polyethylene, polyvinylidene chloride and polyurethane) and is preferably nonbreathable (by adding aluminum foil)
2	Membrane	Controls the release of the drug. It is made of natural or synthetic polymer or synthetic elastomers, and its thickness ranges from about 2 mm to about 7 mm.
3	Adhesive	It binds the components of the patch together and the patch to the skin. It is composed by silicone, rubber, polyvinylacetate, or polyisobutylene, depending on the skin-adhesion properties desired. It may contain permeation enhancers (solvents, surfactants or miscellaneous chemicals) to promote skin permeability by altering its structure.
4	Liner	Protects the patch during storage and is peeled off before use.

Transdermal donepezil therapy

As a small and lipophilic molecule, donepezil (Molecular weight: 379.5, Log P value: 3.08 – 4.11) is considered to be physicochemically well-suited for transdermal delivery [42-44]. Valia KH and Ramaraju VS proposed two types of transdermal delivery systems of donepezil: i) A drug matrix-in-adhesive and ii) A drug reservoir in-adhesive.

The first reservoir-type patch is comprised of a backing film, a drug reservoir, a delivery rate-controlling membrane, and an adhesive layer that contacts the skin. The other type comprises a backing film, an adhesive layer comprising a matrix type adhesive and a protective liner. This second embodiment reduces the lag time, during which the donepezil would otherwise migrate from the drug reservoir into and through the adhesive layer, and thus results in a faster influx of the drug into the patient's blood stream upon application to the patient's skin.

In contrast to the tablets that contain donepezil hydrochloride, the transdermal form of the drug is used as free base in order to obtain the desired delivery rates. As a matter of fact, the hydrophilic donepezil hydrochloride has low skin permeability and, although penetration enhancers can be used in order to favor drug penetration, it is not suitable for transdermal delivery. The patches deliver donepezil through normal skin contact into the patient's blood stream in the range of about 0.5 $\mu\text{g}/\text{cm}^2/\text{hour}$ to about 20 $\mu\text{g}/\text{cm}^2/\text{hour}$ or from about 3 $\mu\text{g}/\text{cm}^2/\text{hour}$ to about 13 $\mu\text{g}/\text{cm}^2/\text{hour}$. The dosage is controlled by the active surface of the patch that comes in contact with the skin, and it can be adjusted by prescribing a patch with a larger or smaller active surface area. Dose size and frequency should be determined by a trained medical professional and depend on many factors, including patient weight and disease severity.

The permeation rate of the donepezil from patches are regulated in such a way that blood-plasma levels obtained in the patient are comparable to the FDA approved blood-plasma levels obtained by oral administration. Patches of donepezil are applied for a period of 1 to 7 days, depending on the severity of the disease and the patient's ability to remember to remove depleted patches and apply new ones.

Eisai Co, Ltd, the maker of AriceptTM in Japan, is currently focusing on clinical development programs for AriceptTM, the major innovations being transdermal patches directed to people with Alzheimer's disease. Phase II clinical trials of a once-a-week transdermal patch formulation of donepezil (which includes a bioequivalence study comparing the currently marketed formulation of donepezil to the transdermal formulation) were conducted in 2009 by Teikoku Pharma USA, Inc (San Jose, CA) [45]. This study was designed to assess skin irritation, skin tolerability, and adhesion of the 350 mg donepezil transdermal patch system on the skin of elderly subjects with Alzheimer's disease who have been on an established, well tolerated oral dose of AriceptTM 10 mg, for a period of at least 2 months [45]. The total application time for the donepezil transdermal patch system is 21 days, which was calculated by dividing the dosage into three 7-day applications to three separate areas of the body (upper back, upper middle arm, and side of torso).

A Phase I clinical trial of the donepezil single dose patch formulation was conducted in 2010 by Eisai Co, Ltd, to compare the pharmacokinetics of the donepezil patch (type A, B, C, D, E) with a single dose of donepezil 5 mg tablets [46]. In addition, Eisai Co, Ltd, conducted a Phase I study in 2011 to evaluate the safety and tolerability of donepezil 16 mg tape when applied repeatedly for 17 days. The treatment was intended to be administered in 2 periods, Period 1 and Period 2. In Period 1, the 5 mg donepezil tablets were administered in a single dose. In Period 2, the tape containing 16 mg of donepezil (which corresponds to the 5 mg donepezil tablet) was applied without interruption for 17 days. A washout period of at least 8 days was followed between Periods 1 and 2. A posttreatment examination was performed at least 21 days after the last removal of the tape in Period 2 [47]. The results have not yet been published.

In February 2010, Eisai Co, Ltd, concluded license and option agreements with Teikoku Pharma USA regarding the development and marketing of a donepezil patch formulation.

In September 2010, the US FDA agreed to review the New Drug Application (NDA) of a weekly transdermal patch formulation (a once-weekly administration formulation) of Aricept™ [48]. This NDA was submitted to the FDA for approval of the treatment for mild, moderate, and severe stages of Alzheimer's disease. The new formulation, if approved, would be marketed by Eisai US, a subsidiary of Eisai Inc, and co-promoted with Pfizer Inc.

In April 2011, the FDA declined approval for the transdermal patch formulation of Eisai's Alzheimer's treatment Aricept™. Even if Teikoku Pharma USA decided to withdraw the NDA on April 17, 2012, Eisai and Teikoku Seiyaku continued to move forward with the development of a once daily Aricept™ transdermal system (Phase I) for the Japanese market based on the exclusive license agreement between the two companies concerning Japan research, development, and marketing rights [49].

CONCLUSION

Transdermal drug delivery is helpful for topical and local action of the drug. At present, the first option for the treatment of Alzheimer's disease focuses on decreasing the cholinergic deficiency in the central nervous system (CNS) with ChEIs like rivastigmine, galantamine, tacrine and donepezil, which compensates for the deficiency of Ach in the CNS. Donepezil is a non competitive, reversible and selective inhibitor of brain AchE. Under regulatory review the donepezil is available in 5 and 10 mg conventional immediate release tablets, 23 mg of sustained release formulation, and in a latest dry syrup formulation.

After the oral administration of donepezil, the huge variations were associated in plasma levels with regular gastro intestinal symptoms including nausea, vomiting, diarrhea, constipation, anorexia, abdominal pain and abdominal distention. For the patients who have difficulties swallowing solids or liquids, a transdermal drug delivery may offer great advantages over conventional delivery methods of ChEI.

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