Expert Opinion

Drug delivery strategies for Alzheimer's disease treatment

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Introduction: Current Alzheimer's disease (AD) therapy is based on the administration of the drugs donepezil, galantamine, rivastigmine and memantine. Until disease-modifying therapies become available, further research is needed to develop new drug delivery strategies to ensure ease of administration and treatment persistence.

Areas covered: In addition to the conventional oral formulations, a variety of drug delivery strategies applied to the treatment of AD are reviewed in this paper, with a focus on strategies leading to simplified dosage regimens and to providing new pharmacological tools. Alternatives include extended release, orally disintegrating or sublingual formulations, intranasal or short- and long-acting intramuscular or transdermal forms, and nanotechnology-based delivery systems.

Expert opinion: The advent of new research on molecular mechanisms of AD pathogenesis has outlined new strategies for therapeutic intervention; these include the stimulation of α-secretase cleavage, the inhibition of γ-secretase activity, the use of non-steroidal anti-inflammatory drugs, neuroprotection based on antioxidant therapy, the use of estrogens, NO synthetase inhibitors, and natural agents such as polyphenols. Unfortunately, these compounds might not help patients with end stage AD, but might hopefully slow or stop the disease process in its early stage. Nanotechnologies may prove to be a promising contribution in future AD drug delivery strategies, in particular drug carrier nano- or microsystems, which can limit the side effects of anti-Alzheimer drugs.

Keywords: Alzheimer's disease, drug delivery devices, drug delivery systems, pharmaceutical formulations, therapeutic strategies

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1. Introduction

Alzheimer's disease (AD) is an irreversible progressive neurodegenerative disorder of the CNS that gradually impairs patient memory and cognition in the geriatric population [1]. Although the etiology of the disease is still unclear, many factors are thought to play a crucial role in its pathogenesis, among them oxidative stress, abnormal proteins and excessive metal ion accumulation in brain, and reduced acetylcholine (ACh) levels [2].

Early in the pathogenesis of AD, there is a progressive deposition of β-amyloid (Aβ)-peptide in the hippocampal and cerebral cortical regions. This deposition is associated with the presence of neurofibrillary tangles (NFTs) and senile plaques. NFTs are formed mainly by aggregates of hyperphosphorylated microtubular tau proteins, whereas senile plaques are complex extracellular lesions in which the Aβ-containing core is surrounded by reactive microglia, fibrillary astrocytes, interleukins and dystrophic neuritis [3,4]. Alzheimer's disease brain tissues are also characterized by neuroinflammatory changes that, together with Aβ deposition and induction of glutathione depletion, might increase the levels of reactive oxygen

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Article highlights.

- In this review, the authors discuss the new delivery systems applied to, or in development for, the treatment of Alzheimer's disease. Treatment strategies are classified according to the route of administration and the active principle to be delivered, focusing on drug delivery strategies that could lead to simplified dosage regimens and aimed at improving patient's quality of life.
- The AD elected therapeutic option exploits mainly a symptomatic approach based on the use of cholinesterase inhibitors and NMDA receptor antagonists.
- Potential alternatives to conventional oral formulations include extended release, orally disintegrating or sublingual formulations, intranasal or short- and long-acting intramuscular or transdermal forms, and a variety of nanotechnology-based drug delivery systems.
- Until disease-modifying therapies become available, further efforts are needed in the drug delivery science to deliver drug molecules more effectively to the CNS, and at the same time to meet the prerequisites of ease of administration and reasonable treatment persistence.

This box summarizes key points contained in the article.

species (ROS) and account for vulnerability to oxidant attack [5,6]. Management of AD patients challenges both physicians and caregivers [7-9]. The elected therapeutic option exploits mainly a symptomatic approach based on the use of cholinesterase inhibitors (ChEIs) and NMDA receptor antagonists [10]. Moreover, patient compliance and treatment persistence are essential factors to succeed in slowing disease progression and maintaining an acceptable quality of life [11-13]. The goal of this paper is to provide the reader with a critical overview on the new therapeutic protocols and delivery systems applied in the pharmacological treatment of AD. Treatment strategies are classified according to the route of administration and the active principle to be delivered, focusing particularly on drug delivery strategies that could lead to simplified dosage regimens and provide new pharmacological tools aimed at improving the patient's quality of life.

2. Traditional oral-based AD therapies

At present, two classes of medications to treat AD are approved, namely ChEIs and NMDA receptor antagonists. The first choice for the treatment of AD are the ChEIs (the oral formulations of tacrine, donepezil, rivastigmine, galantamine, and the rivastigmine patch), which slow down the degradation of acetylcholine in the synaptic cleft and compensate for its deficiency [14,15]. Tacrine was the first ChEI approved for the treatment of mild to moderate AD, but its hepatotoxic side effects have restricted its use to rare cases [16]. Prolonged and non-physiological activation of NMDA receptors caused by the neurotransmitter glutamate is hypothesized to cause excitotoxic neuronal dysfunction and is considered to be involved in the pathophysiology of AD [17]. In 2003, in the US the FDA approved memantine, a moderate and non-competitive NMDA receptor antagonist, for the treatment of moderate to severe stages of AD [18].

2.1 Donepezil

Donepezil (Aricept®, Pfizer, NY, USA) is a reversible, non-competitive and selective ChEI that produces long-lasting inhibition of brain acetylcholinesterase (AChE) without markedly affecting the peripheral AChE activity [19]. Donepezil was approved in 1996 in the US for the treatment of dementia of the Alzheimer's type and is available as 5 and 10 mg conventional immediate release tablets [20]. Inactive ingredients in 5 and 10 mg tablets are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose and magnesium stearate. The film coating contains talc, polyethylene glycol, hypromellose and titanium dioxide. The main adverse effects are related to the gastrointestinal system, and sleep disturbance has been demonstrated in some patients [21].

2.2 Rivastigmine

Rivastigmine (Exelon®, Novartis, Switzerland) has been available since 1998 in the EU and was approved for use by the FDA in 2000 in the US for the treatment of mild to moderate AD. It is a dual inhibitor of both AChE and butyrylcholinesterase, with side effects being mainly gastrointestinal disorders during the titration phase [22]. Rivastigmine tartrate is available as 1.5 mg (yellow), 3 mg (orange), 4.5 mg (red) and 6 mg (orange and red) capsules and as 2 mg/ml oral solution for conventional oral delivery [23].

2.3 Galantamine

Galantamine was the last of the three major ChEIs to be approved by the FDA, but the first to come off-patent and become available in generic form [24]. Galantamine has been formulated in circular biconvex film-coated immediate release tablets (Razadyne®, Ortho-McNeil Neurologics, Inc., Titusville, NJ, USA, marketed as Reminyl® in some countries) of 4 mg (off-white), 8 mg (pink) and 12 mg (orange-brown) of galantamine free base (corresponding to 5.13, 10.25 and 15.38 mg of galantamine hydrobromide, respectively) and as oral solution of 4 mg/ml galantamine hydrobromide for conventional delivery [25]. Inactive ingredients include colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, talc and titanium dioxide. The 4 mg tablets contain yellow ferric oxide, the 8 mg tablets contain red ferric oxide and the 12 mg tablets contain red ferric oxide and yellow aluminum lake. Galantamine is approved for the treatment of patients with mild to moderate AD [26]. Like rivastigmine, galantamine appears to have similar efficacy to donepezil in patients with AD [27].

2.4 Memantine

The NMDA antagonist memantine was approved in October 2003 in the US for the treatment of moderate to severe stages of AD. Its safety and efficacy are supported by several large-scale, controlled clinical studies [28-30]. Memantine is available as 5 and 10 mg film-coated tablets and as 2 mg/ml oral solution for conventional delivery of memantine hydrochloride (Namenda®, Forest Pharmaceuticals, Inc., St Louis, MO, USA). The current recommendation is that memantine should be administered at a dose of 20 mg, taken as 10 mg twice daily, with a 3-week, 3-step uptitration phase. Despite the relatively simple management of memantine administration (i.e., without regard to day timing or food intake), its plasma half-life (60 – 100 h) could justify a 20 mg once daily dosing strategy [31]. The results of a double-blind, fixed-dose study in moderate to severe AD suggested that 20 mg once daily dosing of memantine is as well tolerated as twice daily [32].

3. Innovative drug delivery systems for AD treatment

Symptomatic anti-dementia therapy is now based mainly on oral administration of the drugs donepezil, galantamine, rivastigmine and memantine, and the transdermal administration of galantamine. Nevertheless, a considerable percentage of patients require help to take their medication and/or experience adverse effects [33]. Until disease-modifying therapies become available, and in response to the limitations of conventional delivery strategies, further research is needed on the development of new strategies to deliver drug molecules more effectively to the CNS, and at the same time ensure ease of administration and reasonable treatment persistence. In addition to the conventional oral formulations (i.e., immediate release capsule or tablet and liquid forms), a variety of delivery strategies could be applied to the treatment of AD. Alternatives to conventional oral formulations include, but are not limited to, extended release (ER), orally disintegrating or sublingual formulations, pulmonary, intranasal or short- and long-acting intramuscular or transdermal forms, and, more recently, a variety of nanotechnology-based drug delivery systems. Although each delivery strategy has its own advantages and disadvantages in terms of effectiveness, ease of administration, cost and patient preference, several studies exploring the attitudes to different drug formulations have highlighted that caregivers, as well as patients, definitely prefer oral administration of medications and show aversion to parenteral forms [34-36]. Moreover, AD patients usually find it easier to follow less frequent dosing schedules (i.e., a once a day regime) with respect to multi-day fractionated administrations. Albeit 'once a day' administration is not the solution to adherence problems, the reduction of the number of daily administrations could represent one of the strategies to follow in order to meet AD patients' preferences [13,37,38].

3.1 Oral and buccal unconventional drug delivery systems

Oral ER formulations (i.e., tablet or capsule ER), affecting the drug release in a controlled manner, allow therapeutic agents that had to be administered several times daily to be administered once a day. Extended release formulations include diffusion- and/or erosion-controlled polymer matrix devices, and osmotic delivery systems. The latter system incorporates an osmotically active component that, expanding on contact with biological fluids, releases the drug at a fixed rate. It is generally recognized that the perspective advantages of the oral ER products include reduced dosing frequency, smooth plasma concentration levels at steady-state that allow one to avoid drug values associated with side effects, stable drug levels, uniform drug effect, and enhanced compliance and convenience. Potential disadvantages include longer lag time to reach peak plasma level, unpredictable or reduced bioavailability, especially in elderly patients, dose dumping and potentially sustained toxicity, dosing inflexibility and increased formulation costs. Moreover, the extended drug release is lost if the device is chewed, crushed, or broken, thus a proper ER is obtained only if the device is swallowed whole.

Patients who find it difficult to swallow tablets and hard gelatine capsules, and consequently do not take their medication as prescribed, might benefit from oral disintegrating formulations. Orally disintegrating tablets (ODTs) are monolithic dosage forms that disintegrate rapidly when placed on the tongue and can be designed for buccal adsorption if avoiding first-pass metabolism is desired or for prolonged adsorption in the gastrointestinal tract (GI). In the latter case the ODTs release coated pellets that undergo a further dissolution process along the GI tract. Although oral disintegrating formulations are more expensive devices than conventional tablets and capsules, they offer several important advantages over conventional forms: i) they can be taken without the need for water or chewing; ii) improved taste, albeit that masking for bitter-tasting drugs may be challenging; and iii) they are more discreet to intake. A successful oral treatment, however, is not practicable in patients who have difficulty swallowing, are unable to take medications orally owing to the presence of feeding and breathing tubes, or are refusing medications. Consequently, alternative drug delivery strategies should be designed for these patients [39].

3.1.1 Donepezil

Donepezil hydrochloride (Aricept) has recently been approved in the US, after a study completed in April 2010 [40], as sustained release (SR) film-coated tablets containing 23 mg of donepezil hydrochloride for once daily oral administration. In this study 23 mg donepezil SR was compared with the marketed formulation of 10 mg donepezil immediate release in patients with moderate to severe AD. Tested patients were required to have been on a stable dose of Aricept 10 mg/day for at least 3 months before screening;

they received either 10 mg donepezil immediate release in combination with the placebo corresponding to 23 mg donepezil SR formulation, or 23 mg donepezil SR in combination with the placebo corresponding to 10 mg donepezil immediate release formulation. A total of ~ 1500 patients were enrolled and the study was conducted in 219 sites (Asia, Oceania, Europe, India, Israel, North America, South Africa and South America). The results indicated that patients on 23 mg/day experienced significant cognitive benefits and that most severely impaired patients experienced global functioning benefits as well [41]. An open-label extension study is now continuing to evaluate the safety and efficacy of long-term administration of 23 mg donepezil SR in patients with moderate to severe AD who completed the previous study with no serious adverse events and no serious adverse drug reactions [42]. Inactive ingredients in 23 mg tablets include ethylcellulose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and methacrylic acid copolymer, type C. The film coating includes ferric oxide, hypromellose 2910, PEG 8000, talc and titanium dioxide.

In 2004, in the US, new ODT formulations containing 5 or 10 mg of donepezil hydrochloride were developed and approved for use in order to favor administration of the medication. For example, Aricept® ODT tablet contains 5 or 10 mg of donepezil hydrochloride, the inactive ingredients are carrageenan, mannitol, colloidal silicon dioxide and polyvinyl alcohol. Also, the 10 mg tablet contains ferric oxide (yellow) as a coloring agent. The ODT formulations allow once daily administration of tablets that are simply dissolved on the tongue of patients who find it difficult to swallow the conventional oral forms. The main drawback of the donepezil hydrochloride ODT is the bitter taste of the drug and the subsequent requirement of taste masking, carried out during the formulation process. With the aim of preparing a non-bitter donepezil hydrochloride ODT for enhanced patient compliance, a new microsphere-loaded tablet formulation has recently been realized [43]. Donepezil hydrochloride has been encapsulated in Eudragit® EPO (Evonik Industries AG, Essen, Germany) microspheres, a pH-sensitive material that dissolves at pH < 5.5. The bitterness induced by the drug in the oral cavity is prevented because the drug is encapsulated in the polymeric matrix and its release from the microspheres in saliva (pH 6.2) is avoided. However, active drug is then rapidly released in the gastric fluids (pH 1.2) owing to complete dissolution of Eudragit EPO microspheres. The ODT formulation contains donepezil hydrochloride microspheres (equivalent to 5 mg of donepezil hydrochloride), polyplasdone NF and low substituted hydroxypropyl cellulose as disintegrating agents, and microcrystalline cellulose, lactose and/or mannitol as diluents plus aspartame and orange flavor for the further enhancement of the tablet's palatability. The results from taste evaluation in human volunteers revealed that the microsphere-loaded ODTs had significantly enhanced palatability. The *in vitro* dissolution and the pharmacokinetics in rats of the above-mentioned ODTs were evaluated and compared with the commercially available Aricept ODT. Both tablets showed comparable dissolution patterns *in vitro* and similar area under curve (AUC) from 0 to 24 h (AUC_{24h}), C_{max} and T_{max} of donepezil hydrochloride *in vivo*, suggesting that the tested microsphere-encapsulated ODTs might give a drug efficacy in rats similar to that of Aricept ODT. So far, this non-bitter donepezil hydrochloride ODT has not been approved for AD treatment.

3.1.2 Galantamine

Galantamine has been formulated in opaque hard gelatin ER capsules of galantamine hydrobromide (Razadyne® ER) and approved for use in 2004 in the US. The capsules contain 8 mg (white), 16 mg (pink), or 24 mg (caramel) of galantamine base. Inactive ingredients include gelatin, diethyl phthalate, ethylcellulose, hypromellose, PEG, titanium dioxide and sugar spheres (sucrose and starch). The pink 16 mg capsule contains red ferric oxide, whereas the caramel-colored 24 mg capsule contains a mixture of red and yellow ferric oxides. Each capsule contains 25% of the dose in an immediate release form and 75% of the dose in a controlled release form [44]. Galantamine extended release capsules of 24 mg administered once daily under fasting conditions are bioequivalent to galantamine immediate release tablets of 12 mg administered twice daily with respect to AUC_{24h} and C_{min}. The C_{max} is reached in 1 h for immediate release tablets and in 4 h for ER capsules [45,46]. In patients with mild to moderate AD both galantamine extended release and galantamine immediate release are superior to placebo as far as cognitive benefits are concerned, but neither of them is associated with improvement of global functioning [47,48]. Adverse events occurred with an incidence of at least 5% for administration of both galantamine extended release and galantamine immediate release and were shown to be dose-dependent and give mostly gastrointestinal problems. For subjects reporting nausea, the mean percentage of days with nausea and the subsequent antiemetic use was lower with galantamine extended release than with galantamine immediate release. In these studies galantamine immediate release and extended release were increased from an initial dosage of 8 mg/day to 16 or 24 mg/day (based on safety and tolerability) in increments of 8 mg/day every 4 weeks, in order to minimize the occurrence of gastrointestinal adverse events. Galantamine ER was safe and generally well tolerated also when a 1-week dose titration schedule was followed (from 8 to 16 mg/day), albeit more gastrointestinal-related side effects were experienced with respect to the accepted 4-week titration schedule [49]. It is recommended to take galantamine ER with food at an initial dosage of 8 mg/day, increasing it to the initial maintenance dosage of 16 mg/day after a minimum of 4 weeks. A further increase to 24 mg/day should be considered after a further 4-week time interval, based on the clinical benefit and tolerability of the previous dosage. On the other hand, in patients with moderate hepatic or renal impairment, the dosage should not exceed 16 mg/day. Patients receiving stable

doses of twice daily galantamine immediate release may switch to once daily galantamine extended release without titration period [50].

Another approach for the administration of galantamine hydrobromide is represented by the system described as a controlled drug delivery oral device, namely IntelliDrug. This system has to be implanted into the oral cavity, built onto a prosthetic tooth crown, or embedded inside a denture. The device, having the size of two molar teeth, consists of a stainless steel, intra-oral module containing an osmotic membrane, a drug reservoir, a triggering mechanism for pushing the drug solution, a drug-level sensor, and a power source. This system is driven by software and may contain electrodes for iontophoretic delivery enhancement [51,52]. The device has been designed for transbuccal delivery (specifically referred to the administration of drugs through the mucosal membrane lining the inner cheek) of galantamine hydrobromide in order to overcome the drawbacks of conventional administration routes. Owing to its relative permeability, robustness and lower tendency to irritation or damage, the buccal mucosa offers the opportunity to deliver pharmacological actives systemically. This mucosa is richly vascularized, accessible for administration and removal of a dosage form, and thus eligible for matching sufficient patient acceptability compared with other non-oral routes [53]. The efficacy of a prototype of the IntelliDrug device has been evaluated in an *in vivo* animal trial following a single galantamine dose delivered through the buccal mucosae and compared with a 10 mg intravenous (i.v.) drug injection. The buccal galantamine bioavailability, the pharmacokinetic and the enhancement effect of iontophoresis have been evaluated as well [54]. As expected, intravenous administration produced a sharp increase in blood galantamine levels that reached a peak 15 min after administration and then underwent a steep decrease. Unlike intravenous delivery, buccal drug delivery elicited a moderate increase in drug blood concentration, reaching a peak after 120 – 180 min and undergoing a moderate decrease in galantamine over time. Overall, although galantamine hydrobromide delivery by means of the IntelliDrug system is not yet approved for AD treatment, an intra-oral device capable of delivering galantamine at the appropriate dosage periods of time, thereby avoiding the first-pass effect and ensuring effective bioavailability, could be of advantage for patients poorly accustomed to conventional AD treatments.

3.1.3 Physostigmine

As physostigmine is readily absorbed from the GI tract and undergoes extensive presystemic metabolism, its oral dosage forms are affected by poor bioavailability, requiring repeated administrations at short time intervals, and causing poor patient compliance [55]. With the aim of overcoming the limitations dictated by the oral delivery of physostigmine, Bolourchian *et al.* proposed a tablet formulation with suitable physical and chemical characteristics for sublingual delivery of physostigmine salicylate [56]. Taking into account the physical limitations connected with sublingual tablets such as hardness and disintegration time, the authors integrated the mixture plan approach and the statistical D-optimal design approach for the development and optimization of the formulation. Tablets were prepared with a constant content of drug (4%), magnesium stearate (1%) and talc (0.2%), whereas polyvinylpyrrolidone (PVP), starch 1500, lactose and sodium starch glycolate were varied within precise proportions in order to ensure significant changes in the corresponding physical properties. Finally, the new formulations were characterized for their hardness, disintegration and dissolution time, friability, drug content and stability. The data collected highlighted the feasibility of sublingual devices for physostigmine salicylate, but so far the formulation has not been tested *in vivo*.

3.1.4 Memantine

In June 2010, memantine was approved in the US as an ER capsule formulation containing 28 mg of memantine (Namenda XR®) for the treatment of moderate to severe dementia of the Alzheimer's type. Each capsule of Namenda XR contains extended release beads with the labeled amount of memantine hydrochloride and the following inactive ingredients: sugar spheres, PVP, hypromellose, talc, polyethylene glycol, ethylcellulose, ammonium hydroxide, oleic acid, and medium chain triglycerides in hard gelatin capsules [57]. This new ER formulation has been developed to improve adherence and efficacy without compromising an excellent tolerability and safety profile [58]. The safety and efficacy of Namenda XR were established in a randomized, double-blind, placebo-controlled trial of 676 outpatients already subjected to a cholinesterase inhibitor treatment. The results indicate that patients treated with this drug experienced statistically significant benefits in cognition and clinical global status compared with placebo. In a study comparing 28 mg once daily Namenda XR with 10 mg twice daily Namenda, C_{max} and AUC_{24h} values were 48 and 33% higher for the XR dosage regimen, respectively. Treatment begins at a low dose (7 mg once a day) and is gradually increased (in 7 mg increments) until the target dose (28 mg once a day or 14 mg once a day for patients with severe renal impairment) is reached.

3.2 Transdermal and injectable depot-forming drug delivery systems

Transdermal delivery may offer considerable advantages over conventional delivery methods for patients who are non-adherent or have difficulties swallowing solids or liquids. Certain adverse effects may be decreased by this route; for example, first-pass effects could be avoided [59], doses could be reduced as a result of the shortened metabolic pathway, and the daily dosing schedule can be simplified. Moreover, when adverse effects become manifest, prompt cessation of drug delivery can be ensured by simple patch removal. As the release is controlled by the device, it is possible to

obtain smooth plasma levels, continuous drug delivery and persistent therapeutic plasma drug concentrations with good tolerability [60-62]. This route of administration can improve patient compliance by facilitating regular drug intake in a patient-friendly manner, especially for patients with chronic neurological diseases. The main disadvantages of transdermal delivery include its high cost, skin sensitization or irritation, and discomfort caused by adhesives. Moreover, only drugs that do not require high blood concentration can be delivered by means of transdermal patches [63,64]. Although this route of administration can improve patient compliance by reducing the frequency of medication schedule, the placement of patches in certain areas, such as the upper back, can make removal by the patient him/herself rather difficult.

A more convenient approach might be represented by the injectable depot-forming drug delivery systems, designed for either intramuscular or subcutaneous injection, able to release the active in a controlled manner for up to 1 month. In the last decade, the development of parenteral sustained release systems for long-term drug delivery has grown rapidly. *In situ* forming implants, such as those generating a semisolid drug depot after subcutaneous injection, are gaining in popularity owing to the inherent advantages of their ease of manufacturing and ease of administration. *In situ* forming implants are injectable drug delivery systems that are in the sol form before administration but transform into macroscopic gels once injected into the body. As a consequence, the drug can be released in a sustained and controlled manner. *In situ* gelation can be obtained in response to a certain stimulus such as temperature modulation, pH change, presence of ions or UV-polymerization [65-67]. Compared with oral formulations, parenteral depot systems allow a smooth plasma level to be achieved and, as a result, minimization of the side effects associated with the rapid increases in drug plasma concentrations that generally follow multiple administrations of actives with narrow therapeutic indices [68]. Further potential benefits are a dose reduction resulting from the avoidance of plasma drug concentration fluctuations, the elimination of bioavailability problems related to absorption and first-pass metabolism, as well as the enhancement of patient compliance by reducing the frequency of application. From a manufacturing point of view, injectable controlled release dosage forms offer the advantage of being relatively easy to manufacture from polymers adapted for this approach. Disadvantages include pain at the injection site, risk of infection and hematoma, administration difficulties in obese or overly thin patients, and lack of dosage flexibility once adverse effects become manifest as the medication cannot be promptly discontinued. Moreover, the use of depot formulations requires trained medical personnel to inject the *in situ* forming device.

3.2.1 *Rivastigmine*

In July 2007, the rivastigmine patch was approved in the US to treat mild to moderate AD and Parkinson-associated dementia, and is considered among the first-line therapies for the disease [69]. The rivastigmine patch (Exelon Patch®) is a matrix diffusion-controlled patch, composed of four layers (**Figure 1**) [70]. The highest layer, the backing film, is colored and has a protective function; the second layer, the acrylic matrix, ensures effective storage of rivastigmine [63]; the next coating, a silicone matrix layer with a silicone polymer, provides good adhesion of the patch to the skin; the release liner is removed and discarded before use. To offer maximum drug exposure, the patch should be applied to the upper back, chest, abdomen, thigh or upper arm (**Figure 2**) [71]. Notably, the patch application site should be rotated on a daily basis (alternating right to left sides of the body), with no reapplication of the patch to an identical area of skin within 14 days [72]. The amount of rivastigmine in the patch is higher than the amount absorbed into the bloodstream, because only 50% of the total loading dose is absorbed over a 24 h application period [73]. There are four patches with different rivastigmine amounts (**Table 1**), but in the EU and US only two sizes are available: the 5 cm^2 patch, loaded with a total dose of 9 mg, which delivers 4.6 mg/day rivastigmine; and the 10 cm^2 patch, loaded with a total dose of 18 mg, which delivers 9.5 mg/day rivastigmine [74,75]. After a lag time of 0.5 – 1 h the transdermal patch is able to maintain plasma concentrations of rivastigmine within the optimal therapeutic window of each patient [31,71]. Therapy starts with a small patch of 4.6 mg/day and, if well tolerated, the dosage may be increased to the recommended maintenance (and maximum approved) dosage of 9.5 mg/day after at least 4 weeks' time interval therapy [70]. The rivastigmine patch could be used also for patients who discontinue or reduce the oral treatment because of tolerability problems, or loss of therapeutic benefit [76]. In particular, the open-label extension to a double-blind, randomized trial in which one group of patients was switched from rivastigmine capsules to rivastigmine patches (the IDEAL study) demonstrated that patients on high rivastigmine capsule doses may be switched directly to the 9.5 mg/day patch, whereas patients on low doses should undergo 4 weeks of 4.6 mg/day patch treatment before raising their dose to 9.5 mg/day (**Figure 3**) [77-79]. In both instances, the first patch should be applied the day after the last oral dose. The rivastigmine patch is generally well tolerated in patients with AD. The most commonly reported adverse events were gastrointestinal disorders, including nausea, vomiting and diarrhea. Nevertheless, their incidence was similar to that of placebo and the rate of discontinuations because of gastrointestinal adverse events was much lower than that recorded for rivastigmine capsule administration [74,77,80]. Overall, the safety profile of rivastigmine is favorable and the improved tolerability offered by the rivastigmine patch suggests that transdermal delivery may be the best way to deliver this drug in AD and Parkinson's disease dementia patients [81]. The relative brevity of the published trials does not allow comment on long-term

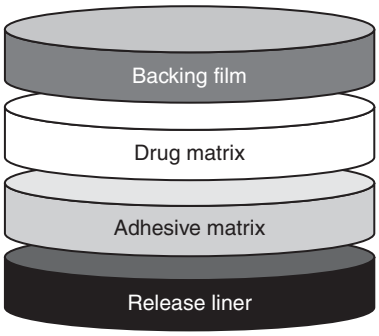

Figure 1. Rivastigmine patch structure.

efficacy or retention rates, and clearly continuing post-marketing surveillance will be required in order to monitor for the emergence of unanticipated side effects, such as cholestatic hepatitis [74,78,82,83]. Clinical trials for assessing the efficacy of the 15 cm^2 rivastigmine patch in patients with severe dementia of the Alzheimer's type, comparing it with the lowest dose of 5 cm^2 rivastigmine patch and for supporting the optimal use of rivastigmine patch in long-term treatment of AD in patients demonstrating cognitive decline at the target maintenance dose of rivastigmine patch are in progress [84-86].

Alternatively to transdermal patches, oleogels containing rivastigmine free base or hydrogen tartrate at concentrations up to 5% (w/w), *N*-stearoyl-L-alanine methyl ester in concentrations up to 10% (w/w) as gelator agent, and safflower oil as the vehicle, were preclinically investigated as *in situ* forming implants for long-term drug delivery with potential use in AD treatment. The injectable devices have been physicochemically characterized and optimized for sustained rivastigmine release both *in vitro* and *in vivo*. Pharmacokinetic studies after subcutaneous injection in rats showed sustained blood levels within the therapeutic range (1 – 400 ng/ml) for 11 days, with 5 times lower peak plasma concentrations for L-alanine-based rivastigmine oleogels when compared with subcutaneous rivastigmine solutions [87]. In a subsequent report, rivastigmine oleogels were obtained by using *N*-behenoyl-L-tyrosine methyl ester as the gelator agent with the aim of improving the mechanical properties of the *in situ* forming device as well as the sustained release of the active. The effects of gel composition (L-alanine versus L-tyrosine), rivastigmine dose and implant volume on rivastigmine plasma concentrations were evaluated after subcutaneous injection. The L-tyrosine-based rivastigmine-loaded oleogel was able to deliver rivastigmine for several weeks, achieving significant inhibition of hippocampal AChE activity in rats. Such a simplified dosing regimen has been proposed as an alternative to the current once a day oral administration of rivastigmine for the treatment of mild to moderate AD, but, so far, it has not been approved for clinical use [88].

3.2.2 *Galantamine*

Among the forefront in transdermal delivery science is the application of microneedle patches. This is a method aimed at increasing skin permeability based on the formation of micropores in the stratum corneum by the use of an array of microneedles. As the thicknesses of stratum corneum and live epidermis are 10 – 40 and 50 – 100 μm in the study reported by Wei-Ze and co-workers, microneedles with a length of 70 – 80 μm were fabricated and used in order to investigate the ability of physical skin pretreatment with microneedle piercing to increase galantamine permeability across rat skin [89]. Histological examination revealed that the microneedles were able to form skin conduits by pressing and swaying against the microneedle backing layer at common pressure. The created conduits acted as a transdermal pathway for transport of galantamine across the skin. *In vitro* diffusion studies showed that the piercing of skin significantly increased galantamine permeability. Moreover, the skin permeability increased along with the increase of insertion force, retention time and microneedle number in a certain range. The skin was not damaged after microneedle applications and the conduits formed did not facilitate the permeation of pathogens into the body across the skin. Microneedle patches were shown to be a useful drug delivery device for the percutaneous administration of hydrophilic molecules, but more investigations are needed to translate these findings into clinical practice.

3.2.3 *Physostigmine*

Physostigmine was the first ChEI to be formulated in a transdermal patch in order to overcome the short half-life and narrow therapeutic window associated with oral and intravenous (i.v.) administration, and to improve patients' compliance [90]. The pharmacokinetic of 30 mg physostigmine patch was investigated in 6 healthy male volunteers and compared with that of an oral solution and an i.v. infusion [91]. The peak plasma drug concentrations observed with the patch were in the therapeutic range and were maintained for ~ 18 h after a single administration. Patches containing 30 and 60 mg of physostigmine were also tested on 204 patients with probable AD, but the efficacy of physostigmine was not superior to that of placebo after a treatment period of 24 weeks. The plasma concentrations obtained (100 pg/ml) were not sufficient to compensate for cholinergic deficiencies in affected brain areas and to produce clinical benefits, and there was not a linear dose relationship between the 30 and 60 mg dosages. This evidence suggests that the dose (up to 60 mg) administered may have been too low to be effective [92,93].

3.2.4 *Phenserine*

The clinically relevant activity of phenserine appeared to be limited partly because of first-pass hepatic and GI metabolism of the drug [94]. To minimize these limitations, a transdermal formulation of phenserine was developed and

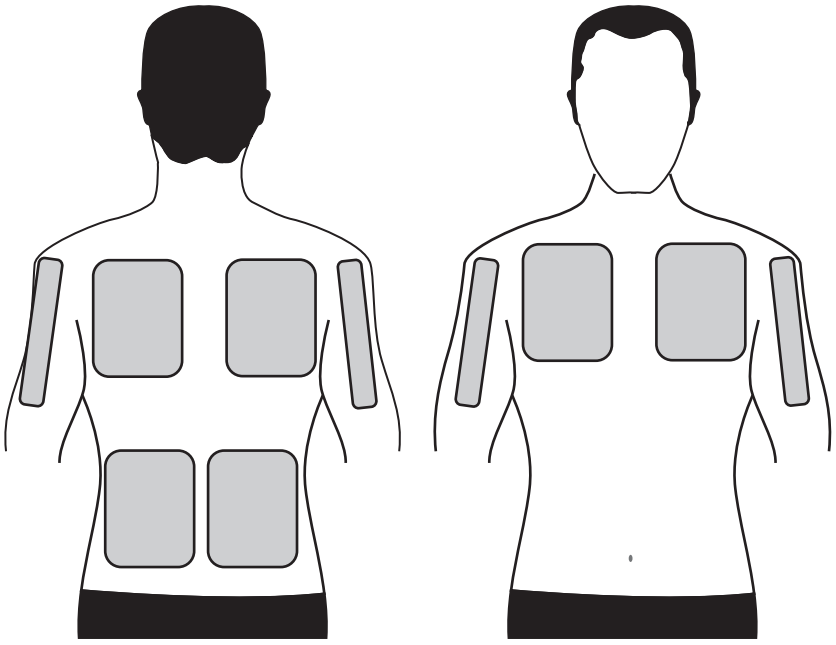

Figure 2. Application sites of rivastigmine patch [72].

Table 1. Features of rivastigmine patches.

Patch diameter (cm^2)	Rivastigmine amount (mg)	Drug delivery rate (mg/24 h)
5	9	4.6
10	18	9.5
15	27	13.3
20	36	17.4

characterized *in vitro* and *in vivo* [59]. Phenserine has been blended into a mixture of melted fatty alcohols (stearyl, cetyl and 1-docosanol), propylene glycol and the permeability enhancer 1-[2-(decylthio)ethyl]azacyclopentane-2-one (HPE-101) at concentrations of 1 – 5% (w/w) in order to form a fatty alcohol propylene glycol (FAPG) ointment. The drug's nature (free base or tartrate), different ointment compositions, and the effect of the permeability enhancer on the *in vitro* drug permeability were tested in order to evaluate the optimal formulation able to reach therapeutic phenserine plasma levels in the rat [95]. Afterwards, the selected transdermal ointment was evaluated *in vivo* for transdermal phenserine permeability, AChE activity, and the effects on cognitive performance in rats with scopolamine-induced cognitive impairment. The *in vivo* results indicated that phenserine ointment reduced AChE activity in both plasma (30% decrease at 8 h) and brain (60% inhibition), resulting in improved cognitive performance of the animals. These findings allow speculation that phenserine delivered transdermally may provide clinical benefits, but more investigations need to be carried out before translating these findings into clinical use for treating AD patients.

3.2.5 *Tacrine*

Tacrine was the first centrally acting oral ChEI approved for use in the US. Transdermal delivery was developed to minimize first-pass metabolism, to reduce incidence of gastrointestinal side effects and hepatotoxicity, and to maximize the effects on memory enhancement by keeping constant the levels of tacrine in the brain [96,97]. Passive permeation through the stratum corneum is difficult because tacrine is a rather lipophilic drug (logP octanol/water 3.3). Therefore, transport is generally facilitated by the use of ion-exchange fibers and iontophoresis. Iontophoresis exploits an electromotive force to facilitate percutaneous absorption of a drug via disorganization of the lipid bilayer, diffusion shunts and/or flip-flop gating model [98]. The ion-exchange mechanism offers the possibility of forming a drug reservoir as charged drugs are bound to the ion-exchange groups of the fiber until they are released by the mobile ions [99]. Therefore, the combination of iontophoresis and ion-exchange fibers may be used to control drug release and to increase drug permeation across the skin. A short-term preclinical study on 10 healthy human volunteers demonstrated that this combination can ensure a constant flux until the current (0.4 mA/cm^2 for 3 h) is turned off with a short lag time (30 min) [100]. The side effects of tacrine delivery during this short study were minimal, mainly confined to transient skin irritation occurring owing to iontophoresis. Unlike oral therapy, no hepatotoxicity was observed. So far none of the above-mentioned transdermal tacrine delivery systems (TDSs) has been approved for use.

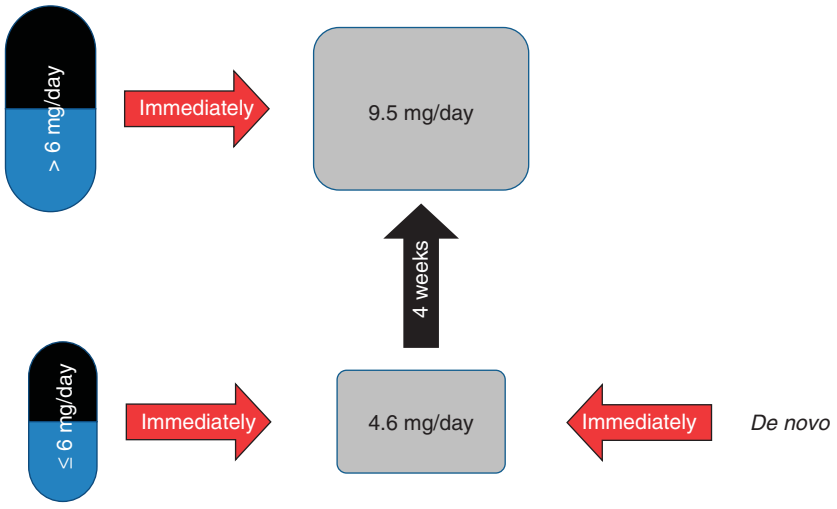

Figure 3. Therapy treatment for *de novo* patients and for patients switching from rivastigmine capsules.

3.2.6 *Nicotine*

At present, many FDA-approved nicotine TDSs are available for nicotine replacement therapy. Each system differs in the technology used to achieve the transdermal delivery of drug, the total loading dose and the patch size. Among these, Nicoderm® (ALZA, MO, USA) and Nicotrol® (Kabi Pharmacia, Sweden) were selected for studying the beneficial effects of nicotine on attention and memory. The Nicoderm system is a rectangular-shaped patch consisting of: i) an outer occlusive backing film; ii) a drug reservoir, which contains nicotine in a matrix of ethylene-vinyl acetate copolymer; iii) a polyethylene rate-controlling membrane; iv) a contact adhesive of polyisobutylene; and v) a protective release liner that covers the adhesive layer and is removed before application (**Figure 4**). The Nicotrol system is a polymer-matrix drug dispersion-type consisting of three distinct layers: i) an outer layer, which is composed of a laminated polyester film; ii) a middle layer, which contains nicotine dispersed in a structural non-woven material and rate-limiting adhesives; and iii) a disposable liner that protects the system and must be removed before use (**Figure 4**) [101]. For both types the amount of nicotine delivered to the patient is proportional to the surface area of the system (**Table 2**). It was found that nicotine administered by means of Nicoderm patches can significantly improve attention in non-smoking subjects without pre-existing attentional impairment and can improve cognitive functions such as verbal learning in healthy elderly non-smoking subjects [102,103]. The nicotine effect was also evaluated in 8 AD subjects over a 4-week period: after 1 week on the 7.5 mg/day Nicotrol patches the subjects were switched to 15 mg/day patches for 2 weeks. Then they were switched back to 7.5 mg/day patches for the fourth week in order to avoid withdrawal symptoms following discontinuation [104]. The results indicated that nicotine administered through a dermal patch did not produce improvement in memory or overall clinical status, but produced a statistically significant improvement in attention among AD subjects. This effect was sustained over the 4 weeks of treatment. As persistence of therapeutic effect is essential for the treatment of a chronic disorder such as AD, these results are promising, but larger clinical trials are necessary in order to confirm the potential therapeutic benefit of nicotinic treatment in AD patients [105].

3.2.7 *17β-Estradiol*

Whereas several trials of oral conjugated estrogens reported no benefit compared with placebo on cognition among women with AD, transdermal administration of estradiol confirmed the favorable neuroprotective effects of estrogens [106-109]. These different results depend on both the hormone type and the route and time of administration. Before menopause, estradiol is the predominant circulating estrogen, whereas after menopause a dramatic decrease in circulating estradiol is observed and AD patients have significantly reduced estradiol levels in the frontal cortex, a region typically affected in AD [110,111]. Thus, in order to mimic more closely the premenopausal state, estradiol may be an appropriate replacement strategy. To exert a neuroprotective effect against the development of AD the estradiol has to be administered in a 'critical period' immediately following the menopause; administration after this period may have no (or negative) effect [112]. The effectiveness depends also on the administration route because, for example, the transdermal route of delivery allows the achievement of steady-state plasma levels of estradiol similar to those found during the early to mid-follicular phase of the menstrual cycle, and avoidance of venous thrombosis and hypertension complications reportedly associated with oral administration [113,114].

An example of an estradiol skin patch used for *in vivo* and *in vitro* studies is Estraderm® (Novartis, Switzerland) [115].

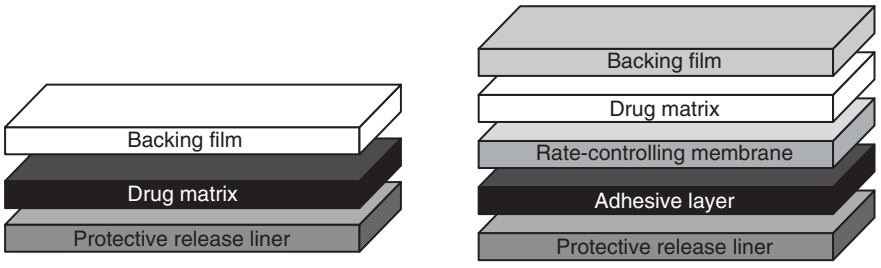

Figure 4. Nicoderm® (left) and Nicotrol® (right) patch structure.

Table 2. Main features of nicotine transdermal patches.

Patch	Dosage rate (mg/day)	Surface area (cm^2)	Total nicotine content (mg)	Bioavailability	Delivery rate ($\mu g/(cm^2\ h)$)
Nicoderm®	7	7	36	68%	40
	14	15	75		
	21	22	114		
Nicotrol®	7.5	10	8.3	95%	31
	15	20	16.6		
	22.5	30	24.9		

This patch has a surface area of 10 or 20 cm^2, contains estradiol (4 or 8 mg) and alcohol (0.3 or 0.6 ml) and releases 0.05 or 0.1 mg of estradiol a day, respectively. It consists of five layers: i) a backing layer of polyester/ethylene vinyl acetate copolymer film; ii) a drug reservoir of estradiol and alcohol gelled with hydroxypropyl cellulose; iii) a rate-limiting ethylene-vinyl acetate copolymer membrane; iv) an adhesive formulation of light mineral oil and polyisobutylene; and v) a protective liner of siliconized polyester film (**Figure 5**). The cognitive and neuroendocrine response to estradiol administration for postmenopausal women with AD was evaluated by using patches of 0.05 and 0.1 mg/day for 8 weeks [109,110]. The results of both studies indicated that estradiol administration has the potential to facilitate both attention and memory for postmenopausal women with AD. Moreover, the improvements in attention and memory decreased as soon as the treatment was discontinued. This effect may be attributed to estrogen-induced modulation of several neurotransmitter systems, such as acetylcholine, serotonin and catecholamines. The effect of estradiol administration on plasma concentration of Aβ for postmenopausal women with AD was also evaluated [116]. In a placebo-controlled, double-blind, parallel-group design study, 20 women were randomized to receive either 0.10 mg/day of transdermal 17β-estradiol or a placebo for 8 weeks. The results supported an effect of estradiol on Aβ-processing for AD women who were hormone replacement therapy-naive. The transdermal estrogen patches were also administered in 27 male patients with advanced dementia for evaluating the efficacy and tolerability as adjunctive treatment for aggressive behavior [117]. The use of transdermal estrogen yielding up to 100 μg/day was not associated with an improvement in aggressive behavior, but a rebound effect after patch removal was described. Nevertheless, small subject numbers, multiple variables and lack of statistical power impair the interpretation of these results, and more studies in this area are needed in order to draw exhaustive conclusions.

3.3 Nasal route

Among the alternative delivery methodologies, intranasal (i.n.) delivery has come to the forefront as an alternative to invasive delivery methods. Nasal administration of pharmacologically active molecules, first developed by Frey in 1991, enables their potential absorption to the CNS bypassing the limitations of the blood–brain barrier (BBB) because of the unique connections that the olfactory and trigeminal nerves provide between the brain and external environment [118]. Possible mechanisms of transport of active molecules may involve a combination of axonal transport from the olfactory neurons of the olfactory epithelium to the olfactory bulb, and of extracellular transport routes involving bulk flow and diffusion within perineuronal channels and perivascular spaces or lymphatic channels directly connected to the cerebrospinal fluid (CSF) [119-123]. Advantages of i.n. administration include targeting of therapeutics to the CNS with rapid achievement of drug levels in the target tissue, and less systemic exposure and fewer side effects with avoidance of first-pass metabolism [124-130]. For a therapeutic to be absorbed and become bioavailable in the CNS after intranasal administration, the drug molecule has to go

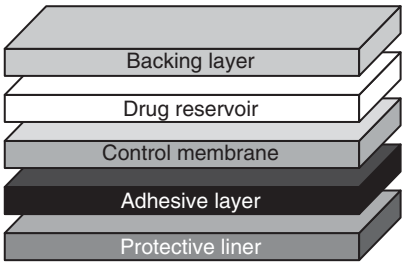

Figure 5. Estraderm® patch structure.

through the mucus layer and cross the epithelial membrane of the nasal cavity, thus bypassing the clearance mechanisms imposed by the mucociliary apparatus, the broad range of metabolic enzymes present in the nasal tissues, and the efflux transporters that reside in the apical area of ciliated epithelial cells and in the submucosal vessels of the human olfactory region [131-135]. Thus, physiological conditions, physicochemical properties of drugs and formulations, and the deposition methodologies of the formulations represent key factors when the aim is the development of a successful nasal medicine.

3.3.1 *Galantamine*

Owing to low solubility (35 mg/ml) and dose volume limitations (100 µl), the commercially available hydrobromide salt of galantamine is not suitable for i.n. dosing [136,137]. The typical oral dose for galantamine is 8 mg and therefore it is necessary to increase its solubility at least to 80 mg/ml. This goal was brilliantly reached by using a counter ion exchange approach, with which the traditional counter ion bromide was replaced with lactate by using an anion exchange column consisting of Q Sepharose [138]. Lactate was chosen because it favors a strong interaction, through hydrogen bonding, with water owing to its hydroxyl and carbonyl groups. Compared with galantamine hydrobromide, galantamine lactate showed remarkable increased solubility (up to ~ 400 mg/ml) and comparable stability and *in vitro* cellular toxicity. To maximize the bioavailability after i.n. administration, galantamine lactate (35 – 80 mg/ml) was formulated with several excipients such as methyl-β-cyclodextrin 30 mg/ml, didecanoyl-L-α-phosphatidylcholine 1.7 mg/ml and edetate disodium dihydrate 2.0 mg/ml [139]. The mixture of these three permeation enhancers resulted in a fourfold increase in the *in vitro* galantamine permeation across the epithelial barrier, high cell viability and low cytotoxicity. This formulation was also tested in a rat pharmacokinetic model, to study the pharmacokinetic profile of the oral versus i.n. administration. The i.n. galantamine had a shortened T_{max} relative to the oral formulation (5 min versus 240 min, respectively) and nearly fourfold increase in C_{max} (12,100 ± 8000 ng/ml versus 3200 ± 200 ng/ml). Finally, the hypothesis of reduced GI-related side effects for i.n. versus oral dosing was tested with a ferret model [140,141]. Clearly, a significant decrease in GI-related side effects was observed when galantamine was administered by the i.n. route. In particular, during the first 4 h after i.n. administration only three emesis and retching events were observed, whereas 34 events were recorded within 4 h after oral administration. Despite the promising results, so far the formulation has not been tested in AD patients.

3.3.2 *Physostigmine*

The physostigmine analogue (3aS)-*cis*-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-pyrrolo-[2,3b]-indol-5-yl-3,4-dihydro-2-isoquinolincarboxylate (NXX-066), which acts as an ChEI and showed potential for treating AD, is well absorbed from the GI tract, but its oral bioavailability is poor to moderate in rats and dogs because of presystemic metabolism [142]. The aims of the study conducted by Dahlin and Björk were, thus, to investigate the systemic absorption of nasally administered NXX-066 in rats and to compare the uptake of the drug into the CSF after nasal or intravenous administration [143]. Nasal administration of NXX-066 resulted in extremely rapid and complete absorption into the systemic circulation followed by a rapid decline of the plasma concentrations. The intravenous and nasal concentration–time profiles of NXX-066 were similar, with the mean values of each pharmacokinetic parameter not differing significantly between the two administration routes. The data collected allowed speculation that, as the oral bioavailability is poor to moderate owing to presystemic metabolism, nasal delivery could be a good alternative to the parenteral route for NXX-066 administration.

3.3.3 *Rivastigmine*

For i.n. administration, rivastigmine was formulated in conventional multilamellar liposomes obtained by the well-known lipid layer hydration method and using cholesterol and soy lecithin as lipid components [144]. The *in vitro* release studies showed that there was an initial burst release followed by a lag phase. The *in vivo* studies showed that intranasally administered liposomes significantly increased the exposure and resulted in a higher concentration in rat brain. As a matter of fact, the AUC (36.13 ± 1.87 mg min/ml) was fivefold higher than orally administered free drug (6.58 ± 0.26 mg min/ml) and almost threefold higher than free drug administrated intranasally (12.99 ± 0.87 mg min/ml). If approved for human use, this sustained release of rivastigmine from liposomes may be used to reduce the frequency of administration.

3.3.4 *Tacrine*

To assess the efficiency of i.n. administration, a tacrine solution in propylene glycol was prepared and drug concentrations in mice blood and brain were determined [145]. The study showed that following intranasal administration, tacrine reached the rabbit brain quickly (T_{max} 60 min) compared with intravenous administration (T_{max} 120 min), suggesting a direct transport into the brain from the nasal cavity. This selective localization of tacrine in the brain may be helpful

in reducing dose, frequency of dosing and dose-dependent side effects. Starting from these data and in order to increase brain bioavailability, a mucoadhesive microemulsion of tacrine was prepared and characterized. The mentioned microemulsion formulation contained a mucoadhesive substance, which favored adhesion to the mucous membranes lining the nasal mucosa and improved drug targeting to the CNS [146]. The results demonstrated rapid and larger extent of transport of tacrine into the mice brain and fastest regain of memory loss in scopolamine-induced amnesic mice after intranasal administration of tacrine microemulsion.

3.3.5 17β-Estradiol

To overcome the low estradiol water solubility (0.008 mg/ml), making feasible the nasal administration of an effective dose (i.e., 0.1 mg in a volume of 0.1 ml), four water-soluble prodrugs have been proposed [147]. They are three phenolic esters, 3-*N*,*N*-dimethylamino butyl ester hydrochloride, 3-*N*,*N*-diethylamino propionyl ester hydrochloride and 3-*N*,*N*,*N*-trimethylamino butyl ester iodide, and one alcoholic ester, 17-*N*,*N*-dimethylamino butyl ester hydrochloride. All of these were significantly more soluble than 17β-estradiol, but only the alcoholic prodrug was found to be chemically stable. Moreover, the rat CSF concentration of estradiol following nasal administration of this compound was higher than that following intravenous administration. These preclinical data suggest that the drug can reach the CSF via a direct pathway through the nasal cavity and that the nasal spray solution is the best formulation for this ester.

Another preclinical attempt to improve the estradiol solubility was encapsulation in chitosan nanoparticles (final concentration 2 mg/ml) [148]. Microdialysis studies showed that estradiol levels in rat CSF administered with estradiol by means of the nasal route (C_{max} 76.4 ± 14.0 ng/ml and AUC 12788.4 ± 4093.6 ng min/ml) were significantly higher than those obtained after i.v. injection, despite the much lower estradiol concentrations in rat plasma after nasal route administration with respect to those measured after i.v. injection. It has been seen that chitosan behaves as a bioadhesive material and binds strongly to the negatively charged mucin through electrostatic interactions, thus increasing significantly the half-time of clearance of estradiol.

3.4 Nanotechnology-based drug delivery systems

A great contribution to the improvement of the therapies for neurodegenerative diseases is expected with the application of nanotechnology to the pharmaceutical sciences. Targeting and localized delivery are key challenges in AD therapy because they allow severe side effects deriving from the distribution of any actives in healthy tissues to be limited. In recent years there has been increasing interest in developing drug delivery systems able to target pharmacologically active molecules near their site of action. Among these, liposomes, polymeric or lipidic micro- and nanoparticles, polymeric micelles, and dendrimers seem to be the most effective for interacting with biological systems at molecular level with a high degree of specificity [149]. Nanotechnology devices take advantage of their tunable size, increased suspendability, and surface tailorability that allows the selective conjugation of active compounds with ligands showing a high affinity to the BBB, and show promise in overcoming the restrictions imposed by the BBB [150,151]. However, there continues to be concern regarding the biocompatibility of nanotechnology-based drug delivery systems, especially in a complex biological milieu such as the brain and the potential dangers associated with their use therein [152]. Both biodegradable and non-biodegradable nanotechnology devices interacting with the surrounding tissue and binding to tissue carriers can trigger dangerous allergic-type immune reactions [153,154]. However, several polymers have been shown to be non-mutagenic, non-cytogenic and non-teratogenic and safe for administration if properly sterilized. Nanotechnology in neurology will dramatically affect the ability to specifically target drugs beyond the BBB, to develop potential regenerative therapies and engineer new advanced diagnostic tools for early diagnosis of the disease. Despite the encouraging promises, none of the nanotechnology-based drug delivery systems reviewed in the following subsections is approved for use in AD patients.

3.4.1 Donepezil

Donepezil has been encapsulated in PLGA microparticles for the design of a controlled drug delivery system. The microparticles were prepared by an oil-in-water emulsion solvent evaporation technique [155]. The results obtained from the *in vitro* release experiments carried out in three different media (water, phosphate buffer solution [PBS] at pH 5.8 and PBS at pH 7.4) showed a release of 98.4 and 49.1% for PBS at pH 5.8 and 7.4, respectively, up to day 30, whereas donepezil-loaded microparticles, injected by subcutaneous infusion in rats, were able to achieve a sustained release of the active in accordance with that of free donepezil by the oral application route (3 mg/day). Although the *in vivo* release mechanism remains to be fully understood and further investigations are needed to characterize completely the *in vivo* behavior of the formulation, the experimental data indicate that donepezil-loaded microparticles might represent a valid means to obtain a sustained drug delivery system requiring only once a month administration.

3.4.2 Physostigmine

To prolong its short half-life (12 – 40 min), physostigmine has been formulated in PLGA microparticles by the spray drying technique [156]. The new physostigmine formulation has been characterized for its *in vitro* release profile, which was biphasic in nature with an initial burst release followed by a sustained release over 1 week. When administered in rats orally, the physostigmine-loaded microparticles were able to prolong the drug half-life to 18 – 23 h and hence allowed higher AUC to be achieved, probably protecting the

sensitive drug from the enzymatic degradation or improving its absorption.

3.4.3 Rivastigmine

Polysorbate 80-coated poly(n-butylcyanoacrilate) nanoparticles have been formulated by the emulsion polymerization method to target selectively rivastigmine to the CNS [157]. *In vitro* the particles released rivastigmine with a biphasic pattern, characterized by an initial burst effect within 30 min followed by sustained release over a period of 24 h. *In vivo* tests were conducted on rats after intravenous injection of free drug, drug-loaded poly(n-butylcyanoacrylate) nanoparticles and drug-loaded poly(n-butylcyanoacrylate) nanoparticles coated with 1% polysorbate 80. A slight increase of rivastigmine concentration was observed for uncoated nanoparticles compared with the free drug (54.8 ± 3.4 ng/ml versus 44.8 ± 3.7 ng/ml). It has been demonstrated that uncoated rivastigmine-loaded nanoparticles are captured by the reticuloendothelial system (RES) and that particles continue to release the drug into the bloodstream, resulting in elevated plasma and brain levels of rivastigmine. The coating with 1% polysorbate 80 of the nanoparticles increased the concentrations of rivastigmine in the brain 3.82-fold when compared with the free drug, indicating potential selective targeting to the CNS.

Taking advantage of the surface tailorability of polymeric nanoparticles, long circulating particles (i.e., PEGylated nanoparticles) have been formulated for rivastigmine delivery as either free base or tartrate salt. The new formulations have been realized by means of the reverse-phase microemulsion technique, the UV irradiation and photo-crosslinked copolymers technique, and by using poly(hydroxyethylaspartamide methacrylate) and PEGylated poly(hydroxyethylaspartamide methacrylate) as copolymers [158]. *In vitro* studies showed that the release profile was affected by the drug loading procedure and the particles' formulation technique. Besides, the rate of release depended on the drug nature (salt or free base) being faster for the tartrate salt and slower for the free base, probably owing to the lower solubility in the aqueous medium of the latter form. *In vitro* biological tests demonstrated the cell compatibility of these delivery systems and their ability to escape from phagocytosis, although *in vivo* evaluations of these formulations have still to be performed.

3.4.4 Tacrine

One of the first nanotechnology-based systems formulated for the treatment of AD was microparticles containing tacrine because its clinical use has been limited owing to associated cholinergic, hepatic and gastrointestinal adverse effects [159]. The aim of the study was to deliver tacrine for a prolonged period of time at a controlled lower concentration with respect to the conventional oral formulation, to reduce hepatic toxicity and bypass the gastrointestinal route [160]. Tacrine-loaded microparticles were formulated by means of the emulsion solvent evaporation procedure and using PLGA of different molecular mass as the polymer, and polyvinyl alcohol (PVA) as the surfactant. *In vitro* studies showed that the release of tacrine from the miscrospheres was strictly dependent on the molecular mass of the polymer. In particular, the higher the molecular mass of the polymer used for the preparation, the lower the rate of drug release. Furthermore, the study suggested that the kinetics of tacrine release from the microspheres was a combination of diffusion and erosion. Despite the promising *in vitro* results, the *in vivo* studies have not been performed yet.

Tacrine has also been encapsulated in magnetic chitosan microparticles of a biodegradable polymer shell containing a magnetic nucleus with the aim of favoring transport of the active to a specific site by means of an external magnetic field [161]. Tacrine brain concentrations have been evaluated after intravenous injection in rats. Despite the magnetic chitosan microparticles increasing the concentrations of tacrine in the brain 5.38-fold when compared with the free drug, tacrine was also found in non-target organs such as liver, spleen and lungs, probably because of phagocytosis of these microdevices by the RES [162]. Tacrine has been also encapsulated in polysorbate 80-coated poly(n-butylcyanoacrylate) nanoparticles by the emulsion polymerization technique [163]. After intravenous injection of tacrine-loaded polysorbate 80-coated nanoparticles, a 4.07-fold increase in tacrine brain concentration was observed with respect to the free drug, thus confirming the ability of polysorbate 80-coated nanoparticles to target the delivery system to the brain.

3.4.5 Nicotine

The potential effect of nicotine to delay the onset of AD has stimulated research on its prospective neuroprotective effects. Several delivery systems have been designed to modulate the delivery of nicotine, such as transdermal patches or intranasal spray. The challenge was to formulate a new system that accomplished only its peripheral and therefore beneficial effects at the CNS level. Therefore, nicotine has been encapsulated by Singh and co-workers into PLA-PLGA microparticles subsequently reincorporated into a crosslinked zinc-alginate-pectinate polyspheric multiparticulate system [164]. As a matter of fact, the *in vitro* release of nicotine from non-reincorporated PLA-PLGA microparticles demonstrated that ~ 100% of the drug was released within the first 30 min, probably owing to the high porosity of the particles. The double-incorporation into a crosslinked zinc-alginate-pectinate system was therefore designed to restrict the rapid diffusion of the drug. The new zinc-alginate-pectinate platform had a high degree of crosslinking, leading to better drug encapsulation and slower drug release. Despite the prospective targeting to the CNS that this formulation promises, further studies, in particular *in vivo* tests, are necessary for the evaluation of the features of this innovative drug delivery system.

3.4.6 *Metal chelators*

Although the etiology of AD is not well understood, there is evidence that oxidative stress is one of the most important risk factors. Oxidation reactions are catalyzed by transition metals such as iron and copper ions [165]; in particular, aluminum(III) has been found in high concentration in both senile plaques and intraneuronal NFTs in the brains of subjects with AD [166-168]. Therefore, chelation therapy is a relatively new approach for the treatment of AD, which aims to reduce oxidative stress and the subsequent neurodegeneration. Unfortunately, the use of chelators has been limited by their toxicity and poor ability in crossing the BBB. In this regard, nanoparticles able to cross the BBB have been formulated for chelator delivery [169]. To be effective in preventing oxidative damage, a chelator agent must be also able to re-cross the BBB once complexed with the metal ion. This goal can be achieved by covalent conjugation of metal chelators to nanoparticles, thanks to the particles' surface modifiability [170]. Monodispersed polystyrene particles have been used to conjugate 2-methyl-*N*-(3′-aminopropyl)-3-hydroxyl-4-pyridinone (MAPHP), which has high affinity for iron, aluminum, copper and zinc ions, and desferioxamine (DFO), which is the only chelator drug approved by the FDA for iron overload. The conjugation did not alter the chelator metal binding ability, and the systems had the potential to cross the BBB and drain excess metals out of the brain, thus protecting against neurodegeneration. Nevertheless, further studies are necessary, in particular to evaluate system toxicity.

The same approach has been also used for the conjugation of D-penicillamine, a copper(I) chelator approved by the FDA for the treatment of Wilson's disease, to 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[4-(*p*-maleimidophenyl) butyramide] (sodium salt) (MPB-PE) and 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[3-(2-pyridyldithio)-propionate] (sodium salt) (PDP-PE) nanoparticles by means of a disulfide or thioether bond [171]. As D-penicillamine is too hydrophilic to cross the BBB and is eliminated rapidly from the blood, D-penicillamine has been conjugated to nanoparticles in order to prolong its half-life and enhance its brain uptake. *In vitro* studies proved that D-penicillamine can be released from the nanoparticles under reducing conditions, and that the free drug is effective in solubilizing copper (I)-Aβ(1 – 42) aggregates. Nevertheless, *in vivo* studies confirming the selective targeting of the chelator to the CNS have not been carried out yet.

4. Expert opinion

Alzheimer's disease is an age-dependent multifactorial neurodegenerative disorder that gradually and subtly impairs memory and cognition in the geriatric population. It has become clear that the processes underlying the pathology involve genetic, environmental and endogenous factors, and that these are the pharmacological targets on which researchers need to focus their attention for the prevention and/or cure of AD. Despite the progress in research, successful treatment of neurodegeneration associated with AD remains elusive and at present the mainstay of current management of AD patients involves drugs that provide only symptomatic therapy (**Table 3**). These agents belong to the following major classes: cholinesterase inhibitors (donezepil, tacrine, galantamine, physostigmine, rivastigmine and phenserine), cholinergic agonists (nicotine) and NMDA receptor antagonists (memantine). The advent of new research on molecular mechanisms of AD pathogenesis has outlined new strategies for therapeutic intervention; these include the stimulation of α-secretase cleavage, the inhibition of γ-secretase activity, the use of non-steroidal anti-inflammatory drugs, neuroprotection based on antioxidant therapy, the use of estrogens, NO synthetase inhibitors, and natural agents such as polyphenols. Unfortunately, these compounds might not help patients with end stage AD, but might hopefully slow or stop the disease process in its early stage.

The management of medical problems can be more complex in patients with AD than in other patients. As concurrent medical conditions are common in older adults, individuals with AD typically are forced to take several medications and, thus, adherence to AD treatments is usually low. Simplifications of drug regimen dosage, which may reduce the daily AD medication administrations and may exploit friendly modes of administration, are key factors to consider when improvements in treatment compliance are desired. Even if oral once daily medications seem to offer many advantages by simplifying drug regimens, important achievements have been reported with alternative devices for drug delivery, such as transdermal patches, which may decrease caregiver stress and, in turn, have a favorable impact on patients' conditions. Moreover, i.n. delivery is an effective alternative to invasive delivery methods, with the advantage of achieving rapid targeting of the drugs to the CNS. Finally, a great contribution to the improvement of AD treatments may arise from the use of nanotechnologies. In particular, targeting and localized delivery by means of drug carrier nano- or microsystems, limiting the side effects of anti-Alzheimer drugs, seems effective at improving AD management. Unfortunately, nanotechnology-based drug delivery systems are still affected by poor stability in the biological milieu, rapid enzymatic degradation, and unfavorable pharmacokinetic properties. According to actual trends, many of the approaches mentioned above have realistic chances of becoming established as therapeutic routine in AD if: i) the potential dangers associated with these new drug delivery systems in humans are well understood; and ii) the social benefits derived from their application outweigh the production costs.

On the other side, as dementia of the Alzheimer's type may be viewed as the final step of a long-lasting pathologic process spanning decades, in order to realize a successful disease-modifying therapy, diagnosis at an early stage of the disease is essentially required. In fact, trying to cure AD in the later stages may not be feasible owing to the difficulties in reversing

Table 3. Traditional drugs and new delivery system for treatment of Alzheimer's disease.

Drug	Dosage	Trade name (manufacturer)	Studies	Details	Ref.
Conventional oral delivery					
Donepezil	5 or 10 mg	Aricept®, Pfizer	Marketed	Once daily tablets for conventional oral delivery of donepezil hydrochloride	[19]
Galantamine	4, 8 or 12 mg	Razadyne®, Ortho-McNeil Neurologics	Marketed	Circular biconvex film-coated immediate-release tablets of 4 mg (off-white), 8 mg (pink) and 12 mg (orange-brown). The starting dose is 4 mg twice a day (8 mg/day) and can be increased to 8 mg twice a day after 4 weeks; a further increase to 12 mg twice a day should be attempted after a minimum of 4 weeks at 8 mg twice a day	[25]
	4 mg/ml	Razadyne®, Ortho-McNeil Neurologics	Marketed	Oral solution for conventional delivery of galantamine hydrobromide	[25]
Rivastigmine	1.5, 3, 4.5 or 6 mg	Exelon®, Novartis	Marketed	Capsules for conventional oral delivery of rivastigmine tartrate of 1.5 mg (yellow), 3 mg (orange), 4.5 mg (red) and 6 mg (orange and red). The starting dose of Exelon is 1.5 mg b.i.d. After a minimum of 2 weeks of treatment, the dose may be increased to 3 mg b.i.d. Subsequent increases to 4.5 mg b.i.d. and 6 mg b.i.d. should be attempted after a minimum of 2 weeks at the previous dose	[23]
	2 mg/ml	Exelon®, Novartis	Marketed	Oral solution for conventional delivery of rivastigmine tartrate	[23]
Memantine	5 or 10 mg	Namenda®, Forest Pharmaceuticals	Marketed	Film-coated tablets for conventional oral delivery of memantine hydrochloride. The starting dose is 5 mg once daily, the target dose is 20 mg/day	[57]
	2 mg/ml	Namenda®, Forest Pharmaceuticals	Marketed	Oral solution for conventional delivery of memantine hydrochloride	[57]
Oral and buccal unconventional drug delivery systems					
Donepezil	23 mg	Aricept®, Pfizer	Marketed	Film-coated tablets for sustained release of donepezil hydrochloride	[19]
	5 or 10 mg	Aricept® ODT, Pfizer	Marketed	Once a day orally disintegrating tablets that dissolve on the tongue for patients who find it difficult to swallow conventional oral forms	[19]
	5 mg	–	Preclinical	ODTs in which domepezil hydrochloride is encapsulated in Eudragit® EPO microspheres for improved tablets palatability	[43]
Galantamine	8, 16 or 24 mg	Razadyne® ER, Ortho-McNeil Neurologics	Marketed	Hard gelatin ER capsules. Each capsule contains 25% of dose in an immediate release form and 75% of dose in a controlled release form	[25]
	–	–	Preclinical	Drug delivery oral device to be implanted into the oral cavity, built onto a prosthetic tooth crown or embedded inside a denture for remote-controlled transbuccal delivery of galantamine hydrobromide	[54]

AD: Alzheimer's disease; b.i.d.: Twice a day; DFO: Desferioxamine; ER: Extended release; i.n.: Intranasal; MAPH: 2-methyl-*N*-(3'-aminopropyl)-3-hydroxyl-4-pyridinone; ODTs: Orally disintegrating tablets.

Table 3. Traditional drugs and new delivery system for treatment of Alzheimer's disease (continued).

Drug	Dosage	Trade name (manufacturer)	Studies	Details	Ref.
Physostigmine	4% w/w of the tablet weight	–	Preclinical	Formulation optimization of physostigmine salicylate tablet with suitable physical and chemical characteristics for sublingual delivery of the active	[56]
Memantine	28 mg	Namenda XR®, Forest Pharmaceuticals	Marketed	Capsules containing extended release beads for once a day administration of memantine hydrochloride	[57]
Transdermal delivery and injectable depot-forming systems					
Rivastigmine	9 or 18 mg	Exelon®, Novartis	Marketed	Transdermal patch able to deliver rivastigmine by means of a matrix diffusion-controlled kinetic	[72]
	5% (w/w)	–	Preclinical	Oleogels containing rivastigmine free base or hydrogen tartrate as *in situ* forming implants for long-term drug delivery	[87]
Galantamine	–	–	Preclinical	Microneedle patch able to alter the barrier property of the skin and improve the galantamine permeation across the skin	[89]
Physostigmine	30 and 60 mg	–	Preclinical	Study on physostigmine transdermal patch with the aim of overcoming the problems associated with oral and intravenous application	[90]
Phenserine	10% w/w of the lyogel	–	Preclinical	Phenserine-loaded lyogel containing penetration enhancers for improving the drug permeability through the stratum corneum	[59]
Tacrine	–	–	Preclinical	Tacrine-loaded ion-exchange devices for percutaneous administration of the active by means of iontophoresis system	[97]
Nicotine	36, 75 or 114 mg	Nicoderm®, Alza, US	Marketed (not approved for AD therapy)	Reservoir transdermal patch for nicotine-controlled delivery	[101-103]
	8.3, 16.6 or 24.9 mg	Nicotrol®, Kabi Pharmacia, Sweden	Marketed (not approved for AD therapy)	Polymer-matrix drug dispersion patch for nicotine-controlled delivery	[101,104]
Estradiol	4 or 8 mg	Estraderm®, Novartis	Marketed (not approved for AD therapy)	Drug reservoir transdermal patch for estradiol delivery	[115]
Nasal route					
Galantamine lactate	35 – 80 mg/ml	–	Preclinical	Galantamine lactate co-formulated with several penetration enhancers for i.n. delivery	[138,139]
Physostigmine analogue (NXX-006)	6.4 mg/ml	–	Preclinical	Chemically modified physostigmine for improved i.n. bioavailability	[143]
Rivastigmine	–	–	Preclinical	Rivastigmine encapsulated in conventional liposomes to be delivered intranasally	[144]
Tacrine microemulsion	–	–	Preclinical	Mucoadhesive microemulsion containing tacrine for improving drug targeting to the CNS via i.n. administration	[146]

AD: Alzheimer's disease; b.i.d.: Twice a day; DFO: Desferioxamine; ER: Extended release; i.n.: Intranasal; MAPH: 2-methyl-*N*-(3′-aminopropyl)-3-hydroxyl-4-pyridinone; ODTs: Orally disintegrating tablets.

Table 3. Traditional drugs and new delivery system for treatment of Alzheimer's disease (continued).

Drug	Dosage	Trade name (manufacturer)	Studies	Details	Ref.
Estradiol	–	–	Preclinical	Chemically modified estradiols (prodrugs) with improved water solubility for improved i.n. delivery	[147]
	0.1 mg/kg 2 mg/ml	–	Preclinical	Estradiol encapsulated in chitosan nanoparticles for improving nasal adsorption and brain targeting	[148]
Nanotechology-based drug delivery systems					
Donepezil	–	–	Preclinical	Donepezil-loaded PLGA microparticles to be injected by subcutaneous infusion and releasing the active for up to 30 days	[155]
Physostigmine	–	–	Preclinical	PLGA microparticles encapsulating physostigmine able to prolong the drug half-life	[156]
Rivastigmine	–	–	Preclinical	Polysorbate 80 poly(n-butylcyanoacrilate) nanoparticles to selectively target rivastigmine to the CNS	[157]
	–	–	Preclinical	Long-circulating nanoparticles for improving rivastigmine half-life	[158]
Tacrine	–	–	Preclinical	PLGA microparticles for tacrine-controlled release	[160]
	–	–	Preclinical	Chitosan-coated magnetic microparticles to be targeted by means of an external applied magnetic field	[161]
	–	–	Preclinical	CNS targeted poly(n-butylcyanoacrylate) nanoparticles	[163]
Nicotine	–	–	Preclinical	Double encapsulation of nicotine in PLA-PLG/crosslinked zinc-alginate-pectinate microsphere	[164]
MAPHP and DFO	–	–	Preclinical	Neuroprotectant polystyrene nanoparticles bearing surface-conjugated metal chelators	[169]
D-penicillamine	–	–	Preclinical	D-penicillamine conjugated to lipidic-matrix nanoparticles for copper(I) brain accumulation therapy	[171]

AD: Alzheimer's disease; b.i.d.: Twice a day; DFO: Desferioxamine; ER: Extended release; i.n.: Intranasal; MAPH: 2-methyl-*N*-(3′-aminopropyl)-3-hydroxyl-4-pyridinone; ODTs: Orally disintegrating tablets.

late phases of the neurodegenerative process. Thus, preventive approaches starting at least several years before the age of onset of clinical symptoms could represent an important strategy if combined with curative treatments; in this case, the progressive neurodegeneration may be functionally reversible, at least up to a certain degree.

Until disease-modifying therapies become available, however, it is undoubtedly necessary to continue the drug delivery mission in developing strategies for an effective brain targeting of symptomatic AD drugs, as the knowledge gained in this regard will be the starting point for the development of delivery strategies of disease-modifying molecules.

Declaration of interest

A Di Stefano, A Iannitelli, S Laserra and P Sozio declare no conflict of interest and have received no payment in preparation of this manuscript.

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