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REVIEW ARTICLE

Overcoming Therapeutic Barriers in Alzheimer's Disease: From Nanotechnology to Microneedles

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SUMMARY

Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which effective pharmacological treatment remains challenging, partly because of the complex disease pathology and the restrictive nature of the blood–brain barrier (BBB). Conventional therapeutic approaches are further limited by unfavorable pharmacokinetic profiles, systemic adverse effects, and treatment-adherence difficulties. Nanotechnology-based drug delivery systems (NDDS) have emerged as promising strategies to address these limitations by improving drug solubility and stability, enabling controlled release, and enhancing drug accumulation in the brain. This review discusses major approaches investigated for BBB-targeting strategies, including optimization of particle size and surface charge, PEGylation, surfactant-mediated transport, and ligand-mediated targeting. It also highlights microneedle (MN)-based delivery as a minimally invasive alternative capable of overcoming the stratum corneum and facilitating systemic administration of therapeutic agents. The integration of nanocarriers into microneedle systems represents an emerging strategy that combines the advantages of transdermal delivery with the controlled-release and brain-targeting potential of NDDS. Recent studies demonstrate encouraging improvements in drug bioavailability, brain accumulation, and therapeutic outcomes; however, evidence for nanocarrier-integrated MN systems in AD remains very limited. Overall, combining nanotechnology, BBB-targeting strategies, and microneedle-based delivery offers a promising framework for overcoming multiple therapeutic barriers in AD and warrants further investigation toward clinical treatment platforms.

Keywords: *Alzheimer's disease, drug delivery system, microneedle, nanotechnology, transdermal administration*

Alzheimer Hastalığında Terapötik Engellerin Aşılması: Nanoteknolojiden Mikroiğnelere

ÖZ

Alzheimer hastalığı (AH), karmaşık patolojisi ve kan-beyin bariyerinin (KBB) kısıtlayıcı yapısı nedeniyle etkili farmakolojik tedavisi hâlâ güç olan ilerleyici bir nörodejeneratif hastalıktır. Ayrıca, geleneksel tedavi yaklaşımları farmakokinetik profiller, sistemik advers etkiler ve tedaviye uyum güçlükleri nedeniyle sınırlı kalmaktadır. Nanoteknoloji temelli ilaç taşıyıcı sistemler (NİTS), ilaç çözünürlüğünü ve stabilitesini iyileştirerek, kontrollü salım sağlayarak ve ilacın beyinde birikimini artırarak bu sınırlılıkların aşılmasında umut vadeden stratejiler olarak öne çıkmaktadır. Bu derlemede partikül boyutu ve yüzey yükünün optimizasyonu, PEGilasyon, yüzey aktif madde aracılı hedefleme ve ligand aracılı hedefleme yöntemleri KBB'yi hedeflemeye yönelik başlıca yaklaşımlar olarak ele alınmaktadır. Ayrıca, stratum korneumu aşabilen ve terapötik ajanların sistemik uygulanmasını kolaylaştıran minimal invaziv bir alternatif olarak mikroiğne (Mİ) temelli uygulamalar üzerinde durulmaktadır. Nanotaşıyıcıların Mİ sistemlerine entegrasyonu, transdermal uygulamanın avantajlarını NİTS'lerin kontrollü salım ve beyin hedefleme potansiyeli ile birleştiren yeni bir stratejidir. Güncel çalışmalar ilaç biyoyararlanımı, beyin birikimi ve terapötik sonuçlar açısından umut verici gelişmeler ortaya koymaktadır. Ancak AH'da nanotaşıyıcı entegre Mİ sistemlerine ilişkin kanıtlar oldukça sınırlıdır. Sonuç olarak nanoteknoloji, KBB hedefleme stratejileri ve Mİ temelli uygulamaların bir arada kullanımı, AH'daki çoklu terapötik engellerin aşılması için umut verici gelişmeler sunmakta ve klinik tedavi uygulamalarına yönelik ileri araştırmalar gerektirmektedir.

Anahtar Kelimeler: *Alzheimer hastalığı, ilaç taşıyıcı sistem, mikroiğne, nanoteknoloji, transdermal uygulama*

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INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide, accounting for 60–80% of all dementia cases (Rajasekhar & Govindaraju, 2018; Alzheimer's Association, 2026). Global dementia prevalence is approximately 50 million and is projected to triple by 2050, driven by aging populations and longer life expectancies (Kim et al., 2024; Rajasekhar & Govindaraju, 2018; Tryphena, Shukla, Khatri, & Vora, 2024). AD is the seventh leading cause of death, while caring for AD patients places a tremendous physical and financial strain on families and caregivers, often requiring long-term support (Bice, Nho, Ertekin-Taner, & Saykin, 2026; World Health Organization, 2026). The intensifying prevalence in low- and middle-income countries further heightens the urgency for cost-effective treatments (Kim et al., 2024).

Although its etiology remains incompletely understood, several hypotheses have been proposed to explain its underlying pathogenesis. AD is defined by extracellular β-amyloid (Aβ) plaques and intracellular hyperphosphorylated tau neurofibrillary tangles (Lo Vecchio, La Torre, Gravina, D'Onofrio, & Greco, 2026). The amyloid cascade hypothesis posits that abnormal Aβ deposition triggers neuroinflammation, oxidative stress, and synaptic dysfunction (Dominguez-Gortaire, Ruiz, Porto-Pazos, Rodriguez-Yanez, & Cedron, 2025). According to the tau hypothesis, pathological tau alterations promote aggregation into neurofibrillary tangles, contributing to neuronal dysfunction and cell loss (Atoki, Aja, Ondari, & Shinkafi, 2023). In parallel, the neuroinflammation hypothesis proposes that inflammatory responses in the brain, characterized by increased cytokines and chemokines, can lead to neuronal damage and cognitive decline (Wong-Guerra, Calfio, Maccioni, & Rojo, 2023). On the other hand, growing evidence indicates that mitochondrial dysfunction plays a critical role in AD pathogenesis (Lo Vecchio et al., 2026). Collectively, these hypotheses highlight the complex and multifactorial nature of AD while identifying promising molecular pathways that may serve as targets for future therapeutic strategies.

CURRENT THERAPEUTIC APPROACHES

AD Treatments

Despite more than a century of research since Alois Alzheimer first described the disease in 1907, the development of therapies capable of modifying or reversing disease progression remains a major challenge (Hein et al., 2025; Lane, Hardy, & Schott, 2018; Liu, Zhang, & Wang, 2024). AD treatment relies on symptomatic medications that aim to temporarily improve or stabilize cognitive function, behavioral symptoms, and daily activities without directly targeting the underlying neuropathological processes.

Currently, the principal pharmacological options are acetylcholinesterase inhibitors (AChEIs), donepezil, galantamine, and rivastigmine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (Tan et al., 2014). AChEIs enhance cholinergic neurotransmission by reducing the enzymatic degradation of acetylcholine and are predominantly used in mild-to-moderate AD, whereas memantine modulates excessive glutamatergic neurotransmission and is generally used in moderate-to-severe stages of the disease (Majidazar, Rezazadeh-Gavgani, Sadigh-Eteghad, & Naseri, 2022; National Institute on Aging, 2025).

Recent advances in the understanding of AD pathophysiology have shifted therapeutic development beyond symptomatic management toward disease-modifying strategies that target the biological processes underlying neurodegeneration. Among these approaches, Aβ monoclonal antibodies have achieved the greatest clinical progress. Lecanemab and donanemab are disease-modifying monoclonal antibodies developed for patients with early symptomatic AD and confirmed amyloid pathology (Cummings, Osse, Cammann, Powell, & Chen, 2024). In parallel, emerging strategies include tau-targeting antibodies and vaccines, inhibitors of tau aggrega-

tion, modulators of neuroinflammation and microglial activity, APOE-directed therapies, metabolic and mitochondrial interventions, and approaches aimed at restoring synaptic function (Bajinka, Jallow, & Ozdemir, 2026). Gene and RNA-based strategies, including antisense oligonucleotides and other nucleic-acid therapeutics, are also being investigated (Anthony, 2022; Bevins et al., 2026).

Therapeutic Barriers in AD

The therapeutic effectiveness of AD drugs depends on achieving sufficient drug concentration in the brain while maintaining acceptable side effects (Wu et al., 2023). These requirements are challenged by the restrictive properties of the BBB, drug-specific pharmacokinetic limitations, and the clinical complexity of an ageing population with progressive cognitive impairment. Understanding these interacting barriers is essential for designing delivery systems that translate pharmacological activity into sustained therapeutic benefit.

The Blood-Brain Barrier: The Principal Delivery Obstacle

The BBB constitutes the principal barrier to drug transport from the systemic circulation into the brain. Its anatomical structure consists of specialized brain microvascular endothelial cells connected by tight junctions, which restrict paracellular diffusion. In addition to this physical restriction, efflux transporters can return drugs to the circulation, while metabolic enzymes provide an additional biochemical barrier. Consequently, systemic drug availability does not necessarily translate into sufficient exposure within the brain (Kadry, Noorani, & Cucullo, 2020; Wu et al., 2023).

Drug physicochemical characteristics strongly influence BBB permeability. Small lipophilic molecules with molecular weights below 400 Da and the capacity to form fewer than eight hydrogen bonds generally exhibit favorable characteristics for passive diffusion across the BBB (Pardridge, 2015). Larger therapeutic agents, including antibodies and nucleic acids, require specialized transport or delivery strategies (Wu et al., 2023). Molecular charge also affects transport: the non-ionized fraction of a compound generally crosses lipid membranes more readily than its ionized fraction (Banks, Rhea, Reed, & Erickson, 2024).

Clinical and Patient-Related Barriers

Advanced age adds substantial variability to AD pharmacotherapy. Age-associated changes in body composition, renal function, and hepatic clearance can alter drug distribution and elimination, requiring more careful dose adjustment (Turnheim, 2003). Coexisting chronic conditions also frequently necessitate polypharmacy, increasing regimen complexity and the potential for drug–drug interactions and potentially inappropriate prescribing (Zhao, Chen, Xu, Fan, & Tian, 2023).

Progressive memory impairment also compromises patients' ability to organize medications, follow dosing schedules, and sustain independent treatment administration (El-Saifi, Moyle, Jones, & Tuffaha, 2018). Also, swallowing difficulties may emerge during the earlier stages of AD and become more pronounced as the disease progresses. Dysphagia presents an additional obstacle to oral administration of solid dosage forms in the elderly population (Mira, Gonçalves, & Rodrigues, 2022). Gastrointestinal adverse effects can interfere with dose escalation and contribute to treatment discontinuation (Alva & Cummings, 2008).

AD treatments are also associated with several important side effects. AChEIs frequently cause gastrointestinal adverse effects, particularly nausea and vomiting, which can contribute to treatment discontinuation. The use of memantine can also cause adverse effects such as dizziness, confusion, constipation, and vomiting (Raina et al., 2008). Conventional oral pharmacotherapy often requires multiple daily doses, which can contribute to poor adherence in patients with cognitive impairment (Varadharajan et al., 2023).

Taken together, these barriers support the development of delivery strategies that combine appropriate systemic exposure, improved brain targeting, acceptable tolerability, and practical long-term administration.

NANO DRUG DELIVERY SYSTEMS (NDDS) IN AD

Nanotechnology-based drug delivery systems (NDDS) provide novel methods of addressing several pharmaceutical and biological barriers relevant to AD, as mentioned previously. By incorporating therapeutic agents into NDDS, their stability, release profiles, pharmacokinetics, and biological distribution can be modified. These properties are particularly important in AD, where therapeutic efficacy depends not only on pharmacological activity but also on achieving sufficient and sustained drug concentration within the central nervous system (Mazahir, Alam, & Yadav, 2024; Mitchell et al., 2021)

General Advantages of NDDS

One of the main advantages of NDDS is their ability to improve the formulation of therapeutically challenging compounds. Encapsulation into lipid-, polymer-, or other NDDS can facilitate the delivery of poorly water-soluble drugs and protect chemically or biologically labile molecules from premature degradation (Tutubala, Egunlusi, Fisher, Dube, & Joubert, 2025). For example, Zhang et al. (2020) encapsulated poorly soluble and unstable curcumin in chitosan-coated PLGA nanoparticles (Zhang, Yang, Wong, Xie, & Ho, 2020), while Neves et al. (2017) employed ApoE-functionalized solid lipid nanoparticles to protect resveratrol from degradation and enhance its brain delivery (Neves, Queiroz, Lima, & Reis, 2017).

For established small-molecule therapeutics used in AD, NDDS formulation may improve pharmacokinetic and delivery characteristics beyond those of the free drug. For example, PLGA nanoparticles provided sustained release and increased brain exposure of donepezil, while mesoporous silica nanoparticles prolonged the systemic residence of rivastigmine and enhanced its brain delivery in preclinical models (Bhavna et al., 2014; Pandey et al., 2018).

Rivastigmine-loaded mucoadhesive polymeric nanoparticles provided sustained drug release compared with the free drug solution and increased brain drug concentrations following intranasal administration (Kalra, Silakari, & Tiwary, 2025). Similarly, donepezil-loaded nanostructured lipid carriers exhibited a biphasic release profile followed by sustained release and significantly enhanced brain bioavailability; after intranasal administration, brain AUC was reported to be 10.5-fold higher than that obtained after intravenous administration of free donepezil (Souza et al., 2026). These findings illustrate how NDDS design can simultaneously modulate drug-release behavior and pharmacokinetic disposition, potentially maintaining therapeutically relevant concentrations for longer periods and improving drug availability at the intended site.

Nevertheless, these effects remain highly dependent on the composition, physicochemical characteristics, and route of administration of the specific formulation. Importantly, however, encapsulation within an NDDS provides opportunities to improve brain delivery, but does not confer efficient BBB permeability, and additional targeting strategies are generally required to promote productive interactions with BBB transport pathways (Roamcharern & Yubolphan, 2026).

BBB Targeting Strategies

Physicochemical Modification

NDDSs' physicochemical characteristics influence their ability to cross the BBB. Modifying NDDS size, surface charge, and morphology can improve brain accumulation (Liu, Wang, Dong, & Lu, 2025). Particle size is a critical factor in the *in vivo* fate of NDDS and their ability to cross the BBB. Generally, particles <200 nm are transported across the BBB better than larger NPs (Roamcharern & Yubolphan, 2026). The influence of particle size on brain delivery was demonstrated using surface-modified PLGA

nanoparticles, with 60-nm particles achieving greater cerebral accumulation than larger counterparts, supporting the potential advantage of smaller nanocarriers for BBB transport (Figure 1.) (Meng et al., 2022).

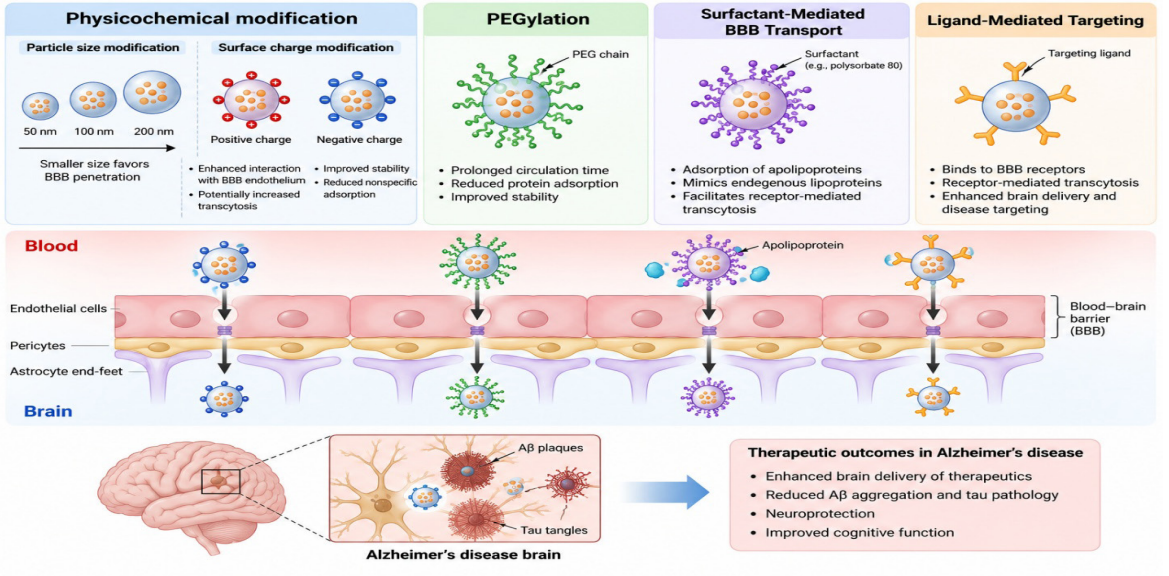

Figure 1. Schematic representation of BBB-targeting strategies in Alzheimer's treatment (generated with AI)

The surface charge of NDDS strongly influences their interaction with the negatively charged brain endothelial cells. Positively charged nanoparticles can enhance electrostatic interactions with the BBB. Cationic polymers have been evaluated to enhance brain delivery. For example, intranasal administration of rivastigmine-loaded chitosan nanoparticles resulted in substantially greater brain drug concentrations than free rivastigmine (Fazil et al., 2012). However, strongly positive surfaces may increase membrane disruption and cytotoxicity. Near-neutral or moderately charged surfaces may offer a more favorable balance between systemic stability and BBB interaction (Kochman et al., 2026). Liao et al. (2012) showed that the negative surface charge of gold nanoparticles (AuNP) was crucial for their interaction with Aβ (Liao, Chang, Yoshiike, Chang, & Chen, 2012). Negatively charged AuNP inhibited and redirected Aβ fibrillization, whereas positively charged amine-functionalized AuNP did not show comparable effects.

PEGylation

PEGylation involves coating or conjugating the nanocarrier surface with polyethylene glycol (PEG) to generate a hydrated steric barrier. This hydrophilic layer reduces aggregation and nonspecific protein adsorption and limits opsonization and recognition by the mononuclear phagocyte system (Le, Vu, Abioye, & Adejare, 2026). Surface hydrophilization with polyethylene glycol (PEG) is widely employed to improve NDDS stability; however, its contribution to brain delivery depends strongly on PEG architecture rather than simply on the presence of a PEG coating. This was demonstrated recently using Angiopep-2-functionalized liposomes bearing PEG chains of 2, 3.4, 5, or 10 kDa. Although shorter PEG chains promoted substantially greater cellular uptake, these formulations showed relatively poor exocytosis and transendothelial transport. In contrast, liposomes with longer PEG chains showed more efficient BBB transcytosis and greater brain accumulation *in vivo*, despite lower cellular uptake (Du et al., 2024).

Sánchez-López et al. (2018) developed memantine-loaded PEGylated PLGA nanoparticles (MEM–PEG–PLGA NPs) for oral administration in AD. The nanoparticles were <200 nm and showed sustained memantine release, were able to cross BBB models both *in vitro* and *in vivo*, and improved memory-relat-

ed outcomes in mice compared with free memantine (Sánchez-López et al., 2018). This strategy has yielded successful results with various drug delivery systems. PEGylated chitosan nanoparticles (Datta, Gajbhiye, & Patil, 2024), gold nanoparticles (Okła et al., 2025), niosomes (Barani et al., 2025) and liposomes have shown successful brain accumulation in AD treatment.

Interestingly, PEG may contribute functions beyond prolonged circulation. Brambilla et al. (2012) demonstrated that the PEG corona of polymeric nanoparticles interacted with monomeric and soluble oligomeric $A\beta_{1-42}$, altering peptide conformation and aggregation kinetics. The authors proposed that long-circulating PEGylated nanoparticles could potentially sequester circulating toxic Aβ species and contribute to a peripheral "sink effect" (Brambilla et al., 2012).

These findings support the concept that surfactant coating can influence BBB transport not only through the engineered surface itself, but also by shaping the biological identity NDDS acquire after systemic exposure.

Surfactant-Mediated BBB Targeting

Surfactant coatings provide another way of modifying NDDS interactions with the BBB. Polysorbate 80 is one of the most investigated examples and can promote the adsorption of circulating apolipoproteins onto the NDDS surface, thereby conferring a lipoprotein-like biological identity that may facilitate recognition by lipoprotein-associated receptors at the BBB (Song, Li, Li, & Li, 2024). In a recent AD study, polysorbate 80-coated donepezil-loaded nanoparticles showed enhanced brain accumulation, while direct binding analysis demonstrated affinity between the coated nanoparticles and ApoE, supporting the proposed role of apolipoprotein adsorption in brain targeting (Tao et al., 2021). Similar benefits have been reported with polysorbate-functionalized silica nanoparticles carrying rivastigmine, which significantly increased the brain-to-plasma concentration ratio and brain uptake clearance compared with the free drug (Fateh Basharzad et al., 2022). These findings support the concept that surfactant coating can influence BBB transport not only through the engineered surface itself, but also by shaping the biological identity nanocarriers acquire after systemic exposure.

Ligand-Mediated Targeting

Functionalizing NDDS with ligands that engage endogenous receptors on brain endothelial cells can achieve more selective transport. This pathway is associated with receptors such as transferrin, lactoferrin, and members of the low-density lipoprotein receptor family (Gopalan, Pandey, Udupa, & Mutalik, 2020; Ouyang et al., 2022).

However, receptor recognition alone does not guarantee productive transport across the BBB. Studies using transferrin-receptor-directed antibodies demonstrated that excessively high binding affinity can favor endothelial retention, lysosomal trafficking, and receptor degradation, thereby reducing transcytosis (Bien-Ly et al., 2014). In addition, disease-associated changes in receptor expression may influence targeting efficiency; nevertheless, transferrin receptor-mediated uptake has been shown to remain functional in experimental models and human tissue exhibiting AD neuropathology (Bourassa, Alata, Tremblay, Paris-Robidas, & Calon, 2019). Effective ligand-mediated delivery therefore depends on the combined effects of receptor availability, ligand affinity and density, intracellular trafficking, and release into the brain.

Overall, successful BBB targeting depends on the coordinated interaction between NDDS design and BBB biology rather than any single modification. Strategies such as PEGylation, surfactant coating, and surface-functionalization influence different stages of the delivery process, but increased endothelial uptake should not be interpreted as equivalent to successful brain delivery.

TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS) IN AD

TDDS represent a promising alternative to oral administration for long-term AD management. By delivering drugs across the skin directly into the systemic circulation, transdermal systems can bypass gastrointestinal degradation and hepatic first-pass

metabolism, reduce fluctuations in plasma drug concentrations, and provide prolonged drug release (Nguyen, Giau, & Vo, 2017; Panoraia et al., 2020). These features may reduce dosing frequency, which is very important for older patients with cognitive impairment, dysphagia, polypharmacy, and difficulties adhering to complex oral regimens.

The transdermal formulations of rivastigmine and donepezil demonstrate the clinical feasibility of this approach. The rivastigmine patch provides continuous drug delivery over 24 hours and produces a smoother pharmacokinetic profile, with lower peak plasma concentrations and fluctuations than oral formulations. This release kinetic is associated with reduced gastrointestinal adverse effects, particularly nausea and vomiting, while maintaining therapeutic efficacy (Kurz, Farlow, & Lefèvre, 2009). Transdermal administration may also facilitate treatment supervision because caregivers can visually confirm patch application. Nevertheless, application-site reactions, including erythema, pruritus, and contact dermatitis, may occur and can affect treatment persistence (Buck et al., 2024).

Despite these advantages, conventional transdermal patches are suitable mainly for potent, relatively small, and sufficiently lipophilic molecules. The stratum corneum constitutes the principal barrier to percutaneous absorption and restricts the delivery of hydrophilic compounds, macromolecules, and drugs requiring relatively high therapeutic doses (Prausnitz & Langer, 2008). Variability in skin integrity, hydration, age, application site, and patch adhesion can further influence drug absorption (Singh & Morris, 2011).

Microneedle-Based TDDS

Microneedle-based TDDS may address some of these limitations by creating microscopic pathways through the stratum corneum. Microneedle arrays are designed based on skin anatomy to enhance molecule transport across the skin. The outermost layer of the skin, stratum corneum that has a thickness of 10–20 μm, is dead tissue that forms the main barrier to drug transport. The layer that lies below, the viable epidermis, is a tissue containing living cells and nerve endings, but no blood vessels (Bariya, Gohel, Mehta, & Sharma, 2012). The next layer below is the dermis, which contains living cells, nerves, and blood vessels. This means that microneedles, which can provide transport pathways across the stratum corneum to the dermis, are painless, since they do not reach nerves found in deeper layers (Henry, McAllister, Allen, & Prausnitz, 1998). Even microneedles longer than 100 μm do not cause pain because of their small size, sharp tips, and rapid application to the skin (Prausnitz, 2004).

Most of the studies have focused on making microscopic holes in the skin by inserting solid microneedles made of silicon or metal. In this "poke and patch" approach, microneedles are applied onto the skin to create microchannels, and then a patch containing the drug is applied onto the same site. The second mechanism is "coat and poke", where the needles are first coated with drug and then inserted into the skin. There is no drug reservoir on the skin surface; all the drug is on the needle itself, coated on the microneedle surface in a water-soluble matrix that dissolves off the microneedles into the skin (Karataş & Sonakin, 2007; Prausnitz, 2004; 2017). Another variation, defined as "poke and dissolve" approach, provides drug release by dissolution of the microneedles in the skin. The microneedles used are water-soluble and release their encapsulated drug by dissolving in the skin (Prausnitz, 2017; van der Maaden, Jiskoot, & Bouwstra, 2012). The last approach, known as "poke and release", features a controlled release of the drug from the microneedles by using materials that serve as a drug depot (van der Maaden et al., 2012). Drugs are encapsulated in the patch backing or/and in the microneedles to enable slow drug release while the patch is adhered to the skin (Donnelly et al., 2012). Patches and microneedles are often made of hydrogels that swell, but do not dissolve, allowing the drug to diffuse out of the backing through the microneedles and into the skin (Prausnitz, 2017).

Recently, dissolvable microneedles were particularly attractive because their drug-loaded polymeric matrix dissolves after insertion, enabling minimally invasive administration without leaving sharp waste. These systems can accommodate compounds with limited passive skin permeability, modulate release profiles, and potentially combine transdermal administration with NDDS engineered for BBB transport (Prausnitz, 2004; Ita, 2017).

Preclinical studies have investigated microneedle-mediated delivery of AD therapeutics, including donepezil and rivastigmine (Ilyas et al., 2024). However, while microneedles alone significantly improve drug delivery and patient compliance, they do not promise an improvement regarding brain delivery.

NDDS-INTEGRATED MICRONEEDLE SYSTEMS

NDDS-integrated microneedle systems represent a hybrid drug delivery strategy that combines the ability of microneedles to overcome the stratum corneum barrier with the controlled release and targeting strategies of NDDS (Figure 2.). Despite the limited number of studies related to NDDS-integrated microneedle systems, the findings reported are highly promising for AD patients (Table 1.).

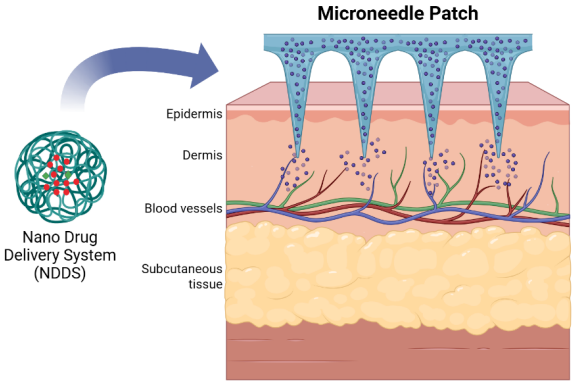

Figure 2. Schematic representation of NDDS-integrated microneedle systems (Created in BioRender. Mucaj, S. (https://BioRender.com/wrzyy4a) is licensed under CC BY 4.0.)

Ruan et al. (2024) developed a nanocarrier-integrated dissolving microneedle platform to improve nose-to-brain drug delivery (Ruan et al., 2024). The toothbrush-like microneedle system consisted of hyaluronic acid supported by a tannic acid-cross-linked gelatin base and was designed for intranasal application. The cyclodextrin-based metal-organic frameworks (CD-MOF) were used to encapsulate huperzine A (Hup A) and were further stabilized with stigmasterol and surface-functionalized with lactoferrin. These modifications enhanced the system's physicochemical stability and biocompatibility while promoting efficient brain-targeted delivery of Hup A. The developed delivery system significantly improved the aqueous solubility of Hup A, resulting in enhanced *ex vivo* transnasal permeation of Hup A in modified Franz diffusion cells. Enhanced brain delivery of Hup A translated into improved learning and memory in scopolamine-treated rats, accompanied by greater AChE inhibition and reduced oxidative stress.

Monou et al. (2024) combined two manufacturing approaches: digital light processing (DLP) 3D printing for microneedle fabrication, and electrohydrodynamic atomization (EHDA) for coating (Monou et al., 2024). The study addressed a recognized gap, most coated microneedle research focuses on single-drug systems, by attempting simultaneous delivery of two therapeutically complementary agents: rivastigmine and N-acetyl cysteine (NAC), a neuroprotective antioxidant. They coated microneedles by electrospraying with PLGA nanoparticles, one batch encapsulating rivastigmine and another encapsulating NAC. The simulation of injection showed that 438-479 μm-long microneedles successfully dissolved in artificial skin and delivered the dyes approximately 2000 μm deep. The platform demonstrated adequate mechanical robustness, effective skin penetration, sustained dual-drug delivery, and acceptable biocompatibility, positioning it as a promising approach for combination pharmacotherapy in neurodegenerative conditions such as AD.

Suriyaamporn et al. (2026) developed a transdermal delivery system for progesterone (PG) aimed at slowing AD progression in postmenopausal women (Suriyaamporn et al., 2026). The authors combined two advanced technologies: solid lipid nanoparticles (SLNs) to enhance drug solubility and encapsulation, and liquid crystal display (LCD)-based degradable hydrogel microneedles to bypass the stratum corneum barrier. The optimized microneedles, measuring 756.98 ± 14.78 μm in length, successfully penetrated the skin barrier. The SLNs had a mean particle size of 308.91 ± 1.66 nm, with a PDI of 0.19 ± 0.08 and a zeta potential of −30.03 ± 1.19 mV. *In vivo* evaluation demonstrated successful transdermal delivery of PG. Furthermore, PG-SLN-loaded microneedles exhibited neuroprotective effects on neuronal cells. The system demonstrated favorable mechanical, biological, and pharmacokinetic profiles, and the authors propose it as a promising patient-friendly alternative to injection-based hormone therapy for AD management in postmenopausal women.

Permana et al. (2024) developed rivastigmine-encapsulated SLNs to improve its lipophilicity and BBB permeability, and then loaded them into a thermosensitive gel (TG) that solidifies upon contact with skin temperature, ensuring prolonged contact at the application site (Permana et al., 2024). The application site was pretreated with polymeric dissolvable microneedles. SLNs' particle size was below 200 nm and produced sustained drug release over 72 hours. The dermal drug concentrations achieved by MN pretreatment and intradermal injection were comparable and approximately 55-fold greater than those achieved by gel application alone, demonstrating that microneedle-created microchannels are essential for meaningful drug penetration into the skin. This approach produced superior pharmacokinetic profiles compared to oral and intravenous routes, was well-tolerated, and showed evidence of non-systemic brain targeting.

Madani et al. (2024) developed a novel DDS for telmisartan (TMN), an angiotensin II receptor blocker that has attracted attention as a potential alternative therapy for AD (Madani, Syauqi, Permatasari, Putri, & Permana, 2024). However, TMN's very poor water solubility severely limits its oral bioavailability, and the presence of the BBB further restricts its access to brain tissue. To overcome both obstacles simultaneously, the authors first converted TMN into nanosized crystals (NC) and then loaded these nanocrystals into dissolving microneedles (DMN) intended for application to the facial skin, where the trigeminal nerve provides a more direct anatomical route to the brain than systemic circulation. The *in vivo* comparison of TMN-NC-DMN, TMN-DMN, Oral, and patch control groups showed that TMN-NC-DMN produced the highest C_{max} (1.27±0.09 μg/mL) and the largest AUC (79.91±6.09). Relative bioavailability of TMN-NC-DMN compared to oral administration exceeded 3000%, reflecting the dramatic difference between first-pass-affected oral absorption of a poorly soluble drug and needle-assisted intradermal delivery of nanocrystals. In brain tissue, the contrast was even more striking: TMN-NC-DMN achieved a brain C_{max} of 0.73±0.04 μg/mL compared to values below 0.02 μg/mL for all other groups. The AUC in brain tissue for TMN-NC-DMN was approximately 48-fold greater than for DMN containing plain TMN, and roughly 91-fold greater than for oral administration.

Table 1. Summary of NDDS-integrated MN studies in AD treatment

Drug	NDDS type	MN composition	Key findings	Experimental model	Ref.
Huperzine A	Cyclodextrin-based metal-organic frameworks reinforced with stigmasterol and functionalized with lactoferrin	Hyaluronic acid-formed dissolvable microneedles	Enhanced nose-to-brain delivery of Hup A translated into improved learning and memory in scopolamine-treated rats; produced higher AChE inhibition and reduced oxidative stress.	*In vivo* behavioral study and pharmacodynamic test	(Ruan et al., 2024)
Rivastigmine and N-acetyl cysteine	Polymeric nanoparticle	Solid coated microneedles	Microneedles coated with drug-loaded nanoparticles effectively penetrated the skin; drugs accumulated in the deepest layer of skin.	Artificial skin evaluation; *In vitro* characterization	(Monou et al., 2024)
Progesterone	Solid lipid nanoparticles	Hydrogel dissolvable microneedles	*In vivo* studies showed significantly higher transdermal drug delivery compared to the other formulations. The neuroprotective ability in neuronal cells was higher for the drug-loaded MN group.	*In vitro* neuroprotective study; *In vivo* skin permeation and irritation test	(Suriyaamporn et al., 2026)
Rivastigmine	Solid lipid nanoparticle and thermosensitive gel	Solid microneedles for pretreatment	MN pretreatment achieved dermal drug concentrations 55-fold higher than gel application alone.	*Ex vivo* dermatokinetic study; *In vivo* biodistribution study	(Permana et al., 2024)
Telmisartan	Nanocrystal	Dissolvable microneedles	TMN-NC-DMN enhanced systemic and brain exposure, achieving the highest C_{max} and AUC, over 3000% relative bioavailability versus oral administration, and approximately 48- and 91-fold greater brain AUC than plain TMN-DMN and oral TMN, respectively.	*Ex vivo* permeation study; *In vivo* plasma and brain pharmacokinetic study	(Madani et al., 2024)

CONCLUSION

Despite advances in understanding the complex pathophysiology of AD, effective treatment remains challenging. Conventional pharmacotherapy is limited by several factors, including low brain bioavailability, limited BBB transport, systemic adverse effects, and difficulties with treatment adherence. These limitations highlight the need for drug-delivery strategies capable of improving therapeutic efficiency while minimizing systemic effects.

NDDS offer considerable potential to address these challenges by improving drug stability, providing controlled or sustained release, and modifying the pharmacokinetic and biodistribution profiles of therapeutic agents. Microneedle-based delivery systems provide a complementary approach by overcoming the stratum corneum and enabling minimally invasive administration of therapeutic agents. Integration of NDDS with microneedles is particularly promising, as microneedles can facilitate transdermal administration while NDDS provide drug protection, sustained release, and, when appropriately engineered, enhanced brain targeting. Although studies investigating NDDS-integrated microneedles for AD remain limited, the available findings demonstrate encouraging improvements.

Despite these advantages, translation from experimental systems to clinical application remains a major challenge. Long-term safety remains a major concern, particularly regarding the potential accumulation of nanocarriers in tissues, their biodegradation profiles, and possible chronic inflammatory or immunological

responses following repeated administration. Comprehensive long-term toxicological and biocompatibility studies are therefore essential to establish their safety.

Furthermore, formulation stability represents a critical challenge, as nanocarrier aggregation, drug leakage, degradation of active compounds, and changes in microneedle mechanical properties during storage may compromise therapeutic efficacy and product shelf life. Appropriate stability testing and optimized storage conditions are necessary to maintain consistent performance.

Another important limitation is manufacturing reproducibility, particularly during large-scale production. Ensuring uniform nanocarrier distribution, consistent drug loading, reproducible microneedle geometry, and adequate mechanical strength across manufacturing batches is essential for reliable drug delivery. Standardized fabrication protocols, robust quality-control procedures, and compliance with Good Manufacturing Practice (GMP) requirements will be crucial for regulatory approval and clinical implementation.

Addressing these limitations through systematic preclinical investigations, standardized manufacturing processes, and well-designed clinical trials will be essential to facilitate the safe and effective translation of nanocarrier-integrated microneedle systems into clinical practice.

Furthermore, the physiological complexity of the BBB and the heterogeneity and progressive nature of AD should be considered when translating results from experimental progressive models to patients. The evidence remains limited, and further research is required to establish reproducibility, long-term dermal safety, manufacturing scalability, and the relationship between enhanced systemic exposure and actual drug concentrations in the brain.

AUTHOR CONTRIBUTION STATEMENT

Conceptualization (SM); investigation and literature research (SM, AA, TG); data curation and interpretation (SM, AA); writing – original draft (SM, AA); writing – review & editing (TG, RNG); project administration (TG); supervision (RNG).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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