*EJPMR, 2026, 13(8), 560-566* **Review Article** **Impact Factor: 8.158**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

**ISSN (O): 2394-3211**
**ISSN (P): 3051-2573**
**Coden USA: EJPMAG**

# ADVANCES IN SOLID LIPID NANOPARTICLES FOR ALZHEIMER'S DISEASE MANAGEMENT

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**DOI:** https://doi.org/10.5281/zenodo.21885768

**How to cite this Article:** Vignesh B*, Gowthaman. R.[1], Prakash M. R.[2], Sathishkumar M.[3] (2026). Advances In Solid Lipid Nanoparticles For Alzheimer's Disease Management. European Journal of Pharmaceutical and Medical Research, 13(8), 560–566.



**Article Received on 17/07/2026** **Article Revised on 07/08/2026** **Article Published on 10/08/2026**

**ABSTRACT**

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by cognitive decline, loss of memory, and neuronal damage linked to the accumulation of amyloid-β plaques and aggregation of tau proteins. Despite comprehensive research efforts, existing treatment methods only offer relief from symptoms and do not stop the advancement of the disease, mainly due to obstacles in delivering drugs effectively across the blood-brain barrier (BBB). Drug delivery systems based on nanotechnology, particularly solid lipid nanoparticles (SLNs), have emerged as promising solutions to address these issues. SLNs present benefits such as enhanced drug stability, increased bioavailability, controlled release, and targeted delivery to the brain. This review discusses the pathophysiology of AD, the primary barriers to drug delivery, including BBB limitations, and various techniques for preparing SLNs like high-pressure homogenization and solvent-based methods. Additionally, it explores the mechanisms for targeting the brain, which include intranasal delivery.

**KEYWORDS:** Alzheimer's Disease, Solid lipid nanoparticles, Blood-Brain Barrier, Drug Delivery, Nanotechnology.

## 1. INTRODUCTION

Alzheimer's disease (AD) is a neurological disorder that causes irreversible dementia syndrome that gradually damages neurons.[1,2] AD is more prevalent in older adults and increases with age.[3] Currently affecting 32.6 million people globally, it is predicted to almost quadruple every 20 years in the absence of new treatments, reaching 78 million by 2030 and 139 million by 2050.[4] Behavioural, mental, and other intellectual capacities deteriorate as a result. Memory loss results from the death of brain cells.[5] Alzheimer's Disease is a neuropathological condition brought on by the build-up of intraneuronal tau (τ) protein neurofibrillary tangles and the extracellular aggregation of amyloid beta (Aβ) plaques.[6] The patient's CSF fluid and plasma contain high amounts of Aβ, which is produced by the division of type I membrane proteins such amyloid precursor protein (APP). Therefore, the dual-target therapy for AD involves suppression of p-τ fibrils and depletion of Aβ plaque deposition. There are no specific diagnostic methods or medications to treat this incurable illness. Currently available treatments for AD merely lessen symptoms.[7] The current treatment plan improves cognitive function and momentarily reduces symptoms, but it does not stop or decrease the progression of the illness. Furthermore, most medicines are provided in traditional oral dosage forms, which have negative side effects and lack brain specialization, which lowers patient compliance. Additionally, AD is a degenerative metabolic illness linked to cardiovascular risk factors as obesity, diabetes, hypertension, and atherogenic dyslipidaemia.[8] AD can be brought on by exposure to toxins in the environment, genetics, mutations, trauma, and metabolic disorders like obesity and diabetes.[9] Nanotechnology's tremendous potential is opening new avenues for human disease diagnosis, treatment, and cure.[10] The most complicated illnesses, such cancer and neurological diseases, are treated using drugs developed using nanotechnology. Through extremely effective signal transduction techniques, nanotechnology can aid in the early identification of AD. The process of transforming and amplifying a biological signal to record

it is known as signal transduction. The development of a target-based therapy (TBT) is currently of interest because the standard medications used for AD can only slow the disease's progression; they cannot cure it.[11,12]

## 2. CHALLENGCES IN DRUG DELIVERY FOR AD

The best-protected organ in the body is thought to be the brain. The brain is surrounded by several protective barriers, such as the skull, meninges, cerebrospinal fluid, and blood-brain barrier. These components aid in maintaining the brain's health and protecting it from both internal and external damage. However, these protective barriers make it more challenging for therapeutic medications to enter the brain when the brain is ill.[13] A brief discussion is given of the main barriers, such as the blood–cerebrospinal fluid barrier (BCFB), the blood–brain barrier (BBB), and multidrug resistance proteins (MDRPs).

### 2.1. BLOOD BRAIN BARRIER RESTRICTION

The blood-brain barrier (BBB) restriction is one of the primary barriers to getting medicines into the brain to treat neurological conditions like Alzheimer's disease. The BBB is a highly selective biophysical barrier that develops by close contacts between astrocytes, pericytes, and brain capillary endothelial cells. This barrier safeguards the brain from toxic substances that can enter the circulatory system. Despite the BBB's limited shape and selective permeability, most drugs cannot enter the brain. Approximately ninety of small-molecule medications and almost all large molecules (proteins, peptides, and antibodies) cannot penetrate the blood-brain barrier. Additionally, efflux transporters including P-glycoprotein constantly pump several pharmaceuticals back into the bloodstream, decreasing drug build-up in brain tissue.[14,15,16]

## 3. SOLID LIPID NANOPARTICLES FUNDAMENTALS

With the profound knowledge acquired in the many domains of biotechnology, biomedical engineering, and nanotechnology, the field of novel drug delivery systems is developing at an exponential rate.[17] Nanotechnology, or the creation of nanoscale structures containing the API, is used in several of the more modern formulation techniques.[18] The National Nanotechnology Initiative (NNI) defines nanotechnology as the study and application of structures that are approximately between 1 and 100 nm in size. Solid Lipid Nanoparticles (SLNs) are the primary topic of this article. Compared to conventional colloidal carriers including emulsions, liposomes, and polymeric micro and nanoparticles, SLNs, which were first developed in 1991, offer a superior alternative carrier system.[19] Figure 1 represents the solid lipid nanoparticles.

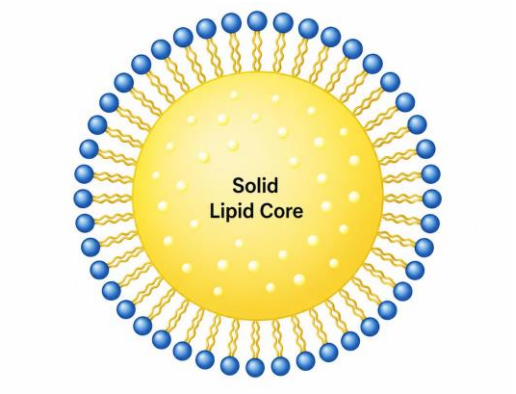


**Figure 1: Solid Lipid Nanoparticles.**

### 3.1. METHOD OS PREPARATION OF SOLID LIPID NANOPARTICLES

**1. High weight homogenization.**[20,21]

1.1. Hot homogenization.

1.2. Cold homogenization.

**2. Ultrasonication/fast Homogenization**

2.1. Test Ultrasonication.

2.2. Shower Ultrasonication.

**3. Solvent evaporation method.**
**4. Solvent emulsification-diffusion method.**
**5. Supercritical fluid method.**
**6. Microemulsion based method.**
**7. Spray drying method.**
**8. Double emulsion method.**
**9. Precipitation technique.**
**10. Film-ultrasound dispersion.**

### 3.2. HIGH PRESSURE HOMOGENIZATION

For the first time, SLNs are produced using this dependable and potent method. A liquid at high pressure (100–2000 bar) is forced through a small opening (a few microns) using high pressure homogenizers. The fluid accelerates to a very high velocity (more than 1000 km/h) over a very small distance. Particles are disrupted down to the submicron range by extremely high shear stress and cavitation forces. 5–10% lipid content is frequently used, even though up to 40% lipid content has been examined. Hot homogenization and cold homogenization are the two forms of HPH. In both situations, a preparatory step entails dissolving or dispersing the medication in the lipid melt to incorporate it into the bulk lipid.

### 3.3. SOLVENT EVAPORATION METHOD

A water-immiscible organic solvent, such as cyclohexane, is used to dissolve the lipophilic substance and emulsify it in an aqueous phase. When the solvent evaporates, the lipid precipitates in the aqueous media, resulting in a dispersion of nanoparticles with a mean size of 25 nm. High pressure homogenization was used to emulsify the solution in an aqueous phase. By evaporating under lower pressure (40–60 mbar), the organic solvent was extracted from the emulsion.[22]

### 3.4. SOLVENT EMULSIFYING DIFFUSION METHOD

This method can produce particles with average sizes between 30 and 100 nm. The most significant benefit of this method is the absence of heat during preparation. In this method, lipids are typically dissolved in the organic phase in a water bath at 50 °C. An acidic aqueous phase is then utilized to modify the zeta potential to create coacervation of SLN, which is then easily separated by centrifugation. The SLN suspension was manufactured swiftly. The dispersed system can then be centrifuged and resuspended in distilled water.[23,24,25]

## 4. MECHANISM OF BRAIN TARGETING USING SLNs

### 4.1. INTRANASL DELIVERY PATHWAY

These chitosan NPs significantly lowered piperine-induced nasal irritation in a rat model without having any adverse effects on the brains. This work was the first to show that PIP's benefits in AD were caused by its anti-inflammatory and anti-apoptotic properties. Additionally, the authors created mucoadhesive chitosan nanoparticles (NPs) that effectively, safely, and non-invasively delivered PIP to brains at levels equivalent to oral treatment, but at 5% of the oral dose, providing a way to prevent PIP side effects.[26]

### 4.2. RECEPTOR MEDIATED TRANSPORT

Understanding the endogenous transport systems used at the blood-brain barrier (BBB) to move proteins, metabolites, and nutrients between the blood and the brain can help design ways for delivering biologics to the brain. Figure 1 depicts the main molecular transport pathways at the BBB. In the absence of TJ disruption, paracellular diffusion is not a suitable target for biologic administration since TJs effectively eliminate it. Hydrophilic small molecule nutrients including glucose and amino acids are transported via carrier-mediated transport (CMT).[27] Large molecule biologics have not been successfully transported by CMT, which tends to be size and stereo selective. However, CMT has been used to transport small molecule pharmaceuticals to the brain by linking the drug to the natural CMT ligand.[28] Small compounds that are lipophilic and weigh less than 600 kDa can easily permeate the endothelial plasma membrane (PM). Nevertheless, many lipophilic substances are recognized by efflux pumps like p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein-1 (MRP-1) at the apical (blood-facing) PM of ECs, which then efflux them back into the blood.[29]

## 5. SLNs PHYTOCHEMICAL AND NATURAL COMPOUND

### 5.1. CURCUMIN LOADED SLNs

Curcumin has been studied and shown to have a variety of biological activities in recent decades, including neuroprotective properties. Despite this potential, curcumin is known to have low bioavailability, is prone to oxidation and biodegradation, and does not reach the biological system. Therefore, this restriction can be circumvented by incorporating it into nano capsules to enable simple BBB crossover.[30] Using in silico modelling approaches, a class of high molecular weight glycolate polyethylene nanocarriers was created that bind to Ab1-42 and can change their conformations in blood.[31] The scientists suggested that by attaching to harmful types of Ab, these particles act as "nano sinks"[32] The manufacture of water-soluble curcumin nanoparticles coated with polylactic-co-glycolic acid (PLGA) and conjugated with Tet-1 peptide was reported by Mathew in 2012. The components used in this work made it extremely important. Due to its broad range of bioactivity, including anti-AD activity, curcumin is one of the most used natural compounds.

## 6. COMPARISON OF SLNs WITH OTHER NANOCARRIER

### 6.1. LIPOSOMES

Since their discovery in the 1960s, liposomes have gained significant attention because of their unique characteristics, which include non-immunogenicity, biodegradability, low toxicity, flexibility, and biocompatibility.[33-35]

Liposomes with the curcumin derivative, or with both the curcumin derivative and anti-TrF, were found to strongly bind to amyloid plaques in brain samples taken from Alzheimer’s patients after death. Additionally, the authors discovered that liposome’s containing curcumin derivatives did not stop Ab aggregation or block Ab deposit staining. However, the brain-targeting ability was unaffected by the presence of a curcumin–PEG–lipid conjugate, indicating that these multifunctional NLs may be effective AD theragnostic.[36]

### 6.2. LIPID BASED NANOPARTICLES

LBNs are lipid-based nano delivery devices that can carry drugs or genetic material into the body. Stability, bioavailability, and pharmacokinetic acceptability are further benefits of LBNs. Other industries, such as agriculture, nutrition, cosmetics, medical imaging, and other cutting-edge fields like nanoreactors, have also employed LBNs.[37] Lipid-based nano-delivery systems, or LBNs, can deliver medications or genetic material into the body. The FDA has given LBNs permission to provide vaccines and drugs.

LBNs are vital for effectively delivering and preserving mRNA to cells, and they are currently in the news as key components of the COVID-19 mRNA vaccines.[38] Exosomes, liposomes, SLNs, and NLCs are examples of LBNs that have garnered interest in the field of CNS medication delivery. The four types of LBNs that will be discussed in our review paper are shown in Figure 2. In addition to benefits like high biocompatibility, ease of production, prolonged release of cargo, and improved solubility of the hydrophobic medication, LBNs enable precise and sustained drug delivery to the lesion site due

to the improved BBB targeting and penetration for AD treatment.[39]

## 7. RECENT CLINICAL AND PRECLINICAL ADVANCES

### 7.1. IN VITRO MODEL

The disease model can also be replicated at the cellular and molecular levels using in vitro models. Nevertheless, the robustness of the in vitro models is not as strong as that of the in vivo models.

#### 7.1.1. Neuroblastoma cell line

When treated with different treatments, the neuroblastoma cell lines, also referred to as SH-SY5Y cell lines, may generate neuronal cells that function as neurons. The subcloning method is used to produce SH-SY5Y cell lines from neuroblastoma. Schwann cells and neuroblasts make up neuroblastoma. Consequently, novel therapeutic drugs for the treatment of AD can be developed using these cell lines.[40]

#### 7.1.2. iPSC-Derived Cell Lines.

One well-known paradigm for research on AD is the production of induced pluripotent stem cells (iPSC) from AD patients and their differentiation into neuronal cells. Human-induced PSC can revitalize this subject by bridging the gap left by conventional models' inability to recreate the complicated form of SAD. This in vitro model may be able to replicate the microenvironment of an AD patient's brain.[41] The model may be based on pathological features such as iPSC-centered NFTs and amyloid plaques. This model can be used to investigate AD Pathophysiology and identify possible treatments for the illness. Depending on the patient's origins, the model may be based on either familial or sporadic AD.[42]

### 7.2. IN VIVO ANIMAL MODEL

#### 7.2.1. Aged Rat Model.

When compared to younger rats, older rats exhibit hippocampal, temporal lobe, and neocortex damage, which leads to learning and memory impairment. Because it is noninvasive and mimics the clinical symptoms of late-onset/aged sporadic AD, this model is chosen over other chemical-induced models. Rats between the ages of 15 and 20 months could be used in this model. Given the clinical characteristics of the condition, this model is more pertinent.[43] Additionally, neuroinflammatory cytokines, oxidative stress, insulin resistance, and mitochondrial dysfunction arising from old age-related phenomena including glucose and energy metabolism, obesity, physical inactivity, etc. have been shown to be associated with aging-induced dementia. Additionally, this model generates tau pathology and amyloid genesis like those seen in other AD models. It has been demonstrated that exercise, intermittent fasting, and a few other antiaging techniques can reverse these negative aspects of AD, improving synaptic plasticity and memory formation.[44]

#### 7.2.2. High-Fat Diet-Induced Model.

Insulin resistance, obesity, and diabetes mellitus are frequently modelled using a high-fat diet. Nonetheless, it has also been suggested that it be called a cognitive dysfunction model in a few recent studies. Apart from the peripheral distortion of insulin sensitivity, giving rats or mice fat-loaded meals for nearly 10–14 weeks in place of a regular diet may also partially cause central insulin resistance,[45] 25% fat, 20% protein, and 50% carbohydrates make up the fatty diet.[46] It has long been known that dementia and AD are associated with abnormal brain insulin signalling. This model contains a fundamental aspect of insulin resistance that is essential to assessing memory and enhancing treatment approaches.

Additionally, obesity brought on by a high-fat diet impairs appropriate blood flow to brain areas, lowering the availability of glucose and oxygen and leading to vascular dementia. Additionally, high dietary fat intake has been linked to cognitive deterioration brought on by diabetes and hypertension.[47] By upregulating APP, which is responsible for neuronal death, fat-associated cholesterol contributes to the development of senile plaques.[48] An imbalance in the lipid profile and glucose-transport inhibition may be additional processes contributing to memory loss. Additionally, by reducing antioxidant enzymes and raising proinflammatory cytokines, the high-fat diet AD model worsens oxidative stress and neuroinflammation.[49]

## 8. FUTURE PERSPECTIVE

Conventional treatment strategies fail to address AD properly due to the involvement of a plethora of physiological factors and the multifactorial nature of the disease. Unfortunately, AD treatment outcomes are disappointing despite research a effort, which highlights the gaps that exist between promising research outputs and proper implementation in clinical trials. Mitochondrial dysfunction can be a big shot to target amelioration of AD. Although the mechanisms responsible for the Pathophysiology of AD have not been determined, nanotechnology provides probably means of managing dis-ease. Thus, there is a pressing need to investigate nanotechnology-based methods of treating AD, because this approach offers a realistic strategy for improving cognitive skills and delaying disease progression. Magnetic nanoparticles are an exciting field to investigate, with a plethora of current and future technology uses as well as unsolved scientific issues. Two other types of drug delivery technologies that ought to be investigated further for CNS drug transport are dendrimers and nano emulsions.

## 9. CONCLUSION

Thus, Alzheimer's disease continues to be one of the most significant health problems worldwide due to its complex Pathophysiology and the lack of effective disease-modifying treatment. Conventional drug delivery systems are limited by low bioavailability and the

difficulty of effectively penetrating the blood–brain barrier, resulting in less-than-optimal therapeutic effects. Thus, Solid lipid nanoparticles (SLNs) have appeared as a potential nanocarrier system that can overcome these barriers by improving drug stability, controlled release, and site-specific targeting to the brain. Moreover, they are also suitable candidates for neurological applications because they can encapsulate hydrophilic and lipophilic drugs and have biocompatibility. Advanced targeting approaches, such as intranasal administration and receptor-mediated transport, increase their ability to deliver drugs efficiently to the brain. Curcumin-loaded Solid lipid nanoparticles (SLNs) have also shown considerable promise in improving therapeutic efficacy in various AD models. Despite such promising advances in preclinical studies, further clinical trials are required to establish safety, efficacy, and long-term outcomes. Therefore, Solid lipid nanoparticles (SLNs) constitute a novel and promising avenue in Alzheimer's disease care and nanomedicine therapeutic strategy development.

## 10. ACKNOWLEDGMENTS

The authors are thankful to The Erode College of Pharmacy, Erode (Tamil Nadu, India) for providing the necessary facilities to carry out this work. The authors also express their sincere gratitude to Mr. R. Gowthaman, Department of Pharmaceutics, for her valuable guidance and constant support during the preparation of this manuscript. The cooperation of faculty members and library staff is gratefully acknowledged**.**

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