

# Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease

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**Abstract:** Alzheimer's disease is a neurological disorder that results in cognitive and behavioral impairment. Conventional treatment strategies, such as acetylcholinesterase inhibitor drugs, often fail due to their poor solubility, lower bioavailability, and ineffective ability to cross the blood–brain barrier. Nanotechnological treatment methods, which involve the design, characterization, production, and application of nanoscale drug delivery systems, have been employed to optimize therapeutics. These nanotechnologies include polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, microemulsion, nanoemulsion, and liquid crystals. Each of these are promising tools for the delivery of therapeutic devices to the brain via various routes of administration, particularly the intranasal route. The objective of this study is to present a systematic review of nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease.

**Keywords:** Alzheimer's disease, polymeric nanoparticles, solid lipid nanocarriers, microemulsions, liquid crystals, targeted delivery, nose-to-brain

## Introduction

Alzheimer's disease (AD) is an acquired disorder of cognitive and behavioral impairment that is an incurable disease with a long and progressive course.<sup>1</sup> In AD, plaques develop in the hippocampus,<sup>2</sup> a structure deep in the brain that helps to encode memories, and in other areas of the cerebral cortex that are used in thinking and decision making.

In the US, an estimated 5.2 million people of all ages have AD. This disease is the sixth leading cause of death in the US overall and the fifth leading cause of death for those aged 65 years and older. Deaths from Alzheimer's increased by 68% between 2000 and 2010, while deaths from human immunodeficiency virus (HIV), stroke, and heart disease decreased by 42%, 23%, and 16%, respectively. By 2050, the number of people aged 65 years and older with AD may nearly triple from 5 million to a projected 13.8 million unless medical breakthroughs are made to prevent, retard, or stop the disease progression.<sup>3</sup>

There are several limitations associated with present therapy, and the intranasal strategy seems to be a promising route for delivery of drugs to brain.<sup>4</sup> Currently approved drugs for treating the cognitive impairments in AD are based on neurotransmitter or enzyme modulation.<sup>4</sup> Acetylcholinesterase (AChE) inhibitors are associated with gastrointestinal adverse effects like nausea and vomiting that most commonly lead to discontinuation of treatment.<sup>5,6</sup> Tacrine has a short half-life and needs four administrations per day.<sup>7</sup> In addition, patients who used the drug required periodic blood monitoring due to hepatotoxicity.<sup>8</sup> Also, galantamine and rivastigmine exhibit a half-life of 7 and 2 hours, respectively. The use of memantine can cause adverse

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**Table 1** Summary of the pharmacokinetic parameters of the cholinesterase inhibitors and memantine

Drug	Bioavailability (%)	t <sub>max</sub> (h)	Protein binding (%)	Half-life (h)	Hepatic metabolism
Tacrine <sup>7</sup>	17–37	0.5–3	75	1.3–7.0	CYP1A2, CYP2D6
Donepezil <sup>7</sup>	100	3–5	96	60–90	CYP2D6, CYP3A4
Rivastigmine <sup>7</sup>	40	0.8–1.7	40	2	Non-hepatic
Galantamine <sup>7</sup>	85–100	0.5–1.5	18	5–7	CYP2D6, CYP3A4
Memantine <sup>10,11</sup>	100	3–7	45	60–80	

**Abbreviations:** CYP, cytochrome P450; t<sub>max</sub>, time to maximum serum concentration; h, hours.

effects as dizziness, confusion, constipation, and vomiting.<sup>9</sup> A summary of pharmacokinetic parameters of drugs used in AD are shown in Table 1.

Therapy failure frequently occurs due to the unfavorable pharmacokinetics and pharmacodynamics of drugs.<sup>12</sup> Pharmacotherapy failure is the result of inadequate physical chemistry of drugs (such as hydrophobicity), unfavorable absorption by biological membranes, unfavorable pharmacokinetic parameters (such as intense and plasma metabolism), instability of drugs (oxidation, hydrolysis, or photolysis), and toxicity to tissues (hepatotoxicity, neurotoxicity, or kidney toxicity).<sup>12–14</sup> The use of drugs in nano-platforms or nanodevices results in the enhancement of their pharmacokinetics and pharmacodynamics, as well as they can to exhibit minimal toxicity.<sup>15,16</sup> On the one hand, an essential aspect in nanomedicine development is the controlled release of drugs into disease sites.<sup>12,14,17,18</sup>

The effectiveness of a treatment can be increased by incorporating nanotechnology-based drug delivery systems.<sup>19,20</sup> Some of these new platforms, which aim to improve the bioavailability, pharmacokinetics, and pharmacodynamics of drugs while reducing their side effects, are shown in Table 2.

## AD pathophysiology

AD is histopathologically characterized by a massive synaptic loss and neuronal death observed in the brain regions responsible for cognitive functions, including the cerebral cortex, hippocampus, entorhinal cortex, and ventral striatum.<sup>55</sup> In the brain parenchyma of patients with AD, fibrillar amyloid deposits located on the walls of blood vessels are associated with a variety of different types of senile plaques, the accumulation of abnormal tau protein filaments, and the subsequent formation of neurofibrillary tangles, neuronal and synaptic loss, glial cell activation, and inflammation.<sup>55</sup> Two hypotheses have been proposed for the etiology and pathophysiology of AD: the first hypothesis pertains to amyloid cascade neurodegeneration, whereas the second pertains to the dysfunction of the cholinergic system: tau aggregation, metal-mediated toxicity, and inflammation.

According to the amyloid cascade neurodegeneration hypothesis, AD begins with the proteolytic cleavage of the amyloid precursor protein (APP) and results in the production, aggregation, and deposition of  $\beta$ -amyloid (A $\beta$ ) and amyloid plaques (Figure 1A).<sup>56,57</sup> The deposition of A $\beta$  is increased in patients with AD when there are mutations in APP and presenilin (PS).<sup>56,58</sup> An increase in metal-mediated neurotoxicity is also associated with the deposition of A $\beta$ .<sup>59</sup> When the concentration of A $\beta$  is high, insoluble amyloid fibers are formed in the brain. These fibers may be complexed with zinc and copper, thereby aggravating the neuronal toxicity.<sup>60</sup> Copper has shown the ability to increase A $\beta$  aggregation, and an in vitro study showed that the A $\beta$ -copper complexation resulted in the formation of neurotoxic hydrogen peroxide.<sup>61</sup> Furthermore, metals such as copper, iron, and zinc have been found in the amyloid deposits in the brains of AD patients.<sup>62</sup> The use of metal chelators in the postmortem tissues of AD patients could dissolve these amyloid plaques.<sup>63</sup> An in vivo study with an animal model of AD also showed that chelating agents could solubilize amyloid plaques.<sup>64</sup>

According to the cholinergic hypothesis, the dysfunction of the cholinergic system is sufficient to produce a memory deficit in animal models that is similar to AD.<sup>65</sup> Rossor et al and Henke and Lang reported that the brains of patients with AD showed the degeneration of cholinergic neurons and a reduction in cholinergic markers, whereas the activities of choline acetyltransferase (ChAT) and AChE were reduced in the cerebral cortexes of patients with AD.<sup>66,67</sup> A study reported by Soinen et al showed that AD patients carrying the apolipoprotein E (APOE)  $\epsilon$ 4 allele have a more severe cholinergic deficit than the AD patients without the APOE  $\epsilon$ 4 allele.<sup>68</sup>

Phospholipase A2 (PA2) is the enzyme responsible for the synthesis of chemical mediators of inflammation and is also responsible for the conversion of phosphatidylcholine to choline.<sup>69,70</sup> However, PA2 has been reported to decrease in the frontal and parietal cortexes of AD patients,<sup>71</sup> resulting in decreased levels of choline. Because choline is converted to acetylcholine by ChAT and AChE, its deficit contributes to cholinergic deficiency and AD progression.<sup>70</sup>

**Table 2** Summary of nanotechnology-based systems applied in the treatment of Alzheimer's disease

Nanotechnology-based systems	Drug or active ingredients	Major applications	Route of administration	References
Polymeric nanoparticles	Tacrine	High concentrations of tacrine achieved in the brain Reduced the total dose required for the therapy	Intravenous	21
	Rivastigmine	High concentrations of rivastigmine achieved in the brain	Intravenous	22
	Peptides TGN and QSH	Targeted delivery to amyloid plaques	Intravenous	23
	Fibroblast growth factor	Increased ChAT	Intranasal and intravenous	24
	Unloaded polymeric nanoparticles	Increased biodistribution with intranasal administration	In vitro	25, 26
	Rivastigmine	Disaggregation of A $\beta$ (A $\beta$ <sub>1-42</sub> ) Improved learning and memory capacities	Intravenous	27
	Rivastigmine	Improved bioavailability	Intranasal	28
	Idebenone	Enhanced uptake into the brain Increased drug stability Decreased drug reactivity	In vitro	29
	Piperine	Increased AChE enzyme activity	Intraperitoneal	30
	Curcumin and donepezil	Reduced plaques and tangles in the brain Increased concentration of drugs in the brain	Intranasal	31
Solid lipid nanoparticles	Vinpocetine	Improved memory and learning in mice	Oral route	32
	Resveratrol	Enhanced bioavailability compared to the free drug Improved cerebral bioavailability	Oral and intraperitoneal	33
	Ferulic acid	Improved memory	In vitro	34
	Huperzine A	Higher protective activity on neurons Permeation through abdominal rat skin No primary irritation observed	In vitro Skin application	35
	Curcumin	Improved cognitive functions Increased AChE activity	Oral route	36
	Rivastigmine	Increased biodistribution in the brain	Intranasal	37
	Rivastigmine	Higher concentrations in hippocampus, cortex, and olfactory region Enhanced drug pharmacodynamics in mice	Oral route	38
	Beta-sheet blocker peptide	Improved cognitive functions and memory	In vitro	39
	Curcumin	Prevented amyloid aggregation Crossed a BBB model	In vitro	40
	Transferrin MAb and PAA	Crossed a BBB model by transcytosis pathway	In vitro	41
Liposomes	Curcumin-PEG derivative	Increased brain targeting Higher affinity by senile plaques Ability A $\beta$ aggregation	Intravenous Ex vivo In vitro	42
	Curcumin-phospholipid conjugate	Intaken by the BBB model Strongly labeled A $\beta$ deposits	Ex vivo	43
	Lipid-curcumin derivatives	Stained the A $\beta$ deposits in brain of mice	Hippocampal injection	44
	Galantamine and a ligand-functionalized peptide <sup>a</sup>	Higher affinity for A $\beta$ <sub>1-42</sub> fibrils Uptake into PC12 neuronal cells	In vitro In vitro	45

(Continued)

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Nanotechnology-based systems	Drug or active ingredients	Major applications	Route of administration	References
	Rivastigmine	Highest AChE inhibition Enhanced bioavailability	Intranasal	46
	Rivastigmine	Highest AChE inhibition	Intravenous	47
	Rivastigmine	Drug permeated through cultured Caco-2 cells	Oral route and intraperitoneal	48
	Folic acid	AChE inhibited in the brain	Oral route	49
	<i>Ginkgo biloba</i> extract	Absorbed through the nasal cavity Accumulated in the brain	Intranasal	50
		Increased the activities of antioxidant enzymes		
	<i>G. biloba</i> extract	High concentration of flavonoid glycoside biomarker in the brain	Oral	51
Nanoemulsions	Curcumin	Improved memory and learning	Intranasal	31
	Huperzine A	Improved cognitive function	Transdermal	35
	$\beta$ -Asarone	Improved bioavailability	Intranasal	52
	<i>Tabernaemontana divaricate</i>	Stable formulations	Transdermal	53
		Increased skin permeation and retention		
Microemulsions	Tacrine	Rapidly absorbed through nose to brain	Intranasal	54
		Improved memory		
Liquid crystals	<i>T. divaricate</i>	Stability of drug in formulations Increased skin permeation and retention	Transdermal route	53

Note: Peptide not specified in the reference.

Abbreviations: AChE, acetylcholinesterase; BBB, blood-brain barrier; ChAT, choline acetyltransferase; MAb, monoclonal antibody; PAA, peptide analog of apolipoprotein; PEG, polyethylene glycol.

The main function of tau protein is to promote the association of tubulin monomers in order to form microtubules, which modulate the functional and structural organization of neurons.<sup>72</sup> In AD, tau protein is abnormally phosphorylated and thus the microtubules disaggregate, accumulating in the cell body and forming intracellular filaments that lead to the disorganization of the neuron cytoskeleton.<sup>73,74</sup> This results in the blocking of the intracellular trafficking of neurotrophic proteins and other functional proteins, resulting in the loss or decline in dendritic or axonal transport in neurons (Figure 1B).

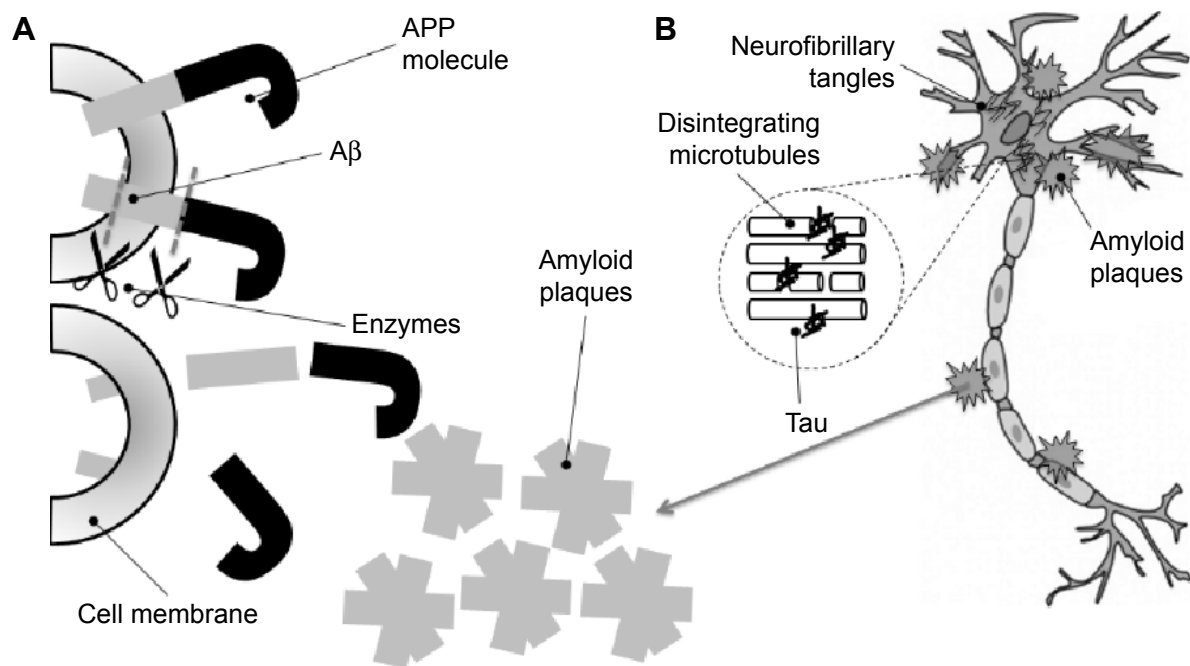
In AD, the reactive astrocytes are increased,<sup>75,76</sup> and there is a high expression of PA2. Astrocytes are able to release proinflammatory molecules, such as interleukins (ILs), prostaglandins, leukotrienes, thromboxanes, coagulation factors, complement factors, and proteases.<sup>77–80</sup> The activated microglia cells have also been shown to be abundant in the brains of patients with AD.<sup>76,79</sup> These cells produce a variety of neurotoxic compounds, including superoxide radicals, glutamate, and nitric oxide.<sup>81</sup> The exposure of microglia cells to A $\beta$  results in the release of proinflammatory factors, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>82</sup>

A number of complex mechanisms are involved in the genesis and progression of AD. Recent advances in the understanding of the molecular control of these various pathways will allow for a more accurate diagnosis and assessment of AD prognosis and may lead to more novel approaches to finding new molecular targets for AD treatment and prevention.

## Diagnosis and treatment of AD

AD is a clinical diagnosis;<sup>83–86</sup> however, the differential diagnosis of AD is based on the diagnosis of depression, which occurs in approximately 30%–50% of patients with AD. Depression in patients committed with AD are more often features motivational disturbances, such as fatigue, psychomotor slowing, and apathy, whereas depression in geriatric patients without cognitive impairment tends to feature mood symptoms, such as depressed mood, anxiety, suicidality, and disturbances in sleep and appetite.<sup>87</sup> Commonly used instruments for assessing depression were designed for use in other patient populations and may be less reliable in patients with AD.<sup>87</sup> Olin et al have proposed the inclusion and exclusion of provisional affective and behavioral diagnostic criteria in identifying AD in patients with depression.<sup>88</sup>

Ancillary imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI) and, in selected



**Figure 1** Formation of amyloid plaques (A) and neurofibrillary tangles (B) in the neurons in Alzheimer's disease.  
**Abbreviations:** Aβ, β-amyloid; APP, amyloid precursor protein.

cases, single-photon emission CT (SPECT) or positron emission tomography (PET), can also be used in the diagnosis of AD.<sup>89</sup> Brain MRI or CT scanning has indicated the use of structural neuroimaging to detect lesions that may result in cognitive impairment. In patients with AD, brain MRIs or CT scans can show diffuse cortical and cerebral atrophy, but these findings are not diagnostic of AD.<sup>89</sup>

Images obtained from CT scans can show the changes in the rate of atrophy progression,<sup>90</sup> longitudinal changes in brain size,<sup>91</sup> and enlargement of the third and lateral ventricles.<sup>92</sup> This approach can be useful in diagnosing AD. MRI measurements of the cerebral structures (hippocampus, amygdala, lateral ventricles, third ventricle, and basal forebrain) yield a prediction rate of 77% for the conversion of questionable AD to AD.<sup>93,94</sup> PET scanning is helpful for understanding the pathogenesis of AD, making the correct diagnosis, and monitoring the AD progression and response to drug treatment.<sup>95</sup> PET scanning involves the introduction of a radioactive tracer into the human body, usually via intravenous injection. PET measures glucose-dependent physiological processes in brain by using 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG).<sup>96,97</sup> Patients with AD have a temporoparietal glucose hypometabolism, which correlates with the severity of dementia and can be evaluated using FDG PET.<sup>96,98,99</sup> In 2012, florbetapir F18 was approved by the US Food and Drug Administration (FDA) as a diagnostic imaging agent. It is indicated for PET brain imaging of Aβ

neuritic plaques in adults under evaluation for AD or other conditions related to cognitive decline.<sup>100–103</sup> In 2013, the FDA approved flutemetamol F18. Like florbetapir F18, this drug attaches to Aβ in the brain and produces a PET image that can be used to assess the presence of Aβ, as evidenced in a clinical Phase II trial.<sup>104</sup>

Laboratory tests can be used to exclude other possible causes for dementia<sup>89</sup> such as cerebrovascular disease, cobalamin deficiency, syphilis, or thyroid disease.<sup>105–107</sup> Cerebrospinal fluid (CSF) analysis can be useful in identifying dementia caused by other factors, including infections in the central nervous system (CNS) such as neurosyphilis, neuroborreliosis, and cryptococcosis.<sup>108</sup> The CSF levels of tau and phosphorylated tau are often elevated in AD, whereas amyloid levels are usually low. The reason for this is not known, but perhaps amyloid levels are low because the amyloid is deposited in the brain rather than the CSF.<sup>86</sup> Other diagnosis tools include genotyping mutations in the genes for APOE, APP, and PS. A recent study has reported that plasma levels of APOE ε4 are associated with the risk of dementia independent of the APOE genotype.<sup>109</sup> These genotype tests provide assessments to patients with AD and provide the key elements used in genetic counseling for the disease.<sup>110</sup>

The use of nanotechnology as a diagnostic tool depends on the detection of amyloid peptides (Aβ), which are used as targets in the development of biological markers for the diagnosis of AD.

Polymeric nanoparticles (NPs) have been prepared and encapsulated with radio-labeled  $^{125}\text{I}$ -clioquinol (5-chloro-7-iodo-8-hydroxyquinoline [CQ]), a drug with amyloid affinity, to improve its transport to the brain and amyloid plaque retention of  $^{125}\text{I}$ -CQ. Radio-iodinated CQ NPs have been demonstrated to be promising delivery vehicles for in vivo SPECT or for use as a PET amyloid imaging agent.<sup>111</sup>

The use of thioflavin-T entrapped in polymeric NPs has been described for use as a probe to detect A $\beta$  in senile plaques.<sup>112</sup> The photoconversion of fluorescent thioflavin-T as a model drug was achieved in tissues fixed 3 days after injection, and thioflavin-T delivered from nanospheres was predominantly found in neurons and microglia. These data suggest that drugs delivered by NPs might target A $\beta$  in the brain.<sup>112</sup>

The current pharmacological approach to AD treatment is based on vascular prevention and symptomatic therapy with cholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) antagonists.<sup>113</sup> Cholinesterase inhibitors are included in drugs such as donepezil, rivastigmine, galantamine,<sup>113</sup> and tacrine.<sup>114</sup> These drugs act by inhibiting the action of AChE and optimizing the levels of acetylcholine available for postsynaptic stimulation.<sup>115</sup>

Memantine is an NMDA antagonist that acts as a non-competitive glutamate receptor antagonist.<sup>116,117</sup> Glutamate-related excitotoxicity resulting from an excessive activation of neuronal amino acid receptors<sup>118</sup> is involved in the pathophysiology of AD.<sup>119</sup> Memantine acts on the glutamatergic system by blocking NMDA receptors and this blocking effects on glutamate activity reduction on brain cells and blocking the activity of the neurotransmitter.<sup>120,121</sup> At normal levels, glutamate is conducive to memory and learning, but if levels are too high, glutamate appears to overstimulate nerve cells, killing them through excitotoxicity.<sup>122</sup> The interaction of memantine with NMDA receptors plays a major role in the symptomatic improvement that the drug produces in AD. Moreover, there is no evidence as yet that the ability of memantine to protect against NMDA receptor-mediated excitotoxicity has a disease-modifying effect in AD, although this has been suggested in animal models.<sup>123</sup>

Winslow et al have reported conflicting evidence about the benefits of selegiline, testosterone, and ginkgo (*Ginkgo biloba*) for the treatment of AD, and no evidence supports the beneficial effects of vitamin E, estrogen, or nonsteroidal anti-inflammatory drug therapies.<sup>114</sup> Nevertheless, the inflammatory pathways in AD<sup>124,125</sup> and treatment with anti-inflammatory molecules has the potential to delay, prevent, or treat AD.<sup>125,126</sup>

## Nanotechnology-based drug delivery systems

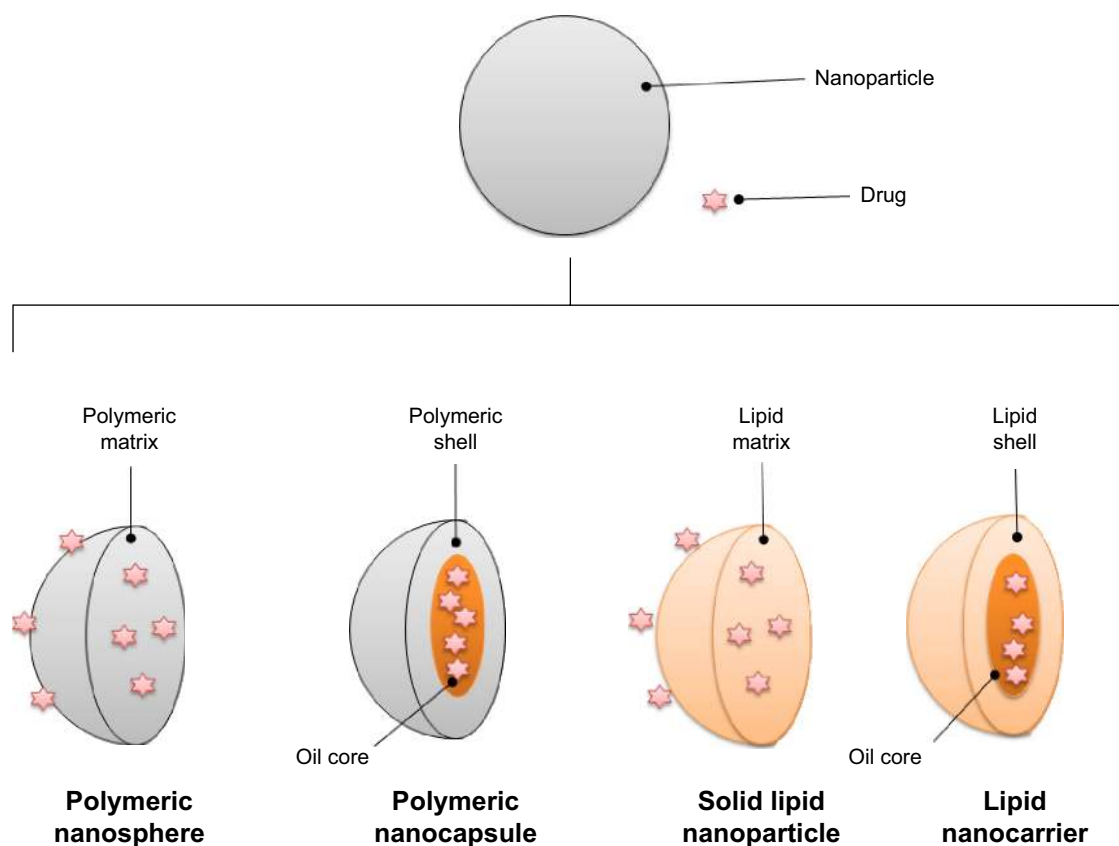
Treatment options are limited mainly due to the inability of drugs to cross the blood–brain barrier (BBB)<sup>127–129</sup> or their poor solubilities by oral route.<sup>130,131</sup> Many strategies have been developed to overcome the BBB, such as drug delivery systems, liposomes, polymeric and solid lipid NPs (SLNs), solid lipid carriers, liquid crystals (LCs), microemulsions (MEs), and hydrogels.<sup>127–129,132–134</sup> The physicochemical characteristics of drugs, such as its hydrophilicity or lipophilicity, ionization, high molecular weight, poor bioavailability, extensive metabolization, and adverse effects, can result in its failure as a pharmacotherapeutic.<sup>127,135</sup> These limitations can be overcome by the use of intranasal administration, which offers an alternative, noninvasive means of drug delivery to the brain because drugs delivered this way can bypass the BBB and directly transport drugs to the CNS.<sup>136,137</sup>

## Polymeric NPs

NPs are defined as particulate dispersions or solid particles with sizes ranging from 1 to 1,000 nm.<sup>138</sup> The structural organization of a nanosystem is based on its composition: the presence of compartments within nanocapsules<sup>139</sup> leads to oily or aqueous cores surrounded by thin polymer membranes,<sup>140</sup> whereas nanospheres provide a matrix-based organization of the polymeric chains (Figure 2).<sup>139</sup>

NPs have been prepared using several methods, including polymer polymerization,<sup>141,142</sup> ionic gelation or coacervation,<sup>143,144</sup> emulsion solvent evaporation,<sup>145–148</sup> spontaneous emulsification or solvent diffusion,<sup>149,150</sup> nanoprecipitation,<sup>151,152</sup> spray drying,<sup>29,153</sup> supercritical fluid technology,<sup>154</sup> and particle replication in non-wetting templates (PRINT).<sup>155–157</sup>

Drug delivery across the BBB to the brain may provide a significant advantage over currently used strategies without damaging the BBB.<sup>158,159</sup> The transport mechanism of NPs across the BBB can be explained by the increased retention of the NPs in the brain blood capillaries in combination with the adsorption of the NPs to the capillary walls. These events lead to a higher concentration gradient, which increases the transport across the endothelial cell layer and thus enhances the delivery to the brain.<sup>160</sup> Transport can also be facilitated through the inhibition of the efflux system<sup>160</sup> by using polysorbate 80 as the coating agent.<sup>161,162</sup> NPs may induce local toxic effects on the brain vasculature, leading to a limited permeabilization of the brain endothelial cells.<sup>160</sup> The use of a surfactant to solubilize the lipids of the endothelial cell membrane can enhance drug permeability across the



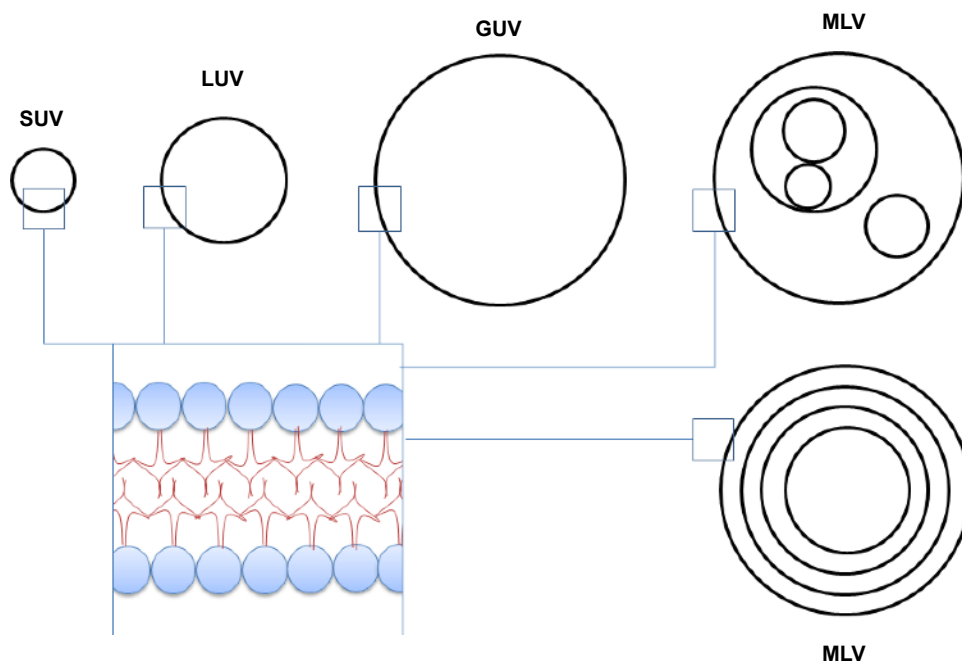
**Figure 2** Schematic differences between nanocapsule, nanostructured lipid carrier, polymeric nanoparticle, and solid lipid nanoparticle drug delivery systems.

BBB. The NPs could permeate the BBB through the tight junctions, which are open between the endothelial cells of the brain blood vessels.<sup>158,160,163</sup> Endocytosis by the endothelial cells followed by the release of the drugs within these cells facilitates delivery to the brain.<sup>164,165</sup> Transcytosis can also facilitate transport through the endothelial cell layer.<sup>166–168</sup> Finally, a combination of the effects described above can be used (Figure 3).<sup>158,160,163</sup> NPs can also be administered nasally to promote absorption<sup>169</sup> and delivery to the brain.<sup>160,170,171</sup> Other technological strategies include coating NPs with polyethylene glycol (PEG),<sup>172</sup> polymers, or antibodies to improve nasal absorption.<sup>173</sup> Surface modification of the NPs with mucoadhesive polymers can increase the retention time of NPs delivered via the nasal route.<sup>174</sup>

Wilson et al<sup>21</sup> developed polysorbate 80-coated poly(*n*-butyl cyanoacrylate) NPs loaded with tacrine, which were prepared by emulsion polymerization. The concentrations of tacrine in the lungs and kidneys were not significant when compared to both groups. The authors suggested a mechanism for delivery of the coated polysorbate 80 NPs to the brain via the interaction between the polysorbate 80 coating and the endothelial cells of the brain microvessels.<sup>21</sup> In another study, Wilson et al<sup>22</sup> developed poly(*n*-butyl

cyanoacrylate) NPs coated with polysorbate 80 for the targeted delivery of rivastigmine to the brain in order to treat AD. Animal studies were performed by injecting the NPs into mice. The concentration of tacrine in the brain was approximately 170 ng/mL when the coated NPs were used, and this result was significant ( $P < 0.001$ ) relative to the use of uncoated NPs or the free drug. The authors suggest that the mechanism for delivering the coated polysorbate 80 NPs to the brain is the interaction between the polysorbate 80 coating and the endothelial cells of the brain microvessels.<sup>22</sup> This specific role of the polysorbate 80 coating in targeting NPs to the brain was proposed and studied by Sun et al.<sup>175</sup>

Zhang et al<sup>23</sup> developed a dual-functional NP drug delivery system based on a PEGylated poly(lactic acid) polymer containing two targeting peptides, TGN and QSH, conjugated to the surfaces of the NPs. TGN specifically targets ligands at the BBB, while QSH has good affinity for  $A\beta_{1-42}$ , which is the main component of amyloid plaques. In this study, the optimal maleimide/peptide molar ratio was 3 for both TGN and QSH on the surface of the NPs. These NPs were delivered to amyloid plaques with enhanced and precisely targeted delivery in the brains of AD model mice.<sup>23</sup>



**Figure 3** Schematic representation of types of liposomes and enlarged view of the layers of phospholipids.

**Abbreviations:** GUV, giant unilamellar vesicle; LUV, large unilamellar vesicle; MLV, multilamellar vesicle; SUV, small unilamellar vesicle.

The use of intranasal NPs to deliver basic fibroblast growth factor (bFGF) to the brain for the treatment of AD was also studied by Zhang et al.<sup>24</sup> In this study, bFGF was entrapped in NPs conjugated with PEG and polylactide-polyglycolide (PLGA) and *Solanum tuberosum* lectin (STL), which selectively binds to *N*-acetylglucosamine on the nasal epithelial membrane to facilitate brain delivery. The NPs were prepared using the emulsion solvent evaporation method. The intranasal administration of the STL-modified NPs (STL-bFGF-NPs) resulted in a 1.7–5.17-fold greater distribution of the formulation in the brain than the intravenous administration of the NPs. The distribution of the formulation using intranasally administered STL-bFGF-NPs was also 0.61–2.21-fold greater than an intranasally administered drug solution and 0.19–1.07-fold greater than intranasally administered unmodified NPs. The activity of ChAT in mice showed a significant increase ( $P < 0.05$ ) in the group treated with NPs via the intranasal route compared to the AD control group. These findings indicated that ChAT activity in the hippocampus of AD rats treated with bFGF-loaded STL-conjugated NPs was higher than in the rats treated with unconjugated NPs. The STL-conjugated NPs could effectively facilitate the direct transport of bFGF into the rat brain with reduced peripheral adverse effects following intranasal administration.<sup>24</sup> Based on these requirements, PEG–PLGA copolymer NPs that feature a PEG-rich surface around the PLGA core are ideal for intranasal administration because the PEG-rich surface has

been demonstrated to prevent the NP aggregation typically observed when the uncoated PLGA NPs come into contact with the nasal mucosa.<sup>176</sup>

Poly[(hexadecyl cyanoacrylate)-*co*-methoxypoly(ethylene glycol) cyanoacrylate] NPs were formulated by Brambilla et al.<sup>25,26</sup> The authors investigated the effects of these NPs in slowing down or disrupting the aggregation process in vitro through kinetic studies performed with the  $A\beta_{1-42}$  peptide or corresponding oligomers by capillary electrophoresis. The capillary electrophoresis experiments showed that these NPs could link the  $A\beta_{1-42}$  peptide both under its monomeric and soluble oligomeric forms. These NPs were also shown to influence  $A\beta_{1-42}$  peptide aggregation, which was confirmed by thioflavin-T assays.

Joshi et al<sup>27</sup> used a modified nanoprecipitation method and an emulsion polymerization method to prepare rivastigmine-loaded PLGA and PBCA NPs, respectively. The administration of rivastigmine formulations in saline-treated animals did not result in any noticeable improvement in learning and memory capacities, whereas the administration of different rivastigmine-loaded NPs in scopolamine-treated mice antagonized the scopolamine-induced amnesia, as evidenced by a significant decrease ( $P < 0.05$ ) in escape latency.

Fazil et al<sup>28</sup> prepared chitosan NPs using an ionic gelation method to enhance the bioavailability and uptake of rivastigmine to the brain via intranasal delivery. Using confocal laser scanning fluorescence microscopy, their findings showed



that the concentration of rivastigmine in the brain following intranasal administration was found to be significantly higher at all times compared to the administration of a rivastigmine solution via the intravenous or intranasal route.<sup>28</sup>

Amorim et al used the spray-drying technique to develop idebenone-loaded chitosan and *N*-carboxymethylchitosan NPs.<sup>29</sup> Although the authors did not study the use of these NPs in the treatment of AD, the beneficial effects of idebenone for the treatment of AD<sup>177,178</sup> and its role as an antioxidant in AD progression<sup>55,58,179–181</sup> have been well documented in clinical trials. The incorporation of idebenone in chitosan or *N*-carboxymethylchitosan NPs was shown to preserve the antioxidant efficiency, especially at higher polymer-to-drug ratios. The NPs showed a tenfold increase in drug stability compared to the free drug. These results showed a severe reactivity of free idebenone that was similar to the positive control, indicating a significant potential for corrosion or irritation. On the other hand, the incorporation of idebenone in polymeric NPs showed a decrease in drug reactivity.<sup>29</sup> Because chitosan and *N*-carboxymethylchitosan exhibit mucoadhesive properties,<sup>182–187</sup> these results revealed that NPs are potential carriers for the nasal delivery of hydrophobic and irritating drugs such as idebenone due to the high first-pass metabolism of idebenone<sup>188</sup> after oral administration.

## Solid lipid carriers

SLNs are typically spherical, with average diameters between 10 and 1,000 nm when dispersed in water. SLNs possess a solid lipid core matrix that can solubilize lipophilic molecules.<sup>189</sup> The lipid core, typically consisting of triglycerides (eg, tristearin), diglycerides (eg, glyceryl behenate), monoglycerides (eg, glycerol monostearate), fatty acids (eg, stearic acid), steroids (eg, cholesterol), or waxes (eg, cetyl palmitate),<sup>190</sup> is stabilized by surfactants, though the combination of emulsifiers might be more efficient at preventing particle agglomeration.<sup>190</sup> Though SLNs are formed by a matrix lipid, a new generation of NPs can be produced using a blend of solid lipids with a liquid lipid, termed nanostructured lipid carriers (NLCs),<sup>189,191</sup> in order to minimize the drug expulsion associated to SLNs (Figure 2).

SLNs or NLCs are prepared from lipids, an emulsifier, and water or solvent by using different methods such as high pressure homogenization,<sup>192,193</sup> an ultrasonication/high-shear technique,<sup>194–198</sup> the solvent evaporation method,<sup>199,200</sup> the solvent emulsification-diffusion method,<sup>201–204</sup> the supercritical fluid method,<sup>205,206</sup> the ME-based method,<sup>207–209</sup> the spray-drying method,<sup>210–212</sup> the double emulsion method,<sup>213</sup> or the precipitation technique.<sup>214</sup>

The BBB can be overcome through the use of SLNs or nanocarriers lipids for the delivery of drugs to the brain, as these formulations can penetrate the BBB<sup>194</sup> or be used intranasally to bypass the BBB. The use of cationic lipids can be a strategy to improve mucoadhesion in the nasal cavity by promoting electrostatic interactions with mucus<sup>215</sup> in addition to mediating the adsorptive-mediated transcytosis of cationic NPs across the BBB.<sup>216</sup> Coating NPs with surfactants can be an alternative strategy for delivery across the BBB. The transport of surfactant-coated NPs across the BBB may occur through endocytosis mediated by the endothelial cells of the brain capillaries.<sup>217–219</sup>

Piperine SLNs with a polysorbate 80 coating were prepared by the emulsification-solvent diffusion technique.<sup>30</sup> These NPs were experimentally assessed in ibotenic acid-induced AD in mice. The results showed an increase in AChE activity and improvement in cognition, which were superior to the result shown for donepezil. Histopathology studies also revealed a reduction in plaques and tangles.<sup>30</sup>

Sood et al<sup>31</sup> developed curcumin/donepezil-loaded NLCs for delivery to the brain via the intranasal route. The results demonstrated a higher concentration of drugs in the brain via intranasal delivery compared to intravenous administration. A mouse model showed improved memory and learning compared to the group treated with the free drug. Nevertheless, the levels of acetylcholine were improved and oxidation damage was reduced in the groups treated with NLCs.<sup>31</sup>

Zhuang et al<sup>32</sup> formulated vinpocetine-loaded NLCs using a high-pressure homogenization method for improved oral bioavailability. Pharmacokinetic studies showed a twofold increase, threefold increase, and 0.35-fold decrease in the maximum concentration, maximum time, and elimination constant in plasma, respectively, relative to a suspension of vinpocetine. The authors concluded that the NLCs showed a relative drug bioavailability of 322% in rats after oral administration compared with the administration of free drug in suspension, further demonstrating that these NLCs can be used to load drugs with poor water solubility. AD-based clinical trial has shown that vinpocetine is a drug with potential use in the treatment of cognitive impairment and memory.<sup>220</sup> However, a 2003 Cochrane Review determined that the results were inconclusive.<sup>221</sup>

NLCs with oil-based cores loaded with resveratrol were developed by Frozza et al in order to improve cerebral bioavailability.<sup>33</sup> The results showed 2.5-fold, 6.6-fold, and 3.4-fold greater drug concentrations in the brain, liver, and kidneys, respectively, of mice treated with the NLCs relative to those treated with free resveratrol.<sup>33</sup> Additional

important data showed that mice treated with an intracerebral infusion of  $A\beta_{1-42}$  had memory deficits that were reduced only by the treatment with drug-loaded NCLs with oil-based cores.<sup>33</sup> Recently, a study using resveratrol confirmed the accumulation of this drug *in vivo* and the neuroprotective action of a kinase against  $A\beta$  plaques.<sup>222</sup> This study demonstrates the emerging therapeutic potential of resveratrol in AD.

Bondi et al<sup>223</sup> developed ferulic acid-loaded SLNs using the ME technique as a potential treatment for AD. In this study, unloaded SLNs showed no cytotoxicity against human neuroblastoma, but they showed the ability to penetrate into these cells. Cells treated with ferulic acid-loaded SLNs showed a greater reduction in the production of radical oxygen species than cells treated with the free drug.<sup>223</sup> These findings demonstrate that drug-loaded SLNs possess a higher protective activity than the free drug against oxidative stress induced in neurons, suggesting that these SLNs are potentially excellent carriers for transporting cholinergic agent drugs into the cells.

Patel et al proposed a study to comparatively evaluate the *in vitro* and *in vivo* behaviors of huperzine A-loaded lipid-based nanocarriers.<sup>35</sup> Huperzine A is a well-tolerated drug that has been shown in a clinical study to effectively reverse or attenuate cognitive deficits.<sup>224</sup> Huperzine A was loaded on SLNs and NLCs, which were prepared using the ME technique before the nanocarriers were dispersed on a gel. *Ex vivo* permeation studies were carried out, and the results showed that NLCs had increased permeability through the abdominal rat skin relative to SLNs. A primary irritation test in rabbit model indicated the safety of applying the drug-loaded nanocarrier-based gel to skin. The *in vivo* efficacies of the nanocarrier-based formulations were also tested in a scopolamine-induced amnesia model. A significant improvement in cognitive function was observed in mice treated with the nanocarrier-based formulations compared with the control group. A decrease in cognitive function was observed upon oral delivery of a drug suspension compared with the transdermally administered nanocarrier. These findings showed a reduced transfer latency over the period of 3 days, which indicated the sustained and controlled release of the drug from the developed nanocarriers when administered via the transdermal route.<sup>223</sup>

Studies have demonstrated that curcumin decreases the *in vitro* and *in vivo*  $A\beta$  formation from APP and also inhibits the aggregation of  $A\beta$  into pleated sheets.<sup>225–228</sup> Curcumin has been incorporated into SLNs and NCLs for other therapeutic purposes.<sup>229–234</sup> Kakkar et al evaluated curcumin-loaded SLNs

for brain delivery in rats via the oral route.<sup>36</sup> The results showed that drug-loaded SLNs increased the activity of AChE compared to the free drug, and the concentration of curcumin was increased by twofold in the brain compared to the free drug when both treatments were orally administered. Although a cerebral ischemic reperfusion injury animal model was used in the study, these SLNs can be used for drug release in the brain for the treatment of AD.<sup>36</sup> SLNs and NCLs that are chosen as drug carriers and administered *in vivo* can be transported to the CNS<sup>34,165,194,235–238</sup> and may be useful in the treatment of AD.

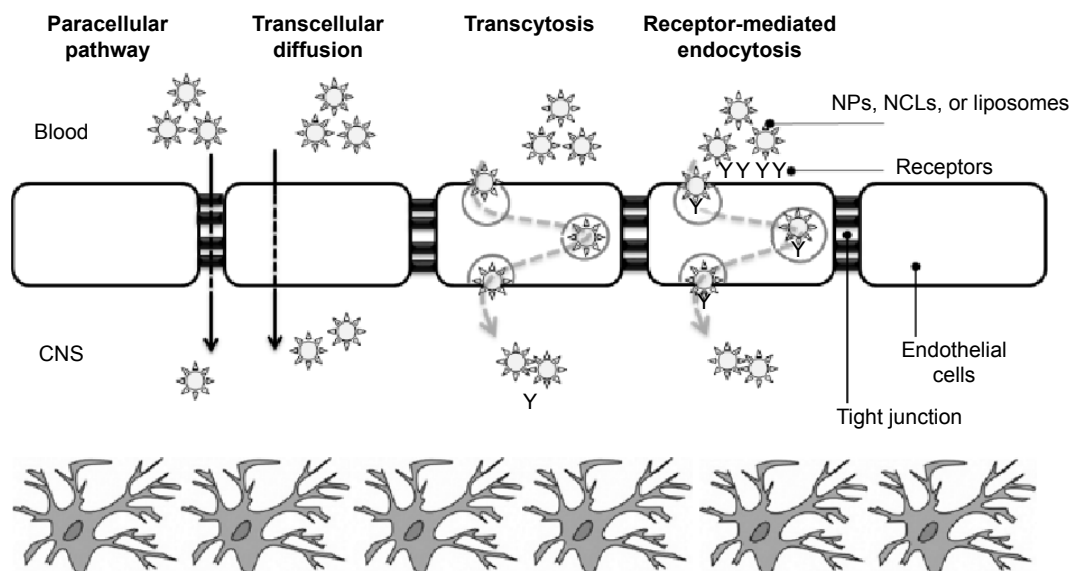
## Liposomes

Liposomes are vesicles consisting of one or more phospholipid bilayers concentrically oriented around an aqueous compartment<sup>239</sup> that serve as carriers of lipophilic or hydrophilic drugs.<sup>240,241</sup> Various processes can be used to prepare liposomes, such as hydration of a thin lipid film<sup>242–244</sup> followed by agitation,<sup>245–248</sup> sonication,<sup>249–254</sup> extrusion,<sup>251,255–258</sup> high-pressure homogenization,<sup>259–262</sup> or reverse-phase evaporation.<sup>263–266</sup>

Liposomes may contain a single lipid bilayer or multiple bilayers around the inner aqueous compartment and are therefore classified as unilamellar and multilamellar, respectively.<sup>267</sup> Liposomes are classified by their lamellar size as small unilamellar vesicles with diameters of 20–100 nm, large unilamellar vesicles with diameters exceeding 100 nm, giant unilamellar vesicles with diameters up to 1  $\mu\text{m}$ , oligolamellar vesicles with diameters of 0.1–1  $\mu\text{m}$ , and multilamellar vesicles with diameters up to 500 nm (Figure 4).<sup>268</sup>

In the literature, liposomes are classified as niosomes, transfersomes, ethosomes, and phytosomes. Niosomes are formed by self-assembly of nonionic surfactants in an aqueous dispersion and they are flexible and more stable than liposomes, which reduces the flux of drugs in comparison to conventional liposomes.<sup>269</sup> Transfersomes are deformable vesicles composed of phospholipids<sup>270</sup> that are usually administered via the transdermal route.<sup>271</sup> Ethosomes are either conventional liposomes or are transfersomes containing up to 10% ethanol, which can promote the solubilization of hydrophilic drugs.<sup>272</sup> Phytosomes are produced by binding individual components of herbal extracts to phosphatidylcholine.<sup>273</sup>

Yang et al formulated rivastigmine liposomes and cell-penetrating peptide (CPP)-modified liposomes to improve the distribution of rivastigmine in the brain, enhance the pharmacodynamics via intranasal administration, and minimize side effects.<sup>37</sup> The results showed that the concentrations of rivastigmine across the BBB were significantly



**Figure 4** Main pathways for nanosystems to cross the blood–brain barrier to target to brain.

**Abbreviations:** CNS, central nervous system; NCLs, nanostructured lipid carriers; NPs, nanoparticles.

different after 8 hours, reaching higher concentration values when CPP liposomes and liposomes were used compared to the free drug. The biodistribution of rivastigmine in the cerebellum was not found when free drug was administered intranasally or intravenously. The average rivastigmine concentration in CNS cerebral tissues was higher following intranasal administration of modified liposomes compared with liposomes, and the average rivastigmine concentration was significantly higher for the modified liposomes in the hippocampus, cortex, and olfactory region at 15 minutes to 60 minutes. The authors suggest that rivastigmine-loaded liposomes, especially-modified liposomes, improve the brain delivery and enhance pharmacodynamics with respect to BBB penetration and the nasal olfactory pathway into the brain after intranasal administration.<sup>37</sup>

In a study designed by Kumaraswamy et al, liposomes were obtained using the thin-film hydration technique.<sup>39</sup> Thermal studies showed that the beta-sheet blocker was located in the hydrophobic core, where it acted to lower the surface tension. This property made these liposomes a suitable therapeutic agent for the prevention of amyloid aggregation by binding with A $\beta$  in the brain.<sup>39</sup>

Many techniques are used to target liposomes across the BBB. These strategic techniques include the conjugation of drugs and monoclonal antibodies against endogenous receptors in the BBB<sup>173,274,275</sup> or liposomes or other nanodevices coated with polysorbate 80, cationic macromolecules, peptides, or antibodies against BBB receptors or A $\beta$  peptides<sup>173,276–279</sup> to cross the BBB and to be targeted to the brain.

Liposomes functionalized with an anti-transferrin receptor antibody can cross the BBB. The functionalization of liposomes gave higher values of uptake and permeability across the barrier model in comparison to non-decorated liposomes.<sup>280</sup> Liposomes were functionalized with a modified cell-penetrating TAT peptide, which increased the permeability of curcumin-loaded liposomes across a BBB model.<sup>40</sup>

Mono- and dual-decorated liposomes were prepared by immobilization of anti-transferrin monoclonal antibody (MAb) against transferrin receptor in BBB and a peptide analog of apolipoprotein (PAA) to target low-density lipoprotein receptor in BBB. The major results showed liposome uptake and transport across the human microvascular endothelial cells (hCMEC/D3) used as a model barrier was significantly affected by decoration with PAA or MAb, and that the double immobilization with ligands in the liposomes exerted an additive effect in the BBB targeting. The mechanism of targeting was confirmed to be vesicle transcytosis. In vivo study was carried out in mice, and the results showed that MAb and dual ligands (MAb and PAA) increased brain targeting compared to nontargeted liposomes. The authors appointed a contradiction between in vitro and in vivo results. PAA was found to target BBB and increase the in vitro targeting potential of MAb-decorated liposomes, but not in vivo, because in vitro studies were carried out in the presence of serum proteins in the middle of cell culture, revealing their important role in targeted-nanoformulation performance.<sup>41</sup>

Another published study explored the use of MAb in liposomes loaded with curcumin analog. This study compared

the ability of both curcumin analog- and curcumin-loaded liposomes and showed a high affinity for senile plaques on postmortem brain tissue of AD patients. The ability of both liposomes to delay A $\beta$ <sub>1-42</sub> peptide aggregation was confirmed. However, the decoration of the curcumin-derivative liposomes with the MAb improved significantly the intake by the BBB cellular model. These results prove the potential of such multifunctional liposomes for application in AD treatment and diagnosis.<sup>42</sup>

Curcumin-conjugated liposomes were developed and the results showed significant amounts of labeled A $\beta$  deposits in postmortem brain tissue of AD patients. In vivo injection in the hippocampus and in the neocortex of mice showed that curcumin-conjugated nanoliposomes were able to specifically stain the A $\beta$  deposits.<sup>43</sup> Thus, these liposome formulations can be applied in diagnosis and targeted drug delivery in AD.

Curcumin derivative maintaining the planarity was developed to obtain conjugated liposomes. Surface plasmon resonance experiments indicated that the liposomes exposing the curcumin derivative had extremely high affinity for A $\beta$ <sub>1-42</sub> fibrils, likely because of the occurrence of multivalent interactions, whereas those exposing non-planar curcumin did not bind to A $\beta$ <sub>1-42</sub>.<sup>44</sup>

Ligand-functionalized nanoliposomes for targeted delivery of galantamine have also been designed. The major result revealed by confocal microscopy was that the ligand-functionalized nanoliposomes facilitated galantamine uptake into PC12 neuronal cells.<sup>45</sup> Nevertheless, in vivo uptake studies should be performed as well as testing in animal models of AD to demonstrate the effectiveness of the nanosystem.

Liposomes were prepared by the lipid hydration method to sustain the effect of rivastigmine in the brain. Rivastigmine-loaded liposomes and rivastigmine solution were administered via the subcutaneous route in an aluminum chloride-induced Alzheimer's model. Both formulations improved the deterioration of spatial memory induced by aluminum chloride, with liposomes having a superior effect. Though the rivastigmine solution significantly attenuated AChE activity, rivastigmine-loaded liposomes succeeded in normalizing AChE.<sup>38</sup>

The delivery of liposomes to the brain can be attained via the intranasal route to overcome the BBB,<sup>169,281,282</sup> and liposomes can cross the BBB by transport lipid-mediated free diffusion or lipid-mediated endocytosis.<sup>283</sup> Rivastigmine-loaded liposomes were prepared using the lipid hydration method for delivery into the brain via the intranasal route. Intranasally delivered liposomes were compared to the

orally delivered free drug group. The results showed that maximum concentration was tenfold higher in plasma and the half-time was significantly different for the intranasally delivered liposome group compared to the intranasally delivered free drug group or the orally delivered free drug group.<sup>46</sup> Rivastigmine-loaded liposomes were administered orally and intraperitoneally in an AD animal model, and the results showed the highest AChE inhibition with the use of rivastigmine–sodium taurocholate liposomes.<sup>47</sup>

The transport of rivastigmine-containing liposomes across Caco-2 cells has also been studied. The highest cumulative amount of rivastigmine to pass through the Caco-2 cell cultures was found for the rivastigmine–sodium taurocholate solution compared to the rivastigmine–sodium taurocholate liposome. Rivastigmine liposomes and molecular solutions were also administered to animals and the AChE activity calculated using blood and brain tissue samples, and the highest value of AChE inhibition was observed for the rivastigmine and sodium taurocholate liposomes.<sup>48</sup>

Folic acid niosomes were prepared using different non-ionic surfactants and cholesterol via the lipid hydration technique, and ex vivo perfusion studies were performed using a rat model. The drug was found to be absorbed through the nasal cavity at the end of 6 hours.<sup>49</sup> Folic acid has been associated with an improvement in the response of cholinesterase inhibitors in people with AD.<sup>284</sup>

Freeze-dried niosomes loaded with *G. biloba* extract were developed with improved oral bioavailability. The in vivo distribution of GbE niosomes in the rat showed that the flavonoid glycoside biomarker content in the brain was significantly higher for the niosome group than for the *G. biloba* extract tablet group.<sup>51</sup> Change in pharmacokinetic behavior, in vivo distribution, and higher accumulation in the brain with the use of the plant drug extract or AChE inhibitor drugs indicate the pharmacotherapeutic uses of niosomes in diseases affecting the brain. Phytosomes containing *G. biloba* were administered to rats via the oral route. Compared to a sodium nitrite treatment, these phytosomes were able to increase the activities of antioxidant enzymes in all the brain regions.<sup>50</sup> However, many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that *G. biloba* has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.<sup>285</sup>

## Surfactant-based systems

Surfactant-based drug delivery systems are different drug delivery systems in which surfactant molecules are

self-aggregated, usually in the presence of water, to form structures with variable parameters depending on the concentration of the surfactant, the presence of salts, or the temperature. These aggregates become more organized even when oils or other components such as other surfactants are added to the surfactant–water system.<sup>286</sup> Thus, MEs, nanoemulsions (NEs), and lyotropic LC mesophases with different geometries can be generated.<sup>286,287</sup>

MEs are usually thermodynamically stable isotropic liquids formed by mixing oil, water, and surfactants together. NEs, by contrast, are conventional emulsions that contain very small particles. The droplet sizes of MEs are between 10 and 140 nm,<sup>288</sup> which results in optically transparent and thermodynamically stable systems.<sup>289,290</sup> NEs are up to 140 nm in diameter and are not transparent and less thermodynamically stable than MEs (Figure 5).<sup>290</sup> The two systems are very different because NEs are formed by mechanical shearing and ME phases are formed by self-assembly.<sup>291</sup>

Other parameters can distinguish MEs from NEs: MEs are more stable in long-term storage than NEs; MEs can be agitated, cooled, or heated and then returned to their original conditions, whereas NEs cannot return to their original conditions; MEs have a homogeneous droplet size while NEs have a range of heterogeneously sized droplets; and MEs may or may not contain spherical droplets due to the lower interfacial tension while NEs consist of spherical droplets due to the large Laplace pressure acting upon them.<sup>290</sup>

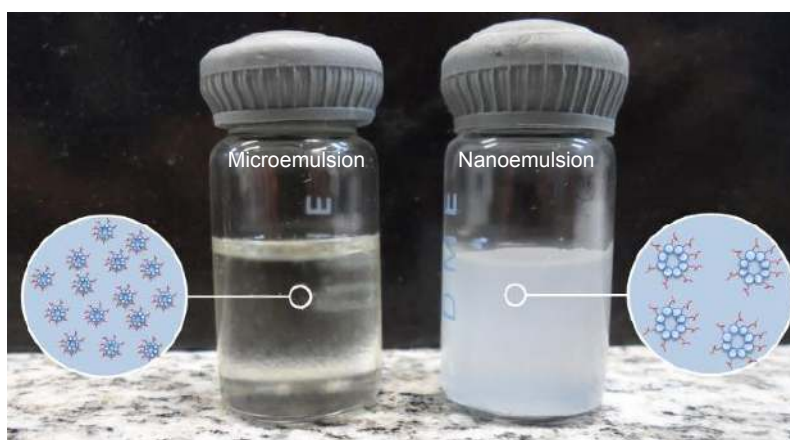
MEs are formed from spontaneous mixtures of oils, water, and surfactants,<sup>292,293</sup> though it is often necessary to apply stirring or heating<sup>292,294</sup> to facilitate the formation of MEs due to kinetic energy barriers that must be overcome or mass transport limitations that inhibit their spontaneous formation.<sup>290</sup> NEs are formed using the input of some external

energy provided by high-pressure homogenizers,<sup>295–297</sup> microfluidizers,<sup>298</sup> and sonication methods<sup>299</sup> to convert the mixture into a colloidal dispersion or phase inversion. Spontaneous emulsification methods<sup>296</sup> can then be used to form NEs.

NEs containing curcumin were developed for intranasal delivery, and the results from behavioral experiments showed improved memory and learning in the group treated with curcumin-loaded NEs compared with the group treated with the pure drug.<sup>300</sup> MEs were developed for transdermal delivery in order to manage AD, and mice given MEs containing huperzine A showed improved cognitive functions compared to mice given the drug in suspension via the oral route.<sup>35</sup> An ME-based patch for the transdermal delivery of huperzine A and ligustrazine phosphate was developed, and the results showed that, unlike the monotherapy, the combined therapy had a synergistic effect against amnesia induced in mice by 9 days after administration.<sup>301</sup>

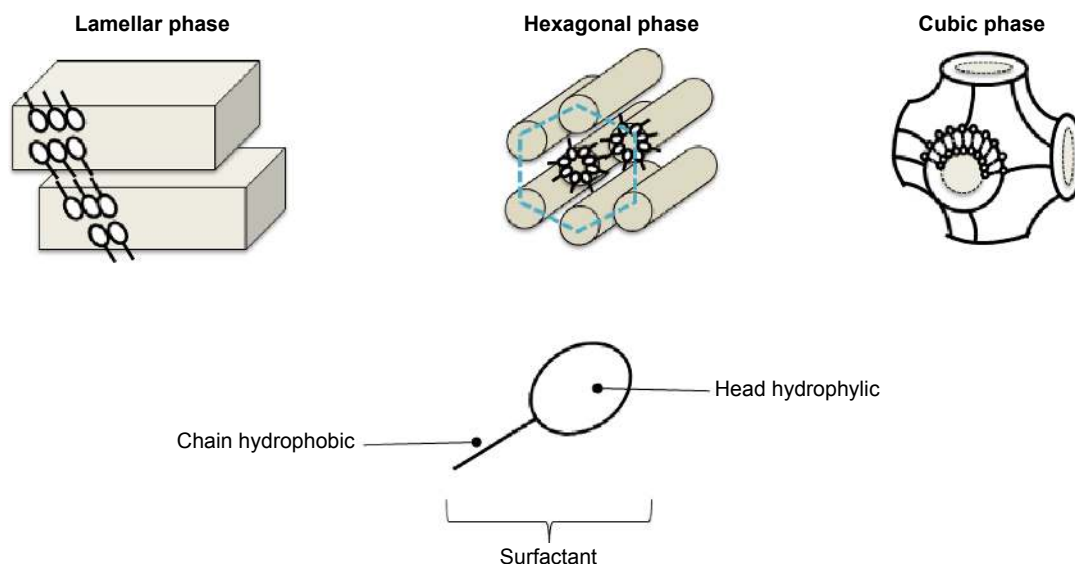
The intranasal administration of  $\beta$ -asarone-loaded MEs resulted in a ratio of  $AUC_{\text{brain}}/AUC_{\text{plasma}}$  that was significantly higher compared to intravenous administration.<sup>52</sup> Another study was developed, in which an anticholinesterase alkaloidal extract from *Tabernaemontana divaricata* was loaded into MEs. The results showed a good stability of the MEs and an AChE activity of more than 80% by 180 days. Moreover, the skin permeation and retention of the formulation increased within 24 hours after transdermal delivery of the extract.<sup>53</sup>

Tacrine-loaded MEs showed a rapid absorption and nose-to-brain transmission that was twofold higher than that of an intranasally administered drug solution. A larger amount of tacrine was transported into the brains of scopolamine-induced amnesic mice after the intranasal



**Figure 5** Photograph of microemulsion and nanoemulsion.

**Note:** Enlarged areas show schematics of the size of droplets formed.



**Figure 6** Schematic representation of lamellar, hexagonal, and cubic liquid crystal mesophases formed by surfactant molecules' self-assembly.

administration of tacrine-loaded MEs. These mice also showed the fastest recovery of memory loss.<sup>54</sup>

LCs consist of matter in a state with properties between those of conventional liquids and those of solid crystals.<sup>302</sup> In other words, LCs have the structural behavior and rigidity of a solid combined with the mobility, disorder, and fluidity of an isotropic liquid.<sup>303</sup> Lyotropic mesophases can be considered to be micelles with ordered molecular arrangements characterized by alternating hydrophobic and hydrophilic regions.<sup>304</sup> By increasing the concentration of surfactants, lamellar, hexagonal, and cubic liquid-crystalline forms can be generated (Figure 6).<sup>305</sup>

The lamellar phase is formed from bilayers separated by layers of surfactants and solvents, which forms a one- or two-dimensional network.<sup>306</sup> In the hexagonal phase, the aggregates are formed by the arrangement of long cylinders that form two- or three-dimensional structures.<sup>307</sup> Lyotropic cubic phases have more complicated structures consisting of a curved, bicontinuous lipid bilayer that extends in three dimensions to generate two interpenetrating, but non-contacting, aqueous nanochannels.<sup>308,309</sup>

Self-assembly systems display phase transformations and notable in situ thickening after administration. These systems are also of interest in relation to drug delivery to the body cavities.<sup>305</sup> The intranasal administration of LCs can be interesting due to the dilution of LCs in nasal fluid, which promotes the phase transition to a hexagonal or cubic LC that can prolong the residence time of the formulation in contact with the mucosa.<sup>310</sup> In the case of LC phases, the mechanism of mucoadhesion most likely involves the rheological properties of the system, which are similar to those of in situ gelling

vehicles.<sup>311</sup> Due to their high viscosity, hexagonal and cubic phases have been suggested as mucoadhesives. However, the viscosity of cubic phases can hinder their nasal administration. To circumvent this handling problem, precursor formulations of liquid-crystalline mesophases have been proposed.<sup>312</sup> Numerous studies have shown that MEs and lamellar phase can be used as a precursor of the hexagonal or cubic phases<sup>310,311,313–317</sup> after the stimuli in situ.

LC systems significantly increased the transdermal delivery of the *T. divaricata* extract at 24 hours. When loaded into an LC system, an alkaloidal extract from the *T. divaricata* stem may act as an alternative percutaneous formulation for enhancing the acetylcholine level in patients with AD.<sup>53</sup>

The nasal administration of LCs in the treatment and management of AD is a tool that has been unexplored by researchers. LCs have been shown to be an optimal system for intranasal administration; in situ gelation occurs by dilution by nasal fluid and results in increased residence time in the nasal cavity and targeting of drugs to the brain.

## Remarks and challenges

Approximately 15 million people worldwide are currently afflicted by AD.<sup>3</sup> This number is expected to increase fourfold by 2050.<sup>3</sup> Nanotechnology offers the potential for designing drug delivery systems with many properties. In the context of treating AD, these types of nanosystems could efficiently carry and deliver drugs and other neuroprotective molecules to the brain.<sup>4,318,319</sup> The intranasal route plays a role in overcoming the BBB and targeting the drugs directly to the brain.<sup>282,319–325</sup> However, the oral, dermal, and intravenous routes can be used to administration of nanodevices

to target to the brain passing by BBB<sup>276,326–329</sup> to enhanced bioavailability, pharmacodynamic properties, and decreased adverse effects of these drugs to maximize pharmacotherapy in patients with AD.

Though the registry of patents for nanotechnology-based products is currently increasing,<sup>323,330,331</sup> clinical trials are needed to evaluate their clinical efficacy and potential toxicological effects to human health.<sup>332</sup> In the near future, neurologists and patients will benefit from suitable nanotechnology-based drug delivery systems that could lead to improved therapeutic outcomes with reduced costs. Although there are no clinical studies on the use of nanotechnology to treat AD, nanotechnology is also predicted to alter health care in neurology, providing novel methods for identifying AD<sup>19</sup> and customizing a patient's therapeutic profile.

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## Author contributions

BFS made substantial contributions in conceiving this review, searching the bibliographical data, conducting the analysis, and critically revising it for important intellectual content. MPDG and MC conducted the analysis and revised it critically for important intellectual content. All authors gave final approval of the version to be published.

## Disclosure

The authors report no conflicts of interest in this work.

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