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Recent development of prospective surface-engineered nanoparticles in the management of neurodegenerative disorders

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Abstract

Clinically, the therapeutic outcomes in neurodegenerative disorders (NDs) by drug treatment are very limited, and the most insurmountable obstacle in the treatment of NDs is the blood–brain barrier (BBB), which provides the highest level of protection from xenobiotics. A great deal of attention still needs to be paid to overcome these barriers, and surface-engineered polymeric nanoparticles are emerging as innovative tools that are able to interact with the biological system at a molecular level for the desired response. The present review covers the potential importance of surface-structure-engineered nanoparticles to overcome the BBB for good bioavailability, and the evaluation of drug therapy in NDs.

Keywords: BBB, conjugation, neurodegenerative disorders, surface-modified nanoparticles, transcytosis

Introduction

Neurodegeneration, which is the persistent and progressive loss of the function and structure of neurons, is a frequently occurring condition including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, and Huntington's disease (HD). In all cases of degenerative disorders, the aggregation of protein is a distinctive feature. The interesting observation in all the conditions mentioned above is that nearly the same type of protein has been found to be involved in different disorders of ND, seemingly following the same pathway in different disorders, while involvement of environmental factors (heavy metals, pesticides) is also speculated in different NDs (Cicchetti et al. 2009).

Among NDs, the conditions of AD and PD are the most prevalent (Zhou 2010), and both lead to high mortality and morbidity in developed countries (Hebert et al. 2001, 2003). Despite the presence of different well-developed diagnostic and treatment tools, successful treatment still seems to be challenging. Due to an increase in the aging population, the number of patients with AD and PD may also rise in the coming years. On the other hand, although a number of drugs have been developed to treat NDs, only a few of them reach the market (Pardridge 2002). The limited potential of many pharmaceutical entities results in unsatisfactory treatment. In neurodegeneration, the death of a specific type of neuron is the result of multiple deleterious molecular and cellular events, rather than a single pathological factor. A number of strategies have been employed in recent years, including the direct surgical administration of drugs into the brain, osmotic opening of the tight junctions, reversible disruption of the blood–brain barrier (BBB) by different nanocarriers, the use of prodrugs, and carrier-mediated transport (Wagner et al. 2012, Pardridge 1988, Neuwelt 1989, Begley 2004), followed by the use of polymeric nanoparticles and solid lipid nanoparticles, which are able to cross the BBB. Nanoparticles not only cross the BBB, but also protect the active drug from degradation and minimize the side effects (Kreuter et al. 1995). Alternative routes of delivery are the intraventricular/intrathecal route and the olfactory pathway. The surface modification of nanoparticles by apolipoprotein is also an effective way to cross the BBB (Kreuter et al. 2007, Petri et al. 2007).

Blood–brain barrier

The BBB is a specialized biological, highly dynamic, and physically efficient protective barrier interface between the blood and the central nervous system (CNS). Tight junctions, consisting of barrier cells called capillary endothelial cells, hinder the transcellular passage, while adherent tight junctions restrict para-cellular flux of charged molecules and molecules of high molecular weight over the brain parenchyma, while low molecular weight lipophilic molecules are able to enter the CNS by passive diffusion (Paolino et al. 2010). The BBB comprises the brain microvascular endothelial cells (BMECs), pericytes, and astrocytes, and neuronal processes

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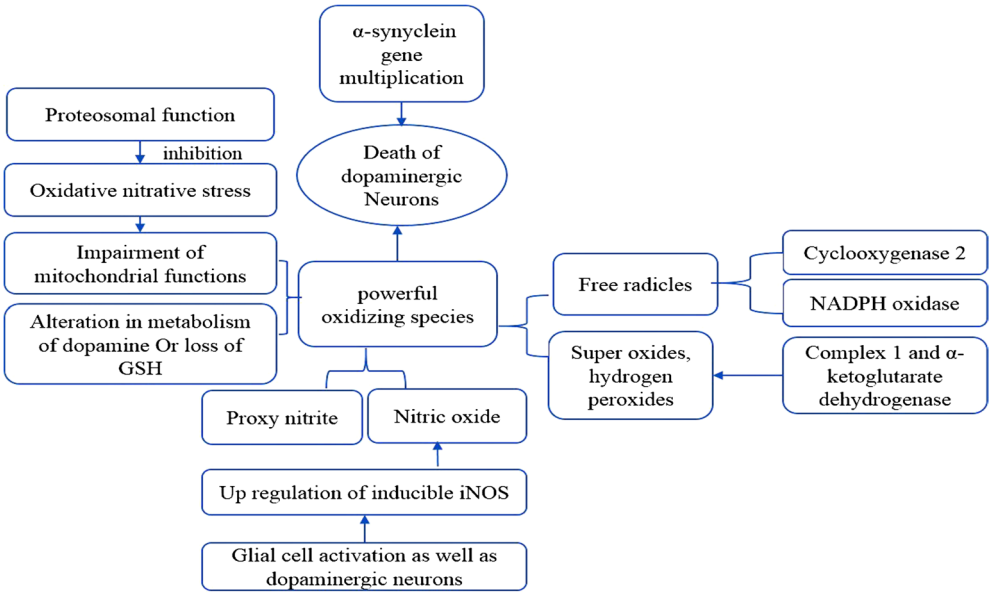

Figure 1. Different pathways leading to oxidative stress in PD.

that cover most parts of the brain side of BMECs. Permeability across the BBB is limited because of the BMECs, and only receptor-mediated and carrier-mediated transporters are allowed in through the blood side (luminal), along with various efflux transport systems (Brightman 1977, Banks and Kastin 1990, Tamai and Tsuji 2000). It has also been shown that the BMEC express a different type of enzyme which is also used to develop the restriction across the BBB (Bodor and Buchwald 1999). Tight endothelial cells were found to have a gap size of up to 600 nm in diameter in tumor-implanted mice (Hobbs et al. 1998). The BBB functions to protect the brain against xenobiotics, cytotoxins, peripheral neurotransmitters, and microorganisms.

A variety of strategies have been tried to overcome the BBB, for example, invasive techniques or implantation, drug modification, permeability enhancement (Patel et al. 2009), and coupling of drug with a substance which can pass the BBB. Small lipophilic molecules (with a molecular weight less than 400–500 Da) are able to cross, while the charge-bearing hydrophilic molecules require a gated channel, ATP protein, or receptor to cross the BBB (Pardridge 2006). The transporters yet to be identified are for the sugars, amino acids, nucleosides, monocarboxylic acids, organic anions, and organic cations, and include the organic cation transporters, organic anion transporters (polypeptides), glucose transporters, peptide transporters, ATP-binding cassette, and P-glycoprotein, which are mostly expressed in brain. Various efflux transporters (ASCT2, NET, OAT3) are present at the albuminal site of the endothelial cell membrane and they are used to efflux the metabolites and neurotoxic compounds that are developed in the brain (Ohtsuki and Terasaki 2007). Among different approaches that do not interfere with route functioning are the receptor and adsorption-mediated transcytosis, the most attractive mechanisms to facilitate the transport across the BBB (Bhaskar et al. 2010). For successful brain delivery, many tasks need to be considered, for example, surface decoration, prolonged half-life, bypassing reticuloendothelial uptake (RES), biocompatibility and non-immunogenicity, protection from enzymatic degradation, and the different orders of targeting (cell-, tissue-, and organ-specific) that can be achieved.

Neurodegenerative disorders

Alzheimer's disease

AD is a brain disorder causing the most common type of dementia in the elderly, and is characterized by the formation two protein aggregates—neurofibrillary tangles and senile plaque—which are the main factors in the progressive neuronal degeneration and death. The senile plaques are developed by deposition, in the human brain, of fibrils of amyloid-β peptide, derived from the proteolytic processing of the amyloid precursor protein. Neurofibrillary tangles are a complex filamentous network, and tau protein was found to be the major component of this complex network. Cyclin-dependent kinase (Cdk5) and glycogen synthase kinase (GSK3β) have been shown to be involved in tau phosphorylations. Cdk5 is associated with neurogenesis and plays an important role in brain development. Extracellular amyloid loading induces the deregulation of protein kinase, which results in tau hyper-phosphorylation, further triggering cascades of events that lead to neurodegeneration; as evidenced, inhibition of Cdk5 and GSK3b exhibits protection against neurodegeneration, which, along with oxidative stress, constitutes an important factor in the modification of the general signaling pathway in neurons, causing the neurodegeneration and leading to structural and biochemical abnormalities, which seem to be related to the pathogenesis of AD (Maccioni et al. 2001).

Parkinson's disease

PD is a state of progressive degeneration of midbrain nigrostriatal dopaminergic neurons, which results in a reduction in dopamine (DA) level in the brain, characterized by motor

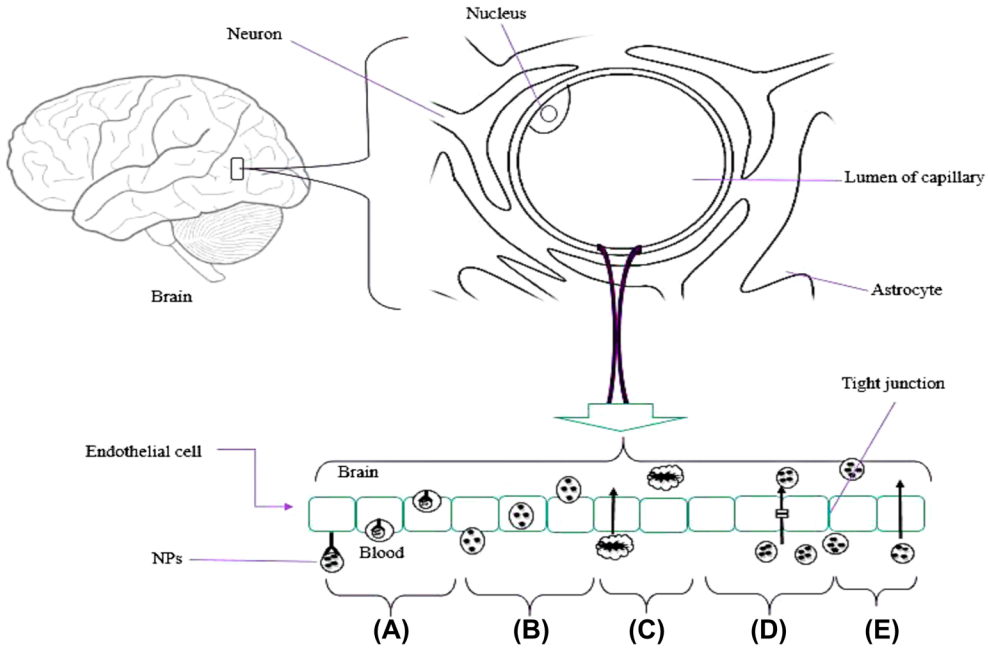

Figure 2. Different mechanisms of nanoparticle transport across the BBB (A) Receptor-mediated transcytosis (B) Adsorption-mediated transcytosis (C) Transcellular pathway (D) Paracellular transport (E) Passive diffusion.

and non-motor symptoms. Selective degeneration of the nigrostriatal dopaminergic pathway is one of the key features known of PD, and the key motor symptoms of PD are the bradykinesia and rigidity. The highly affected areas in the brain include the basal ganglia, brainstem, and cerebellum, which may be associated with tremors. Substantia nigra pars compacta (SNpc) neurons were found to form the nigrostriatal dopaminergic pathway, and the loss of SNpc neurons results in striatal DA deficiency, which is responsible for most symptoms of PD; the striatal DA deficiency or striatal damage may result in the syndrome of Parkinsonism.

The first hereditary connection was linked to the protein α-synuclein, and its genetic locus on chromosome 4 is now known as PARK1. Other additional loci, namely PARK2 through PARK12, have also been implicated. The mutation in the α-synuclein gene leads to the amino acid substitution, as was seen in a family with an early-onset autosomal form of PD; α-synuclein is considered to be a major factor in the pathogenesis of PD (Polymeropoulos et al. 1997, Spillantini et al. 1997). Currently, the first choice of therapy is the dopamine agonist levodopa; others are the peripheral decarboxylase inhibitors carbidopa and benserazide, dopaminergic agonists such as bromocriptine, pergolide, pramipexole, MAO inhibitors such as selegiline, and dopamine facilitators such as amantadine.

Huntington's disease

HD is a devastating chronic autosomal dominant, progressive and fatal ND cause by a single mutation on the HTT gene, resulting in the repeat expansion of CAG trinucleotide (36 or more repeats), which encodes the huntingtin protein (containing more than 3000 residues). HD is characterized by weight loss, behavioral changes (chorea, dementia), dystonia, severe motor impairments, and cognitive dysfunction, as a result of brain atrophy and progressive loss of striatal neurons. Neuronal loss has also been observed in the thalamus, subthalamic nucleus, and substantia nigra pars reticulate in advanced cases of HD (Ferrante et al. 1985, Rubinsztein 2002). Pathologically, HD is characterized by neuronal loss in the cortex and striatum, and the other highly affected area includes the hippocampus. The mutation of the HTT gene in production of huntingtin protein further develops the aggregates within cells, which ultimately produce the toxic, insoluble, and filamentous neuronal intra-nuclear inclusions (NIIs) in the nucleolus of the cell (Gil-Mohapel et al. 2011). For the symptomatic management of movement disorder in HD, the most widely used drugs are olanzapine, risperidone, quetiapine, sulpiride, haloperidol, clonazepam, and sodium valproate. The psychiatric symptoms of HD are managed with aripiprazole, citalopram, fluoxetine, paroxetine, sertraline, venelafaxine, limotrigine, and carbamazepine.

Mechanisms involved in penetration of nanoparticles through the BBB

Adsorptive-mediated transcytosis

Adsorptive-mediated transcytosis is associated with interaction between ligand and charge at the luminal surface of endothelial cells. Penetrating peptides and cationic proteins, for example, albumin, are generally used for surface modification of the developed nanocarrier to enable it to cross the BBB.

Receptor-mediated transport

Endothelial cells of the BBB express the receptor-mediated transport (RMT) system to transport the large molecules by transcytosis to the CNS. It develops the vesicles and dispenses their content on the luminal site of the BBB.

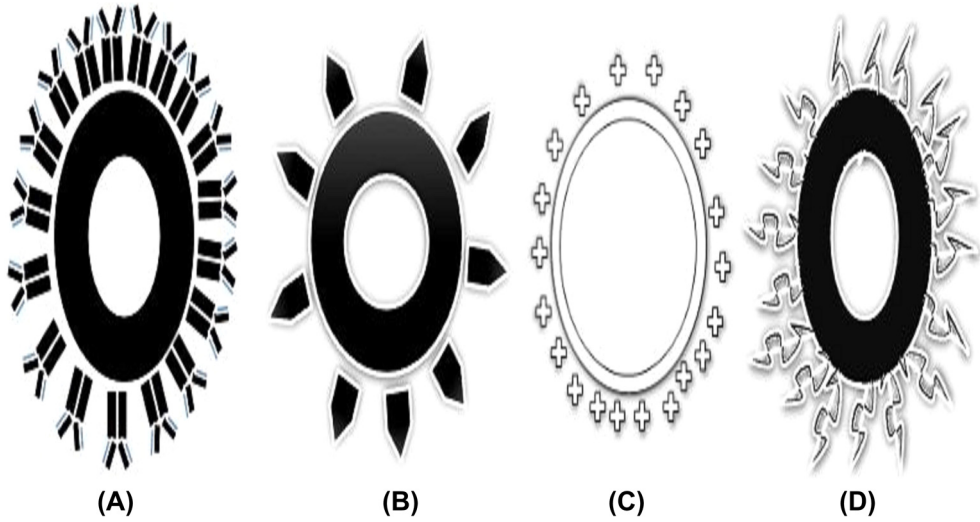

Figure 3. Surface-modified nanoparticles (A) Antibody-coated (B) Ligand-appended (C) Cyclodextrin-modified (D) PEGylated nanoparticle.

RMT of large molecules covers the proteins, nanoparticles, enzymes, liposomes, and genes. RMT is a mechanism based on the receptors expressed at the BBB (endothelial cells) which recognize a few substances and allow them across the BBB; for example, apolipoprotein E (Apo E), transferrin, macroglobulin, and monoclonal antibodies including the OX26, RD3, and R17217 are the biomolecules used for the surface modification to act as a directive unit across the BBB (Kim et al. 2007). Various strategies have been used to overcome the BBB, and among them, RMT has been found to be effective, in various studies. The RMT system is designed in such a way that the drug-loaded carrier is appended with the suitable ligands which have high affinity to the receptors, for example, insulin receptors, low density lipoprotein receptors, and transferrin receptors present at the drug entry sites of BBB.

Carrier-mediated transport

Carrier mediated transport (CMT) allows a few small molecules, hormones, and amino acid nutrients across the BBB, in a concentration gradient manner. A CMT transporter is capable of selecting the substrate and carrying it via uni- or bidirectional mono-, co-, or counter transport. The transport rate is associated with substrate affinity toward the transporters (De Boer and Gaillard 2007, Smith 1993). Many reports have been published in recent years concerning this area, on the structural similarities between the endogenous transporter substrate and the therapeutic molecules (Tamai et al. 2000).

Importance of surface-modified nanoparticles

Nanoparticles used for the delivery system are of 10–1000 nm in size, with the capacity for drug delivery to different parts of the body; nanoparticles have gained a lot of attention in recent decades for use in delivery across the BBB, because they are easy to modify according to the physiological requirement, and help in increasing the understanding of receptors, which would facilitate great development in nanotechnology and polymer chemistry. Among different nanocarriers, nanoparticles have been extensively exploited in drug delivery across the BBB and a few of them are under clinical trials.

The number of different scientific studies based on surface modification of the nanoparticles for application in brain drug delivery has drastically increased in the recent past few decades, and the nanoparticles are designed in such a way that they are able to overcome many of the problems associated with the traditional carriers. The properties which make surface-modified nanoparticles as a first choice of carrier are, for example, their ability to maintain the integrity

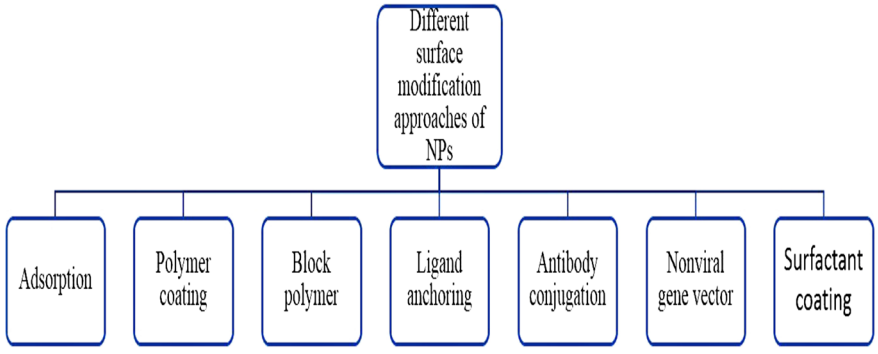

Figure 4. Different surface modification techniques.

Table I. Advantages of surface-modified nanoparticles over unmodified nanoparticles (Huang et al. 2013, Gaoet al. 2006).

Surface-modified nanoparticles	Unmodified nanoparticles
Modified nanoparticles exhibit higher cellular uptake and gene expression in brain cells	Low uptake, which results to low gene expression
By surface-functionalization of nanoparticles to improve the absorption by increasing the retention (with adsorption on capillary walls leading to high concentration gradient) time at tight endothelial junctions on nasal administration	Absorption of unmodified nanoparticles were found to be 2.5-fold less than surface-functionalized nanoparticles
Surface-functionalized nanoparticles are able to deliver the drug site-specifically at the concentration required, are able to open the tight junctions and minimize the side-effects associated with the drug	Unmodified nanoparticles lack site-specificity
Surface-modified nanoparticles offer significant improvement over traditional nanoparticles in terms of efficiency and effectiveness	Are of less importance because of lack of control of over release, uncontrolled bio-distribution
These nanoparticles are able to bypass the RES uptake	Traditional carriers as such are taken up easily by the RES

of the loaded protein, peptide, gene, MAbs and many more payloads; site-specific delivery, which minimizes the severe side-effects associated with model drug; better uptake by the endothelial cells, ability to cross the BBB and modify the function of the efflux pump, and excellent control over the release of the drug for a longer period of time. All these characteristics make the drug efficacious and effective and may minimize the resistance to some extent. More specifically, the surface-modified nanoparticles are able to deliver the drug into the CNS by opening the tight endothelial junctions or by direct transport by transcytosis, or by retaining at the BBB and improving the absorption against the concentration gradient across the endothelial cell layer, or by solubilizing the lipid on the membrane of endothelial cells and on particle coating (Barbu et al. 2009).

Polymeric nanoparticles represent a potential means for transport across the BBB, and are designed in such way that they target the different receptors present at the BBB, ultimately enhancing the brain uptake by endothelial cells. Nanoparticles of different levels of hydrophobicity are effectively coated with a plasma component, for example, albumin or immunoglobulin, and can also be selected on the basis of their ability to bypass the phagocytic cells (Moghimi et al. 2001, Ogawara et al. 2001, Furumoto et al. 2004). The other different approaches in the area of surface modification include the use of PEG and its derivatives. Various studies support the observation that coating reduces the uptake of nanoparticles in the liver and increases their circulation time (Leu et al. 1984, Ilium et al. 1986, Douglas et al. 1986, Peracchia et al. 1998, 1999, Gref et al. 1994).

Properties required by nanoparticulate carriers to cross the BBB

While considering the successful brain uptake of the drug, lipophilicity is the main factor for transport across the BBB; however, high lipophilicity leads to trapping inside the membrane, which results in a reduced rate of transport. On the other hand, the transport of a substance through the BBB is inversely proportional to its molecular weight, which seems to be a great limiting factor in crossing the BBB. Limited transport was observed in the case of ionization of acidic molecules, while ionization of the basic group has no significant effect. Log P values between − 0.2 and + 1.3 were shown to be optimal for the successful transport through the BBB. Negative charge-bearing hydrophobic molecules promote protein adsorption and activate the complement system (Moghimi et al. 2001). However, in other studies, it has been reported that positive charge-bearing nanoparticles may interact with negative charge-bearing cells that lie in the outer layer of the BBB.

Surface-modified nanoparticles in neurodegenerative disorders

The dual-function nanoparticles, based on the PEGylated poly(lactic acid) (PLA) polymer conjugated with targeting, cell-penetrating peptides on the surface, have been shown to be valuable targeting tools for diagnosis and therapy. The development of effective strategies to enhance the short interfering RNA (siRNA) nose-to-brain delivery system, combined with cell-penetrating, peptide-modified nano-micelles (cell penetrating peptides or CPP) comprising the polyethylene glycol-polycaprolactone (MPEG-PCL) copolymer conjugated with the cell-penetrating peptide, and the *in vivo* results, all show that MPEG-PCL increases the nose-to-brain delivery as compared to the intravenous route of administration, which shows the cell penetrating property of CPP along with the modified micelles (Kanazawa et al. 2013). The nanoparticles capable of permeating the BBB to target the cerebrovascular Aβ proteins are developed as immuno-nanovehicles, which are chitosan-coated PLGA nanoparticles conjugated with the novel anti Aβ antibody. Studies show the enhanced uptake at the BBB and better targeting of the Aβ protein, which, along with chitosan, enhances the aqueous dispensability and stability and finally enables successful delivery of the therapeutic and diagnostic agent to the cerebral vascular amyloid (Jaruszewski et al. 2012). Superparamagnetic iron oxide nanoparticles (SPIONs), used in magnetic resonance imaging for AD are made efficient contrast agents for AD using 1,1-dicyano-2-[6-(dimethylamino)naphthalene-2-yl]propene (DDNP) carboxyl derivative to functionalize the SPION surface. The DDNP–SPIONs are prepared by conjugating the DDNP carboxyl derivative to oleic acid-treated SPIONs through ligand exchange. The combination was found to induce the fluorescence enhancement of the DDNP–SPIONs and displayed tremendous promise for use as a contrast agent for MRI of AD (Zhou et al. 2014). A novel nanohybrid (surface-modified fluorescent nanocrystal) prepared by using l-glutamic and l-aspartic (as surface-capping agents) quantum dots bio-conjugated with the surface-active neurotransmitter moieties can function as a potential biomarker in cell signaling and cell targeting (Mansur et al. 2013). Vitamin E (D-α-tocopheryl polyethylene glycol 1000 succinate, TPGS)-modified PLGA nanoparticles were prepared as a promising carrier to treat neurological symptoms associated

Table II. Various pharmaceutical approaches to overcome the BBB.

Approach	Description	References
Colloidal carrier	Colloidal carriers offer an attractive and promising approach that could deliver drugs site-specifically, enhance the bioavailability, mask the physicochemical properties of the drug, and protect from enzymatic and gastric degradation. Examples include the nanoparticles, liposomes, and emulsions	Karanth and Murthy (2008)
Lipidization	It is a method of converting small hydrophilic molecules into lipid form in order to gain allowance by the BBB	Pardridge (2007), Rautioa and Chikhale (2004)
Modification of carrier	Surface modification is mainly carried out to eliminate the problem associated with conventional carriers and to enable advanced therapy. In this method, the surface of the carrier is modified either by adsorption or conjugation with polymer, amino acids, antibodies, ligand, monoclonal antibodies, PEG, or copolymer	Patel et al. (2009), Immordino et al. (2006), Cosco et al. (2009), Paolino et al. (2010), Licciardi et al. (2010)
BBB disruption	This method involves the reversible breaking down of tight endothelial junctions, which allows the passage of drug across the barrier (for example, mannitol or arabinose alkyl glycerol, or a bradykinin analog), and surgical implantation of polymeric carrier to improve drug concentration in the brain. Hynynen and coworkers reported that low frequency ultrasound bursts can reversibly disrupt the BBB. However, just after disruption, other xenobiotics may also inter into the CNS along with the drug (Hynynen et al. 2006)	Blanchette and Fortin (2011), Neuwelt et al. (2008), Borlongan and Emerich (2003), Erdlenbruch et al. (2003)
Modulation of efflux transporter	The Pgp transport function can be modulated by down- regulating the Pgp expression at the transcriptional and translational level or chemical inhibition of the transporter function, for example, laniquidar, zosuquidar, tariquidar, quinidine, quinine, cyclosporin, verapamil	Czeisler and Janigro (2006), Su and Sinko (2006)
Use of block polymer	The Pluronics block polymers are used for nanoparticle preparation. They are inert, possess intermediate hydrophilic and lipophilic properties, which enables them to bypass the RES uptake and enhances the drug transport across the BBB by acting on various transporters	Batrakova et al. (2001), Begley (2004)
Endogenous transporter	The conjugation of transporter to the carrier system that creates a mimic of the endogenous nutrient are easily able to cross the BBB, for example mannose liposomes, thiamine-coated nanoparticles	Juillerat-Jeanneret (2008), Vauthier et al. (2003)
Polymer coating	On coating, different types of functions can be Achieved, for example, PEG coating to bypass the RES uptake, poloxamer coating to stabilize the nanoparticles, and coating of polysorbate 80 to enhance the permeability	Gref et al. (1994)
Intra nasal delivery	Recently, it was shown through various studies that the drug is directly transported from the olfactory portion to the CNS. It offers rapid absorption and bypasses first-pass metabolism in the liver	Chou and Donovan (1998), van Laar et al. (1999)
Direct drug delivery	The delivery of drug directly to the intraventricular and intracerebral routes or reservoirs and catheter implantation. In case of injection, the response may be for a shorter duration of time because of total renewal of fluid within 5–6 hours	Chauhan (2002)
Prodrug approach	This technique is targeted to enhance the permeability and lipid solubility by esterification or amidation of amino, carboxylic acid, hydroxyl group-containing molecules. Increment in lipophilicity may enhance the diffusion across the BBB	Temsamani et al. (2000)

with neurological disorders. TPGS is well known as an emulsifier, and degradation of nanoparticles may release the TPGS component, which has a synergistic activity (Jalali et al. 2011). The lactoferrin (Lf)-conjugated PEG-co-PCL nanoparticles are found to enhance the cellular accumulation in 16HBE14o-cells of the brain (cerebellum, olfactory tract, olfactory bulb, and hippocampus) through both caveolae-/clathrin-mediated endocytosis, and to enhance the biodistribution of protein and peptide in different parts of the brain by noninvasive nasal brain delivery in AD (Liu et al. 2013). The peptide-ligand functionalized nanoliposomes were produced to facilitate the neuronal cell uptake of galantamine-loaded nanoliposomes, and the final formulation aided neuron accumulation, confirmed by fluorometry and confocal microscopy (Mufamadi et al. 2013). Odorranalectin (OL) (small non-immunogenic peptide)-conjugated modified cubosomes, prepared by incorporating maleimide-PEG-oleate and Gly14-Humanin (S14G-HN), serve as a model drug for AD. Here, the OL is used to eliminate the non-immunogenic character as compared to other lectins, and offers a novel, effective, and noninvasive system for brain drug delivery, especially for peptides and proteins (Wu et al. 2012). Curcumin, a fluorescent molecule, has high affinity for the Aβ peptide but faces the problem of low solubility in clinical use. Nanoliposomes are conjugated with curcumin, exposed at the surface of the nanoliposomes. The *in vivo* study has revealed that curcumin-loaded nanoliposomes are able to specifically stain the Aβ deposits in brain tissue in AD, which finally leads toward its application in diagnosis and site-specific delivery in AD (Lazar et al. 2013). The poly(ethylene glycol)-*block*-polylactide (PEG-*b*-PLA) nanoparticles are able to interact with the Aβ peptide, and were suitably stabilized by the sodium cholate and PEG, in a simple new approach for AD (Brambilla et al. 2011). PLGA nanoparticles coated with Tween 80 can deliver estradiol to the brain upon oral administration. In an ovariectomized (OVX) rat model of AD, the nanoparticles were able to prevent the expression of amyloid β. It was observed that Tween 80-coated nanoparticles administered orally result in the same brain estradiol concentration as achieved by i.m. injection of estradiol, but lower brain estradiol concentration was observed with the administration of uncoated nanoparticles (Mittal et al. 2011). Strategies to improve the drug delivery to brain include the use of e peptide sequence—*THRPPM-WSPVWP*—in the gold nanoparticle–*CLPFFD* conjugate. This sequence interacts with the transferrin receptor in microvascular endothelial cells of the BBB and leads to permeability of the conjugate in brain, in AD (Prades et al.

2012). A 12-amino acid peptide (denoted as pep TGN) is displayed by the bacteriophage clone 12-2. The pep TGN was covalently conjugated onto the surface of poly(ethylene glycol)-poly (lactic-co-glycolic acid) (PEG-PLGA)-based nanoparticles, with great potential for site-specific delivery across the BBB. The cellular uptake and brain-targeting index of Pep TGN-modified nanoparticles was found to be significantly higher than that of unmodified nanoparticles (Li et al. 2011). The formulation of chitosan nanoparticles into SNVs enhanced their transcytosis-mediated uptake at the BBB endothelial cells and their accumulation in various regions of brain. Such types of nanoparticles are capable of delivering the therapeutic agent across the BBB to target the amyloid beta (Agyare et al. 2008). Rhodamine B isothiocyanate, a fluorescent probe, was used to label angiopep-conjugated poly(ethyl glycol)-co-poly (E-caprolactone) nanoparticles as a brain-targeting drug delivery system in mice, and the study results demonstrate that the ANG-PEG-NP significantly enhances the uptake by the brain capillary endothelial cells (more specifically, accumulation of ANG-PEG-NP at a higher extent in the cortical layer, lateral ventricles, and hippocampus) compared with that of PEG-NP through caveolae and clathrin-mediated endocytosis. Elaboration of this issue is important for the future development of ANG-PEG-NP drug delivery system in brain-targeting in NDs (Xin et al. 2012). The ApoE is adsorbed on to the surface of polysorbate 80 (Tween-80)-coated nanoparticles which may be able to enter the BBB (Kreuter 2001).

Furthermore, receptor-mediated transcytosis is confirmed by using the Apo E-related nonsense sequences, as these are unable to transport drug across the BBB (Michaelis et al. 2006). The BBB crossing potential can also be confirmed by the data of HAS nanoparticles modified by Apo E in different parts of brain and neurons just 15 min after intravenous injection (Zensi et al. 2009); on comparing this with PEGylated nanoparticles which were found in endothelial junction and were absent in different parts of brain after 30 min of injection. This is evidence of the unspecificity of PEGylated nanoparticles (Wagner et al. 2012).

Surface-decorated nanoparticles play an important role in the management of PD, and research scientists studying therapeutic formulations are paying great attention towards efficient nanoparticle uptake, targeted delivery, minimizing the unnecessary distribution to areas other than the targeted organ, and many more such effects. More specifically, OL was recently identified as a small molecule with the least immunogenicity as compared to other molecules, and was found to have good potential when used as a ligand with PEG-PLA nanoparticles to enhance the nose-to-brain delivery of the peptide urocortin. The results show increased brain delivery of surface-modified nanoparticles and enhanced therapeutic effects, further suggesting that this could be carrier of interest for CNS delivery (Wen et al. 2011). In another study, the nanoparticles were developed by conjugation of Lf with PEG-PLA nanoparticles (lactoferrin thiolated and conjugated to the maleiamide function surrounding the PEGylated nanoparticles), and the presence of ligand on the surface of the nanoparticles was confirmed. The murine studies suggest more pronounced accumulation of surface-modified nanoparticles than unmodified nanoparticles, and such kinds of approach are able to attenuate the lesion in the striatum in PD (Hu et al. 2011).

Among different therapeutic approaches, gene therapy is also considered promising to effectively treat PD, but the BBB limits the choices. Lf-modified nanoparticles are used as gene vectors because of their BBB-crossing potential. *In vivo* study results show that multiple intravenous injections of Lf-modified nanoparticles obtained higher GDNF expression for a longer period of time, with significant improvement in locomotor activity and reduction in neuronal loss (Huang et al. 2010). SNCA (gene encoding the alpha synuclein protein) targeting is another important treatment strategy in PD, but the challenges are to maintain efficient delivery without any toxicity and side effects. Such a goal was achieved by developing polyethylene glycol-polyethyleneimine as a vector for alpha synuclein siRNA delivery to PC12 cells in PD. The study shows that these nanoparticles have low toxicity with high transfection efficiency, and seem to have remarkable potential for gene delivery in PD (Liu et al. 2014). Among various approaches, a new innovative approach is the fabrication of surface-modified polymer-lipid hybrid nanoparticles for the intranasal delivery of ropinirole hydrochloride. Such kinds of nanoparticles were developed with the aim of achieving sustained release, avoiding hepatic first pass metabolism, and enhancing the therapeutic efficacy. The results from the *in vivo* studies show good retention at nasal mucosa, sustained release pattern, and therapeutic efficiency. This type of carrier was found to be safe and stable for intranasal delivery of nanoparticles for effective treatment of PD (Pardeshi et al. 2013).

As previously discussed, in HD, the toxic huntingtin protein is expressed, and the use of SiRNA to inhibit the mutant protein was found to be an approach with good potential. Such an approach consists of modifying β-cyclodextrin nanoparticles as neuronal SiRNA delivery vectors, and the results revealed that such nanoparticles are stable in the brain and are able to reduce the expression of the huntingtin protein in rat striatal cells and in humans, while simultaneously limiting toxicity. From the *in vivo* results, it was reported that these modified nanoparticles are may be a vector of choice in NDs (Godinho et al. 2013).

Different techniques of surface modification for the management of neurodegenerative disorders

Conjugation

The conjugation of nanoparticles with a directing unit is a creative approach to deliver the drug in a temporally and spatially controlled manner, which enhances the efficacy and minimizes the side effects by site-specific delivery. Polymer-drug conjugates were first introduced in the 1970s, and pre-clinically evaluated in the 1980s. The conjugation of PLGA with lectins involves the covalent coupling of PLGA with the ligand or other polymer. Most commonly, the polymer is suitably converted to an ester form by a reagent like N-hydroxy succinimide, in which lectin forms the covalent bond with the NH_2 of lectin; in the same way, the amine group

Table III. Various studies on surface-modified nanoparticles and their potential to overcome.

Polymer	Modification	Drug	Used animal	Objective of modification	Comment	References
PEG-substitute d lysine	Plasmid DNA compacted with PEG-substituted lysine	DNA	Rat	To measure the transfection potential in CNS disorder	Results shows that nanoparticle s are able to bypass the BBB, and transfect and express the encoded gene	Harmon et al. (2014)
PLA	PEG coating along with ligand	Peptide (QSH)	Mice	BBB targeting	Promising tool for diagnosis and therapy	Zhang et al. (2014)
PCL	PEG conjugation with cell-penetrating peptide	siRNA	Rat	Good cell-penetrating property in nose to brain delivery	Intranasal delivery of final formulation was found to be effective in comparison with the i.v route	Kanazawa et al. (2013)
PLGA	Nanoparticles modified by conjugation with Aβ antibody.	Anti-Aβ antibody	Cellular cerebral amyloid angiopathy model	Enhance uptake at BBB and Aβ targeting	Capable to delivering the drug to the cerebrovascular amyloid	Jaruszewski et al. (2012)
1,1-dicyano-2-[6-(dimethyl amino)naphthalene-2-yl] propene (DDNP)	DDNP conjugate with carboxyl derivative to oleic acid-treated SPIONs	Contrast agent		MRI imaging	Promising contrast agent of Alzheimer's disease in MRI	Zhou et al. (2014)
l-glutamic and l-aspartic as surface capping agents	Bio conjugated with the surface active neurotransmitter			Biomarker, cell signaling	potential biomarkers in cell targeting and signaling applications	Mansur et al. (2013)
PLGA	TGPS coating			Drug delivery along with Vitamin E	In Vitamin E and the associated neurological disorder	Jalali et al. (2011)
PEG-CO-PCL	Lactoferrin coating	Neuro protective peptide	Mice	To enhance the uptake drug nanoparticles in the brain along with the bio distribution	In neurological disorder	Liu et al. (2013)
PLGA	Tween 80 coating	Estradiol	Rats	To improve the oral bioavailability. Successful in preventing the expression of amyloid beta-42	In AD therapy	Mittal et al. (2011)
PEG-PLGA	Pep TGN	Coumarin 6 (fluorescent probe)	Mice	Site specific delivery to brain. To increase cellular uptake	These modified nanoparticle s are of good potential to overcome the BBB	Li et al. (2011)
Chitosan	A polyamine-modified F (ab') portion of IgG4.1, an anti-amyloid antibody.	Antibody	Mice	SNV capable of permeating the BBB. To target cerebrovascular amyloid in AD and cerebrovascular amyloid angiopathy (CAA)	Nanoparticles are a good option for protein and peptide to cross the BBB	Agyare et al. (2008)
poly(ethy l glycol)-co-poly (E-caprolact one)	Angiopep conjugate	Rhoda mine B (fluorescent probe	Mice	To enhance of selective uptake of nanoparticles. Receptor-mediated transcytosis	Promising approach for the therapy and diagnosis of neurological disorders	Xin et al. (2012)
PEG-PLA	Lactorferrin conjugation	Urocortin (peptide)	Mice	To identify the application of ligand-conjugated nanoparticles in PD	Better uptake (by clathrin-mediated endocytosis) of surface modified nanoparticles as compared to unmodified nanoparticles, and lesions in striatum were attenuated	Hu et al. (2011)
PEG-PEI Polyethylene glycol-polyethylene imine	PEG-PEI siSNCA complex	siSNCA	PC12 cells	To develop and characterize PEG-PEI siSNCA as a vector to target PC12 cells for Parkinson's	Nanoparticles had low toxicity and high transfection efficiency, and successfully suppressed the SNC mRNA expression	Liu et al. (2014)
PEG-PLA	Odorranalectin conjugation	Urocortin (peptide)	Rats	To increase brain delivery, and to enhance the therapeutic effects	Such type of modification enhances the brain delivery. Could be a potential carrier for CNS drug delivery	Wen et al. (2011)
DGL dendrigraft poly-L-lysine	Angiopep-conjugated nanoparticles	Gene	Rats	To evaluate the neuroprotective effects	Modified nanoparticles exhibit the higher cellular uptake, and gene expression in brain cells of rats	Huang et al. (2013)
Silica	Conjugation	Gene	Mice	Cationic charge will enhance the binding with negatively charged plasmid	To introduce the gene into the dopaminergic cell of substantianigra and parscompecta	Bharali et al. (2005)
PEG-PLGA	Odorranalectin conjugated to PEG-PLGA	Urocortin peptide	Mice	To enhance the nose-to-brain delivery and reduce immunogenicity of traditional lectins associated carrier	Such a modification enhance brain delivery, along with therapeutic effects	Wen et al. (2011)
Poly(amidoamine) derivative	Lactoferrin conjugation	Gene therapy	Rats	To develop the polymer ligand conjugate to overcome the BBB	High gene expression for longer period of time, improvement in locomotor activity, and reduced neuronal loss	Huang et al. (2010)
β-cyclodextrin	Amphiphilic β-cyclodextrin (oligosaccharide based molecules)	siRNA	Mouse	To develop an efficient, nontoxic delivery vehicle to the CNS	Developed carrier was shown to be able to reduce the expression of Huntingtin protein in striatum, with limited toxicity	Godinho et al. (2013)

of chitosan can be replaced by the thiol group. The chitosan-nanosphere-conjugated PEG bearing the OX26 monoclonal antibody has an affinity towards the transferrin receptor, as was seen by electron microscopy in the brain of mice, and it seems to be a promising carrier for the transport of anti-caspase peptide (DEVD-FMK) into the brain (Aktas et al. 2005). Among the different types of lectins, OL was found to be smallest lectin with low immunogenicity among the members of the traditional lectin family, capable of enhancing the nose-to-brain delivery and to reducing the immunogenicity of traditional lectins. Urocortin peptide was used as a macromolecule model drug and its therapeutic efficacy on rats was evaluated. The results suggest the increment in brain delivery and enhanced therapeutic effects in PD (Wen et al. 2011). The maleimide-mediated (to enhance nasal absorption) wheat gram agglutinin (lectin)-functionalized PEG-PLA nanoparticles, with intranasal administration, was found be present in different areas of brain tissue, at a quantity two-fold that of unmodified nanoparticles), as proved by the fluorescent marker. Such techniques offer an effective noninvasive system for protein and gene delivery to the brain (Gao et al. 2006).

Surface-modified nanoparticles as non-viral gene vectors

Angiopep-conjugated dendrigraft poly-L-lysine nanoparticles were prepared to investigate the potential application in gene delivery in PD by taking advantage of the affinity of angiopep (a ligand) towards the low density lipoprotein receptor protein-overexpressed luminal site of the BBB. Angiopep-modified nanoparticles exhibit higher uptake and gene expression, and apparent recovery of dopaminergic neurons, as compared to unmodified nanoparticles; such an approach may be attractive for long-term gene therapy in different NDs (Huang et al. 2013). Bharali and coworkers have shown the ability of nanoparticles to effectively traverse the biological barrier and transfect cells *in vivo*; more specifically, organically modified silica nanoparticles surface-functionalized with amino groups (as a non-viral vector), for efficient *in vivo* gene delivery. After fours week of fluorescent visualization, the transfection was observed in the substantia nigra, and the level of this non-viral vector was equal to that of the viral vector **(**Bharali et al. 2005).

Surfactant coating

The concept of surfactant-coating of nanoparticles was first introduced by Troster and coworkers who hypothesized the body distribution of coated nanoparticles (Tröster and Kreuter 1988). On the basis of this, later work carried out by same group studied the *in vivo* distribution of surfactant-coated nanoparticles of PMMA of a size of 131 nm (Tröster et al. 1990). In the later phase, different types of surfactant, including the different types of poloxamers 188, 407, 184, 338, and 908, and polysorbate 20, 60, and 80 were being widely used to identify the possible relationship between the surface property of nanoparticles and their bio-distribution. The potential of surfactant-modified nanoparticles was confirmed first by the developing the P80-coated poly(butyl cyano acrylate) nanoparticles to effectively cross the BBB and achieving good therapeutic response as compared to intravenous administration of the same. Poly(butylated cyano acrylate) nanoparticles were among the carriers which were studied in various drug delivery applications, and surface-functionalization by polysorbate 80 was shown to enable crossing of the BBB by receptor-mediated endocytosis on adsorption of the apolipoprotein from blood (Friese et al. 2000).

On the mechanistic aspects, different explanations for how these surfactant-modified nanoparticles work have been published, which are as follows: as these nanoparticles increase the retention time or their adsorption, the concentration gradient in the wall of the capillaries enhances the transport, solubilizing the lipid of the endothelial cell membrane, opening tight junctions to enhance the paracellular transport, and inhibiting the efflux system (Kreuter 2004, 2005). Iron chelator (2-methyl-N-(3-aminopropyl)-3-hydroxyl-4-pyridinon) (MAPHP)-conjugated nanoparticles also behave like lipoprotein particles by preferentially adsorbing apolipoprotein A-1 and are able to cross the BBB by mimicking low density lipoprotein (LDL), to facilitate the removal of nanoparticles to remove iron from the brain tissue (from paraffin sections). Through the same (LDL) transport system, metal ion concentration is reduced at the disease-affected area (Liu et al. 2006).

Polymer coating or PEGylation

PEG chains were first linked to the PLA nanoparticles by Gref and coworkers (Gref et al. 1994). Subsequently, PEG was chemically linked with poly(hexadecyl) cyanoacrylate nanoparticles. Both these PEGylated nanoparticles significantly prolong the blood circulation time and minimize their uptake by liver. Dextran-coated nanoparticles have also been used in different biomedical applications (Huong et al. 2009).

Nanoparticles coated with PEG have gained a lot of attention. The protective properties of PEG on nanoparticles was demonstrated by Torchilin (Torchilin 1998). Minakshi and coworkers introduced a novel strategy for synthesizing peptide-tagged polyethylene glycol, PEGylated chitosan polymer, to develop nanoparticles for siRNA delivery. From a mechanistic point of view, the conjugation of monomethoxy PEG, at the C2 hydroxyl group of the chitosan polymer, with conjugation of PEG to a cell-penetrating peptide transactivator of transcription (TAT), attenuates the neurodegeneration (Malhotra et al. 2013).

Block polymer

A number of amphiphilic diblock copolymers like MePEG-PLA were synthesized by ring-opening polymerization of D,L-lactide, initiated with the hydroxyl group of methoxy poly(ethylene glycol), with stannous octoate used as catalyst. The chemical structure of the conjugate was confirmed by NMR **(**Zhang et al. 2004).

Effect of formulation variables on the functioning of surface-modified nanoparticles

It has been observed in various studies that on conjugation, the particle showed an increase in diameter. During formulation, it is necessary to consider that the flexibility of the directing unit (ligand) might enhance the receptor recognition and binding capacity (Olivier et al. 2003). The ligand

density on the surface of nanocarrier has a great effect on the brain uptake of the nanocarrier. The neuronal cell uptake of ligand-appended nanoparticles at 37°C (which is important for normal cellular functioning) was higher as compared to that at 4°C (at this temperature, all active, energy-consuming transport processes are stopped) (Wagner et al. 2012), suggesting the uptake of nanoparticles in a temperature-dependent manner. With regard to the concentration, at 37°C, probe-labeled ligand-appended nanoparticles showed an increase in size with an increase in concentration, while at 4°C, on increasing the concentration, saturation concentration was easily achieved at lower dose of both ligand-appended nanoparticles and non-ligand-appended nanoparticles, showing no significant difference between the two types of nanoparticles. In a qualitative uptake study using fluorescent microscopy, the ligand-appended nanoparticles showed higher fluorescent intensity than that of the non-ligand-appended nanoparticles. Sometimes, the complex formation between fluorescent dye and the copolymer may produce negative results, and the incubation time may also affect the fluorescence (Demeule et al. 2002). The best way to enhance the circulation time is PEGylation, and on increasing the density of PEG on nanoparticle surface, the RES uptake can be avoided to a higher extent. Jalali and coworkers used the PLGA nanoparticle with vitamin E (d-α-tocopheryl polyethylene glycol 1000 succinate, TPGS) as an effective emulsifier for the delivery of drugs (both hydrophilic and lipophilic) to the brain. In addition to having the desired surface morphology, several studies have demonstrated the effect of TPGS as an absorption enhancer, and vitamin E is also a free radical scavenger in the brain (Amano et al. 1994, Jalali et al. 2011).

Conclusion

Different kinds of surface modifications of nanoparticles are of great interest from the pharmacological as well as pharmaceutical points of view, offering an impressive resolution not only for the NDs but also for different types of life-threatening diseases. These modified nanocarriers can potentially act at a molecular level to attenuate the premature death of neurons and also afford the observation of the molecular basis of the disease and the associated events which may give rise to new pathways of disease-causing factors. The targeting ability of nanoparticles can be improved without affecting the normal physiological body events, by selecting the ligands which simulate already existing compounds in our body, and these ligands, though from an external source, have an affinity toward the specific receptor present at the target site. In neurodegeneration, the gap developed by the neuronal loss can be filled by developing artificial cells in order to retain the long term memories. The developed nanocarriers are also associated with some serious problems, more specifically, the reversible disruption of the BBB allows the entry of endogenous as well as foreign particles. Such aspects need to be considered in the design and development of nanocarriers, and such disruptions can also be modified for the limited entry of specific carriers and the required nutrients.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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