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Reviews

# Nanoparticles for drug delivery to the central nervous system

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**Abstract** Treating central nervous system (CNS) disease is a huge challenge because of the presence of various obstacles. These obstacles, including blood-brain barrier as the major one, prevent the drug from penetrating into brain, which results in the low efficacy of many potential therapeutic agents. Therefore, a variety of novel strategies have been proposed to overcome the barriers and deliver drugs in a sufficient quantity to the CNS. One of the possibilities is drug delivery to the brain using nanoparticles. Nanoparticles delivery systems can penetrate the barriers and target to the CNS by modifying the surface and attaching groups to them, besides, the methods of preparation are generally simple and easy to scale-up. This review intents to detail the nanoparticles used for drug delivery to the CNS.

***Keywords:*** Drug delivery; Central nervous system (CNS); Blood-brain barrier; nanoparticles

## 1 Introduction

The blood-brain barrier (BBB) is well known as the major hindrance, which impedes the effective delivery of the pharmaceutical to the brain. It is formed at the level of the endothelial cells of the cerebral capillaries and characterized as its endothelial tight junction and a complete absence of pinocytic activity [1]. The limited access of drugs to the brain is due to the unique property of BBB. Only small molecules with high lipid solubility and low molecular mass of less than 400-500 Da , actually cross the BBB. US researchers recently have uncovered a second barrier beyond the BBB that might prevent some agents from reaching their target cells in the brain [2]. Finding ways to breach this, these barriers is the focus of many scientists in the world. Those novel strategies called drug delivery systems (DDS), which can make drugs released in a time-controlled and site-specific way, have been developed from this. Various drug delivery and targeting systems, including polymer-based systems, liposome-based systems, intelligent delivery systems, nanoparticles and carbon nanotubes, are currently under study. Potential advantages of these systems include: (1) continuous maintenance of drug delivery levels in a therapeutically desirable range; (2) reduction of harmful side effects because of the targeted delivery to the tissues; (3) increase of the bioavailability of drug, leading to decreased amount of drug needed [3,4].

## 2 Nanoparticles for drug delivery to the CNS

A variety of novel strategies have been proposed to improve the permeability of drugs into the CNS, including blood-brain barrier disruption, alternative routes to CNS drug delivery, chemical drug delivery, biological drug delivery [5, 6]. One of the possibilities to deliver drugs to the brain is the employment of nanoparticles. The term "nanoparticle" may be defined as a submicron drug carrier system [7]. Nanoparticles are polymeric particles made of natural or artificial polymers ranging in size between about 10 and 1000 nm (1 μm). Drugs or other groups may be dissolved into the nanoparticles, entrapped, encapsulated and/or adsorbed or attached. The aim in using nanoparticles is to the increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes and / or to protect them against enzyme inactivation [7]. Use of nanoparticles for drug delivery has some advantage because of their properties: small size and biodegradable materials for nanoparticle preparation [7]. Nanoparticles and be synthesized from preformed or from a monomer during its poly merization, as in the case of alkylcyanoacrylates. Three

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major strategies have been evolved to produce nanoparticles, including emulsion polymerization, dispersion polymerization and interfacial polymerization/denaturation and desolvation [8].

## 2.1 Polysorbate 80-coated nanoparticles

The earliest drugs were transported across the BBB using nanoparticles were Dalargin and Loperamide. The studies show that these molecules themselves do not exhibit any therapeutic effect after intravenous injections science they cannot cross the BBB. But, after adsorption onto the surface of poly (butyl cyanoacrylate) (PBCA) nanoparticles further coated with the detergent, polysorbate-80 (PS-80), a dose and time dependent analgesic effect was obtained [7,9]. The mechanism behind the translocation of those nanoparticles into the brain remains, however, not fully understood. Olivier *et al* have suggested that Polysorbate 80-coated PBCA nanoparticles could lead to an opening of the tight junctions between the endothelial cells. The drug could then permeate through the tight junctions in free form or together with the nanoparticles in bound form [7,9]. However, Kreuter *et al* have come up with different mechanisms based on both *in vivo* and *in vitro* studies: (1) the binding of nanoparticles to the inner endothelial lining of the brain capillaries could provide a drug concentration gradient, thus improving passive diffusion and (2) brain endothelial cell uptake of nanoparticles may occur through endocytosis or transcytosis [7]. Recently it was shown that nanoparticles overcoated with polysorbate 20, 40, 60, or 80 but not other surfactants adsorb apolipoprotein E. It was also concluded from the results of the tail-flick in mice that only nanoparticles overcoated with polysorbate 20, 40, 60, or 80 induced an analgesic effect with Dalargin. In addition, coating of the Dalargin-loaded nanoparticles with apolipoprotein E or B without polysorbate 80 induce a lower antinociceptive effect than with polysorbate 80 alone. However, the antinociceptive effect was even higher when both polysorbate 80 and apolipoprotein E or B overcoating. From these results it is concluded that when polysorbate coating the nanoparticles intravenous injected, the surface of nanoparticles becomes further coated with adsorbed apolipoprotein E or B [7,9]. It is thought that the final product is mistaken for low-density Lipoprotein (LDL) particles by the cerebral endothelium and is internalized by the LDL uptake system [10]. Doxorubicin is one of the most important anticancer drugs, but it is not used against brain tumors due to a failure to cross the barriers. After binding to poly (butyl cyanoacrylate) nanoparticles and coating with polysorbate 80 very considerable doxorubicin concentrations (6 Ag/g) were detected in the brain after intravenous injection at a level of 5 mg/kg doxorubicin to rats. Intravenously injected doxorubicin-loaded polysorbate 80-coated nanoparticles were able to lead to 20-50% cure in rats with intracranially transplanted glioblastomas that typically kill the rats within 10-20 days [9,11]. Other molecules, such as MRZ 2/576, were also adsorbed onto the polysorbate 80-coated nanoparticles and prolonged duration of the anticonvulsive activity was obtained [12].

## 2.2 Pegylated nanoparticles

Cationic bovine serum albumin (CBSA) conjugated with poly(ethyleneglycol)-poly(lactide) (PEG-PLA) nanoparticle (CBSA-NP) is a novel drug carrier for brain delivery which has been developed and its effects have been evaluated. The study results showed that CBSA-NP was a promising brain drug delivery carrier with low toxicity. The copolymers of methoxy-PEG-PLA and maleimide-PEG-PLA were synthesized by ring opening polymerization of d, l-lactide initiated by methoxy-PEG and maleimide-PEG, respectively, which were applied to prepare pegylated nanoparticles by means of double emulsion and solvent evaporation procedure. Native bovine serum albumin (BSA) was cationized and thiolated, followed by conjugation through the maleimide function located at the distal end of PEG surrounding the nanoparticle´s surface. CBSA-NP had a round and regular shape with a mean diameter around 100 nm. The qualitative and quantitative results of CBSA-NP uptake experiment compared with those of BSA-NP showed that rat brain capillary endothelial cells (BCECs) took in much more CBSA-NP than BSA-NP at 37℃, at different concentrations and time incubations. After a dose of 60 mg/kg CBSA-NP or BSA-NP injection in mice caudal vein, fluorescent microscopy of brain coronal sections showed a higher accumulation of CBSA-NP in the lateral ventricle, third ventricle and periventricular region than that of BSA-NP. There was no difference on BCECs´ viability between CBSA-conjugated and -unconjugated pegylated nanoparticles [13]. Pegylated -poly (hexadecylcyanoacrylate) (PEG-PHDCA) nanoparticle is another kind of copolymer, which has been studied to treat several CNS diseases. The PEG-PHDCA copolymer was achieved by the synthesis of a cyanoacrylate monomer substituted with PEG and its co-polymerization with hexadecylcyanoacrylate in a 1:4 ratio [14]. PEG is attached to the hydrophobic block with a covalent bond, which makes PEG desorption impossible. PEG-PHDCA nanoparticles have more significant permeability than PS-80 nanoparticles mentioned above and other kinds of nanoparticles, and besides, they have long-circulating properties [15,16]. The results of tests showed that PEG-PHDCA nanoparticles did not display any toxicity towards the BBB. Accumulation of PEG-PHDCA nanoparticles into the brain tumor and a lower extend into the normal brain tissue have been observed in tests[17].

## 3 Conclusions

1. Nanoparticles were found to be helpful for the treatment of the disseminated and very aggressive brain tumours.

2. Polysorbate 80-coated nanoparticles and pegylated nanoparticles are very promising materials for drug delivery to CNS. Using these materials as carriers for drugs to the brain, higher permeability and prolonged duration were obtained.

3. Mechanism of nanoparticle-mediated drug transport to the brain has not been fully understood yet. Many scientists came up with different opinions. It is thought that several mechanisms may work in combination.

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