Chapter 5
CNS Targeted Nanoparticle Drug Delivery: CNS Drug Delivery

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ABSTRACT
The idea of formulating brain permeable nanoparticles stems from the need to treat various neurological disorders like Parkinson’s disease, Alzheimer’s disease, schizophrenia, depression and brain tumors. Neuropeptides, antibiotics, anticancer drugs and many CNS active drugs cannot cross blood brain barrier (BBB). Studies have revealed that when these drugs are loaded onto nanoparticles they not only cross BBB, but also exhibit decreased side effects. The drug can be dissolved, dispersed, encapsulated inside the nanoparticle or attached on to surface of nanoparticles. In 1995, dalargin was the first drug to be delivered across blood brain barrier (BBB) using polysorbate 80 coated nanoparticles. The size of nanoparticles is usually between 10-1000nm. For crossing BBB it should be less than 300 nm.

INTRODUCTION
In the past few years, several high profile global pharmaceutical companies have shutdown major research activities within the neuroscience area. This is because the development of new psychotherapeutic drugs has become a high risk activity with
little success. CNS drug development takes considerable amount of time. Out of 5000 potential candidate molecules, only 250 reach pre-clinical evaluation. Out of 250 reaching the pre-clinical stage, 10 reach clinical development. Out of these 10 molecules entering clinical development, only one gets approved by the regulatory authorities and gets to the market. The time for development of one drug molecule takes 12-15 years. The cost of developing a new drug is typically US$10-15 billion. Moreover, CNS drugs usually fail at later stage of clinical trials, after significant investment has been made (Wegner & Rujescu, 2013). The new drug molecule should possess desired pharmacological activity, selectivity at receptor site to avoid undesirable side effects, optimal bioavailability, ability to penetrate the blood-brain barrier. The BBB and the efflux transporters are the main cause of failure of most of the CNS drugs under clinical trial.

Ehrlich and his colleagues very the first to describe the existence of blood-brain barrier (BBB) in 1885. They showed that intravenous injection of acidic dye tryptan blue was not able to color brain and spinal cord. This gave an indication of presence of some barrier which separated the CNS from rest of the body (Ehrlich, 1885). The existence of a barrier at the level of cerebral vessels was first postulated by Bield and Kraus (1898) and Lewandowsky (1900) based on the observation that the intravenous injection of cholic acids or sodium ferrocyanide had no pharmacological effects on the CNS, whereas neurological symptoms occurred after intraventricular application of the same substances. After the development of electron microscope, it was found that cerebral endothelial cells were morphologically different from other endothelial cells in the body. The tight junctions between the endothelial cells forms the cellular basis of BBB. The brain capillary endothelial cells are surrounded by astrocytes, microglial cells, pericytes. BBB protect brain from general circulation and toxic substances. Astrocytes are periendothelial structures which play an important role in brain homeostasis. They are involved in maintenance of potassium ion levels, inactivation of neurotransmitters, regulation and production of growth factors and cytokines (Ehrlich, 1885). Damage to the BBB or alterations in transport systems may facilitate pathogenesis of many CNS diseases, including HIV-associated CNS dysfunction. HIV-1 infection can result in neuropathologic changes in about one half of infected individuals and also can result in damage to the BBB. HIV-1 and the HIV-1 viral proteins, Tat and gp120, cause alterations in the integrity and function of the BBB through both paracellular and transcellular mechanisms (McRae, 2016).

**Mechanisms of Transport Across BBB**

The transport of solute molecules across the BBB membrane takes place by four different mechanisms:
On the Internalisation, Intraplasmodial Carriage and Excretion of Metallic Nanoparticles in the Slime Mould, Physarum Polycephalum

Development of Gelatin Films with Designed Antimicrobial Peptide and Silver Nanoparticles

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