REVIEW ARTICLE

In-Situ Gels for Brain Delivery: Breaching the Barriers

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Abstract: The blood-brain barrier (BBB) regulates blood and chemical exchange in the central nervous system. It is made up of brain parenchyma capillary endothelial cells. It separates the interstitial cerebrospinal fluid from the circulation and limits brain drug entry. Peptides, antibodies, and even tiny hydrophilic biomolecules cannot flow across the BBB due to their semi-permeability. It protects the brain from poisons, chemicals, and pathogens, and blood cells penetrate brain tissue. BBB-facilitated carrier molecules allow selective permeability of nutrients such as D-glucose, L-lactic acid, L-phenylalanine, L-arginine, and hormones, especially steroid hormones. Brain barriers prevent drug molecules from entering, making medication delivery difficult. Drugs can reach specific brain regions through the nasal cavity, making it a preferred route. The *in*-situ gels are mucoadhesive, which extends their stay in the nasal cavity, allows them to penetrate deep and makes them a dependable way of transporting numerous medications, including peptides and proteins, straight into the central nervous system. This approach holds great potential for neurological therapy as they deliver drugs directly to the central nervous system, with less interference and better drug release control. The brain affects daily life by processing sensory stimuli, controlling movement and behaviour, and sustaining mental, emotional, and cognitive functioning. Unlike systemic routes, the nasal mucosa is extensively vascularized and directly contacts olfactory sensory neurons. Compared to the systemic circulation, this improves brain bioavailability of medications. Drugs can be delivered to the brain using *in-situ* gel formulations safely and efficiently, with a greater therapeutic impact than with traditional techniques.

Keywords: Alzheimer's, blood-brain barrier, poloxamer, thermo-responsive, *in-situ* gel, chitosan.

1. INTRODUCTION

The brain is a sensitive, intricate, and delicate organ [1]. It is a part of the central nervous system (CNS). It is linked to a wide range of processes, such as interpreting sensory stimuli, regulating movement and appropriate behaviour, and maintaining mental, emotional, and cognitive functions, significantly influencing an individual's daily life [2]. However, individuals may suffer from certain brain disorders, such as brain tumours, neuroinflammation, neurodegenerative diseases, or neuropsychiatric disorders, either due to genetic, biological, or environmental causes or a brain injury [3]. To restore brain health, it needs treatment. Typically, the treatments involve drug substances entering the brain. The presence of brain barriers limits the entry of any molecules into it, thereby obstructing the transportation and delivery of drugs [4]. Due to their impermeable nature, these barriers also help maintain the brain's microenvironment by ensuring a secure blood flow, which regulates the pH within the brain tissue [5].

The blood-brain barrier, the cerebrospinal fluid-brain barrier, and the blood-cerebrospinal fluid barrier are the three primary barriers between the cerebrospinal and brain parenchyma [6]. The blood--brain barrier (BBB), a semi-permeable membrane barrier located at the interface of the blood and cerebral tissue, is a key regulator of the interchange of blood and chemicals in the central nervous system [7]. Capillary endothelial cells in the brain parenchyma create it. It divides the interstitial CSF from the circulation and restricts the passage of medicines or other neuroactive substances into the brain [6]. The paracellular protein seals and maintains the BBB, which is mainly made up of brain endothelial cells and is regenerated *via* interactions between pericytes and glia [8], along with the astrocytes, the pericytes, the neurons and the basement membrane, which result in the formation of the structure called the neurovascular unit [9]. The BBB's semi-permeability prevents large molecules, including peptides, antibodies, and even minuscule hydrophilic biomolecules, from passing through it [10]. It guards the brain against harmful substances like toxins, chemicals, and pathogens [11], and cells enter through the blood into the brain tissue. However, it allows selective permeation of the nutrients, such as D-glucose, L-lactic acid, L-phenylalanine or L-arginine through BBB-facilitated carrier molecules [10]; and the hormones, particularly the steroid hormones [12].

Despite being crucial for normal and healthy physiology, the BBB remains an impediment to the delivery of drugs to the brain [10]. Tight junction proteins (TJs), efflux, and metabolic processes of the BBB are the main inhibitors of drug translocation through the BBB. The TJs let the molecules pass according to their polarity, ionisation, lipophilicity, or other physical or chemical properties. Simple diffusion, endocytic flux, and the ratio of inward-outward transportation affect how quickly medicines move through cells. Peptidase, transferase, P450 enzymes, and multidrug transporter proteins are examples of metabolising enzymes that control how drugs are metabolised and transported across the BBB [6, 13], as depicted in Fig. (**1**).

The cerebrospinal fluid-brain barrier (CSF-BB) is located in the choroid plexus (CP) of the ventricles [14]. The structural unit of the CSF-BB is the TJs situated in the upper part of the arachnoid epithelial layer and the CP epithelium's intercellular space, which express P-glycoprotein, a protein linked with multidrug resistance and breast cancer resistance [15]. Compared to the BBB, the CSF-BB is relatively more porous due to the epithelium's pores and vesicles. It creates an enormous protein filter, enabling some water-soluble substances to cross it and thus enter the CSF determined by an inverse proportion of their molecular weights [16].

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