A PERSPECTIVE REVIEW ON APPLICATIONS OF NANOPARTICLE MEDIATED DRUG DELIVERY TO THE CNS

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ABSTRACT

Delivery of drugs into the brain is one of the most interesting and challenging areas of research. The blood-brain barrier (BBB) is a highly selective semipermeable membrane that separates blood from the brain in the central nervous system. It acts as a barrier to protect the brain from microbes, neurotoxins and other chemical substances and also blocks the entry of many drugs into the brain. An estimated 6.8 billion people die every year from CNS diseases like Parkinson's disease, Alzheimer's disease, sclerosis, brain stroke, dementia and others. According to WHO, one billion people are affected worldwide, about 50 million suffer from epilepsy and 24 million suffer from Alzheimer and other dementias. This indicates the importance of the delivery of drugs into the brain for treating various neurological diseases and psychological disorders. In drug targeting, a concept was introduced by Dr. Paul Ehrlich as a 'magic bullet' that gave tremendous hope for the researches to deliver drugs into the brain. This review discuses about various drug targeting strategies and applications of nanotechnology in designing drug delivery systems with the ability to cross through the BBB for treating neurological diseases.

Keywords: BBB, CNS, Brain target, Nanoparticles, TDDS, Neural diseases

INTRODUCTION

Worldwide, Alzheimer's and Parkinson's disease are the most commonly caused neurodegenerative diseases. Stroke is one of the second leading cause of death and the third leading cause of disability. An estimated 6.8 billion people die every year from central nervous diseases like Parkinson's disease, Alzheimer's disease, sclerosis, brain stroke, dementia and others [1, 2]. According to WHO, one billion people are affected worldwide, about 50 million suffer from epilepsy and 24 million suffer from Alzheimer's and other dementias.

The primary phase in the therapy of neural illness is the diffusion of drugs across the BBB. The safe, appropriate and targeted delivery of drug compounds into the brain is a challenging and exceptional goal for achieving optimal therapeutic outcomes against neural diseases [3]. There are various drug targeting strategies into the brain. Nanoparticle is considered one of the most efficient carriers to transport the therapeutic agent to the targeted site [4].

Blood-brain barrier

Human brain is the most delicate and complicated organ in the body that is protected by a membrane called the blood-brain barrier (BBB). The BBB is a highly selective semipermeable membrane that separates the circulating blood from the brain in the central nervous system [5, 6]. This barrier protects the brain neurons from harmful toxins, microbes and other chemicals that exist in the blood. This barrier also blocks the diffusion of drugs into the brain.

The BBB is composed of tightly connected endothelial cells and a discontinuous layer of pericytes. Endothelial cells consist of specific proteins TJs and AJs [7]. TJs proteins include claudins, occludens, zona occludens, junction adhesion molecules (JAMs).

Our human brain consists of about 100 billion neurons. The capillaries may be 7-10 μm in diameter. The BBB does have any intracellular and valvar gaps and the entry of any compounds into the brain is very limited [8, 9]. The BBB only enables the passage of ions or neurotransmitters responsible for the impulse conduction. However, nanoparticles (NPs) coupled with polymeric materials, can pass through the BBB and promotes the delivery of drugs into the CNS [10].

Dr. Paul ehrlich's magic bullet concept

Dr. Paul Ehrlich, a German-jewis physician introduced a concept named as magic bullet concept in 1990. For a drug to act on a particular targeted site, it requires a proper carrier [11, 12]. This carrier has to be bound with the drug and should reach the site of action to produce its therapeutic effect but it should not affect the non-targeted sites or non-diseased cells [13].

Dr. Paul Ehrlich termed that a carrier-drug complex should act only on the targeted site just as the bullet target a specific point [14]. This concept gave tremendous hope for scientists for achieving the passage of drugs through the BBB.

Substance transport across the BBB

Because of the presence of BBB, which limits the entry into the brain, prevents the brain from diseases and does not allow the access of various pharmaceutical agents into the brain. The BBB blocks the passage of even tiny molecules to enter into the brain [15]. It only allows the passage of ions or molecules that are responsible for the impulse conduction and synthesis and release of neurotransmitters.

The passage of molecules across the BBB occurs through two processes. They either pass through the endothelial cells or is termed as trans cellular transportation or the pass in between the endothelial cells and it is termed as paracellular transportation.

There are various drug targeting strategies to pass through the BBB. These are enlisted in table 1. There are mainly two techniques non-invasive and invasive techniques. Each technique has different approaches and may have advantages and disadvantages within itself. Hence for a successful target of drugs to the CNS is based on the proper selection of these approaches [16].

Nanoparticles acts an efficient carrier for the transport of pharmaceutical compounds to the brain. Several nano-formulations are used to penetrate through the BBB. The nanoparticles penetrate through the tight junctions between the endothelial cells and allow the drug to pass through the BBB [17].

Various drug targeting strategies to the CNS

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Table 1: Approach and strategies for central nervous system drug delivery

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Techniques for the drug delivery to the CNS	Approaches	Strategies	References
Non-invasive techniques	Chemical	Lipophilic analogues Prodrugs Chemical drug delivery system Molecular packing	[18]
	Biological	Receptor-mediated delivery of chimeric peptides Viral vector Cell-penetrating peptide-mediated delivery	[19]
	Colloidal	Micelles and microemulsions Nanospheres and nano-capsules Liposomes SLNs Dendrimers Polyetheleneimine derivatives	[20]
Invasive techniques	Pharmacological	Intracerebral implants Intraventricular/intrathecal/interstitial delivery Biological tissue delivery	[21]
	Blood-brain barrier disruption	Convection-enhanced delivery Osmotic blood-brain barrier disruption strategy Biochemical blood-brain barrier disruption strategy Ultrasound mediated blood-brain barrier disruption strategy	[22]
	Alternative routes	Olfactory and trigeminal pathways Intranasal delivery Intophoretic delivery	[23]

Nanoparticles

Nanoparticles are colloidal carriers. They may be the natural or synthetic origin. The natural NPs are either prepared from chitosan or albumin. Synthetic NPs are prepared from polymeric materials like polyethyleneimine (PEI), polyalkylanoacrylates (PAA), poly-lactic glycolic acid (PLGA), dendrimers. NPs are also synthesized from inorganic materials like gold and silica.

Nanoparticles are developed to regulate the release and safeguard of drugs from enzymatic or chemical degradation and to improve its therapeutic efficacy. Several kinds of nanoparticles can be used to deliver drugs and genes to the CNS [24].

Characteristics of nanoparticles

Molecules with high lipophilicity and small size can passively pass across the BBB. Lipophilicity of NPs are often associated with the permeability and solubility of a compound. Lipophilicity, however, is a two-edged sword. Most drug parameters are affected by lipophilicity [25]. Increased lipophilicity leads to the formation of compounds with rapid metabolism, low solubility and poor absorption. In such cases, nanotechnology can be used for the delivery of these pharmaceutical compounds. New strategies were developed for the delivery of nanoformulations (fig. 1.).

Nanoparticle mediated drug delivery [26]

The nanoparticles due to their mean particle size, zeta potential and hydrophilicity play a major role for the transport of drugs. Due to their small size, they can be easily penetrated through the BBB. To increase the permeability of NPs they are coated with surfactants like polysorbate 80. This enhanced the permeability of drugs like loperamide, tubocurarine and doxorubicin [27]. Attachment of ligands such as shielding ones can increase their circulation time in the blood whereas targeting ligands enhances the targeting potential.

Claudia *et al.* An experiment was carried out on mice. Meloxicam, a drug used in the treatment of memory impairment cannot diffuse through the BBB. Hence, it is loaded with nano-capsules and was found to induce memory impairment in mice [28].

Gurthork *et al.* an effective nanosystem was developed for efficient drug delivery to the brain. The designed a liposomal drug delivery system for transferring levodopa (used to treat Parkinson's disease) through the BBB.

Various nanoformulations were developed in order to increase the permeability and efficacy of drugs. These are enlisted in table 2.

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Table 2: Various nanoformulations for the CNS drug delivery

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S. No.	Title	Journal name	Author	Year/volume/Issue	Nano formulation (TDDS)	Conclusion
1.	Polymeric nanoparticles for drug delivery to the CNS	Advanced drug delivery	Toral patel	2011/12/006	PBCA nanoparticle coated with polysorbate 80 were loaded with dalargin (opiod activity)	Dalargin-loaded PBCA diffuses through the BBB and reaches the targeted site.
2.	Polymeric nanoparticles for drug delivery to the CNS	Advanced drug delivery	Toral patel	2011/12/006	PLA nanoparticles loaded with breviscapine (flavonoid)	PLA-loaded breviscapine penetrates the BBB
3.	Nanoparticles for brain drug delivery.	ISRN biochemistry	Massimo	2013	Rifampicin drug loaded with NPs	Expt. carried out on mice showed better permeability of rifampicin into the brain
4.	Nano formulations for drug delivery	biopharmaceutics	wang	2015	Synthesis of DU-FUdR to overcome the limited access of drug FUdR and incorporated with SLN	The result showed that D0-FUdR-SLN had brain target efficiency *in vivo*.
5.	Nanoparticle mediated drug delivery	Journal of controlled release	claudia	2016/34-47	NGF loaded with PBCA NPs	Improved uptake to brain regions. Reversed Scopolamaine-induced amnesia and improved cognition and memory.

Fig. 1: Development of new strategies based on NPs for drug delivery into the CNS

Conclusion and future prospects

NPs are well suited for the diagnosis and therapy of brain disorders owing to their physical, chemical and biological characteristics [29]. The ability to use this technological strategy for the therapy and diagnosis of CNS illnesses was hopeful. Several nanoformulations are being investigated using polymer-based techniques and nanomaterials [30].

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declare none

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