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Intranasal Delivery of Nano Neurotherapeutics: A Meta Opinion

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Abstract

The most stringer barrier for the delivery of neurotherapeutics *in-vivo* is presented by the blood-brain barrier which limits the access of neurotherapeutics to the CNS effectively. Intranasal delivery of neurotherapeutics is one of the promising endeavors to surmount the blood-brain barrier, designated as direct nose to brain transport, by the passage of neurotherapeutics along the olfactory and trigeminal nerve pathways. The outstanding findings obtained from the nanomedicines in the preclinical studies for the treatment of CNS disorders via intranasal administration have harnessed the scientists from various research groups to walk around the nano neurotherapeutics for the effective management of CNS disorders. Currently, 33 nanotherapeutics and 67 commercialized nanodevices are on the market but none of them is a nano neurotherapeutic. This could be attributed to the fact that though the researchers have obtained outstanding preclinical findings but these were followed by the disappointing clinical results. To conclude in summary, the authors want to mention here that the development of targets-specific nano pharmaceuticals delivered via non-invasive intranasal route of administration might present some hope to the development of novel neurotherapeutics for major CNS disorders. According to our assessment, in order to come out with a newly designed neurotherapeutic with optimized physicochemical, pharmacological, and pharmacokinetic properties, it requires several parameters to be studied in silico, *in-vitro*, and *in-vivo*, keeping in mind the complex nature of the brain.

Keywords: Nanotechnology; Nanomedicine; Neurotherapeutics; Intranasal; Drug delivery; CNS disorders; Nose to brain

Abbreviations: NIH: National Institute of Health; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; nm: Nanometers; PLGA: Poly (lactic-co-Glycolic Acid)

Introduction

Nanotechnology is a multidisciplinary field where Nano refers to the scale of objects measured in nanometers (nm) means one nanometer is one billionth, or 10^{-9}, of a meter. The dimensions of nanoparticles are similar to biomolecules, such as proteins (1–20 nm), DNA (~diameter 2 nm), virus (~20 nm), cell surface receptors (~10 nm), hemoglobin (~5 nm), cell membrane (~6–10 nm). Therefore scientists with diverse interests and backgrounds have clutched their attention to work with and understand properties of materials on a nano scale and apply them in medicine [1]. Nanomedicine comes along one of the most important disciplines of nanotechnology and according to National Institute of Health (NIH), the term nanomedicine refers to highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of various diseases [2,3]. National Nanotechnology Initiative defines nanotechnology as the production of materials in the scale between 1 and 100 billionths of a meter (1-100 nm) at least in one dimension [4].

The last 20 years have witnessed an outburst in research on the development of novel drug delivery systems. Among them, the multiparticulate drug delivery systems have broad prospects in the pharmaceutical field [5]. Researchers from various disciplines have been harnessed by the superior outcomes obtained from such nanocarrier systems viz. greater therapeutic efficacy and reduced dosing frequency [6]. At the University of North Carolina, a chemistry Professor Joseph De Simone once said about nanoparticles that you want to deliver it where you want it, when you want it, without wasting it [7]. A very first report was published on the designing a specified drug

delivery system to achieve selective targeting of drugs and was originated from the perception of Paul Ehrlich, who proposed a hypothesis of magic bullet concept [8]. Neurotherapeutics represents second largest segments of the total drug market accounting for a total market share of US $56 billion, and will be growing substantially in the recent years, majorly because of the rapidly increasing population with CNS disorders. However, neurotherapeutics takes longer time to be there in the market. This is attributed to the rigorous restrictions set down by the physiological barriers in the CNS [9-11].

Drug delivery via nasal route has been practices since ancient times for systemic effects. Nasal drug delivery has now been recognised as an excellent platform for the delivery of neurotherapeutics. Large surface area, porous endothelial membrane, high total blood flow, ready accessibility, and avoidance of hepatic first pass metabolism are few of the major reasons for drug delivery across nasal mucosa. Henceforth, the intranasal delivery of neurotherapeutics is attaining the great deal of attention of the researchers, now-a-days [12,13].

Animal and human investigations have proved that, transport of exogenous materials directly from nose to brain is a potential route for bypassing the blood-brain barrier [14,15]. Nose to brain drug delivery is most likely mediated along the olfactory and/or trigeminal nerve pathways, located at the roof of the nasal cavity as its neuroepithelium is the only part of the CNS that is directly exposed to the external environment. Thus, better targeting action can be achieved due to direct movement of drug from the submucosal space of the nose into the cerebrospinal fluid (CSF) compartment of the brain [16,17]. Again, the novel nasal administration devices have proven their proficiency in the delivery of neurotherapeutics or nano neurotherapeutics so as to achieve the site-specific action. The performance of the nasal administration device depends on three major attributed viz. quality, safety and efficacy [18].

The most attractive area of research in drug delivery, now-a-days, is the design of nanocarriers for targeted drug therapy. In author's opinion, the nanotechnology-mediated delivery of CNS acting drugs (in general designated as nano neurotherapeutics) via intranasal route of drug administration is the topic of great attention in the today's research. Extensive clinical efforts are still needed so as to bring the nano neurotherapeutics to the shelves for the well being of society.

Intranasal Delivery of Nano Neurotherapeutics: Research at a Glance

There is ample of literature is available demonstrating the extensive investigations published on the theme nanotechnology-based delivery of neurotherapeutics via intranasal route of administration. The nanoparticulate formulations have been developed and evaluated for the brain targeting ability of neurotherapeutics in the treatment of variety of CNS disorders [19]. Our research group is investigating the potential of nanotechnology-based nose to brain drug delivery systems in the management of various CNS disorders since last decade. The major nanoparticulate formulations we have developed in our laboratory include the solid lipid nanoparticles [20], and polymer-lipid hybrid nanoparticles [21], polyelectrolyte nanocomplex [22,23], and N,N,N-trimethyl chitosan-based mucoadhesive nanoparticles [24] for the management of Parkinson's disease, and PLGA-based nanoparticles [25] for the treatment of Schizophrenia.

The intranasal delivery of nano neurotherapeutics has also been explored globally for various other nano formulations viz. chitosan nanoparticles of venlafaxin [26], estradiol [27], and ropinirole [28], nano emulsion of zonisamide [29], risperidone [30,31], olanzapine [32,33], polymeric micelles of zolmitriptan [34], micro emulsion of tacrine [35], and so on.

Conclusion and Future Perspectives

The CNS disorders (mainly brain cancers, neurodegenerative disorders and cerebrovascular disorders) have threatened the human health with high mortality rates. According to the WHO statistics, CNS disorders constitute about 12% of total deaths globally. Thus, the field of development of neurotherapeutics for the treatment of CNS disorders is growing rapidly in the pharmaceutical sector, now-a-days. However, poor permeability and distribution of neurotherapeutics within the CNS led to the little clinical success of the neurotherapeutics as an effective treatment strategy for CNS disorders. There a number of strategies available to enhance the brain targeting ability of neurotherapeutics and intranasal drug delivery is one of the promising avenue to unlock the limitations posed by the other routes of drug administration or other formulation strategies. In general, the trend for the effective brain targeting of neurotherapeutics follows the below-mentioned sequence:

Nasal mucoadhesive nanoparticles > Nasal solution > Intravenous nanoparticles > Intravenous solution

Nano technological interventions could be able to improve the brain targeting ability of neurotherapeutics. Thereby, nano neurotherapeutics would be useful to reduce the gap between preclinical and clinical investigations, to increase the success rate of neurotherapeutics in clinical studies and further, their scale-up and commercialization aspects. The current findings indicate that the development of nano neurotherapeutics will certainly occupy the pharmaceutical market, the only query is when? To conclude in summary, the authors want to mention here that the development of targets-specific nano pharmaceuticals delivered via intranasal route of administration might present some hope to the development of novel neurotherapeutics for major CNS disorders. In order to come out with a newly designed neurotherapeutic with optimized physicochemical, pharmacological, and pharmacokinetic properties, it requires several parameters to be studied in silico, In-vitro, and In-vivo,

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keeping in mind the complex nature of the brain.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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