Nose to Brain Drug Delivery: A Recent Update

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Abstract

Drugs used to treat brain or central nervous system disorder suffer from short fall of absorption and reaching brain due to blood brain barrier and cerebro spinal fluid barrier. Intra nasal administration of brain targeted drug delivery system is gaining popularity to circumvent blood brain barrier and enhance drug availability in brain. It also shows promising reduction of systemic adverse effect incurred by the drug. However there are major limitation of this route which restrict its success of application. Despite different dosage forms such as micro or nano emulsion, gel, in situ gel etc the intra nasal route is still lacking wide applicability. This short review aims to highlight some important features related to nose to brain drug delivery along with its potential challenges that need to overcome. It has focused on few interesting or significant articles on the matter published within last 4-5 years.

Keywords: Nose to brain; In situ gel; Intra nasal; Blood brain barrier; Nano emulsion

Introduction

Reaching brain or CNS is a potential challenge

The unique structure of brain relative to other organs of human body is the outer liquid cover called cerebrospinal fluid (CSF) and inner microvascular layer called blood brain barrier (BBB) [1]. These two barriers form a sophisticated protection system for brain to preserve its physiological nature and shield from external threats such as toxins or pathogens. The BBB forms the interface between blood capillaries and brain tissue. It has its own unique nature which allows selective access of necessary nutrients and hormones while restrict entry of other external materials including therapeutic agent or drug [2]. Any drug that needs to reach central nervous system (CNS) requires crossing BBB. Almost all large drug molecules and most of the small molecules cannot enter brain or CNS after oral or systemic administration. Active transport and passive diffusion through endothelial cells are the two principal mechanisms by which molecules can enter the brain. But problem is that the endothelial cells of capillaries present in the BBB are effectively precluded by very stringent and tight junctions [3]. Therefore other than modified form of drug delivery especially designed for CNS, normal oral or parenteral route of drug administration is not capable enough to make the drug available at the site. This problem is much higher in case of water soluble C.

Naso-mucosal site of drug absorption

Structurally nose is divided in two different nasal cavities by a septum. Each cavity consists of three regions named as vestibule, respiratory region and olfactory region. Functionally, the nasal cavity plays an important protective role to filter, warm and humidify the inhaled air before it reaches the lower airways. It provides a supply and conditioning of air to lungs. Any inhaled particles or microorganisms are trapped by the hair of the nasal vestibule or by the mucus layer covering the respiratory area of the nasal cavity. The mucociliary clearance mechanism of the mucus layer gradually carries such particulates to the back of the throat, down the esophagus, and further into the gastrointestinal tract. Nasal mucosa also have the metabolic capability of converting endogenous materials into compounds that are eliminated more readily [4]. For drug absorption by nasal mucosa and delivery to brain involves the olfactory neural cells, or axons, are unmyelinated cells and are interspaced between supporting cells. They originate at the olfactory bulb and terminate at the apical surface of the olfactory neuroepithelium. Nanoparticles of sufficiently small size or modified formulations could potentially be transported via axons through the olfactory bulb into the olfactory cortex and from there to the caudal pole of the cerebral hemisphere and into the cerebrum and the cerebellum. Hence, these are all potential delivery sites for nose to brain drug transport route via the olfactory epithelium [5]. Different researchers have published their reports in recent times describing improved or better absorption potential trough nasal mucosal route compared to conventional oral or parenteral routes.

Formulations intended for nasal delivery to target brain

Different type of formulations have been developed and studied for naso-mucosal drug delivery to brain such as micro or nano emulsion, nasal gel or thermo responsive nasal gel etc. Some recent reports on nasal emulsion for brain targeted delivery include microemulsion formulation of Rivastigmine [6], Palperidone microemulsion [7] or more recent curcumin micro-emulsion by Shinde and Devrajan [8] or nanoemulsion formations of Quetiapine [9]. All of the articles reported promising drug absorption via nasal route. Among other intra-nasal delivery platforms, gel formulation is very popular in pharmaceutical researchers. Gel formulation can retain on any application site more longer time than solution due to imparted viscosity. For intra nasal application inclusion of bioadhesive polymer helps to retain the dosage form more pronged period of time onto nasal mucosa. There are some polymers that can be converted to gel form by altering pH or temperature. The list includes synthetic as well as natural polymers [10]. A delivery system which is solution in normal temperature but converted into gel at elevated temperature can also retain longer onto mucosal epithelium as well as enhances patient compliance in term of easy administration, measurable dosage etc. Such kind of system is termed as in situ gelling drug delivery platform. In situ nasal thermoresponsive gel delivery system has been developed with many drugs such as Ropinirole [11], Levadopa [12], Midazolam

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to enjoy the advantages. Moreover the absorption pathways is not also very clearly demonstrated and established. Therefore there is necessity of more studies to exploit this route extensively and successfully.

**References**