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Intranasal Drug Delivery of Frovatriptan Succinate–Loaded Polymeric Nanoparticles for Brain Targeting

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ABSTRACT

The objective of the present study was to develop polymeric nanoparticles (PNPs) of frovatriptan succinate for brain targeting by nasal route. Double emulsion method was used to increase the entrapment efficiency of hydrophilic drug, and formulation was optimized by central composite design to achieve critical quality attributes namely particle size, zeta potential, and entrapment efficiency. Optimized batch was evaluated for surface morphology, *in vitro* release, permeation across nasal mucosa, stability, histopathology, and brain tissue uptake study. Prepared PNPs were found to be smooth with particle size of 264.4 ± 0.04 nm, zeta potential −35.17 ± 0.07 mV, and 65.2 ± 0.06% entrapment efficiency. PNPs showed biphasic release pattern, initial burst release followed by sustained release up to 72 h. *Ex vivo* diffusion study using goat nasal mucosa at pH 6.8 revealed that PNPs permeation across nasal mucosa was about 3 times more than the pure drug solution, and quick delivery of PNPs in brain region was confirmed by fluorescence microscopic evaluation in male Wistar rats after intranasal administration. Histopathology studies further revealed integrity of nasal mucosa after treatment with PNPs. The investigation indicated that hydrophilic drug, frovatriptan succinate can be successfully entrapped in PNPs to target brain via nasal delivery, and thus it could be an effective approach for nose to brain delivery.

Introduction

A migraine is a neurovascular throbbing headache on one side of the head followed by nausea, vomiting, photophobia, and phonophobia.[1,2] About 6% of men and 18% of women suffer from migraines. Approximately 80% of migraineurs have family history of migraine (American Headache Society).[3] Migraine is diagnosed by the pulsatile quality of headache, unilateral location, and disabling intensity.[4] Exact mechanism of migraine is not known. However, it is believed that serotonin (5 hydroxytryptamine) receptors play important role in pathogenesis of migraine. Migraine is divided in 2 parts namely migraine with aura and without aura. Migraine without aura is characterized by headache at unilateral location and aggravation by or avoiding daily activities like walking. During aura phase, 5-hydroxytryptamines (HT) concentration in the blood decreases, leading to migraine complications. Reserpine which depletes serotonin level stimulates migraine attack in patients. Therefore, a new class of serotonin receptor agonist (5 hydroxytryptamine) targeting 5-HT 1B/1D receptors was discovered.[5,6]

Frovatriptan, seventh triptan available in market, acts mainly on 5-HT 1B/1D receptor. In spite of having long half-life (26 h) and being potent drug, it is still categorized as low efficacy triptan due to slow onset of action.[7] It is currently available in the market as fast dissolving film and film-coated tablet. Current dosage forms exhibit limitations like slow onset of action, low bioavailability (10%-30%), and adverse effects like coronary vasospasm, sensation of pain, chest tightness, and numbness in fingers. Film coating tablet likely to be given by per oral route suffers from disadvantages of multiple dosing. The reason behind this can be that frovatriptan being a hydrophilic drug is unable to pass the blood-brain barrier.[1,8-11] The aforementioned problem associated with the drug can be overcome by directly targeting the drug to the brain. It can be achieved by invasive targeting strategies like intracerebral implants, intraventricular/intrathecal delivery, and disrupting blood-brain barrier. These strategies suffer from disadvantage of patient compliance.[12] Nose to brain delivery via the olfactory pathway bypassing the blood-brain barrier seems to be the best option for fast onset of action, increased bioavailability, and decreased side effects. From last few decades, nasal route is considered as noninvasive, convenient, safe, and reliable route for brain targeting.[9]

Drug will reach the brain region from nasal cavity via olfactory and trigeminal nerves present in nasal cavity.[13] Although olfactory

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