Trans-nasal Zolmitriptan Novasomes: in-vitro preparation, optimization and in-vivo evaluation of brain targeting efficiency

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Abstract

Migraine attack is a troublesome physiological condition associated with throbbing, intense headache, in one half of the head. Zolmitriptan is a potent second-generation triptan, prescribed for patients with migraine attacks, with or without an aura, and cluster headaches. The absolute bioavailability of zolmitriptan is about 40% for oral administration; due to hepatic first metabolism. Nasal administration would circumvent the pre-systemic metabolism thus increasing the bioavailability of zolmitriptan. In addition, due to the presence of microvilli and high vasculature, the absorption is expected to be faster compared to oral route. However, the bioavailability of nasal administered drugs is particularly restricted by poor membrane penetration. Thus, the aim of this work is to explore the potential of novel nanovesicular fatty acid enriched structures (novasomes) for effective and enhanced nasal delivery of zolmitriptan and investigate their nose to brain targeting potential. Novasomes were prepared using nonionic surfactant, cholesterol in addition to a free fatty acid. A 23 full factorial design was adopted to study the influence of the type of surfactant, type of free fatty acid and ratio between the free fatty acid and the surfactant on novasomes properties. The particle size, entrapment efficiency, polydispersity index, zeta potential and % zolmitriptan released after 2 h were selected as dependent variables. Novasomes were further optimized using Design Expert® software (version 7; Stat-Ease Inc., Minneapolis, MN), and an optimized formulation composed of Span® 80:Cholesterol:stearic acid (in the ratio 1:1:1) was selected. This formulation showed zolmitriptan entrapment of 92.94%, particle size of 149.9 nm, zeta potential of −55.57 mV, and released 48.43% zolmitriptan after 2 h. The optimized formulation was further examined using transmission electron microscope, which revealed non-aggregating multi-lamellar nanovesicles with narrow size distribution. DSC, XRD examination of the optimized formulation confirmed that the drug have been homogeneously dispersed throughout the novasomes in an amorphous state. In-vivo bio-distribution studies of 99mTc radio-labeled intranasal zolmitriptan loaded novasomes were done on mice, the pharmacokinetic parameters were compared with those following administration of intravenous 99mTc-zolmitriptan solution. Results revealed the great enhancement in zolmitriptan targeting to the brain, with drug targeting potential of about 99% following intranasal administration of novasomes compared with the intravenous drug solution. Zolmitriptan loaded novasomes administered via the nasal route may therefore constitute an advance in the management of acute migraine attacks.