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Augmented Brain Delivery of Cinnarizine Through Nanostructured Lipid Carriers Loaded in situ Gel: in vitro and Pharmacokinetic Evaluation

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Abstract

The study envisaged the development of cinnarizine (CIN)-loaded nanostructured lipid carriers (NLCs) in situ gel, for intranasal delivery to the brain, for migraine treatment. The formulation was prepared and optimized by the solvent-evaporation method and central composite designs. The total lipid concentration (X1), surfactant concentration (X2), and sonication time (X3) were selected as critical material attributes, and the effects of variables were characterized for parameters like zeta potential, particle size, percent entrapment, and in vitro release. Furthermore, the optimized NLCs (OPT-NLCs) were incorporated into Pluronic F-127:Pluronic F-68:Chitosan (19:0.5:0.1) % w/v to form the NLCs loaded in situ gel. The prepared gel (CIN-NLC gel) was evaluated for texture analysis, in vitro profile, and antinociceptive activity in vivo. The optimized NLCs possessed a particle size of 108.9 ± 4.3 nm, a zeta potential of − 39.3 ± 2.12 mV, and entrapment efficiency of 97.7 ± 4.31%. NLCs showed an in vitro release of 87.72 ± 3.29% for 6 h. The gel displayed a mucoadhesive strength of 147 ± 2 g. A significant enhancement in antinociceptive activity was observed via intranasal administration with the gel in both phases (neurogenic pain and inflammatory pain) when compared with pure CIN. The pharmacokinetic parameters revealed an approximately twofold increase in the concentration of CIN in the brain with the CIN-NLC gel (7.63 ± 0.073 μg/ml) when compared with pure CIN (3.78 ± 0.023 μg/ml). The results indicate that intranasal administration of CIN-NLCs in situ gel (CIN-NLC gel) may be a step forward in developing safe, effective, and enhanced drug delivery to overcome the challenges encountered during drug delivery to the brain.

Keywords Central composite designs · NLC · Antinociceptive activity · Migraine · Cinnarizine

1 Introduction

Migraine is a disorder of the nervous system which is evidenced by a throbbing headache, mild to severe, thereby affecting normal activity. Photophobia, phonophobia, nausea, and vomiting generally occur simultaneously with a migraine attack [28]. Migraine has a tremendous health burden on patients and society. Prevalence of migraine varies on factors ranging from age to geographical conditions. It is often observed in the age range of 25–55 years, being more common in women, and is more prevalent in lower socio-economic groups.

The preventive therapy for migraine is aimed at reducing attack severity and frequency, improves the response to treatment, and enables better functionality with reduced disability. In general, prophylactic treatment has limited efficacy and includes the α2-adrenoceptor agonist clonidine, the β-blockers propranolol and metoprolol, the 5-HT2 receptor antagonist methysergide, pizotifen, lisuride, and the calcium channel blockers flunarizine and cinnarizine [38]. Cinnarizine (CIN) inhibits contractions in the vascular smooth muscles and stimulation of hair cell. It also has antihistaminic action. The above actions altogether contribute to the prevention of migraine. Abortive medications are taken to treat the symptoms when the attacks arise [39].

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