ABSTRTACT

The present work is concerned with tailoring and appraisal of a novel nano-cargo; bilosomes (BLS) dual laded with doxylamine succinate (DAS) and pyridoxine hydrochloride (PDH), the first treatment option against gestational nausea and vomiting, for intranasal delivery. This bifunctional horizon could surmount constraints of orally-commercialized platforms both in dosage regimen and pharmacokinetic profile. For accomplishing this purpose, DAS/PDH-BLS were elaborated embedding phospholipid, sodium cholate and cholesterol applying thin-film hydration method based on Box-Behnken design. Utilizing Design-Expert® software, the effect of formulation variables on BLS physicochemical features alongside the optimal formulation selection were investigated. Then, the optimum DAS/PDH-BLS formulation was incorporated into a thermally-triggered *in situ* gelling base. The *in vivo* pharmacokinetic studies were scrutinized in rats for intranasal DAS/PDH-BLS *in situ* gel compared with analogous intranasal free *in situ* gel and oral solution. The optimized BLS disclosed particle size of 243.23 nm, ζ potential of -31.33 mV, entrapment efficiency of 59.18 and 41.63%, accumulative % release within 8 h of 63.30 and 85.52% and accumulative permeated amount over 24 h of 347.92 and 195.4 µg/cm^2 for DAS/PDH, respectively. Following intranasal administration of the inspected BLS *in situ* gel, pharmacokinetic studies revealed a 1.64- and 2.3-fold increment in the relative bioavailability of DAS and a 1.7- and 3.73-fold increase for PDH compared to the intranasal free *in situ* gel and oral solution, respectively besides significantly extended mean residence times for both drugs. Thus, the intranasally harnessed DAS/PDH-BLS could be deemed as a competent hybrid nanoplatform with auspicious pharmacokinetics and tolerability traits.

Keywords: Doxylamine succinate; Pyridoxine hydrochloride; Emesis gravidarum; Intranasal delivery; Bilosomes; Pharmacokinetics.