ABSTRACT

Pharmacokinetic and Pharmacodynamic evaluation of a novel formulation of Curcumin.

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Background: The anti-inflammatory action of Curcumin is already proven but its water insolubility and low bioavailability property limits its use to treat neuro inflammatory diseases. Novel formulation like microemulsion and nano formulations are explored to target the drug molecule to affected site.

Aim: The investigation was aimed at developing an optimal mucoadhesive microemulsion and to evaluate its potential neuroprotective effect against dopaminergic inflammation mediated neurodegeneration using MPTP i.e., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in Parkinsonism following transnasal application.

Materials and Methods: Mucoadhesive microemulsion of Curcumin (CMME) was successfully optimized by Box-Behnken design by manipulating the combined influences of all formulation components on responses like average
globule size, size distribution, viscosity, flux and drug permeation (%). CMMEs were characterized and assessed for ex-vivo naso mucosal permeation, nasal toxicity along with pharmacokinetic evaluations (Brain distribution study). Preclinical study in MPTP induced Male C57BL/6 mice model was also carried out to ascertain the neuroprotective action of optimal CMME. Finally, accelerated stability study of CMME was carried out for 6 months as per ICH guideline (Q8, R2).

**Results and Discussion:** Developed CMME with 0.3 ml of Capmul MCM, 36 % of S\textsubscript{mix} at 2.5:1 (Accenon CC & Transcutol P) and 0.5 % aqueous Sodium hyaluronate was observed to be non ciliotoxic and optically transparent with 57.66 ± 3.46 nm and -16.28 ± 4.11 mV as average globule size and zeta potential respectively. Pdl value (0.261 ± 0.19) and TEM data comparatively revealing narrow size distribution of CMME. *In-vitro* permeation study revealed control permeation of curcumin up to 6 h through nasal mucosa.

Brain distribution study revealed that with single intranasal administration of CMME (2.866 mg of Curcumin/kg), olfactory bulb showed three times more Curcumin uptake over intravenous Curcumin solution (CDS). Higher Brain AUC to plasma AUC fractions were in turn, suggesting an effective CNS transport of Curcumin indicating the brain uptake efficiency.

Findings for gross behavioral and motor activity through open field test and rota-rod test respectively were revealing the significant performance of the developed formulation in CMME treated (nasally) mice. *In vivo* and immunohisto-chemistry study showed significant diminution of MPTP-mediated dopamine depletion for CMME treated mice over plain Curcumin gel and other groups. Furthermore, TH neurons count in the substantia nigra and the density of striatal dopaminergic nerve terminals were found to be significant higher for Curcumin treated groups.
Conclusion(s): Data so obtained revealing the neuro-protective action of CMME against injury induced by MPTP in striatum as well as substantia nigra pars compacta (SNpc) and hence, this approach for brain targeting of Curcumin through intranasal route to treat PD is much more promising.