ABSTRACT

Tight junction, an obstructive unit of the blood brain barrier and presence of efflux transporters primarily P-glyco protein, makes the physiology of the CNS system very complex and thus delivery of drugs across the brain becomes a challenging task. Current conventional mode of drug delivery is still ineffective in treating CNS disorders due to the presence of obstacles, thus resulting into poor concentration of the drug at the target site. Quetiapine and rivastigmine are widely used drugs in the treatment of schizophrenia and Alzheimer’s disease respectively. Oral delivery of quetiapine and rivastigmine prevents the effective concentration at the brain due to presence of biological barriers and extensive first pass metabolism (9% and 36% respectively) and thus resulting into frequent dosing. The aim of the investigation was to develop intranasal microemulsion and mucoadhesive microemulsion system of the quetiapine and rivastigmine to overcome the limitation of poor concentration and obstructive barriers at the target site for improved bioavailability. Optimized formulations of quetiapine and rivastigmine were characterized for various physicochemical and diffusion parameters. It was found that chitosan based mucoadhesive microemulsion showed improved nasal diffusion for both the drugs in comparison to microemulsion and drug solution as a result of enhanced paracellular transport across nasal mucosa. In vitro cell line study demonstrated that chitosan based microemulsion system induced reversible opening of tight junctions and hence showed higher diffusion for quetiapine via paracellular route. Spray pattern and plume geometry data showed satisfactory results with plume length in the range of 10-12 cm, thus confirming the delivery of formulation into posterior nasal segment and hence enhanced delivery to brain via olfactory route. In vivo pharmacokinetic study demonstrated superior nasal bioavailability for both the drugs with chitosan based mucoadhesive microemulsion against individual drug solution, thus revealing the potential of chitosan as permeability enhancer and/or tight junction modulator for preferential nose to brain transport bypassing blood brain barrier. Results of gamma scintigraphy study and in vivo pharmacokinetic parameters showed satisfactory correlation between pharmacokinetic parameters for intranasally administered chitosan loaded microemulsion. Overall, the above findings show promising results in the area of developing noninvasive intranasal route as an alternative to oral route for brain delivery.