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 in the treatment of various CNS disorders. Majority of the drugs used in the treatment of CNS disorders are substrate to P-glyco protein, where current conventional mode of drug delivery is still ineffective thus resulting into poor brain uptake and lower concentration of drug at the site of action. Among several strategies viz., invasive and noninvasive for overcoming the obstructive barriers, noninvasive intranasal delivery bypasses the blood brain barrier and rapidly targets a drug directly to the CNS utilizing pathway along olfactory and trigeminal nerves while minimizing the systemic exposure and avoiding surgical intervention. As per reported literature, drug delivery to CNS through nasal route using mucoadhesive microemulsion based system are gaining ample prominence over other carriers owing to its lipidic nature and helps in achieving higher permeation across biological membranes for drugs with poor bioavailability. It surmounts the rapid nasal mucociliary clearance and prolongs the residence time at the site of absorption.

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. P-glyco protein efflux mechanism also hinders their delivery to brain upon oral and/or intravenous administration.

Hence, in the present investigation, the aim was to develop intranasal microemulsion and mucoadhesive microemulsion system of the selected drug candidates to overcome the limitation of poor concentration and obstructive barriers at the target site for improved bioavailability.

Quetiapine showed highest solubility in Capmul MCM EP, Tween80:Labrasol and Transcutol-P as oil, surfactant and cosurfactant respectively; whereby, Smix ratio 3:1 (Labrasol+Twen80: Transcutol-P) showed highest microemulsion formation region. Optimized formulations of quetiapine loaded microemulsion and mucoadhesive microemulsion were characterized for various physicochemical and diffusion parameters. Quetiapine loaded chitosan microemulsion with spherical globules having mean size of 35.31 ± 1.71 nm showed highest *ex vivo* nasal diffusion of 78.26 ± 3.29% after 8 h with no sign of structural damage. Intestinal
diffusion study also showed higher diffusion as a result of enhanced paracellular transport. *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 study showed circular plume with an ovality ratio closer to 1.3 depicting ideal spray pattern. Following intranasal administration in rat, quetiapine loaded chitosan microemulsion showed higher nasal bioavailability in comparison to microemulsion and drug solution, thus revealing potential of chitosan as permeability enhancer for preferential nose to brain transport bypassing blood brain barrier. Quantitative and qualitative biodistribution data showed satisfactory correlation between pharmacokinetic parameters for intranasally administered chitosan loaded microemulsion.

To confirm the modulation effect of chitosan and to investigate whether the effect exerted by chitosan was irrespective of the type of formulation developed, quetiapine loaded chitosan nanoparticles were formulated and evaluated for diffusion and pharmacokinetic parameters. Comparative outcome between them revealed lower globule size (35.31 ± 1.71 nm), 1.3 times higher *ex vivo* nasal diffusion, 1.4 folds higher $C_{\text{max}}$ in the brain and 1.9 folds higher nasal bioavailability with chitosan based microemulsion against nanoparticles. Overall, it was summarized that the brain delivery of quetiapine was superior with intranasal administration of chitosan microemulsion, thus proving the potential of mucoadhesive microemulsion as preferred delivery system in brain delivery of therapeutics via noninvasive intranasal route.

Similar findings were confirmed with rivastigmine loaded chitosan based microemulsion. It showed highest mucoadhesion strength and hence greater diffusion coefficient was observed. Spherical globules with size of 53.8 ± 0.39 nm showed absence of aggregation and ideal spray pattern. Plume length of 11.6 cm confirmed the delivery of formulation into posterior nasal segment and hence enhanced delivery to brain via olfactory route. Higher values for $C_{\text{max}}$ and direct transport percentage for rivastigmine loaded chitosan microemulsion confirmed the effect of chitosan on modulation of tight junctions which resulted in enhanced paracellular transport. Similarity between the results of gamma scintigraphy study and *in vivo* pharmacokinetic parameters proved the potential of chitosan as tight junction modulator and/or permeation enhancer in preferential nose to brain delivery of therapeutics by overcoming biological obstacles.