ABSTRACT

In present study, we aimed to formulate RT loaded nanoparticles, which will give the best result for improvement of memory, cognitive deficits and prevention against degeneration of hippocampus in Alzheimer's disease. We prepared two types of nanoparticles: Polymeric and Solid lipid nanoparticles. Polymeric nanoparticles PLGA-CS-Tween 80, PLGA-CS-PEGs and PLGA-Soya lecithin-Tween 80 were prepared by emulsification-solvent evaporation, oil-in-water (O/W) single emulsion solvent evaporation method, modified nanoprecipitation technique combined with self assembly respectively. Solid lipid nanoparticles were prepared by modified cold homogenization method. The nanoparticles were evaluated for FTIR, DSC, particle size, polydispersity, zetapotential, *in vitro* drug release, stability study, SEM, behavioral study and histopathology of hippocampus. The FTIR and DSC study demonstrated that there was no interaction between drug, polymers and lipids, which indicated that they are compatible with each other. Using factorial design for optimization we tried to achieve higher entrapment efficiency and drug release with smaller particle size (<200 nm) and narrow polydispersity index, with less number of experiments. The SEM study showed that particles were spherical in shape with smooth/rough surface. The stability study for six months demonstrated that the formulations were stable at refrigerator (3-5 °C) condition, hence is the most suitable condition for the storage of nanoparticles. Administration of optimized formulations of polymeric and solid lipid nanoparticles in Aluminium chloride induced Alzheimer's disease model (Wistar rats) results in noticeable improvement in learning and memory capacity and it antagonized the toxic effect of Aluminium chloride by reduction in escape latency compared to standard drug solution treated animals.

Polymeric nanoparticles treated animal model showed better results compared to solid lipid nanoparticles. The results of AchE activity study showed that, compare to free RT and solid lipid nanoparticles, polymeric nanoparticles treated groups, inhibits AchE effectively, and the reduction of AchE concentration results in slower degradation of Ach. Therefore the concentration of Ach rose in rat's brain, and cholinergic system reached a new equilibrium between Ach and AchE, which improved memory and cognitive deficits of rats under AD. Among prepared nanoparticles PLGA-CS-Tween 80 NPs showed better behavioral and histological results with particle size 143.0 nm, polydispersity 0.164, % entrapment efficiency 79.649±0.167% and *in vitro* drug release 69.30±0.262% (60 h). They can be effective in brain targeting and sustained release of RT for prolong period and can be a significant improvement for treating Alzheimer's disease.

Key words: Brain targeting, PLGA-CS-Tween 80 nanoparticles, PLGA-CS-PEG nanoparticles, PLGA-Soya lecithin-Tween 80 nanoparticles, Solid lipid nanoparticles, Morris water maze, Elevated plus maze paradigm