Summary of the research work

Temozolomide (TMZ) is considered a first choice for Glioblastoma which has the highest mortality rate. Despite 100 % bioavailability, only 20-30 % brain bioavailability is achieved due to the short half-life (1.8 h). We investigated two lipid-based PEGylated nanocarriers (liposomes and lyotropic liquid crystals) with the aim to prolong the plasma circulation time of TMZ. Before starting with the formulation development, an analytical and bioanalytical method was developed and a few preformulation studies were conducted to assist in formulation development. During the formulation various lipids, methods of preparation, and size reduction techniques were screened. Thereafter, the effect of various critical material attributes and critical process parameters on critical quality attributes was studied in detail. The formulations were optimized based on the principles of Quality-by-Design and characterized for particle size distribution, zeta potential, morphology, in-vitro drug release, hemolysis, cytotoxicity, cell-uptake, pharmacokinetics and biodistribution. The nanocarriers (80-150 nm) were found to show a prolonged release up to 24-72 h which successfully prolonged the plasma circulation time (upto 2-fold). Also, upto 1.8-fold reduction in the clearance was observed in comparison to the TMZ. The PEGylated nanocarriers showed better pharmacokinetics and biodistribution in comparison to the uncoated nanocarriers and TMZ alone in rats following intravenous injection. Upto 6-fold increase in brain uptake was achieved at 8 h. Both the nanocarriers were investigated using the industrial feasible techniques which were found to be reproducible. Overall, the observed results revealed the potential of the designed PEGylated nanocarriers in the efficient treatment of glioblastoma.

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