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INTRANASAL ROUTE USING NOVEL POLYMERIC NANOPARTICLES AS POSSIBLE DELIVERY STRATEGY OF DRUGS TO ALLEVIATE ALZHEIMER'S DISEASE

MARISTA BINTI ABD RAZAK

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ABSTRACT

Memantine (MEM) is a NMDA receptor antagonist that has been demonstrated to be effective in the treatment of patients with Alzheimer's disease (AD) does not across the blood brain barrier (BBB) readily. This work attempted to improve the brain targeting efficiency of MEM by encapsulating the drug in the novel cross linked itaconic acid-n-vinylcaprolactam-polyethylene glycol (INP) nanoparticles. A novel INP nanoparticle as a carrier for MEM was formulated using the aqueous dispersion polymerization method (ADP). MEM was loaded in the polymer nanoparticles by remote loading method. MEM loaded polymeric nanoparticles were characterized by Fourier transform infrared spectroscopy (FTIR), wide angle X-ray diffraction (WAXD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Particles size and surface charge on the polymeric nanoparticles were evaluated by Zetasizer. WAXD analysis revealed an amorphous nature of the blend polymeric nanoparticles; probably due to the increased composition of itaconic acid (IA). MEM was completely dispersed at the molecular level in the polymer nanoparticles. The blank nanoparticles showed uniform spherical nanoparticles with size ranging from 80 - 180 nm. The *in vitro* release studies on MEM loaded INP nanoparticles was conducted in phosphate buffered saline (PBS). Analysis was performed with high performance liquid chromatography mass spectrometer (LCMS) coupled to an Agilent 6410 triple quadruple mass spectrometer with an electrospray ionization source. MEM was analysed using a C18 column with an isocratic mobile phase of methanol and water, both acidified with 0.01% formic acid at a flow rate of 0.3 ml/min. The instrument was set to multi-reaction monitoring (MRM) mode using precursor and product ions of 180 and m/z 163 for quantification and confirmation respectively. Quantification was done using external calibrations. The external standard method of calibration was evaluated taking at least eight standard solutions. Calibration curves were obtained by plotting peak areas against concentrations of MEM injected. Cytotoxicity studies conducted on INP-NVC MEM 2 utilizing RPMI 2650 cell line showed no effect on the viability of the cells. *In vitro* studies were conducted utilizing different combination of polymer to incorporate MEM. The *in vitro* drug release profile of INP-NVC MEM 2 was found to be the most efficient and exhibited a biphasic release pattern with an initial burst followed by a sustained release process and utilised in the *in vivo* studies. This release pattern is crucial for drug targeting to the brain where the NPs will degrade and release the drug over a period of time to maintain the optimum therapeutic level. *In vivo* studies conducted in the brain homogenate and plasma of rats indicated that the MEM loaded INP NPs administered intranasal produced a higher drug content (DC) & encapsulation efficiency (EE) as compared to MEM solution administered via the same route or intravenously. Collectively the studies suggested the novel formulation to be effective in delivering the drug to the brain when given intransasal.

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