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Design and development of an implantable drug delivery polymeric scaffold for the treatment of Parkinson's disease

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ABSTRACT

Parkinson's disease, primarily defined as the depletion of dopaminergic neurons in the subtantia nigra of the brain, gives rise to severely debilitating motor symptoms. The pharmacological gold standard treatment for the disease, Levodopa , holds great limitations yet still remains the most effective treatment for the disease for the last 40 years. There has been research into novel drug delivery systems for the treatment of the disease that include the development of implantable devices however none have been introduced onto the market. As the neurodegenerative disorder ravages the younger-aged population so the urgency for the effective chronic treatment of the disease escalates. The field of nanotechnology brings promise for the targeted delivery of drugs which is highly sought after in the treatment of central nervous system disorders. A nano-enabled scaffold device (NESD) incorporating dopamine nanoparticles into a polymeric scaffold for implantation into the brain parenchyma may be able to address and overcome the limitations of the current treatment for Parkinson's disease.

Investigations performed cellulose acetate phthalate dopamine-loaded nanoparticles, employing an adopted emulsification-diffusion approach, produced particles with a notably high drug entrapment efficiency (63.05±0.354%) and desirable controlled drug release profiles (16.23% in 24hr). The employment of an experimental design, namely the Box-Behnken design, allowed for the attainment of optimized nanoparticles with high zeta potentials (.34.00mV), minimal particle size (197.20nm) and extended mean dissolution times (40.96).

Barium chloride was employed to crosslink calcium-alginate scaffolds formulated in an adopted freeze-drying approach. Highly resilient (63.58±5.13) and porous structures (pore sizes of 100-400μm) were developed. A statistical approach employing the Box-Behnken design resulted in the formulation of a candidate barium-alginate scaffold displaying maximum matrix resilience (82.46%) and minimal matrix erosion (18.23%) over in 30 days. In addition, dopamine-loaded nanoparticles were dispersed within the scaffold that formed the NESD with the desired drug release profiles (5.12% in 168hr).

Nanosystems of levodopa, nicotine and dopamine nanofibers were preliminary investigated. Drug release profiles for levodopa (4.21%: in 75hr), nicotine (0.42% in 24hrs) and drug entrapment efficiency for the polymeric nanofibers (75-85%) as well as data from scanning electron microscopy, zetasize analysis and drug release studies proved that these systems hold potential for the treatment of the disease and therefore require further investigation.

Ex vivo cytotoxic studies carried out on the NESD and it's separate entities proved that the NESD was biocompatible with the white blood (70-80% cell viability in 24hr) and carcinomic brain cells (25% cell viability in 48hr) despite literature reports of dopamine being highly toxic in vivo.

Extensive in vivo studies resulted in the development of a protocol for the surgical implantation of the NESD in the parenchyma of the frontal lobe of the rat brain. Scanning electron microscope images showed the gradual bioerosion (26% in 30 days) of the NESD while histological findings of the brain tissue proved clinically insignificant (absence of ischemia or chronic inflammation). Ultra Liquid Performance Chromatography revealed higher concentrations of dopamine in the CSF of rats which received brain implants of the NESD (28%) than in those administered the oral preparation, Sinemet (0.000012%) in 3 days.