

Abstract

An impediment in the long-term treatment and positive therapeutic outcome of psychoses is patient non-compliance to treatment regimens. The cognitive impairment associated with psychoses together with the inability to manage the intolerable side-effects of antipsychotic drug, inevitably predisposes the psychotic patient to non-compliance. Furthermore, the highly restricting Blood-Brain Barrier (BBB) has proved to be a significant limitation for the systemic delivery of antipsychotic drugs to the brain.

The benefits of site-specific drug delivery combined with nanobiotechnology serves to enhance drug therapy by evading the BBB, increasing the bioavailability of the drug, enabling effective drug penetration into the brain, avoiding the need to administer potentially toxic doses of antipsychotic drugs and reducing systemic toxicity. In addition, controlled drug release over a prolonged period will ensure improved patient compliance and reduced rates of relapse. Therefore, the aim of this study was to develop of a drug-loaded Nano-enabled Polymeric Membranous Device (NPMD) for intraparenchymal implantation into the sub-arachnoid space in the region of the frontal lobe of the brain that circumvents the limitations of current antipsychotic modes of treatment.

Chlorpromazine hydrochloride (CPZ)-loaded, polycaprolactone (PCL)-based nanoparticles were synthesized by a novel melt-dispersion technique. CPZ was selected as a model drug owing to the fact that it is a highly hydrophilic, cost-effective antipsychotic drug and its use has declined due to its significantly low bioavailability. The employment of a Face-Centered Central Composite Design resulted in an optimized formulation with a desirable size ($140.30 \pm 3.39 \text{ nm}$), stability in terms of its zeta potential ($-26.40 \pm 2.11 \text{ mV}$) and CPZ entrapment ($8170.23 \pm 173.39 \mu\text{g}$) ($\sim 16\%$). Drug release was biphasic with an initial burst release followed by controlled release over 30 days. Furthermore, no thermo-degradation of the drug and constituent polymers were observed with the novel melt-dispersion technique.

Novel implantable polyamide-ethylcellulose (PA 6,10-EC) composite membranes were prepared by a modified wet-phase inversion reaction employing a dialysis apparatus. Composites were optimized by experimental design, which resulted in highly resilient devices with an unhydrated and hydrated matrix resilience of 74.24 ± 0.88 and $84.35 \pm 1.22\%$ respectively. Furthermore, minimal erosion was observed over a period of 30 days ($3.64 \pm 0.08\%$). The optimized CPZ-loaded, PCL-based nanoparticle formulation was combined with the optimized PA 6,10-EC composite membrane formulation to form the intracranial implantable NPMD to be further evaluated *in vivo*.

A further preliminary study investigated the synthesis of encapsulated or adsorbed essential fatty acids in the form of cod-liver oil (CLO) (Gadus Morrhu) within the CPZ-loaded, PCL nanoparticles to form dual-acting nano-liposhells that combine the benefits of conventional with complementary medicine. The rationale for incorporating CLO was due to its high levels of omega-3 fatty acids, Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA), which have been proven to be neuroprotective with proven benefits in conditions such as schizophrenia. Transmission electron microscopy (TEM) revealed that the nano-liposhells were small and denser when compared to nanoparticles devoid of CLO ($16.50 \pm 6.79 \text{ nm}$ in size). A highest absolute zeta potential of $-30.25 \pm 0.06 \text{ mV}$ confirmed the stability of the nano-liposhells and a highest CLO and CPZ entrapment of $98.26 \pm 0.13\%$ and $6690.55 \pm 207.30 \mu\text{g}$ respectively was determined.

Ex vivo cytotoxicity studies using mammalian Pheochromocytoma (PC12) neuronal cells were carried out on the NPMD and the CLO and CPZ-loaded nano-liposhells as well as both their componential elements. A lactate dehydrogenase (LDH) release assay was undertaken and proved that the NPMD and its componential elements were biocompatible and displayed no significant cytotoxicity ($p > 0.05$). The nano-liposhells and the CLO itself did display significant ($p < 0.05$) cytotoxicity and reduced cell viability by $23.27 \pm 2.40\%$ and $45.68 \pm 6.12\%$ respectively and was attributed to free radical formation by auto-oxidation.

An *in vivo* pilot study explored the surgical intraparenchymal implantation of the NPMD into the brain of the New Zealand White Rabbit model. The study was performed over 30 days and Cerebrospinal Fluid (CSF) as well as blood plasma samples were withdrawn at predetermined intervals to evaluate the release of CPZ from the NPMD using Ultra Performance Liquid Chromatography. Results were compared to a group of rabbits given commercially available CPZ in the form of intramuscular (I.M.) Fresenius Chlorpromazine hydrochloride® 25mg/mL. Results revealed higher levels of CPZ in the CSF ($2.08\text{--}2.92 \text{ ng/mL}$) from the NPMD when compared to the I.M. dose ($0.85\text{--}2.32 \text{ ng/mL}$). Furthermore, miniscule quantities of CPZ from the NPMD were detected in the blood ($\leq 0.95 \text{ ng/mL}$). The CPZ release from the NPMD was far superior to the commercially available form of the drug. Implantation at the site of action allowed for a drastic increase in the CPZ bioavailability. Furthermore, the drug was released in a pseudo-steady state with CSF levels being maintained between $2.00\text{--}3.00 \text{ ng/mL}$ with no fluctuations observed. Ultrasonic imaging was utilized to view the NPMD post-implantation. Rabbits displayed no evidence of motor dysfunction or general brain damage post-implantation for the duration of the study. Histomorphological analysis revealed that the NPMD was biocompatible as no evidences of bleeding, ischemia or major chronic inflammation was observed. Light microscopy was used to characterize the bioerosion of the NPMD midway through as well as at the end of the study and revealed minimal erosion at the termination of the study (14.87%).