AN INTRACRANIAL NEUROCOMPATIBLE NANOCOMPOSITE POLYMERIC DEVICE FOR THE CHRONIC MANAGEMENT OF AIDS DEMENTIA COMPLEX

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ABSTRACT

This study focused on the design, biometric simulation and development of a biodegradable Composite Intracranial Nano-enabled Device (CIND) for the intracranial delivery of zidovudine (AZT) in the treatment of AIDS Dementia Complex (ADC), a common CNS complication of late HIV-1 infection. AZT monotherapy administered orally is the gold standard in managing ADC but has limited bioavailability and significant side-effects. Due to the restrictive Blood-Brain Barrier nanoparticles can be used to penetrate the BBB and provide intracranial drug delivery. The CIND was modulated through biometric simulation and computational prototyping to produce a stable ternary crosslinked scaffold fixated with AZT-loaded alginate nanoparticles.

Keywords: intracranial polymeric device, nanoparticles, blood-brain barrier, AIDS Dementia Complex

INTRODUCTION

AIDS Dementia Complex (ADC), a CNS condition caused by the HIV-1 strain of the retrovirus, is a serious manifestation of HIV/AIDS in both developed and developing countries [1-7]. Drug incorporation into nanosystems is employed to achieve site-specific drug delivery, therefore providing better control of drug release. This improves drug efficacy, pharmacokinetics and pharmacodynamics, attributed to sub-micron distribution of the drug particles improving the physicochemical properties of the encapsulated drug [8]. Intracranial implantation of a drug-loaded nanoparticulate multipolymeric device into the frontal lobe of the brain is anticipated to yield site-specific presentation of the drug, negating the need for the drug to bypass the blood brain barrier. Direct implantation into the brain allows for lower doses of drug to be administered and prevents the occurrence of systemic adverse effects resulting from the systemic circulation of drug molecules. The aim of this study was thus to develop a biodegradable Composite Intracranial Nano-enabled Device (CIND) for intracranial implantation into the frontal lobe, enabling controlled, site-specific delivery of drug molecules, for application in ADC. Zidovudine (AZT) was employed as the model antiretroviral drug.

METHODS

Nanoparticle formulations were prepared using a controlled gelification of alginate approach [9], whereby an aqueous AZT-sodium alginate (0.28%$^{w}/_{v}$) was prepared. $CaCl_2$ (6% $^{w}/_{v}$) was added to the solution in a drop wise manner to facilitate crosslinking. A 0.05% $^{w}/_{v}$ pectin solution and a 10% $^{w}/_{v}$ PVA solution were then added to the crosslinked suspension to ensure optimum formulation stability. Carboxymethylcellulose-poly(ethylene oxide)-epsilon caprolactone (CMC-PEO-ECL) scaffolds were prepared by a novel ternary crosslinking approach of aqueous solutions of CMC, PEO and ECL. Crosslinking solutions (10%$^{w}/_{v}$) of $CaCl_2$, $AlCl_3$ and $Na_2S_2O_3$ were prepared and the polymeric mixture was added drop-wise using a 5mL syringe. The mixture was left to agitate for 1 hour. The resultant crosslinked scaffold was removed and dried overnight at 21°C before curing with 1%$^{v}/_{v}$ HCl in order to minimize swelling. Swelling and erosion studies were performed in PBS (pH 7.4; 20rpm; 37°C) with samples taken at predetermined time intervals. Particle size, zeta potential and surface morphology of the nanoparticles were revealed by ZetaSize analysis, SEM and TEM. Drug Entrapment Efficiency (DEE) and drug release was determined by UV spectroscopy. Textural analysis (TA) was performed to assess the physicomechanical properties of the scaffold (N=3). FTIR spectroscopy elucidated transitions in the molecular assemblage of the CIND formulation. Computer-aided free-form prototyping technology was used to design the CIND via suppositional 3D scaffold modeling using ACD/I-Lab, V12 Structure Elucidator Application (Add-on) biometric software based on the step-wise molecular mechanisms of scaffold and nanoparticle formation, polymer interconversion and AZT-loaded nanoparticle fixation as envisioned by the chemical behavior and physical stability. Prototyping aimed to improve the

CIND design by employing archetype data manipulation to pre-assemble the composite scaffold prior to integrated corporeal manufacturing of the device.

RESULTS

Serial prototyping images enabled the step-wise 3D volumetric construction of the CIND model. A simulated stacked voxel of an optimized CIND prototype model (5×3mm) is shown in Fig. 1a-c. The model permitted the componential porosity (mean pore size=100-500µm) and surface area (A=0.0004cm^3) to be semi-optimized via fine control of the micro-architecture of the CIND. This was significant for nanoparticle fixation and mechano-transduction for controlling the release of AZT. TA revealed a matrix resilience of 12.83% (N=3) (Fig. 2). SEM revealed a porous scaffold matrix (Fig. 3). Scaffolds exposed to 1% $^{v}/_{v}$ HCl exhibited smaller uniform pores and a reduction in swelling due to COONa acidic transition (Fig. 3). TEM images confirmed the strut and pore spaces comprising diminutive cavities for allowing the outward diffusion of the nanoparticles from the scaffold (Fig. 4). Nanoparticles displayed an average size of 119.6nm (PDi=0.816) and a stable zeta potential of 0.419mV (Fig. 5). A DEE value of 63±0.35% was computed for AZT-loaded nanoparticles (Fig. 6). The release of AZT from the CIND displayed an initial lag phase compared to native ALG nanoparticles with no burst effect (Fig. 7).

CONCLUSION

The CIND may provide sustained intracranial drug accumulation at targeted sites within the brain via the controlled migration of the nanoparticles from the device in treating ADC.

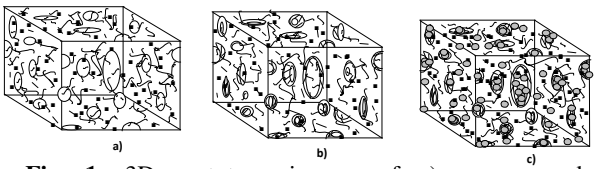

Fig. 1: 3D prototype images of a) a pre-cured crosslinked scaffold, b) a HCl post-cured crosslinked scaffold, and c) AZT-loaded ALG nanoparticles embedded within the scaffold representing the CIND.

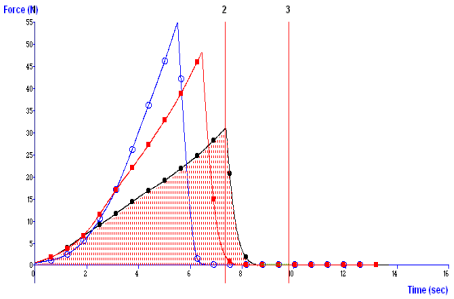

Fig. 2: Typical texture analysis profiles for determining the scaffold matrix resilience.

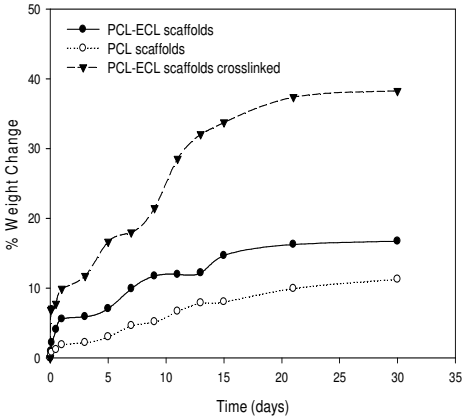

Fig. 3: Mass transitions of the HCl treated CMC-PEO-ECL crosslinked scaffold, indicating degree of swelling.

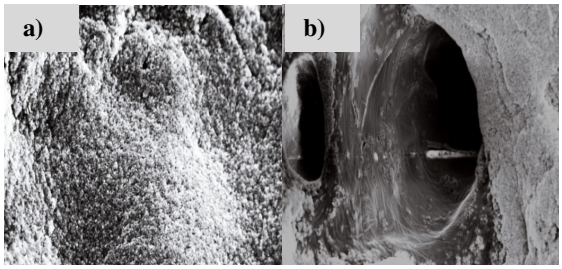

Fig. 4: SEM images of a) densely packed crosslinked scaffold matrix and b) higher magnification porous regions observed within the matrix.

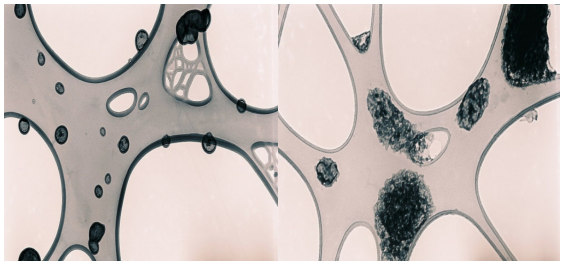

Fig. 5: TEM images of ALG nanoparticles embedded within the composite crosslinked scaffold.

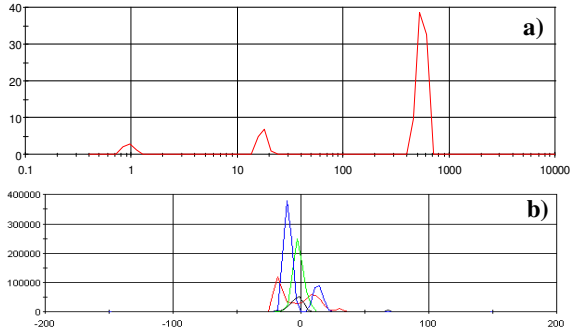

Fig. 6: Typical a) size distribution and b) zeta potential intensity profiles of AZT-loaded nanoparticles.

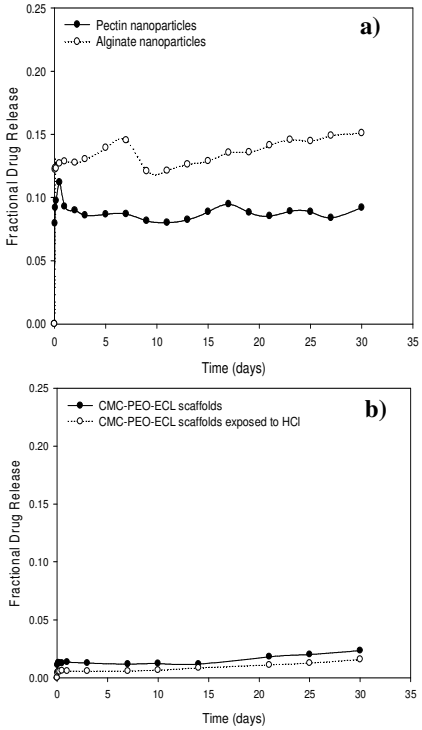

Fig. 7: Drug release profiles of a) native nanoparticles and b) nanoparticles embedded within the HCl treated crosslinked scaffold in simulated cerebrospinal fluid (20rpm, 37ºC, 0.1M PBS, pH7.4).

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