ABSTRACT

Implantable drug delivery devices offer many benefits over other routes of drug delivery. Most significantly, the potential of reducing systematic side-effects and improving patient compliance as drugs are delivered in lesser doses over an extended period. The present work was focused on designing a novel polymeric blend through a judicious combination of polymers. Polymeric material was used for the fabrication of implantable drug delivery devices (IDDDs) with varying geometrical considerations viz. torus and cylinder for the controlled delivery of a model antithrombotic agent, RXB. RXB is an antithrombotic drug used primarily for the prevention of stroke and systemic embolism in the general population of patients with thromboembolic disorders. Even though RXB is often a preferred anti-thrombotic it is associated with some degree of gastrointestinal (GI) bleeding, which is the most common extracranial haemorrhagic complication in patients on oral RXB. This 3D implant formulated is expected to offer an alternative route bypassing the gut, more convenient and safer for RXB delivery especially during long-term use, this device may be widely applied over a range of diseases requiring long-term use of a specific drug. A polyurethane (PU), polyethylene glycol (PEG) and Poly (lactic-co-glycolic acid) (PLGA) blend was used to load the RXB, while hydroxypropyl methylcellulose (HPMC) was used as a supporting material due to its gelation properties. Extrusion and compression-based methods were both utilised for the formulation of the 3D toro-poloidal (RXB loaded PU-PEG-PLGA/HPMC) implantable devices. The RXB loaded PU-PEG-PLGA/HPMC was then characterised using different physicochemical methods such as Fourier-Transform infrared (FTIR) spectroscopy, powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA) studies, all revealing the chemical and compatibility of the formulated components. For comparison 3D porous and non-porous donut shaped implants were also fabricated using compression method. Lastly in-vitro Factor Xa (FXa) assay, in-vitro release profiles, cytotoxicity, and in-vivo drug release studies using New Zealand White Albino rabbits were carried out. The 3D toro-poloidal implantable devices were successfully formulated and characterised using FTIR, PXRD, DSC and TGA, where analysis confirmed the formation of the RXB loaded and HPMC/PU-PEG-PLGA blends, also evident is that the individual structures of the innate polymers were only blended and not altered. Cytotoxicity studies using MTT assay showed no toxicity signs and the FXa activity increased with the increase in RXB concentration. The porous RXB showed much more drug released compared to the non-porous, while both geometries showed controlled sustainable drug release profiles suitable for delivery of potent drugs applied in small doses such as the RXB. The cylinder released the RXB at a constant rate while the donut released the RXB at a consistently increasing rate, both within the therapeutic range. The devices were observed to be having a biphasic release pattern, where an initial burst release was followed by a controlled extended drug release, with an initial burst release and a sustained release from 72 h to day 49. Approximately 97% and 89 % RXB was released on day 49 for donut implants, while only 61.3 % and 66.1 % of the RXB was released from the cylinder, the release was from compressed and extruded 3D implants, respectively. In both the in-vivo and in-vitro RXB release profiles the conventional oral RXB had a bioavailability lower by ±40% and ±32% for in-vitro and in-vivo, respectively, compared to the toro-poloidal 3D implant devices. Correlation of the cytotoxicity and RXB release studies was seen with the in-vitro relative to the in-vivo studies. In conclusion, the 3D toro-poloidal, 3D RXB loaded PU-PEG-PLGA/HPMC implant, has a great potential for personalised medicine, as these devices can be modified into different geometries with different release properties, suitable for both systematic and local drug delivery while avoiding the gut system.