AN IMPLANTABLE SENSOR FOR DISEASE DETECTION AND TREATMENT

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Abstract

Current sensors employed in medicine are used to detect chemical and biochemical abnormalities. Their applications range from biopsy (brain), enzyme-linked immunosorbent assay (ELISA) (spinal fluid), blood (bio-barcode), and sweat and urine bio-diagnostics where the primary focus is the selection of biomarkers that can pinpoint the occurrence of the disease. Emerging sensors for cholesterol detection are based on enzymatic functions, which degrade these molecules, where the signal can be visualized optically by using a transducer. Cholesterol is a steroid metabolite that is employed for the synthesis of steroid hormones, and the establishment of proper membrane permeability and fluidity. Since cholesterol is insoluble in blood, it is transported in the circulatory system within lipoproteins, complex spherical particles which have an exterior comprising of amphiphilic proteins and lipids with outward-facing surfaces that are water-soluble and inward-facing surfaces that are lipid-soluble. Low-density lipoprotein (LDL) is known as 'bad' cholesterol. High-density lipoprotein (HDL) is known as 'good' cholesterol. LDL is linked to cardiovascular conditions such as atherosclerosis and hypertension, which ultimately lead to coronary heart disease, myocardial and cerebral infarction (stroke). An appropriate therapeutic response to a sensor system for cholesterol, specifically LDL, detection implicates the design of an implantable system for stimuli-responsive drug release. The proposed system was designed to detect specific biochemical changes by employing nanoparticles made of glyceryl behenate, polyoxyethylene-polyoxypropylene block copolymer, avidin, biotin and anti-beta lipoprotein antibodies as sensors. This was achieved by coating nanoparticles with antibodies specific to the antigen (i.e. LDL) to create an antibody-conjugated antibody conjugated solid lipid nanoparticles (henceforth known as 'antibody conjugated SLN). Fenofibrate was used as a model drug due to its low water solubility and to its lipophilic properties similar to statins. The antibody conjugated SLNs were of 150nm in size and had a zeta potential of -28mV. Their drug entrapment efficacy was 86%, with a drug release of 16mg/day due to Fickian diffusion and erosion mechanism. The slow release was due semi-crystalline structure determined by XRD and DSC. Antigen responsive hydrogel was designed by incorporation of thiolated antibody conjugated SLN via Traut's reagents, polyethylene glycol diacrylate, methyl acrylic acid and polyethylene glycol 200. The osmotic pump was designed from polyethylene oxide, ethyl cellulose and mannitol. The drug reservoir was synthesized from ethyl cellulose coated gelatin capsule via coacervation phase separation method. The polymeric tube synthesized from ethyl cellulose, methyl cellulose and castor oil was coated with antigen responsive hydrogel. *Ex vivo* studies evaluating intravascular stability of the implant in correlation with mechanical analysis indicated the polymeric tube unstable. An 18-gauge catheter was used for forming an infusion tube as a substitute for the polymeric tube. The implant showed a correlation of Korsmeyer-Peppas drug release during *in vivo* and *in vitro* studies. A constant drug release of 881µg/day was observed during *in vivo*. This played a role in reduction of total cholesterol by means of reduction in LDL sub-fractions by 30%; in correlation with LDL particle enhance clearance from the plasma due to SLN-LDL uptake. An increase by 46% in HDL was observed, which correlated to fenofibrate therapeutic effect. Pharmacokinetic analysis indicated improved mean residence time and efficacy. This indicated that the device could be used for delivery of lipophilic drugs and detection of circulating biomarkers.

Keywords: Cholesterol, biosensor, drug delivery system, Low density Lipoprotein, Solid lipid nanoparticles, antibody, fenofibrate, implantable, biomarkers.