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| **A subdermal implant for controlled release of vitamin D3** |
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| **Background:** Vitamin D deficiency is a prevalent global issue and a risk factor for overall mortality in the general population. Various pharmaceutical formulations, such as vitamin D tablets, capsules, oily drops, are commercially available to address vitamin D deficiency. However, these formulations suffer from poor patient adherence. The aim of this project was to develop a long-acting subdermal implant for controlled release of vitamin D3 over one or more years. Vitamin D3 is highly susceptible to oxidation and initial studies revealed that a subdermal implant formulated by dispersing vitamin D within a silicone elastomer was not stable. Here, we propose a novel reservoir-type subdermal implant platform for sustained release of vitamin D3 offering improved stability. |
| **Methods:** Following a series of pre-formulation studies, a combination of Kolliphor EL ­(a non-ionic solubilizer) and the antioxidant butylated hydroxyanisole (BHA) was selected for subsequent development of the vitamin D implant. The novel reservoir-type subdermal implants were fabricated by mixing vitamin D, BHA and Kolliphor EL and injecting into one-end sealed of medical grade silicone tubing, followed by sealing of the other end. Four different formulations of vitamin D implants were prepared by incorporating equal mass of vitamin D and BHA at concentrations of 3%, 5%, 10% and 20% w/w, respectively. Additionally, three formulations were prepared with a fixed 10% w/w vitamin D content and varied amount of BHA at concentrations of 3%, 5% and 10% w/w. In vitro release testing (IVRT) was conducted at 37 ℃ using a release medium consisting of water with 0.2% w/w Tween 80 and 100 μg/mL EDTA. The release medium was regularly sampled and completely replaced on weekdays (20 mL) or weekends (40 mL) over a total period of 29 days. Content assay was performed on fresh vitamin D implants (initial content assay) and on vitamin D implants after the 29-day in vitro release testing (residual content assay). |
| **Results:** IVRT results demonstrated zero-order release for implants with vitamin D loadings (3%, 5% and 10% w/w) below its solubility limit. The daily release of vitamin D correlated with initial drug loading, ranging from 10 to 60 μg/day over a period of 29 days, which falls within the target dose range of 25 to 100 μg/day. Moreover, the concentration of BHA did not affect the daily release rate of vitamin D. Analysis of the release profiles of BHA indicated that approximately half of the BHA was released within the first four days, and the BHA was nearly depleted after 29-day IVRT. The mass balances of vitamin D indicate successful protection of dissolved vitamin D by the Kolliphor EL-BHA combination within 29-day IVRT.  |
| **Conclusions:** The data supports further development of a novel reservoir-type vitamin D subdermal implant capable of controlled release of vitamin D. |