A subdermal implant for controlled release of dapivirine for HIV pre-exposure prophylaxis (PrEP)

Siqi Wang, Karl Malcolm

School or Pharmacy, Queen's University Belfast, BT9 7BL, United Kingdom

Background: With an estimated 700,000 people dying from HIV-related diseases worldwide each year, there is a need for new prevention methods for preventing sexual transmission of the virus. A silicone elastomer dapivirine (DPV)-releasing vaginal ring was recently approved for HIV pre-exposure prophylaxis (PrEP). DPV is a non-nucleoside transcriptase inhibitor (NNRTI) that blocks the activity of reverse transcriptase and thus stops replication of HIV. With the goal of further expanding prevention methods, here we describe a new reservoir-type subdermal implant offering controlled release of DPV over at least one year.

Methods: Reservoir-type subdermal implants (40 mm length) comprising different DPV loadings (10, 20 and 40% w/w) in the reservoir core were prepared by injecting DPV silicone mix into the lumen of medical grade silicone tubing (dimensions 1.5/2.5, 1.5/3.5, 1.6/3.2 and 2.4/4.0 mm). In vitro release testing (IVRT) was performed at 37 ℃ into water + 0.2% w/w Tween 80 over 246 days. For the first 28 days, the release medium was sampled and completely replaced daily (20 mL), except weekends (40 mL). From day 29–112, the release medium was sampled and replenished weekly (140 mL). After 112 days, IVRT was continued for three formulations (10%,1.5/2.5; 10%,1.5/3.5; 40%,2.4/4.0). From day 112 to present, each implant was placed in 260 mL (20 mL × 13 days) release medium for IVRT, after 13 days the release medium was discarded and replaced with 20 mL release medium for daily sampling at the following day. DPV-loaded implants were also analyzed by DSC to characterize the nature of the drug.

Results: The implants provided zero-order type release of DPV, with daily release rates in the range 5–20 μg/day over 246 days. Based on initial drug loadings, we predict the implants could release at these rates for several years. For implants having the same drug loading (10% w/w DPV) but different dimensions, the observed differences in drug release rate were attributed to the membrane thickness and inner surface area of the implant. DPV releases at a higher rate from the implants with higher inner surface area (2.4/4.0 mm compared to 1.6/3.2 mm) and thinner membrane thickness (1.5/2.5 mm compared to 1.5/3.5 mm). For those implants manufactured with the same dimension but different drug loading, the slightly higher daily release rate of those implants with higher DPV loading might be due to DPV releases from two ends of the implant. The zero-order release profile has achieved for these DPV implants and there was almost no decreasing trend of daily DPV release within the course of 246-day in vitro release testing. DSC data showed that melt onset and peak temperature did not vary with drug loading. DPV solubility in the silicone elastomer was determined to be ~0.981% w/w based on DSC data, indicating that DPV was primarily present in silicone elastomer in the solid crystalline state.

Conclusions: The data demonstrate the possibility of controlled release of dapivirine from a silicone elastomer subdermal implant for long-acting HIV PrEP.