Enzyme and pH Dual Triggered-Tenofovir Release from Nanoparticles in Microparticles System for the Prevention of HIV Transmission

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Purpose
To develop a dual triggered drug delivery system adapted to both enzymatic and pH conditions of the vagina tract during intercourse to prevent HIV transmission. The nanoparticles (NPs) were designed to deliver the drug at simulated human seminal fluid (HSF) pH of 7. However, the microparticles (MPs) matrix was responsive to the presence of prostate specific antigen in the HSF.

Methods
NPs entrapment within MPs matrix (NiMs) occurred in two steps. First, spray-dried pH-responsive tenofovir (TFV)-loaded NPs were optimally synthesized. Secondly, NPs were loaded in gelatin MPs to obtain enzyme responsive MPs using a desolvation method. The synthesized NPs were characterized for particle mean diameter (PMD), zeta potential ($\zeta$), percent drug encapsulation efficiency (EE%). The NiMs were characterized for the degree of swelling using various NPs-gelatin ratios (1:2; 1:3 and 1:4 w/w) and morphology using electron microscopies. Moreover, in vitro drug release test was conducted in simulated physiological conditions. Furthermore, the cytotoxicity and the particle cellular uptake were tested in VK2/E6E7 and End1/E6E7 cell lines by microplate reader and confocal microscopy.

Results
The optimized NPs formula had PMD of 160±26.41 nm, $\zeta$-potential (-24.37±3.45 mV), EE% of 93±7.2%. The NiMs (1:2 ratio) had 0.47±0.1 µm, and -13.87±1.8 mV for PMD and $\zeta$, respectively. Good swelling properties of NiMs (1:2 ratio w/w) were also observed. TEM and SEM images showed a larger number of particles with smooth surface. The release of TFV from NiMs was both pH and Enzyme dependent with 70% of drug release in 30 min. Interestingly, blank and TFV-loaded NiMs exhibited minor toxicity in VK2 and End1 cells. Confocal images provided visual evidence of high particle uptake of both NPs and MPs into vaginal cells.

Conclusion
The data suggested that NiMs could be a promising template for enzyme and pH-responsive vaginal dual triggered and controlled delivery of microbicide to prevent HIV transmission. Future work would determine the in vitro and in vivo efficacy of TFV-loaded NiMs against HIV replication and transmission.