THERMOSENSITIVE-MUCOADHESIVE GEL FOR VAGINAL DELIVERY OF CABOTEGRAVIR FOR HIV TREATMENT

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Background: Cabotegravir (CAB) as one of antiretroviral drugs for HIV treatments. It is currently administered via oral and injection route. However, these routes resulted in several drawbacks, especially low bioavailability and painful administration. Additionally, it has been also reported that in terms of source of infection of HIV transmission, vagina is one of the routes for this transmission. Interestingly, vagina is also reported to be a promising drug delivery route for both localization and systemic purpose. Accordingly, here, we formulated thermosensitive-mucoadhesive vaginal gel containing CAB.

Methods: Thermosensitive-mucoadhesive vaginal gel was prepared using Pluronic F127 (PF127) and Pluronic F68 (PF68) as thermosensitive agents, HPMC as mucoadhesive agent, and PEG as permeation enhancer. The gels were characterized for their gelation temperature, mucoadhesive strength, mucoadhesive time, rheological properties, hemocompatibility, *ex vivo* vaginal permeation and retention ability.

Results: The results showed that, following several optimizations, PF127 and PF68 with the ratio 16% and 6% containing 0.5% HPMC showed thermosensitive properties, showing the gelation temperature around vaginal temperature (35^{o}C). Importantly, the mucoadhesive strength was found to be 10888.89 dyne/cm^2 with more than 8 hours mocoadhesion time. The formulation also showed desired rheological properties for thermosensitive preparations. Essentially, after the addition of PEG as permeation enhancer, the thermosensitive and mucoadhesive properties were affected. Furthermore, hemocompatibility exhibited that all formulations did not cause hemolysis with hemolysis percentage values of <5%. Finally, it was found that the use of 10% PEG in thermosensitive-mucoadhesive vaginal gels resulted in improved permeation and retention of CAB in porcine vaginal tissue in *ex vivo* studies with 6.10% and 17.28 µg/g vaginal tissue of CAB permeated and were retained in the vaginal tissue following 8 h administration of our approach. Following these results, *in vivo* animal studies with suitable model must be conducted.

Conclusions: CAB was successfully formulated into thermosensitive-mucoadhesive gel for vaginal delivery in HIV treatment using PF127, PF168 and HPMC. The use of PEG did not affect the physical properties of the formulation and was able to improve permeation and retention of CAB in porcine vaginal tissue in *ex vivo* studies. Further *in vivo* studies should now be carried out.