Ethylene-vinylacetate Intravaginal Rings for the Prolonged Release of a Combination of Antiretroviral Drug UC781 and Contraceptive Hormone Levonorgestrel

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INTRODUCTION

The lack of success in developing an HIV vaccine has led to the investigation of other methods to control the spread of HIV. The use of microbicides for preventing the transmission of HIV during sexual intercourse represents a promising approach to managing the spread of disease, especially in developing countries. Furthermore vaginal delivery of contraceptive hormones is an acceptable and effective contraceptive approach, and a device that releases both types of active pharmaceutical ingredients (APIs) over an extended period is therefore a potential defense against HIV transmission and unwanted pregnancy.

Intravaginal rings (IVRs) made of cured silicone rubber or EVAc elastomer, and containing APIs are available for contraception[1] and hormone replacement therapy[2]. IVRs with uniformly distributed API throughout the device are termed "matrix" IVRs.

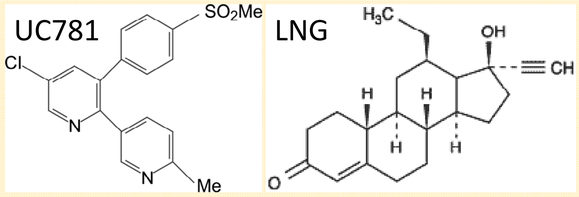
Silicone elastomer vaginal rings containing antiretrovirals (ARVs) are under investigation for the prevention of HIV transmission[3] as they offer the potential for improved user adherence, more constant drug delivery and reduced waste production compared to daily-use gels which are also under evaluation.

In order to evaluate processable thermoplastic elastomers in place of chemically curable silicones to make the IVRs, we chose EVAc (a commodity polymer available in regulatory-appropriate grades). We prepared IVRs containing an ARV (UC781) and a contraceptive hormone (Levonorgestrel), single and together in a combination device, using a commercial injection molding process. We characterized the IVR physical properties and *in-vitro* drug release performance.

EXPERIMENTAL METHODS

A stability-indicating reverse phase HPLC method was developed for both UC781 and LNG following controlled forced degradation of each API (heat, light, acid, base, oxidants) and chromatography optimization.

UC781 and LNG were compounded into molten EVAc for 15 min at 120-140 °C in a Banbury-style batch mixer under yellow light (due to the photo-instability of UC781). The compound was frozen in liquid N_2 and ground in a blade mixer to prepare API-loaded polymer powder for injection molding.



IVRs with 4 mm cross-sectional diameter and 54 mm overall diameter were prepared by injection molding of the ground API/EVAc using an aluminum mold fitted to an AB Instruments piston-type injection molder at 93° C.

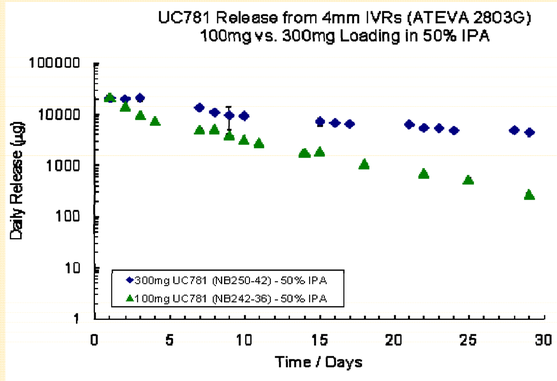
IVRs were prepared with three levels of API (100 mg UC781, 300 mg UC781 and a combination of 25 mg UC781 and 2.7 mg LNG) to investigate effect of API loading on release kinetics.

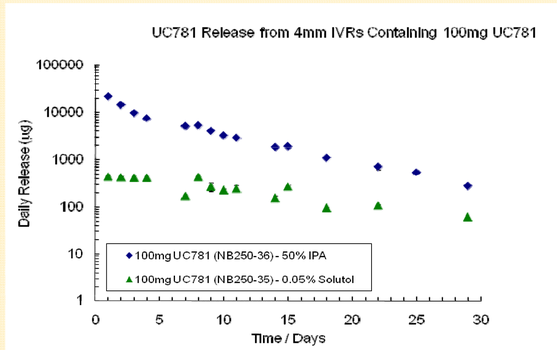
An EZ-Test apparatus fitted with a 10N load cell was used to determine physical properties of IVRs.

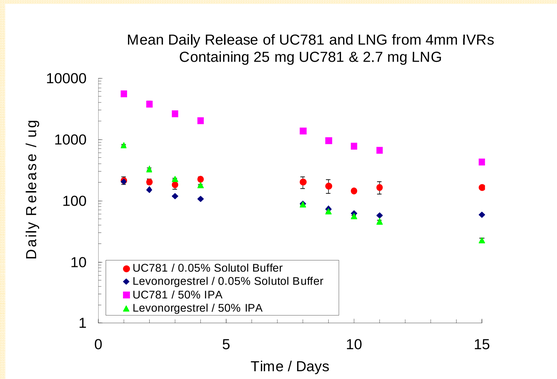
IVRs were incubated in 100 mL IPA:water (1:1 v/v), 2% aqueous Solutol surfactant solution (pH 4.2), and 0.05% aqueous Solutol surfactant solution (pH 4.2), in an incubator/shaker (37 °C, 60 rpm) for up to 30 d, and the release medium was assayed daily for the APIs by reverse-phase HPLC.

RESULTS

Daily Release of API from Various IVRs:







The HPLC method effectively separates UC781 and LNG from their related degradants, and from one another.

The IVRs had physical properties comparable to commercially available contraceptive IVRs (shore hardness ~D30, 10 mm compression force ~ 1 N).

UC781 was released at levels exceeding the solubility limit in 0.05% Solutol, but below the limit in 2% Solutol and IPA:water. Therefore release of UC781 followed approximately first-order kinetics in release media IPA:water and 2% Solutol and approximately zero-order release in 0.05% Solutol. Levonorgestrel showed first-order release kinetics in both 0.05% Solutol and IPA:water, with higher release into the IPA:water medium due to the higher API solubility in that medium.

Initial release of UC781 was as high as 20 mg/d using IPA:water medium. Initial release of Levonorgestrel was 0.8 mg/d using IPA:water medium. Release into aqueous Solutol media was lower due to the lower API solubility

CONCLUSIONS

Injection molding of EVAc is a useful route to preparing intravaginal rings that release therapeutically relevant levels of UC781 in combination with the contraceptive hormone LNG for 30 d. These combination API devices are promising candidates for clinical evaluation.

REFERENCES

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2. http://www.wcrx.com/products/femring/index.php
3. "Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings" *J. Antimicrob. Chemother.,* Nov 2005; 56: 954 - 956.

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