

Ethylene-vinylacetate Intravaginal Rings for Zero-order Release of an Antiretroviral Drug



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ABSTRACT SUMMARY:

Ethylene-vinylacetate (EVA) intravaginal rings (IVRs) containing the antiretroviral Dapivirine, were prepared by injection molding. *In-vitro* release was first-order kinetics, scaled linearly with drug loading and depended weakly on EVA properties. IVRs containing a newly developed microencapsulated drug prepared by a commercially-viable manufacturing processes exhibited zero-order release (90d) and good shelf-stability.

INTRODUCTION:

The lack of success in developing an HIV vaccine has led to the investigation of other methods to control the spread of AIDS. 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.

Intravaginal rings (IVRs) made of cured silicone rubber or ethylene-vinyl acetate elastomer, and containing active pharmaceutical ingredients (APIs) are available for contraception(1) and hormone replacement therapy(2). IVRs with uniformly distributed API (“matrix” IVRs), often exhibit first-order release kinetics with an initial-burst release, which may be undesirable. This can be controlled by containing the API in a reservoir within the IVR (“reservoir” IVRs). Reservoir IVRs inserted vaginally typically release therapeutic levels of drug with zero-order kinetics over a prolonged period (usually 30d), though their manufacturing is more complex compared to a matrix ring design.

Vaginal rings made from cured silicone rubber and containing antiretrovirals are under investigation(3) as they offer the potential for improved patient compliance, more constant drug delivery and reduced waste production compared to daily-use gels.

In order to avoid the curing chemistry required to produce silicone rings, and to investigate the release of antiretrovirals from a different polymer, we used EVA in a commercial injection molding process to manufacture matrix IVRs containing an antiretroviral, and characterized the IVR physical properties and *in-vitro* drug-release performance. EVA is a commodity polymer and available in regulatory-appropriate grades. We also developed a new IVR technology that we term “microreservoir IVR” in which the API is microencapsulated in a polymer prior to blending with EVA and injection molding. Microreservoir IVRs showed zero-order release kinetics over 90d, and shelf-life stability of at least 76d at room temperature, and as such demonstrate a promising technology that combines the ease of manufacture of matrix IVRs with the controlled API release performance of reservoir IVRs.

EXPERIMENTAL METHODS:

Dapivirine was encapsulated in cellulosed acetate phthalate (CAP) by solvent casting from methylene chloride solution followed by grinding in a rotary blade grinder after complete solvent removal.

Neat (or microencapsulated) Dapivirine was mixed with EVA for 15min at 120-150C (depending on EVA grade) in a Banbury-style batch mixer, followed by pelletizing. Various grades of EVA were used to allow investigation of structure-property relationships, and IVRs were prepared with three levels of API (0.2%, 1.3%, 5% w/w) to investigate effect of API loading on release kinetics.

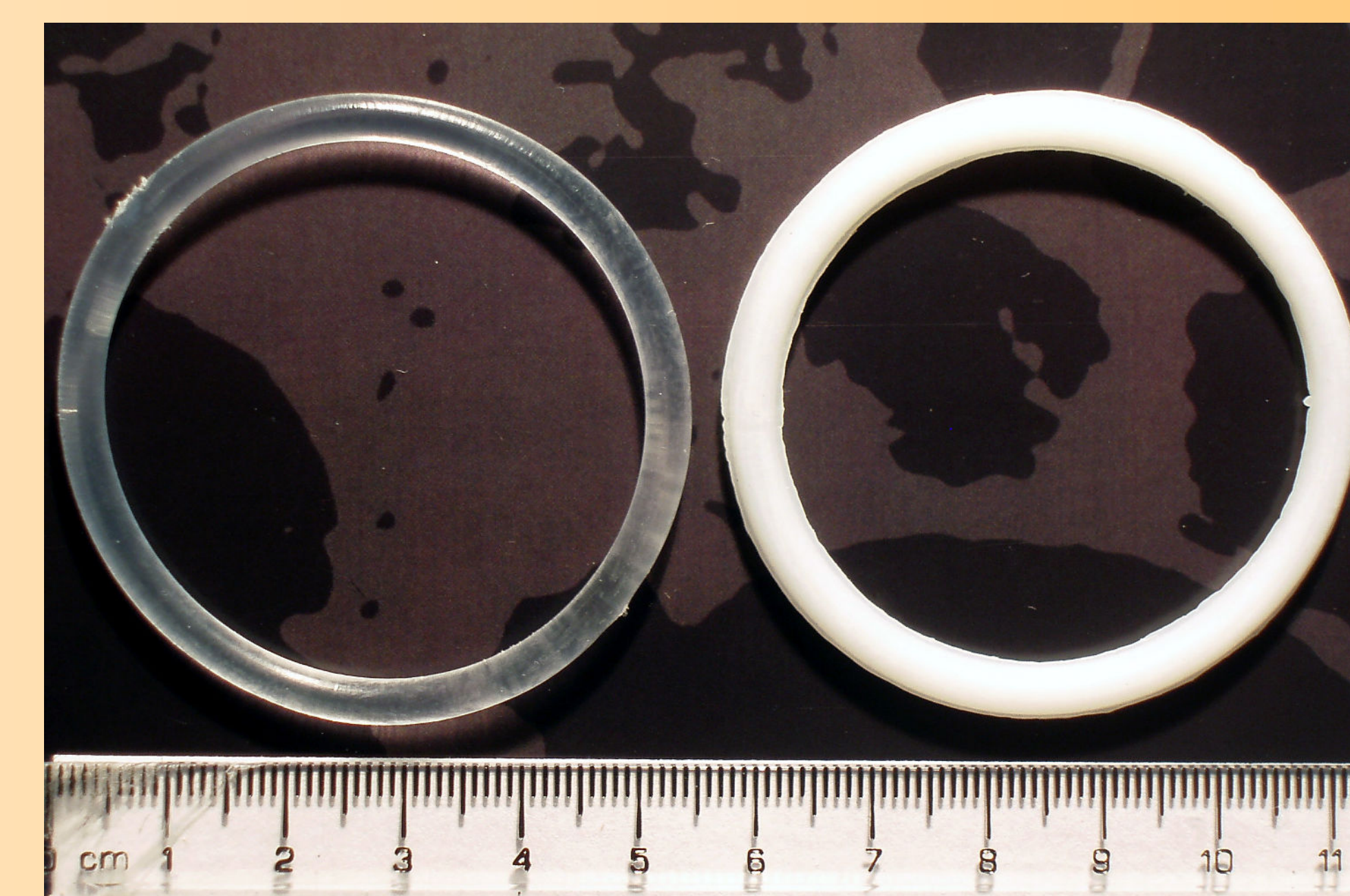
IVRs with 4mm cross-sectional diameter and 54mm overall diameter were prepared by injection molding of the API/EVA pellets into an aluminum mold using a piston-type injection molder at 93C.

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

IVRs were incubated in 100mL IPA:water (1:1 v/v) in an incubator/shaker (37C, 60Hz) and the release medium was assayed daily for API by reverse-phase HPLC, then replaced with fresh medium to maintain sink conditions.



Bench scale ring molder



IVRs: placebo and 25mg Dapivirine active

RESULTS AND DISCUSSION:

High quality antiretroviral-loaded IVRs were readily prepared by simple injection molding.

Dapivirine was released from matrix IVRs for at least 30d, following first order kinetics. Release increased with API-loading (fig.1), but showed almost no dependence on EVA composition (ethylene:vinyl acetate ratio) (fig 2), and weak dependence on polymer melt index (fig 3) over 30d.

Encapsulation of API in CAP yielded particles with an average diameter of 180 microns and almost 100% yield. Microreservoir IVRs prepared from EVA

mixed with these particles showed release levels of API similar to simple matrix rings, but at the same overall loading of API, showed a significantly reduced initial burst, and subsequent release with zero-order kinetics for up to 90d (fig 4).

Microreservoir IVRs that were stored at ambient conditions for 76d showed identical release curves to fresh microreservoir IVRs, indicating that the API remains in the microcapsules in this format, and microreservoir IVRs have promising shelf-stability.

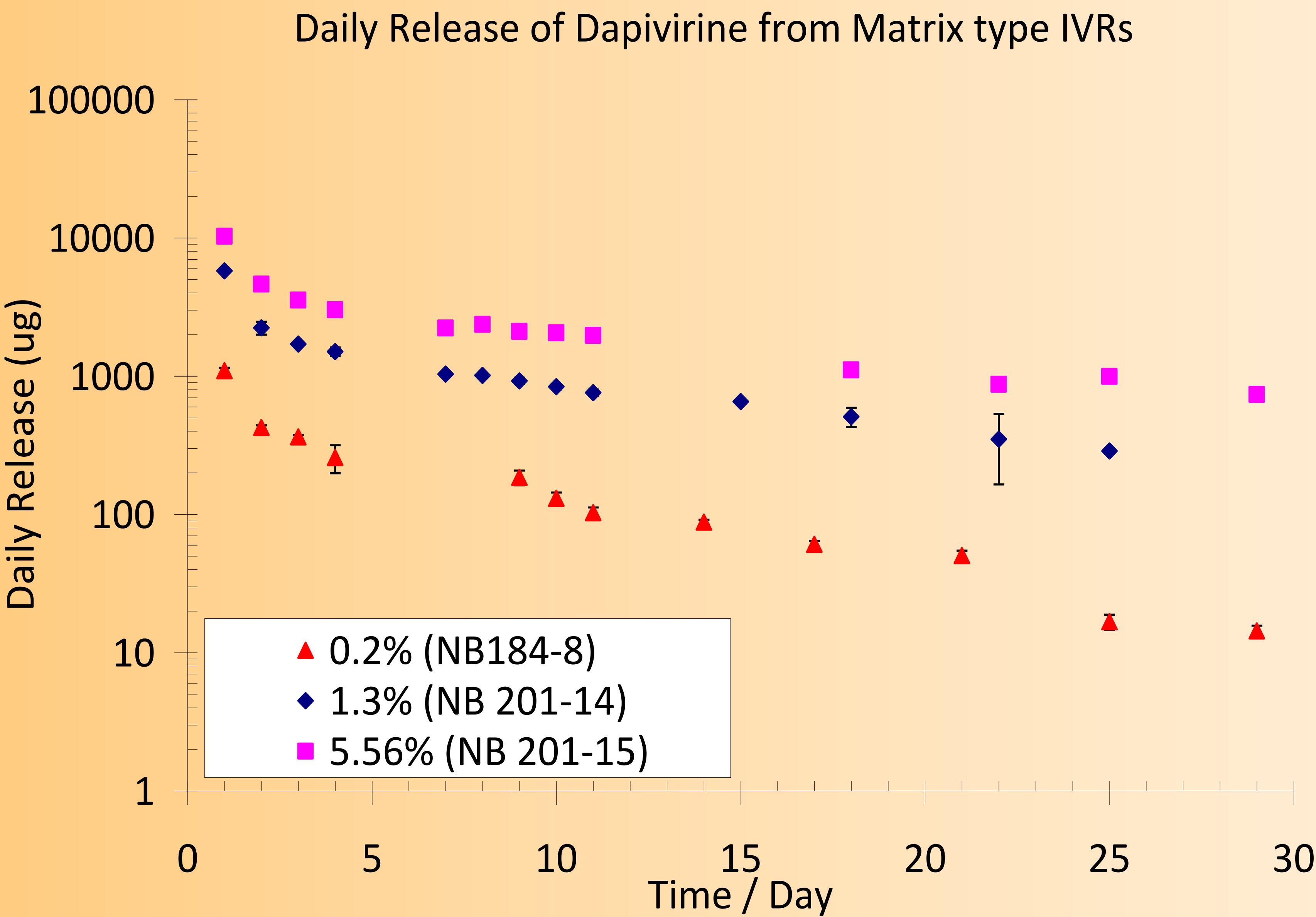


Fig. 1 Release of Dapivirine from EVA IVRs containing 0.2%, 1.3% and 5.56% Dapivirine (4mm Ø, 28% VA, 43g MI)

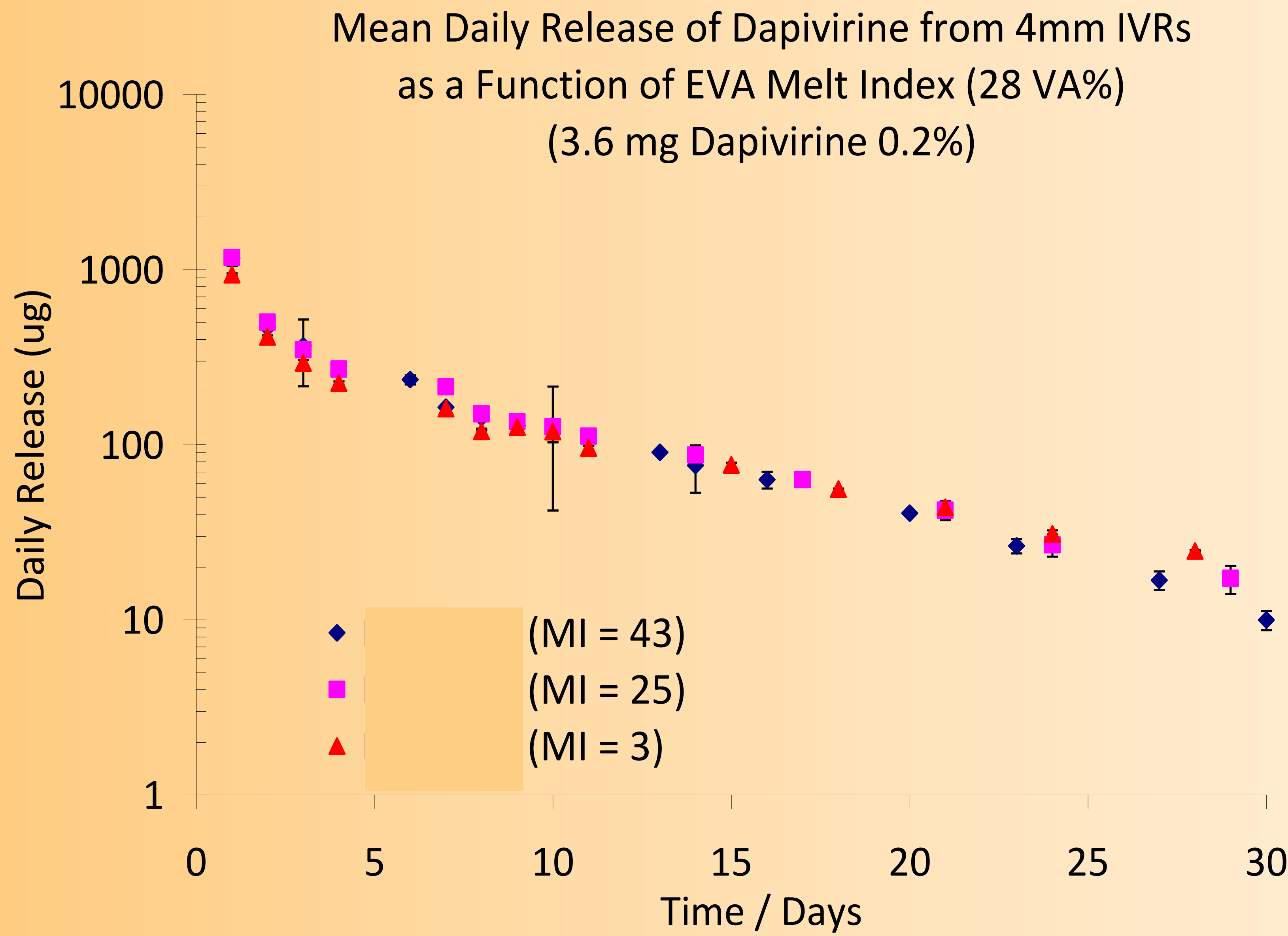


Fig 2. Release of Dapivirine from IVRs made from EVAs with 28% VA and various melt indices (4mm Ø, 3.6mg (0.2%) Dapivirine).

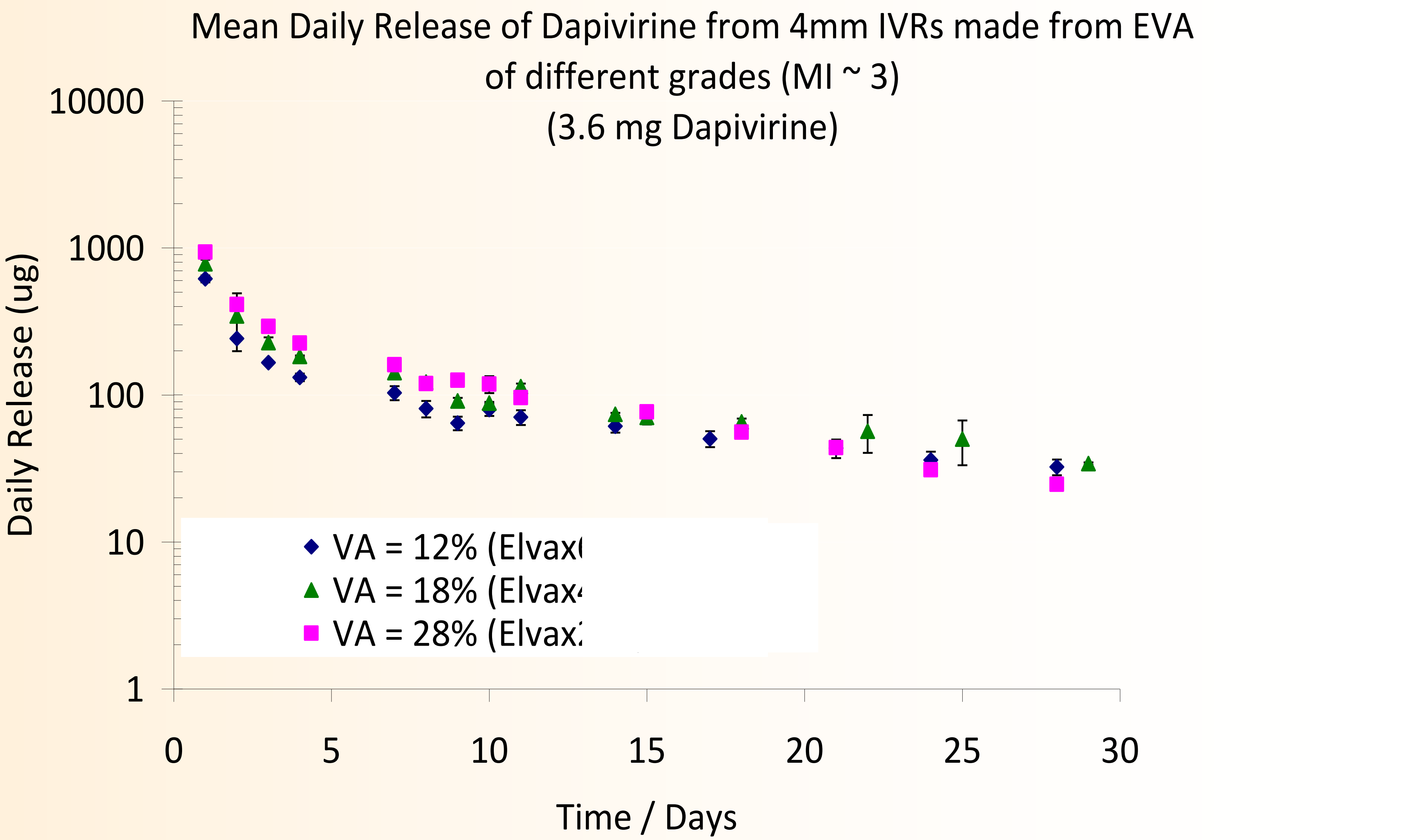


Fig. 3. Release of Dapivirine from IVRs made from various EVAs with melt index of 3 g/10min (4mm Ø, 3.6mg (0.2%) Dapivirine)

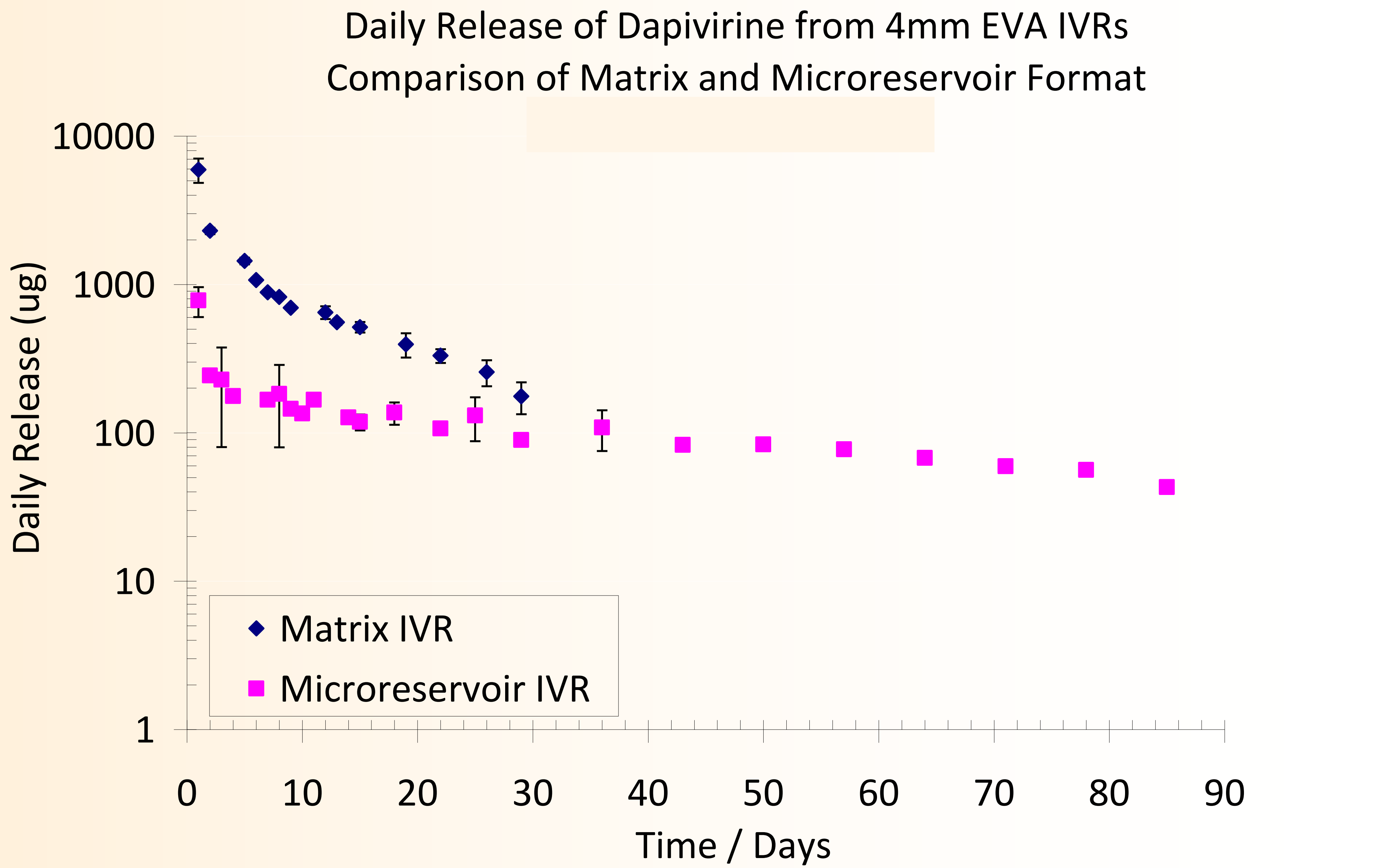


Fig. 4 Release of Dapivirine from EVA IVRs containing 1.3% Dapivirine either in matrix or microreservoir format (4mm Ø, 28% VA, 43g MI)

CONCLUSIONS:

Injection molding of EVA is a useful route to preparing intravaginal rings that release therapeutically useful levels of an antiretroviral API for 30d. Microencapsulation of the API before mixing with the EVA and injection molding is a simple, commercially viable process that yields microreservoir IVRs exhibiting zero order API release over at least 90d with good shelf-stability.

REFERENCES:

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(2) www.wcrx.com/products/femring/index.php
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