VAGINAL APPLICATOR DEVELOPMENT FOR DELIVERY OF MICROARRAY PATCHES CONTAINING RILPIVIRINE FOR HIV PRE-EXPOSURE PROPHYLAXIS

B. Creelman[1], B. Blair[1], C. Jarrahian[1], R. Donnelly[2], G. Austin[1], Y. Moyo[1], A. Rein-Weston[1], E. Saxon[1], D. Zehrung[1]

[1]PATH (www.path.org), [2]Queen's University (www.qub.ac.uk)

BACKGROUND

Health need

Studies of antiretroviral-based HIV pre-exposure prophylaxis (PrEP) have highlighted issues of user compliance with regimens that require daily dosing, particularly in low-resource settings (LRS). Longer-lasting intramuscular injections could obviate compliance issues, but regular access to health care facilities for their administration remains challenging for many women. Longer-lasting and low-cost delivery methods that enable discreet self-administration have the potential to both improve user compliance as well as reduce the frequency of visits to a health care provider.

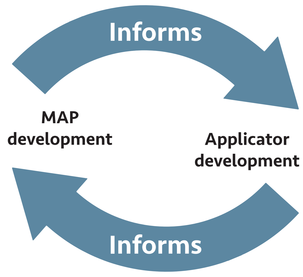
Technology solution

Vaginal delivery of dissolving microarray patches (MAPs) containing a sustained-release, nanoparticle formulation of rilpivirine holds promise for the self-administration of long-acting HIV PrEP. The discreet, easy-to-use form factor of MAPs may also increase user compliance.

Challenges and opportunities in product design

Designing a MAP to be delivered in the vagina (with dynamic and variable geometries, environmental conditions, and tissue characteristics) creates numerous design challenges. Alongside other early learnings, these challenges have underscored the value in pursuing patch and applicator development in parallel. Such concurrent product design allows features unconstrained in one effort (such as the patch's geometry) to be informed by the other (such as the applicator's ideal interface area), and vice versa (Figure 1).

Figure 1. Concurrent design informs requirements.



CONCURRENT PRODUCT DESIGN

Potential functional requirements

Although rilpivirine MAPs remain in the early stages of development, and performance characteristics and specifications for them have yet to be fully defined, the identification and evaluation of desirable functional attributes (Table 1) that can be addressed by the applicator are helping inform the MAPs design process.

Table 1. Functional attributes of MAP applicators.

Attribute	Description
Patch Protection: Physical	The ability of the applicator to provide sufficient protection from physical damage during the insertion procedure.
Patch Protection: Moisture	The ability of the MAP to not prematurely degrade in structure due to exposure to environmental or vaginal moisture (prior to embedment into the mucosa) during the delivery process.
Force Application	The ability of the applicator to apply additional force for embedment of the MAP (over and above the resting force present from the collapsed nature of the vaginal wall).
Delivery Confirmation	The ability of the applicator to provide feedback (visual, auditory, and/or tactile) to the user that the patch has been delivered.
Ease of Use	The ability of the applicator to be used with minimal training.
Self-Administration	The ability of the applicator to facilitate effective self-application of the MAP outside of a health care facility (includes both ergonomically acceptable features for usage as well as guiding placement of MAP).
Patch Delivery	The ability of the applicator to deliver and separate from the patch in a "leave-in-place" delivery process.
Surface Flattening	The ability of the applicator to adapt to surface rugations of the mucosa in a way that maximizes embedment of the array.
Package Combination	The ability of applicator to serve as effective packaging (regarding moisture and physical protection) of the MAP to simplify supply chain requirements.
Discretion	The ability of the applicator to be discreetly stored and used.
Cost	The ability of the applicator to be manufactured at a cost point that does not exclude it from LRS markets.

A FOUR-PHASE DESIGN PROCESS

Phase 1: Initial prototype development

To generate a breadth of applicator design approaches, we conducted multidisciplinary brainstorming sessions and interviews with subject matter experts in engineering, public health, commercialization, midwifery, and industrial design. These design approaches were consolidated into six main concepts (Table 2). Initial prototypes were then constructed for a user study in South Africa that consisted of focus groups of potential users and conversations with local health care providers.

Table 2. Applicator concepts for prototype development.

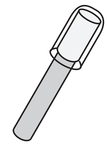
CONCEPTS	MAP INSERTION PROTECTION	APPROXIMATE MAP AREA (cm^2)	FLEXIBILITY OF MAP BACKING	APPLIED FORCE CHARACTERISTIC	FEEDBACK METHODS FOR CONFIRMATION OF SUCCESSFUL MAP DEPLOYMENT
	*Yes*	*2.5*	*Rigid cylinder (or strips)*	*Passive (none)*	*Visual*
	*Yes*	*2.8 (4 strips)*	*Flexible strips*	*User dependent*	*Auditory, tactile*
	*Yes*	*27*	*Rigid cylinder (or strips)*	*Passive (none)*	*Auditory, tactile, visual*
	*No*	*1.5*	*Flexible flat disk*	*User dependent*	*Visual*
	*No*	*3.0*	*Flexible flat disk*	*User dependent*	*Visual*
	*No*	*3.0*	*Rigid flat disk*	*Sustained (low)*	*Visual*

Phase 2: Preliminary downselection

Further downselection to two applicator design concepts (Figure 2) was informed by feedback from both the user study and preliminary assumptions of potential functional characteristics of the patch. In general, feedback from the user study centered on the user's ability to apply direct force, impact on hygiene, discretion of the device, and similarity to current vaginal products.

Figure 2. The two downselected applicator design concepts.

Digital application

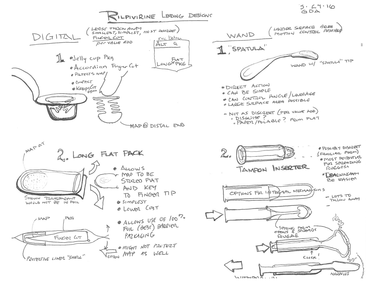


Wand application

Phase 3: Final downselection and prototyping

A final round of prototyping of the digital and wand applicator designs is currently underway. This phase seeks to explore specific design features aimed at addressing the functional requirements of the applicator. Only design iterations maximizing functionality and feasibility will move onto the design testing phase.

Figure 3: Initial refinement of the downselected designs.



Phase 4: Design evaluation

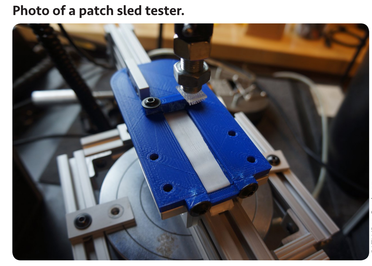
In this upcoming and final phase, the applicator designs will be evaluated for their ability to reliably deliver the MAP into the vaginal mucosa. Testing will focus on verifying the key functional requirements and preliminarily validating the complete delivery process.

DESIGN EVALUATION

Verification

Applicator verification will test how key requirements can be met by the proposed applicator designs. Testing setups will isolate these characteristics for individual evaluation—for example, a sled tester will assess the need for physical patch protection during application (photo).

Photo of a patch sled tester.



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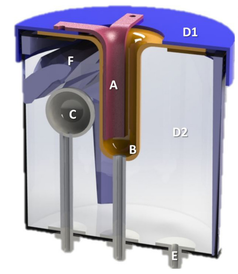
Validation

A vaginal model (Figure 4) has been developed to simulate the full application procedure of MAPs in the vaginal environment. This model is designed to both ergonomically simulate a common environment (Table 3) as well as measure forces experienced by the MAP during application. Key learnings from developing this model are also informing patch-related development efforts.

Figure 4: Cutaway of vaginal model.



A: Excised/synthetic vaginal mucosa

B: Silicone vaginal canal

C: Bladder

D1: Pressure container lid

D2: Pressure container

E: Connection ports for bladder pressure, vaginal secretion, and container pressure source

F: Pelvic bone

Table 3: Vaginal model parameters.

Parameter	Value
Length of canal	8.0 cm
Maximum canal width (lateral)	5.2 cm
Maximum canal depth (anterior/posterior)	3.0 cm
Introitus diameter	~3.0 cm
Intra-abdominal pressure	6.5 mm Hg
Vaginal discharge	5.7 mL / 24 hrs
Vaginal mucosa tissue	Synthetic or excised animal tissue

Pendergrass PB, Reeves CA, Belovicz MW, Molter DJ, White JH. Comparison of vaginal shapes in Afro-American, caucasian and hispanic women as seen with vinyl polysiloxane casting. *Gynecologic and Obstetric Investigation*. 2000;50(1):54–59.

CONCLUSION

Although the work is ongoing, our user-centered process thus far underscores the value of concurrently developing a MAP and its applicator for vaginal delivery or any other route. From product ideation through to user studies, key learnings around the applicator, its functionality and potential use by the end-user—plus appropriateness for the health care system and settings in which it will be used—continue to inform and define design requirements for a MAP product that provides women an effective and discreet method for delivering longer lasting rilpivirine for HIV PrEP.

ACKNOWLEDGMENTS

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