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3D Bioprinted Sustained-Release Platform for Intravaginal Delivery of Probiotics

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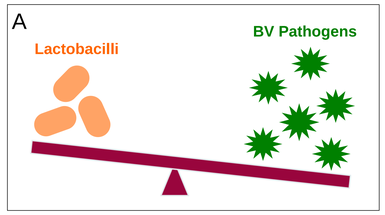
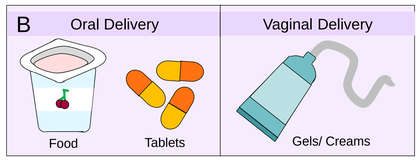
Introduction

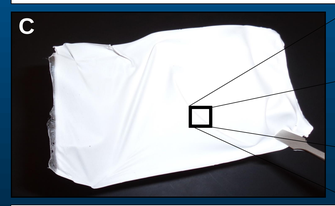
- Bacterial Vaginosis (BV) is the most prevalent vaginal infection, affecting **30%** of reproductive-age women in the United States and worldwide.
- BV is characterized by a shift in the vaginal microbiome from a dominance of Lactobacilli to the overgrowth of vaginal pathogens (specifically *Gardnerella vaginalis).*



- Some common complications include adverse pregnancy outcomes and increased risk for sexually transmitted diseases.
- Current treatment primarily involves antibiotics, but this is ineffective due to high antibiotic resistance and BV recurrence rates of **50%.** Thus, a more permanent cure is sought.
- Lactobacilli probiotics are a promising alternative to antibiotics. They have shown success in reestablishing healthy flora, inhibiting pathogen growth, and reducing recurrence.
- Probiotics have been administered both orally and intravaginally, but vaginal delivery is preferred.



- Unfortunately, present vaginal dosage forms require frequent administration, thereby decreasing user adherence and efficacy.
- Only one sustained-release probiotic dosage form, in the form of pod-intravaginal rings, has been published to date. However this design leads to discomfort and is susceptible to biofilm formation.
- Therefore, an intravaginal probiotic delivery platform capable of sustained release and that offers women flexibility in dosage forms is necessary.



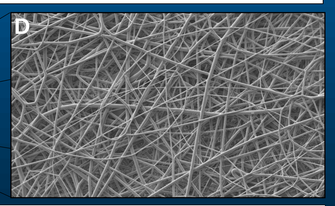


Figure 1. (A) Schematic representing vaginal flora in a BV state. (B) Examples of oral and vaginal dosage forms (C) Electrospun fiber fabricated in lab for vaginal delivery[1]. (D) Fiber at 1,000X magnification[1].

Objective & Methods

- **Objective:** Our goal is to investigate unique 3D bioprinted architectures and identify design parameters that are important for sustaining the intravaginal release of probiotics over several days/weeks.
- **Methods:** PubMed and Google Scholar were used to explore articles that demonstrated sustained release of active pharmaceutical agents through 3D printed platforms.

3D Bioprinting: Proof of Concept for Printing Probiotics

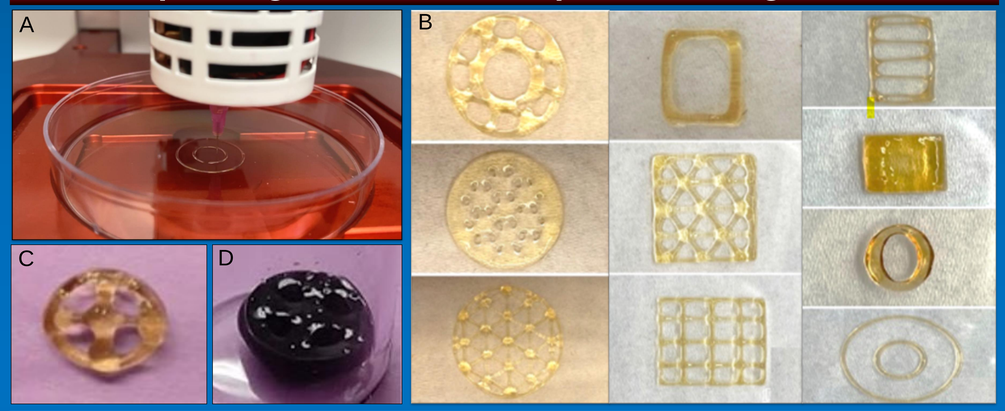


Figure 2. (A) 3D bioprinter[2] and (B) examples of 3D bioprinted shapes[2]. (C) 3D printed probiotic scaffold crosslinked with only $CaCl_2$, compared with[2] (D) scaffold crosslinked with both $CaCl_2$ and genipin[3].

Sustained-Release Architectures

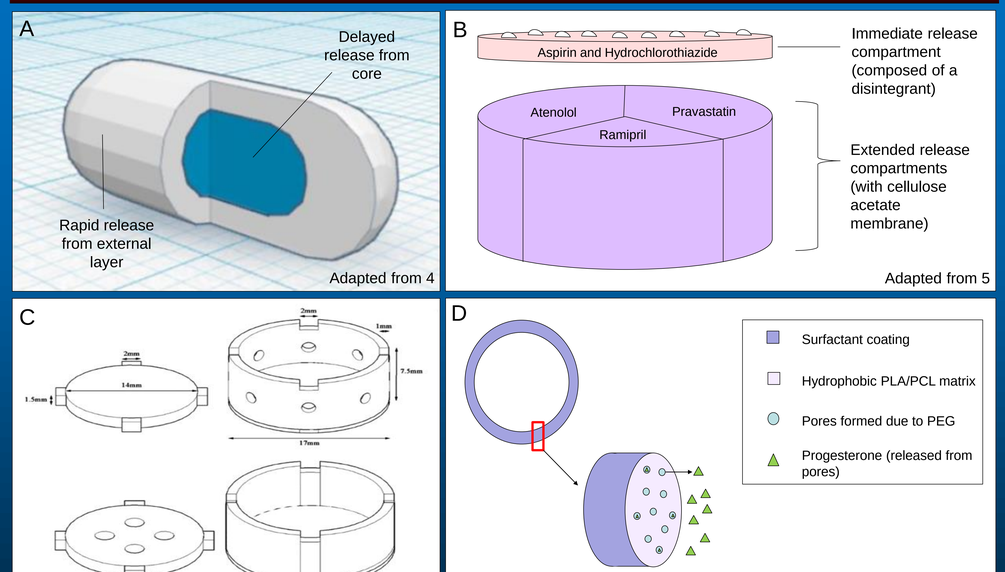


Figure 3. (A) DuoCaplet design demonstrating rapid/delayed release of 2 drugs (acetaminophen and caffeine) loaded in PVA filaments[4]. (B) Polypill (5 drug) design composed of 1 immediate release compartment and 3 sustained-release compartments[5]. (C) Tablet design exploring various hole positions on release of anti-epileptic drugs[6]. (D) Intravaginal ring for controlled progesterone release[7].

Discussion

- Encapsulation of probiotics within a hydrophilic matrix and subsequent coating of the scaffold with a hydrophobic polymer may sustain release and maintain structural integrity for longer time frames. (Fig. 3, B & D)
- Modification of material composition and architecture can yield dosage forms capable of releasing multiple active agents, each with customized release profiles. (Fig. 3, A & B)
  - This suggests that immediate/rapid release of antibiotics followed by the sustained delivery of probiotics may be possible.
- Present architectures focus on release of drugs much smaller than live cells. Diffusion through scaffold and ultimate release of probiotics will be more challenging due to their larger size.
  - Porosity of scaffolds (as in Fig. 3, C) is therefore an important design parameter.
- Present architectures demonstrate release on the order of few minutes to hours. Longer release times may be achieved by exploring other bioinks.
- **Future work** will develop a SOLIDWORKS model; optimize printing parameters and print scaffolds; and assess release profiles, degradation and cell viability.

Design for Delivery Platform

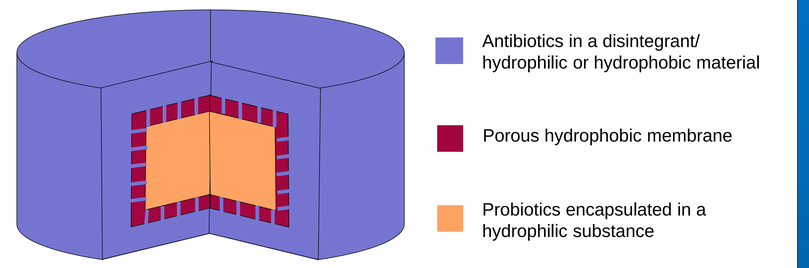


Figure 4. Cross-sectional view: potential design for the dual release of antibiotics and probiotics through the integration of a 2-compartmental porous system with hydrophobic and hydrophilic bioinks.

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2. Pictures kindly provided by Jhanvi Patel (JMSR Lab).
3. Pictures kindly provided by Mark Ryan (JMSR Lab).
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