WITS ADVANCED DRUG DELIVERY (WADDP)

Professor Yahya Choonara and Team

Prof. Pradeep Kumar, Dr. Pavan Walvekar, Dr. Hillary Mndlovu, Dr. Mershen Govender

Professor of Pharmaceutical Sciences

South African NRF/DSI Research Chair

Director: Wits Advanced Drug Delivery Platform (WADDP)

University of the Witwatersrand, Faculty of Health Sciences
Johannesburg, South Africa
W: https://www.wits.ac.za/waddp

WADDP OVERVIEW

- Launched in 2007 focus on Advanced Drug Delivery
- Grown to include Nanomedicine and Regenerative Medicine with Biomaterials
- Largest platform for innovative pharmaceutical sciences research in Africa and only fully integrated R&D platform for pharma PD in Africa
- Graduated >135 PGs, PDs and Pharmaceutical Scientists over 17 years
- Globally competitive with >47 patent filed (28 granted)
- Scholarly activity of >370 ISI-accredited research articles
- Focused on designing 21st Century patient-centric medicines with impact
- Collaborative research with Clinician Scientists
- 2 term-sheets executed and 2 products incubated
- USD7,500,000 in pharmaceutical PD lab infrastructure

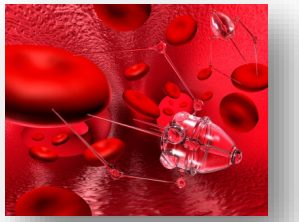
Top 2%
Global Scientists

WADDP
WITS Advanced Drug Delivery Platform

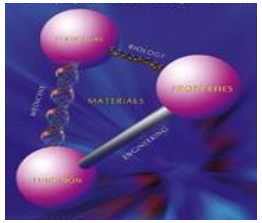
THEMATIC AREAS

Prototyping 21st Century Patient-Centric Platform Therapeutics

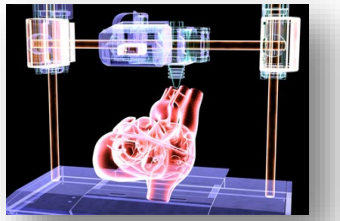
Targeted Drug Delivery



Nanomedicine Prototypes



Functional Biomaterials



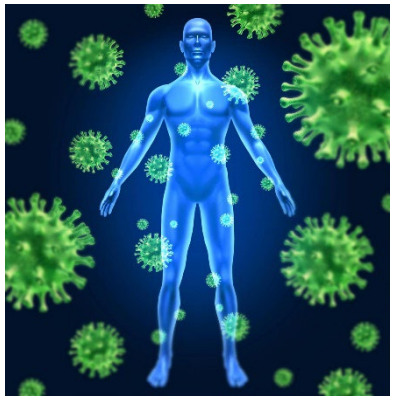
Tissue Engineering

Regenerative Medicine

- **Big Questions**: ↑ impact, unmet Tx needs, contextually relevant, globally applicable
- **Societal Relevance:** Safe, effective and cost-sensitive patient-centric products
- **Critical Mass:** Collaborative innovation, world-class labs, skilled pharma PDs
- **Sustainability:** Translational pharmaceutical sciences research
- **Training:** A needs-based education and training program to mentor pharma PDs

WADDP
WITS Advanced Drug Delivery Platform

THERAPEUTIC FOCUS AREAS

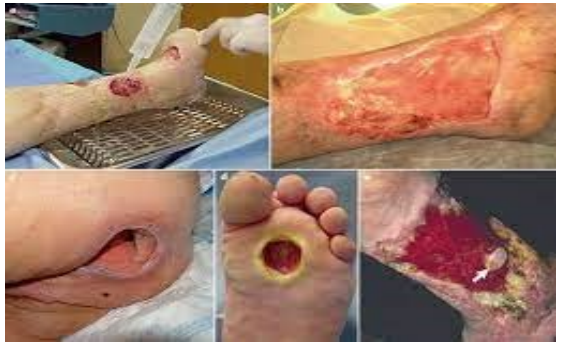


Infectious diseases
(HIV/STIs, TB, nosocomial infection, AMR)

(related opportunistic infections)

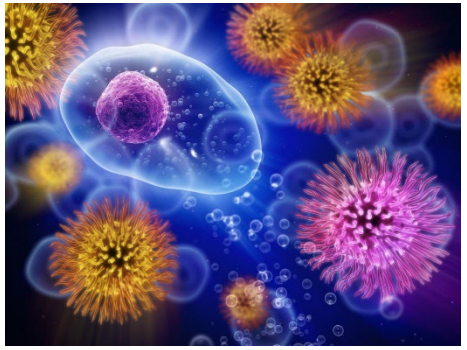
Lifestyle diseases
(diabetes, obesity, cardiovascular, metabolic syndrome)

Cancers
(cervical, ovarian, brain, skin, liver, bladder, osteosarcoma)



Chronic wound healing
(diabetic foot ulcers, venous leg ulcers, burns, cancer wounds)

CNS illnesses
(neurotrauma, SCI, PNI neurodegenerative diseases, substance abuse)

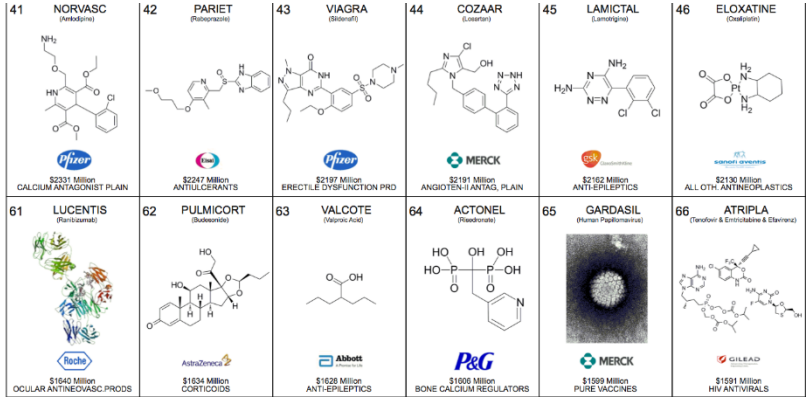


Immune-system diseases
(auto-inflammatory, auto-immune conditions)

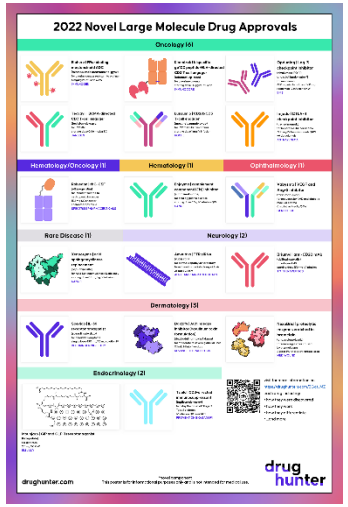
WADDP
WITS Advanced Drug Delivery Platform

FROM MOLECULES

Small Molecule Drugs

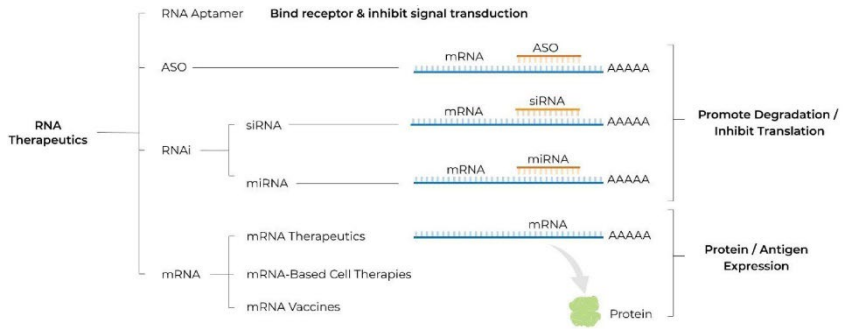


Protein/Peptides



Biomaterials

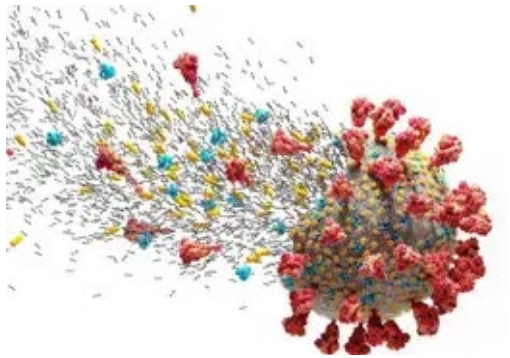
Nucleic Acids



- Biodegradable polymers (PLGA)
- Modified natural polymers (dextrin)
- Celluloses (pectins, alginates)
- Poly(lactide-co-glycolides) (PLGA) for biodegradation
- Poly(methyl methacrylate) (PMMA) for stealth
- Poly(vinyl pyrrolidone) (PVP) for suspensions
- Poly(vinyl alcohol) (PVA) for hydrophilicity
- Poly(ethylene) (PEO) for lack of swelling
- Poly(acrylic acid) (PAA) for bioadhesion
- Poly(ethylene glycol) (PEG) for gelation
- Poly(siloxanes) for insulating ability
- Poly(urethanes) (PU) for elasticity
- Addition polymers (PE)
- Condensation polymers (PA6,10)
- Chain polymerization (PEO)
- Stimuli-responsive polymers
- Natural polymers (collagen)

WADDP
WITS Advanced Drug Delivery Platform

TO MEDICINES: THE VAGITAB (DEVICE)



Destroy/Inactivate Pathogens

Lifecycle Interruption

Block Pathogens from Entering/Replicating

Strengthening Natural Defences in the Vagina (Microbiome)

- Short-acting products rely on patient adherence prior to and/or after coitus
- Long-acting products are invasive and difficult to remove if there is a drug reaction
- Therefore a need for alternate (discreet) ? topical (vaginal) delivery systems to address the gaps in HIV and/or STI treatment/prevention technologies

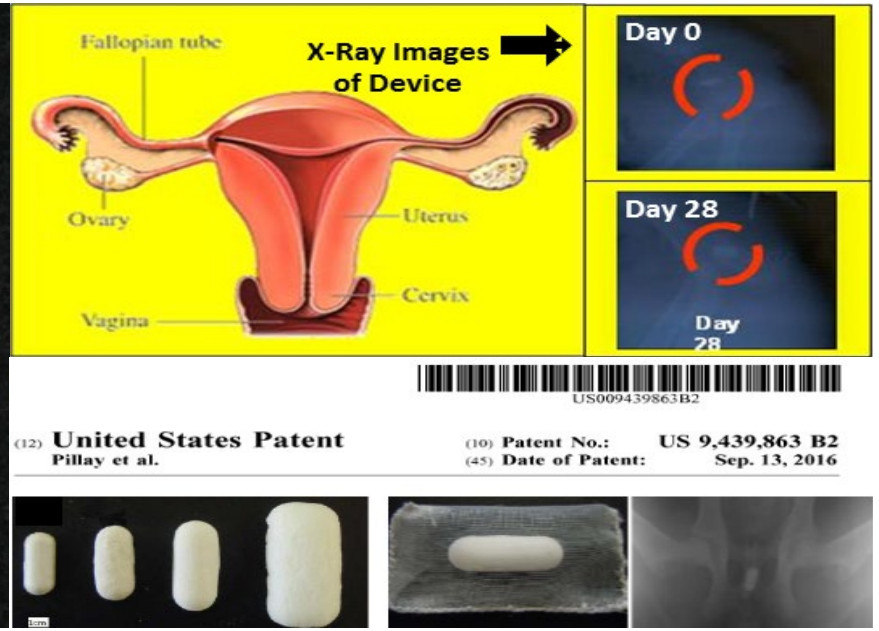
WADDP
WITS Advanced Drug Delivery Platform

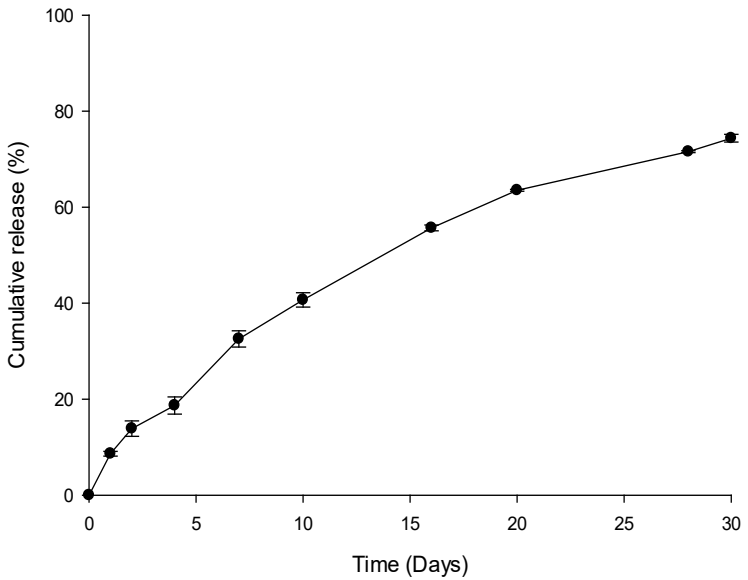
VAGITAB DEVELOPMENT PROPOSITION

- ↑ drug bioavailability
- ✗ pre-mature degradation of single/combination drugs (FDCs)
- ✓ optimal drug release kinetics for either single/combination drugs
- ✓ site-specific drug release within the vagina (↓ drug exposure and side-effects)
- ✓ drug absorption for poorly permeable drugs
- ✓ patient compliance by offering “user-friendly” product technology
- ↓ frequency of drug dosing while maintaining therapeutic efficacy
- ✓ product performance within niche markets (or unmet therapeutic needs)
- Extend patent life or reformulate ‘older’ drugs into more cost-effective ways

WADDP
WITS Advanced Drug Delivery Platform

TO MEDICINES: THE VAGITAB (DEVICE)

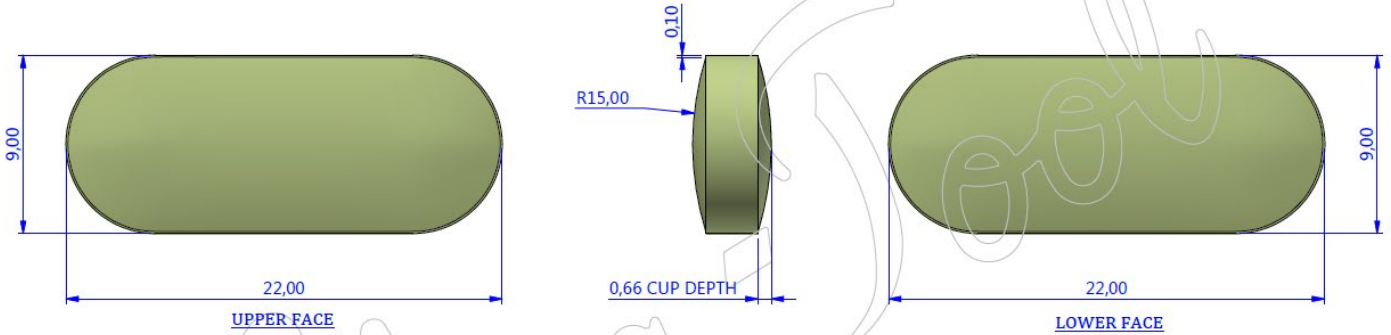




- LA (US9439863B2) and SA (targeted) VagiTab (US9284341B2) developed
- Inserted into the posterior fornix with at 3-4 week barrier formation (LA)
- Not affected by coitus or sperm
- Maintains homeostasis
- Proof of Concept: Prophylaxis and PrEP (HIV and/or STIs)

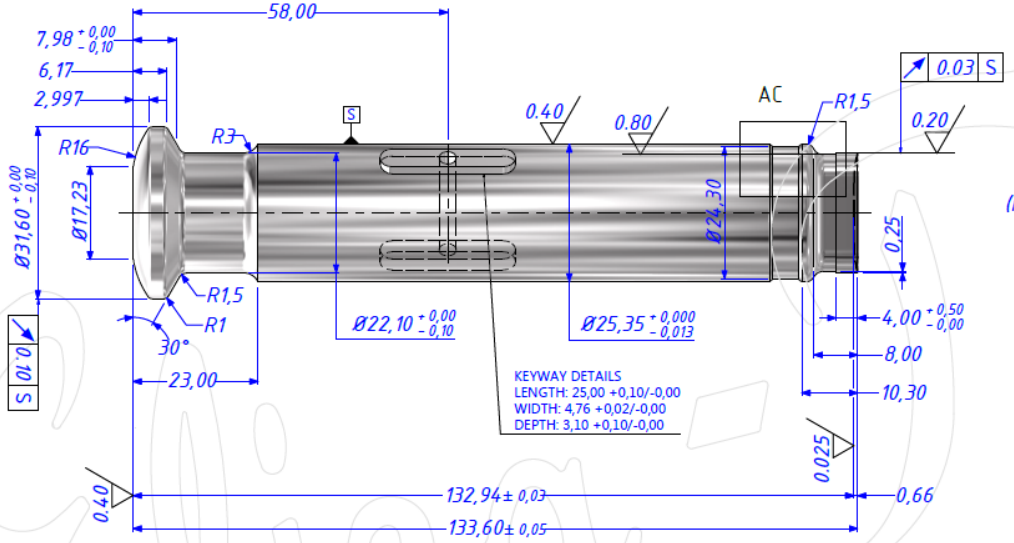
WADDP
WITS Advanced Drug Delivery Platform

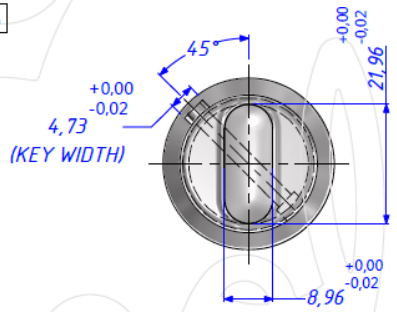
VAGITAB DEVELOPMENT: CAPLET TOOLING



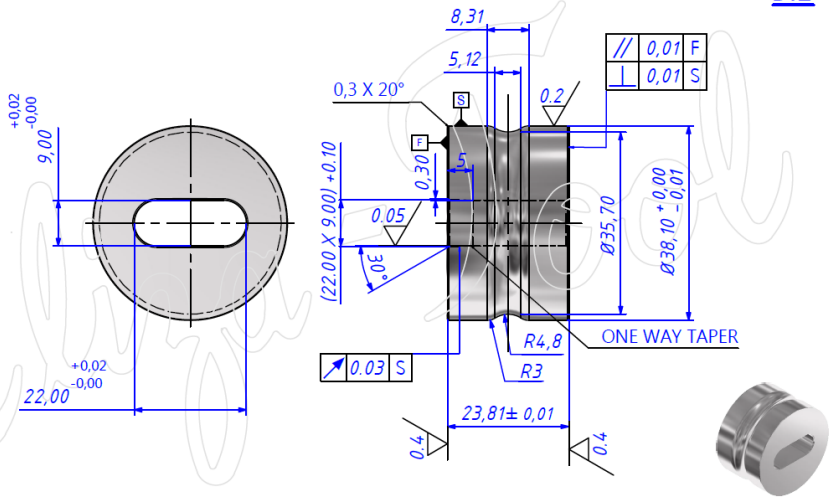
ACTUAL TABLET SIZE

NOTE:
1) DRAWING REFLECTS THE TABLET FACE WITHOUT EXPANSION.
2) RECOMMEND TOOLING TYPE:- D TYPE TOOLING





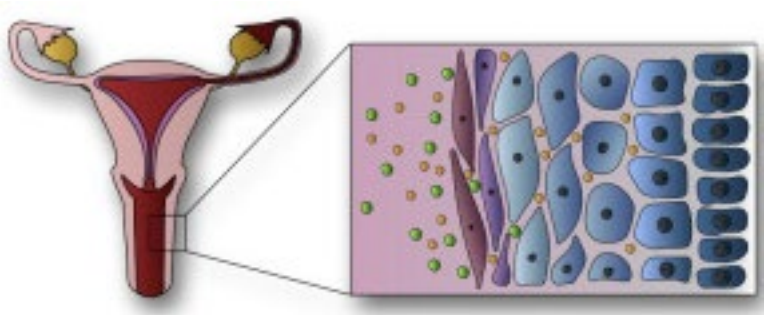
DIE

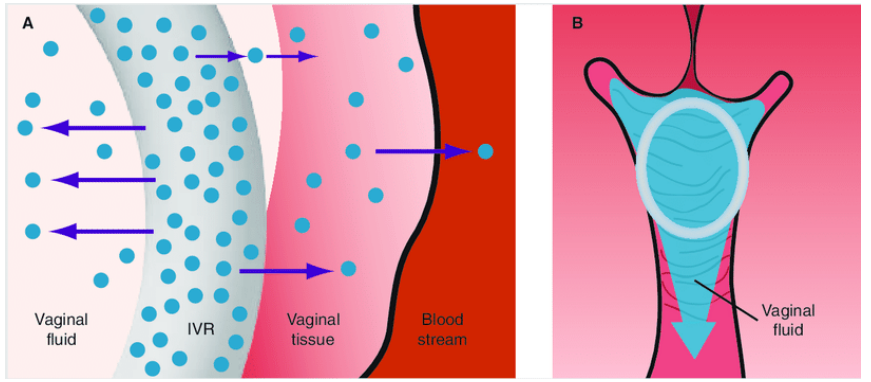


WADDP
WITS Advanced Drug Delivery Platform

THE VAGITAB: MECHANISM OF ACTION

- Self-inserted intravaginally via applicator (patient-centric/discreet, non-messy)
- Provides constant API release over 3-4 weeks
- API reservoir within tissue = Barrier to HIV/STIs transmission (chlamydia, gonorrhoea/trichomoniasis)
- Use of well-known APIs against HIV/STI pathogens
- Can be used as a 1º HIV prevention strategy or MPT depending on APIs included





WADDP
WITS Advanced Drug Delivery Platform

VAGITAB API FORMULATION SUITE

- VagiTab platform versatile to deliver APIs intravaginally

Clinical Target	APIs	Current Dose and Dosage Form
HIV	Carbotegravir	200mg/mL (LA injectable)
	Dapivirine	25mg (vaginal ring)
	Emtricitabine/TFV ALA	200mg/25mg (oral tablets)
	Emtricitabine/TFV DSF	200mg/300mg (oral tablets)
Chlamydia/Gonorrhoea	Azithromycin	1g (tablets/granules)
	Doxycycline hyclate	100mg (capsules)
Trichomoniasis	Metronidazole	250mg/500mg* (tablets)
	Tinidazole	500mg** (tablets)

Notes: ** 250mg orally every 8 hours for 7 days or 500mg twice daily for 7 days*

*** 1g once daily for five days*

WADDP
WITS Advanced Drug Delivery Platform

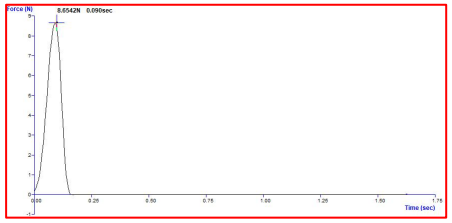
VAGITAB: PRE- AND FORMULATION

Materials: PDLL, PLGA, Kollidon® SR, Mg stearate, porcine gastric mucin, PEG 400, Carbopol 974P NF, pectin (Genu® Pectin DE 55-65%)

API: Tenofovir Alafenamide (TAF) and other APIs

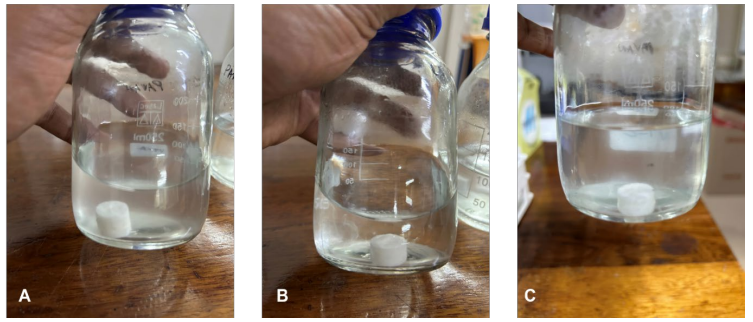
Method: Matrix prepared as per Patent #US9,439,863 B2

- TAF-loaded submicron porous matrix prepared via crosslinking emulsion
- MUC solution added to a PEC/TAF (300mg) blend before CaCl added with PEG 400 to produce the aqueous phase in a 1:4 ratio with cyclohexane and Span 85 added as a surfactant
- The emulsion is centrifuged to separate the cyclohexane and a lyoprotectant added
- The lyophilized powder is blended with PDLL and other excipients for direct compression tabletting (2.5 tons)
- In-process validation tests performed: Friability, Weight Uniformity, Hardness, Stability



Test	Result
Weight Uniformity	772.1mg (± 7.0)
Friability	0.160%
Hardness	8.6542N

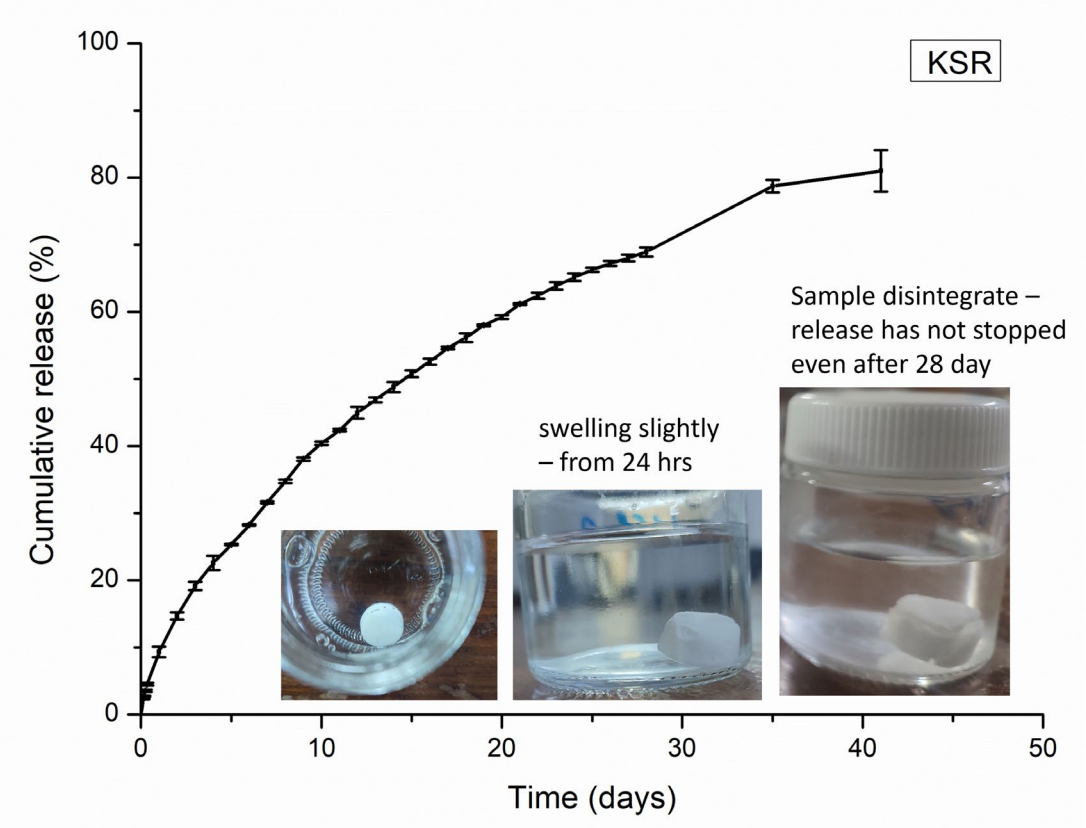
TAF-Poly(D,L-lactide)-VagiTab in SVF on day 9



WADDP
WITS Advanced Drug Delivery Platform

LONG-ACTING VAGITAB PROTOTYPE

- **Test Drug:** Tenofovir Alafenamide (300mg)
- **Test Conditions:** Simulated Vaginal Fluid (pH 4.2; 37°C; 25rpm) in an orbital shaker with 3mL sampling and analysed by UV-Vis (261nm) at various time points



Key points:

- 9.22% @D1
- 31.56% @D7
- 59.22% @D20
- 69.02% @D28
- 80.99% @D41

- Matrix is stable with minimal swelling

- Signs of disintegration at D28

WADDP
WITS Advanced Drug Delivery Platform

CONCLUSIONS AND NEXT STEPS

- VagiTab is versatile and stable
- TAF-loaded VagiTab released ≈70% by D28 in SVF
- Analysis of API release by UPLC/HPLC
- Analysis of the API release via USP IV dissolution apparatus

PATH

USAID FROM THE AMERICAN PEOPLE

PEPFAR U.S. President's Emergency Plan for AIDS Relief

MATRIX Advancing R&D of Innovative HIV Prevention Products for Women

WADDP WITS Advanced Drug Delivery Platform

DELIVERABLES AND TIMELINES

Specific Objective 1: Pre-formulation Studies (April 2023)

Milestone: A variable defined excipient composition and formula.
Go: Well mixed, compatible, and moldable excipient mix.
No go: Non-moldable and non-matrixable excipient mix.

Specific Objective 2: Formulation Evaluation and Optimization (Dec 2023)

Milestone: Optimized formulation with desired release profile.
Go: Drug release and mechanical properties as per clinical requirements.
No go: Release data not meeting the clinical PK requirements.

Specific Objective 3: Stability and Quality Control (April 2024)

Milestone: A stable and scalable VagiTab.
Go: Matrix stable under accelerated stability conditions and matrixable under pharma standards.
No go: Unstable and non-scalable matrix.

WADDP
WITS Advanced Drug Delivery Platform