2021 Women in Science
Fairleigh Dickinson University

Mini-Pharma on Your Desk: 3D Printing of Drug Delivery Systems for Women's Health

Hyunah Cho, Ph.D.
Assistant Professor of Pharmaceutical Sciences
School of Pharmacy and Health Sciences
Fairleigh Dickinson University

Women in Science

Association for Women in Science (http://www.awis.org)

My story


The future
of pharmacy
begins here.

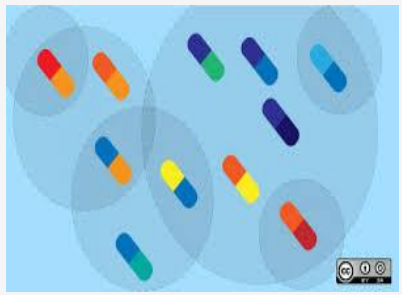

Fairleigh Dickinson University
School of Pharmacy

Why 3D printing

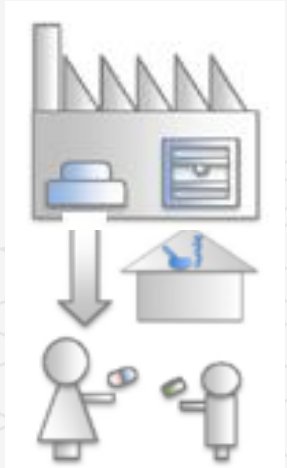
Flexible prototyping technology that has the potential to revolutionize the field of drug delivery.

Personalized medication

fixed-dose **combinations**



On-demand medication

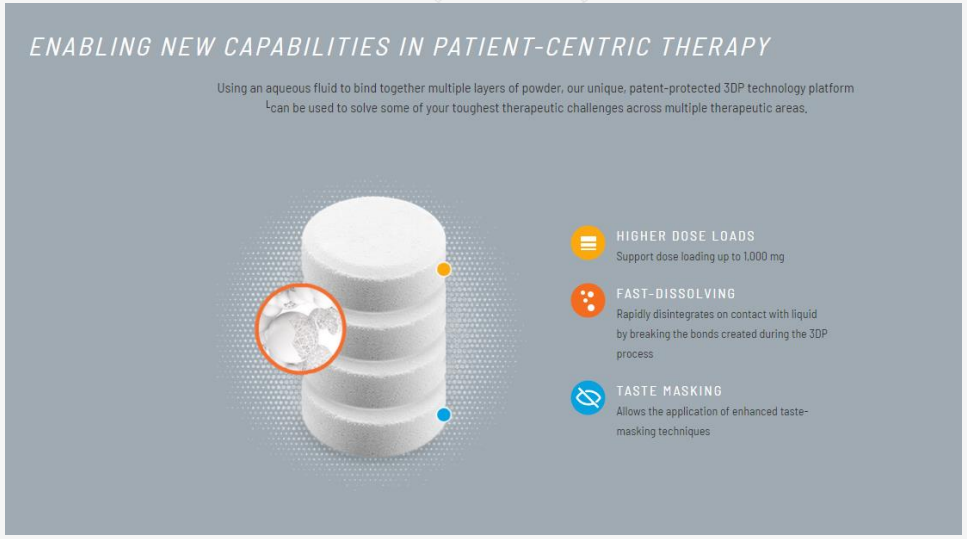


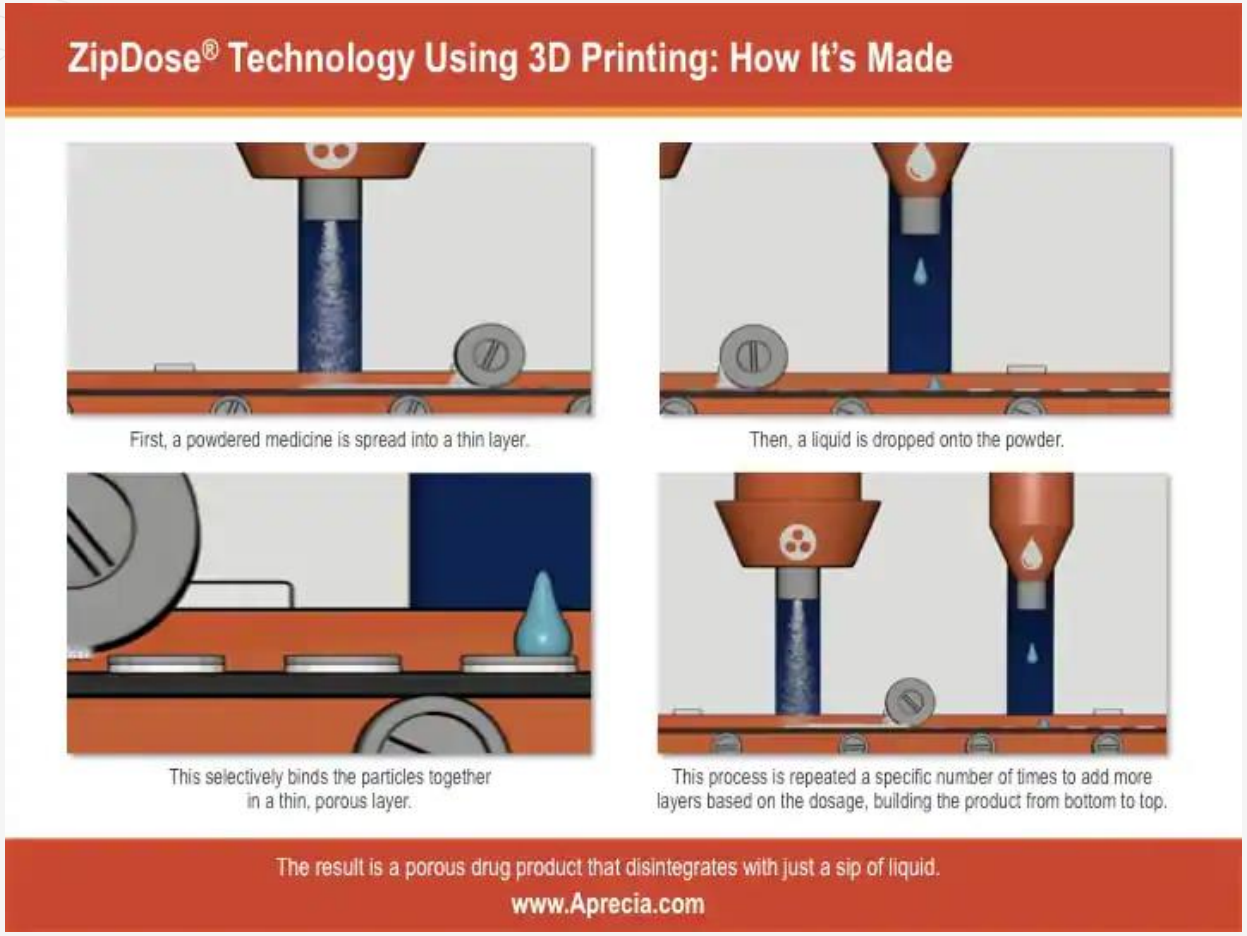
Opportunity to construct **complex geometry**

First 3D-printed tablets

3D printing is a process of making an object from a digital file. This can be achieved in two ways, subtractive manufacturing and additive manufacturing.

In July 2015, FDA approved the first 3D printed tablets called Spritam® (levetiracetam) produced by Aprecia Pharmaceuticals. Spritam is a prescription medication used to treat partial onset seizures in patients 4 years of age and older with epilepsy, designed to ease of swallowing with just a sip of water.



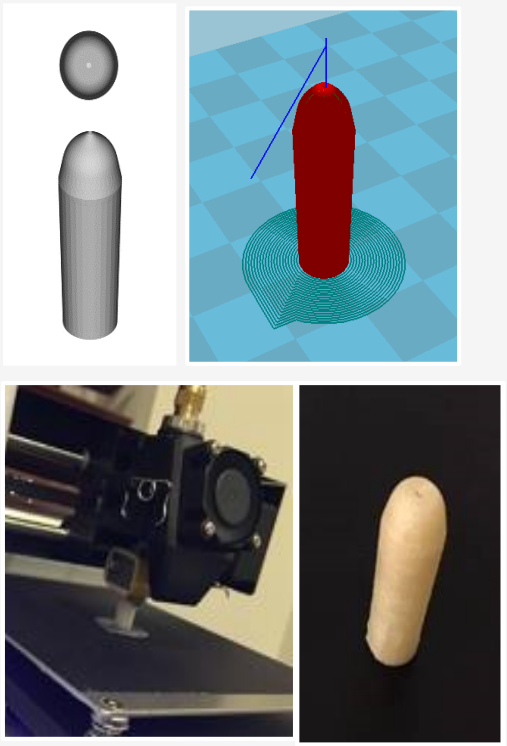


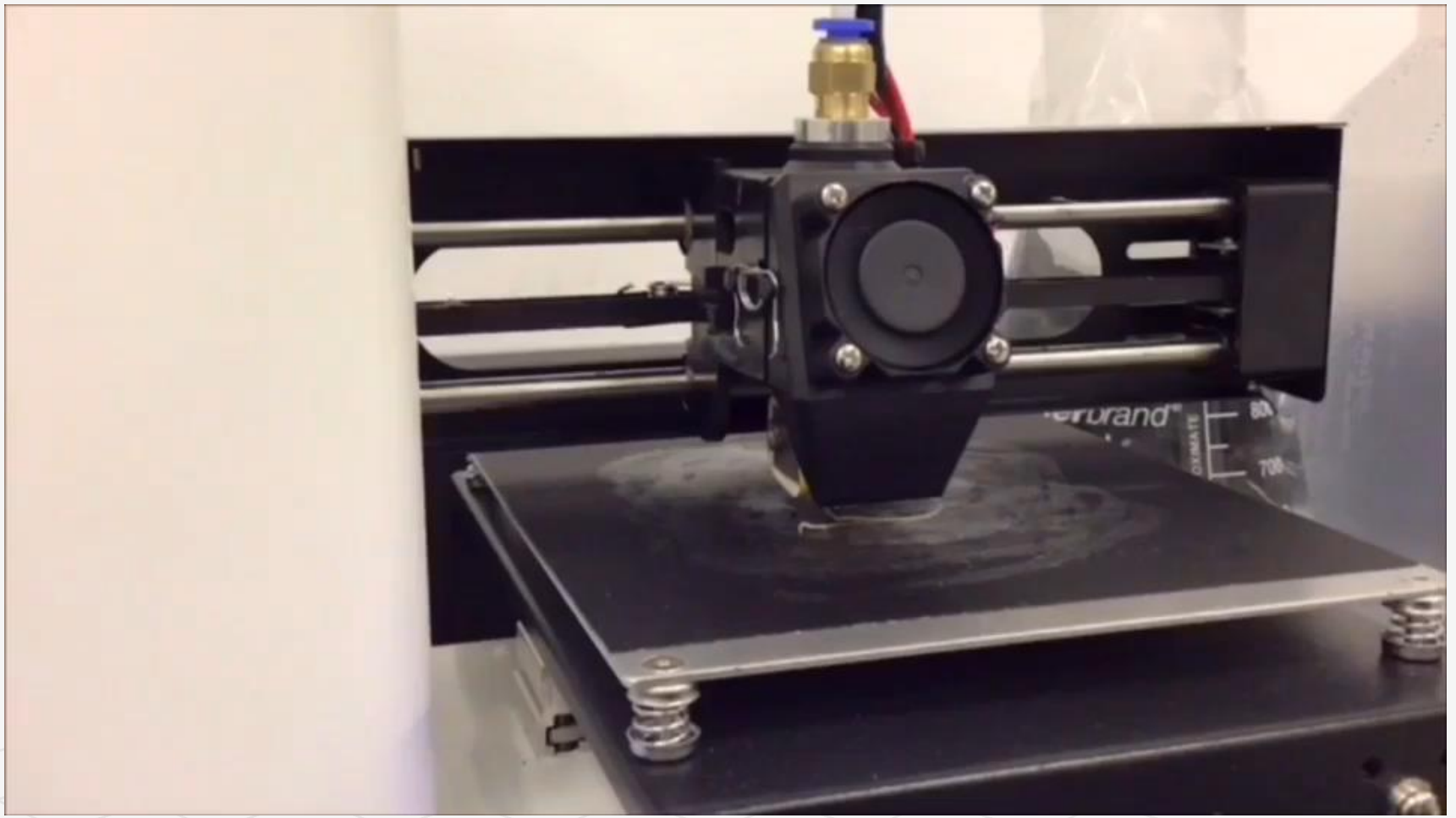
1 Rectal suppositories containing artesunate

Malaria and children

- 1,700 cases of malaria are reported yearly due to travelers and immigrants returning from countries with high malaria transmission rates, such as Africa and South Asia.
- Up to 80% of the children who live in rural areas die before reaching the hospital, due to lack of resources.
- At a community level, access to treatment (e.g., intramuscular injection (IM) artesunate) is still poor, ranging from hours to sometimes days. At this point, the disease may have progressed too far to be treated successfully.
- Rectal artesunate suppository is one of the options for pre-referral treatment of severe malaria, specifically in children under 6 years of age in remote areas.
- Rectal artesunate suppositories can treat young children who cannot take a medication orally due to vomiting or impaired consciousness and are pending transfer to a high-level facility where they can receive complete treatment.
- Rectal artesunate suppositories can treat young children who cannot take a medication orally due to vomiting or impaired consciousness. Single dose of 10 mg/kg artesunate should be given rectally.
- Rectocaps® formulated as 50-mg or 200-mg suppositories. Shelf-life is 24 months, should not be stored above 25°C and should avoid any excursions above 30°C.
- Besides artesunate's low solubility, obtaining the storage stability of the rectal suppositories at elevated temperatures (e.g., 30°C) is important.

Creating 3D-printed suppository shells





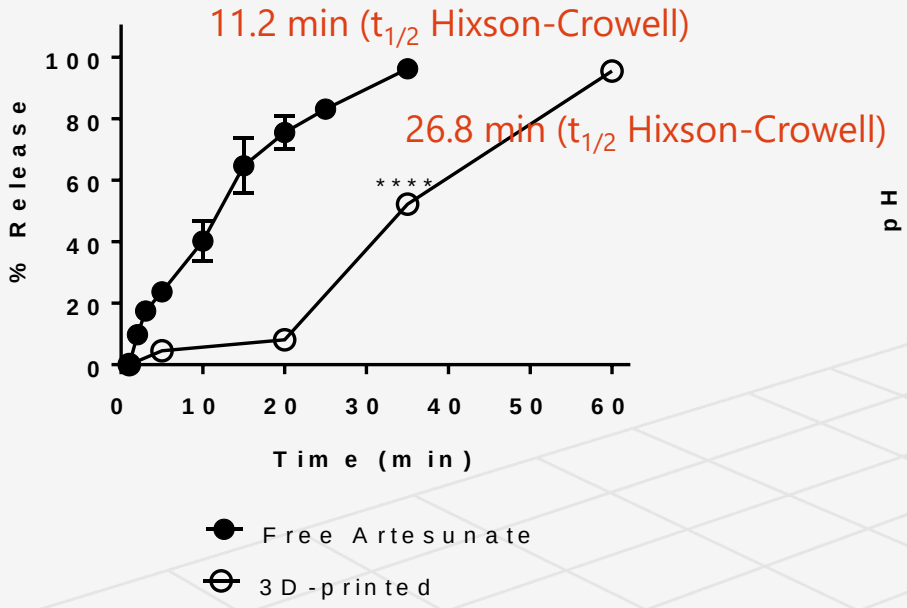
Suzanne Persaud, Sandra Eid, Natalia Swiderski, Ioannis Serris, Hyunah Cho, Preparations of Rectal Suppositories Containing Artesunate, 2020, 12(3) Pharmaceutics, DOI: 10.3390/pharmaceutics12030222

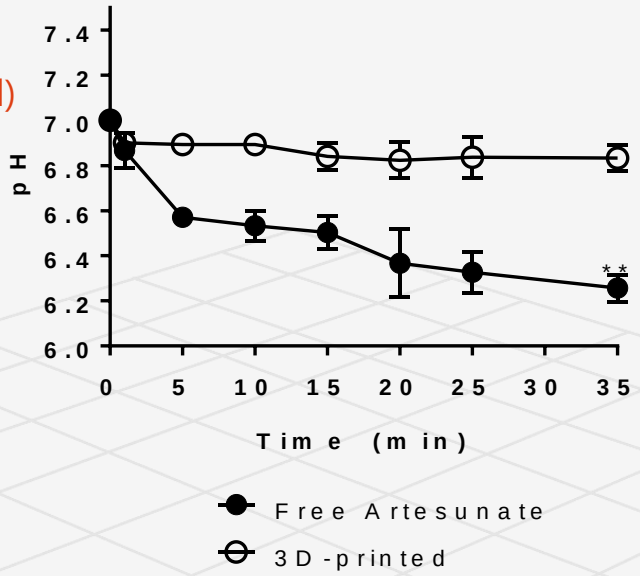
3D-printed PVA suppositories carrying artesunate

Physical properties

Height (mm)	Width (widest) (mm)	Orifice diameter (mm)	Shell thickness (mm)	Cavity diameter (mm)	Shell weight (g)	Artesunate (mg)
24.97±0.01	8.35±0.09	0.53±0.03	1.23±0.03	4.06±0.07	0.71±0.01	60±1

Drug release



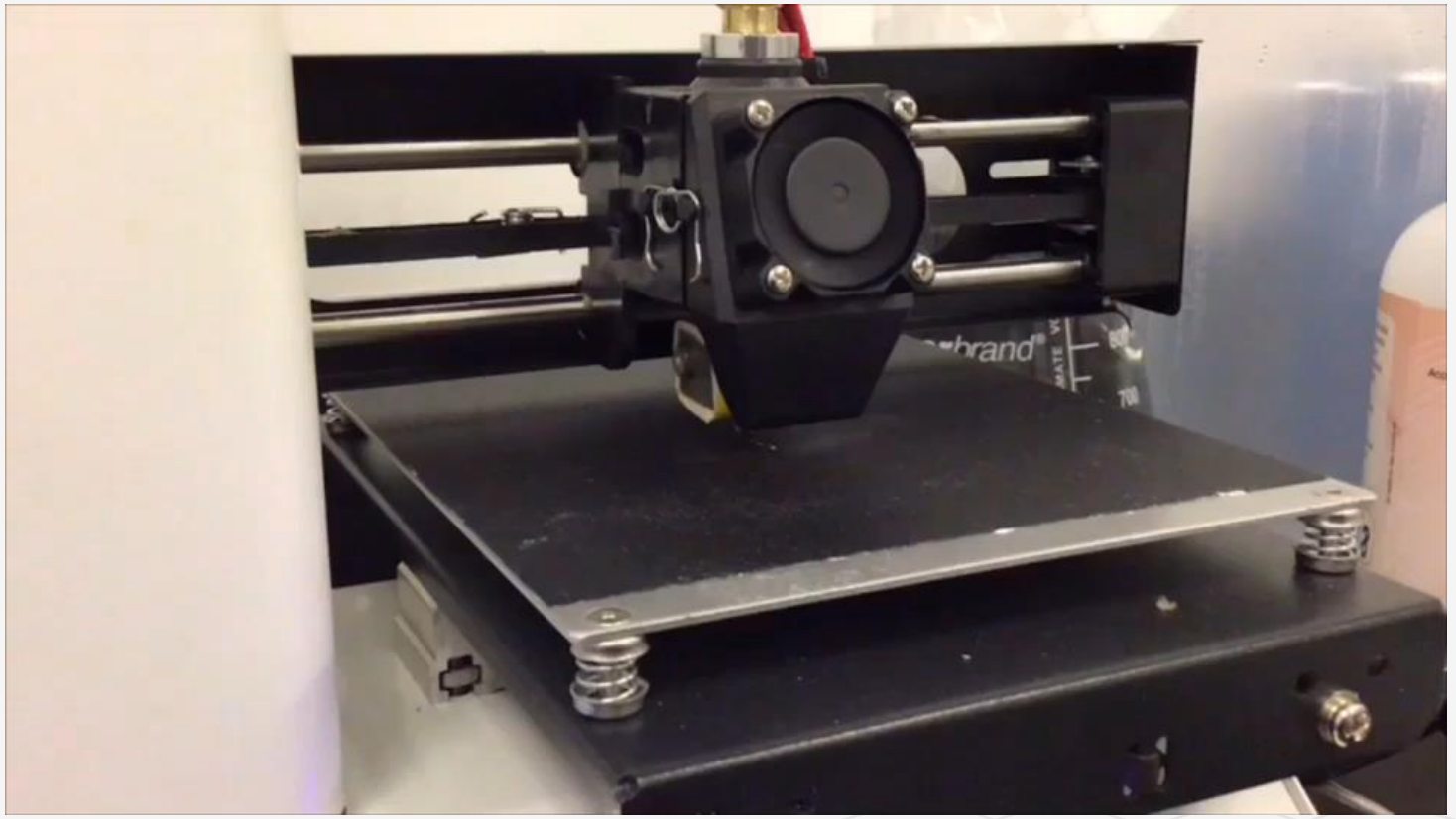


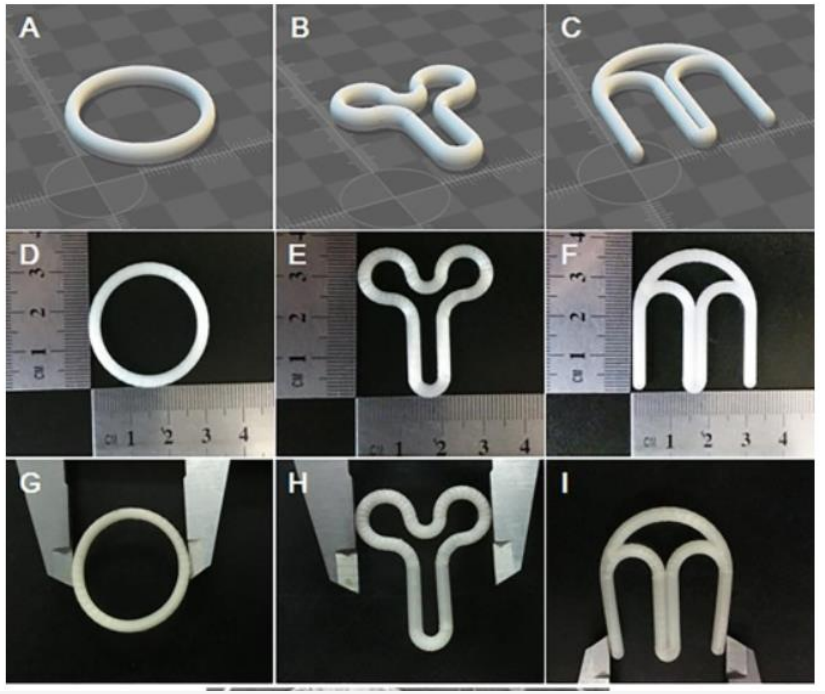
Thermostability (30°C, 35% RH, 6 h)

Types of suppositories	% Remaining	Visual appearance
PEG/free artesunate	90.0 ± 0.5	Soft/partially dissolved
3D-printed	100 ± 0.3	No change

Suzanne Persaud, Sandra Eid, Natalia Swiderski, Ioannis Serris, Hyunah Cho, Preparations of Rectal Suppositories Containing Artesunate, 2020, 12(3) Pharmaceutics, DOI: 10.3390/pharmaceutics12030222

Application: 3D printing of vaginal rings with personalized shapes for controlled release





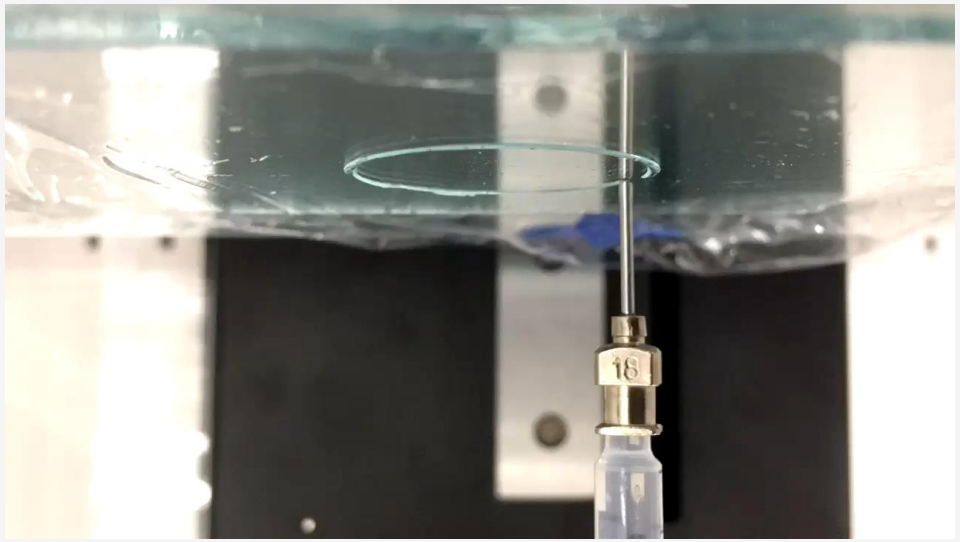
Junhui Fu, Xiang Yu, Yiguang Jin, 3D printing of vaginal rings with personalized shapes for controlled release of progesterone, International Journal of Pharmaceutics, Volume 539, Issues 1–2, 2018, Pages 75-82, https://doi.org/10.1016/j.ijpharm.2018.01.036.

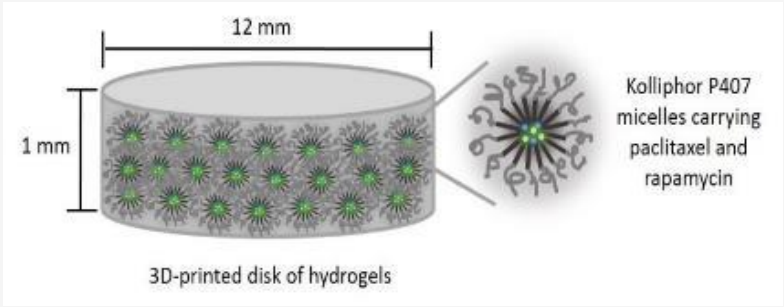
Future application focus on the feasibility of the 3D-printed "personalized PVA vaginal rings" for multi-drug delivery:

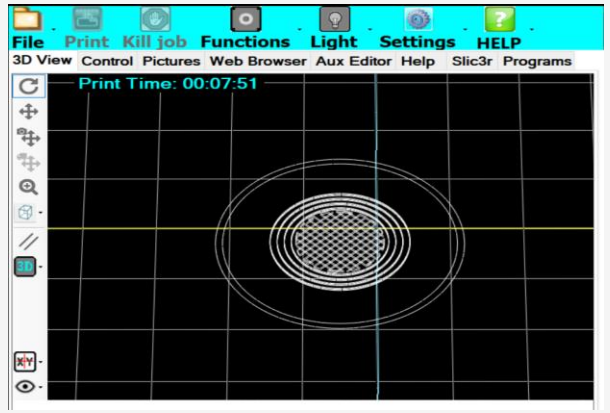
- Incorporation of one drug in the shell and another drug in the "tunnel" of the ring.
- Gradual/sequential delivery of multi-drugs.

2 Solid implants for multi-drug delivery

Customized nanogel discs



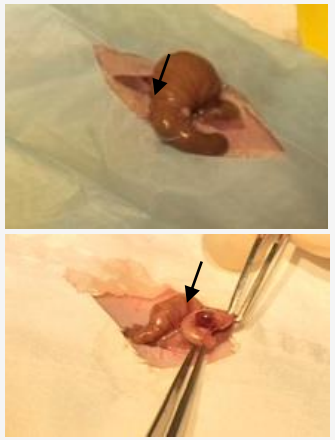




Hyunah Cho, Udayabhanu Jammalamadaka, Karthik Tappa, Christopher Egbulefu, Julie Prior, Rui Tang, Samuel Achilefu, 3D Printing of Poloxamer 407 Nanogel Discs and Their Applications in Adjuvant Ovarian Cancer Therapy, 2019, 16(2) Mol Pharm, DOI: 10.1021/acs.molpharmaceut.8b00836

Application 1: Adjuvant ovarian cancer therapy

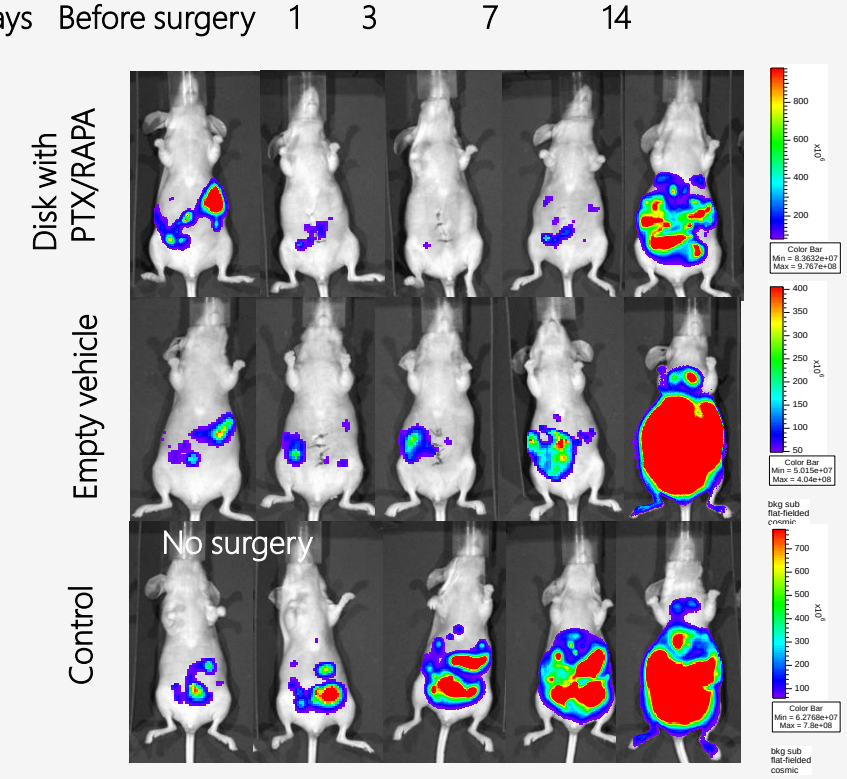
Peritoneal Surgery



Tumor removal

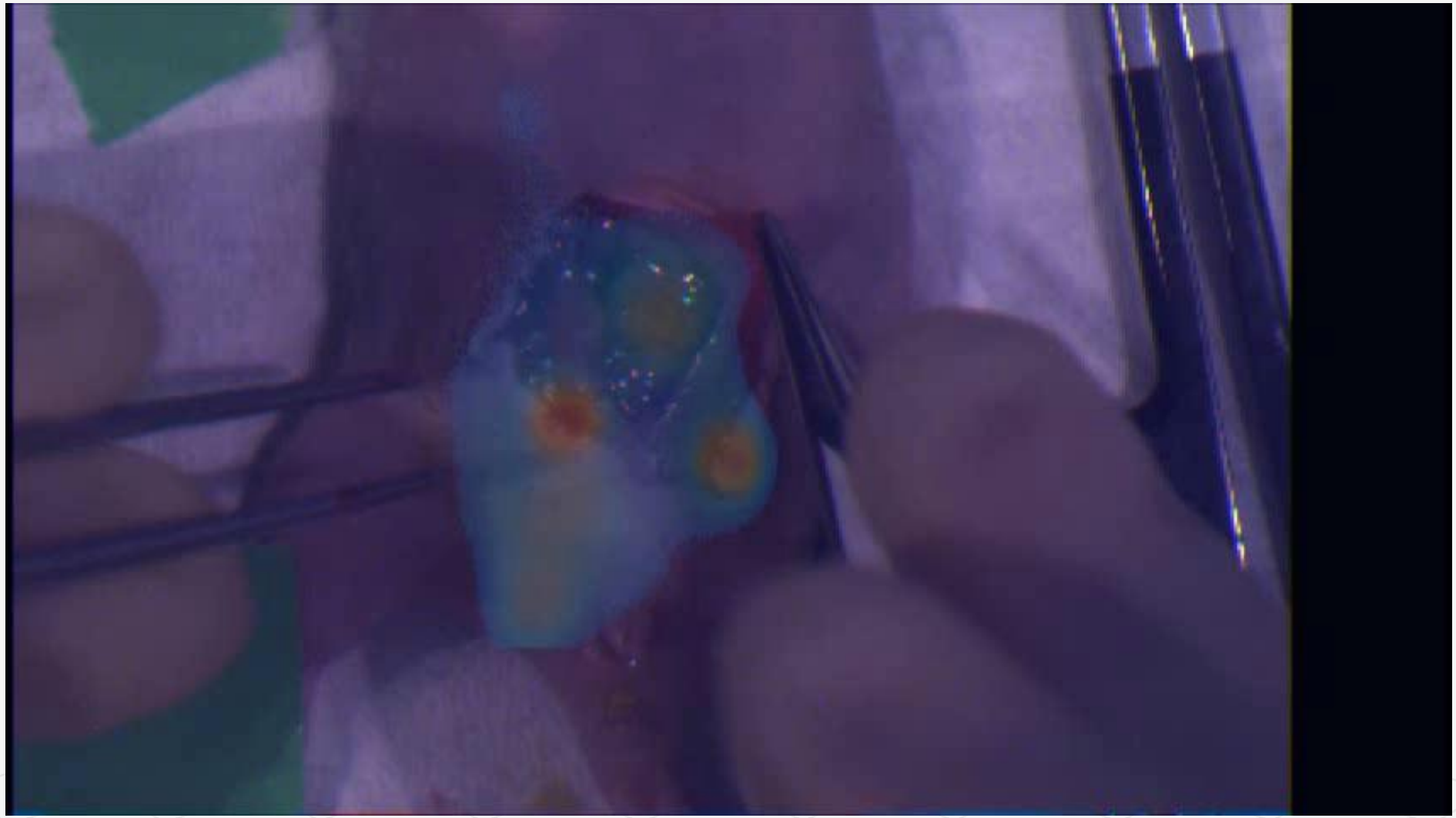
Treatment

Survival



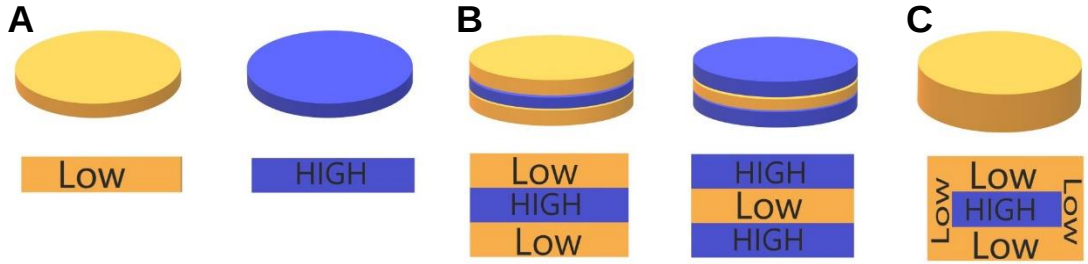
Formulation	Surgery + Disk with PTX/RAPA	Surgery+ Empty vehicle	Control (No surgery/ No treatment)
Median Survival (days)	30	21	14

Application 2: Post-surgical tumor detection

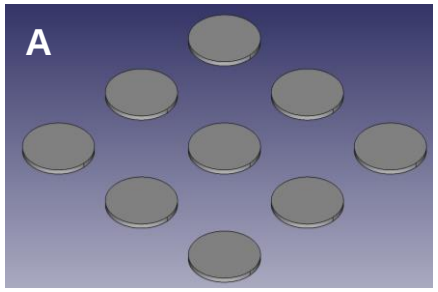


3 Solid implants for controlled drug release

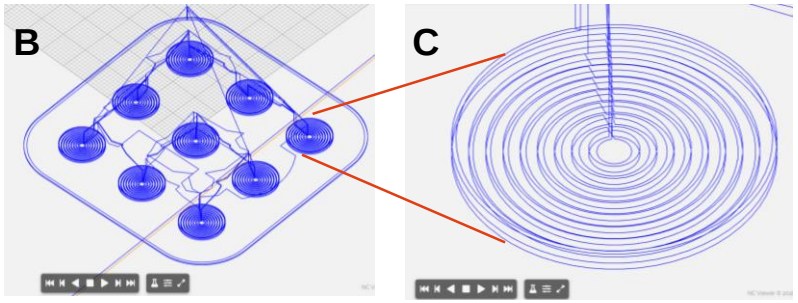
Multi-layered “flexible” films



Drugs were mixed with low MW (12,000-16,000) or high MW (150,000) PLGA polymers. For the PLGA films carrying paclitaxel and rapamycin, a total of 60 mg of paclitaxel was added in the high MW PLGA mixture. A total of 60 mg of rapamycin was added in the low MW PLGA mixture.

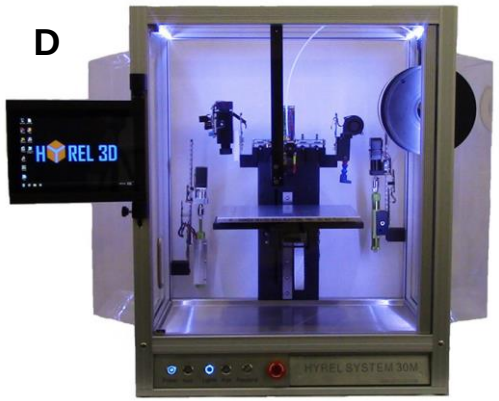


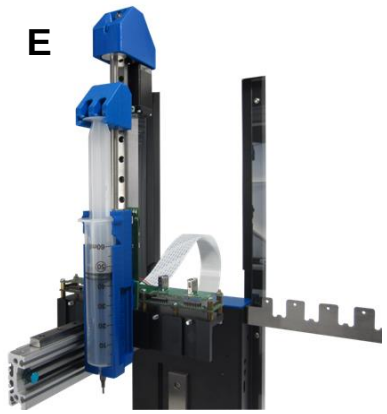
Modeling using CAD software



Convert to Gcode

- Slice into layers
- Tell printer how to print each layer

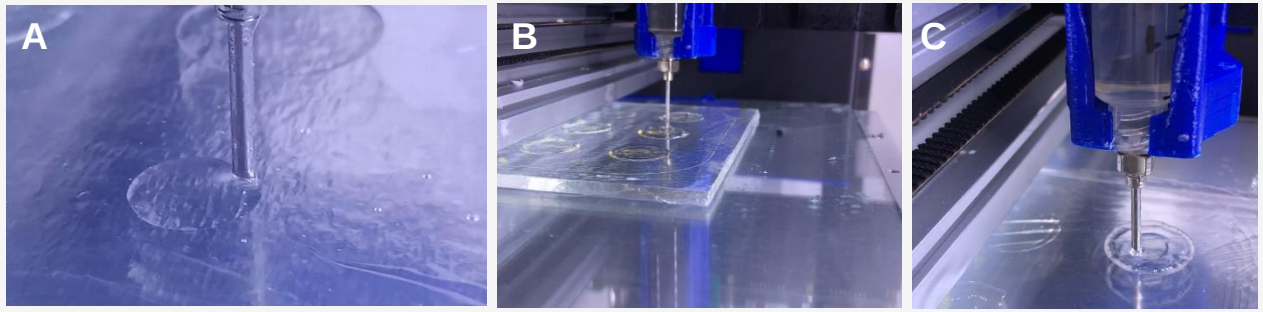




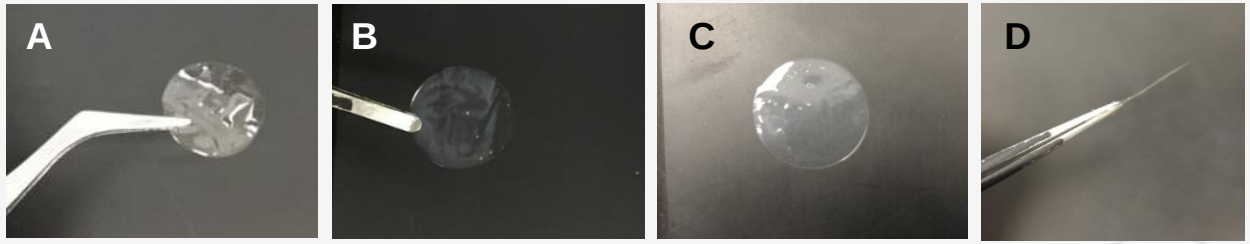
Ioannis Serris, Panagiostis Serris, Kathleen M. Frey, Hyunah Cho, Development of 3D-printed layered PLGA films for drug delivery and evaluation of drug release behaviors. 21(7):256. AAPS PharmSci Tech. doi: 10.1208/s12249-020-01790-1

Multi-layered PLGA films for controlled drug release

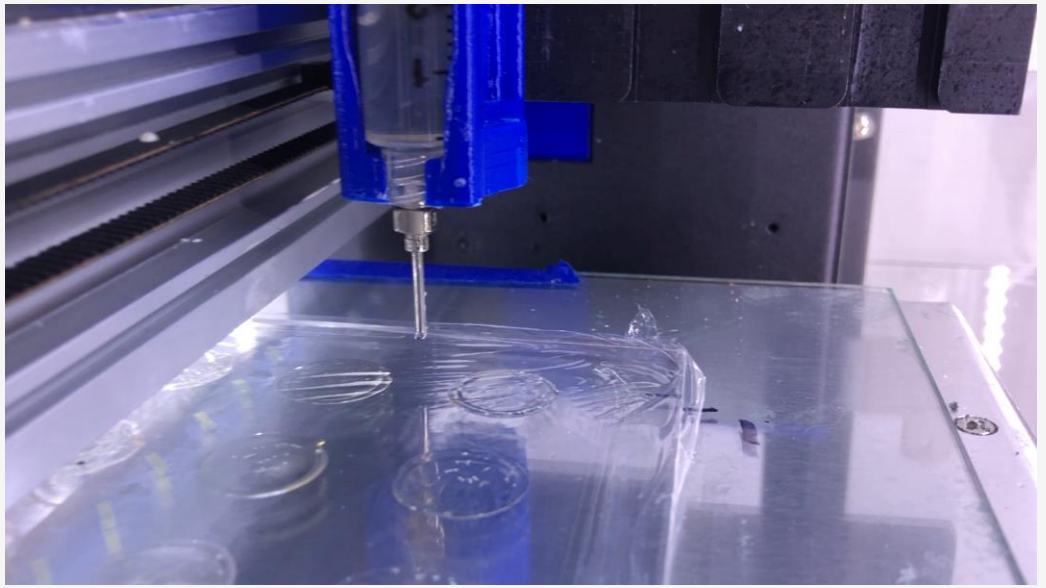
Physical properties



3D printing of bottom layer (A), rim layer (B), and core (C) of core-in-shell PLGA films carrying paclitaxel (core) and rapamycin (shell).



	Diameter (mm)	Weight (mg)	Paclitaxel (mcg)	Rapamycin (mcg)
Low	16 ± 0.5	15 ± 0.0	NA	396 ± 15
High	16 ± 0.3	14 ± 0.1	405 ± 21	NA
L/H/L	17 ± 0.5	45 ± 0.7	343 ± 13	749 ± 14
H/L/H	16 ± 0.3	48 ± 0.9	609 ± 12	352 ± 8
Core-in-Shell	16 ± 0.3	48 ± 0.8	315 ± 6	918 ± 23

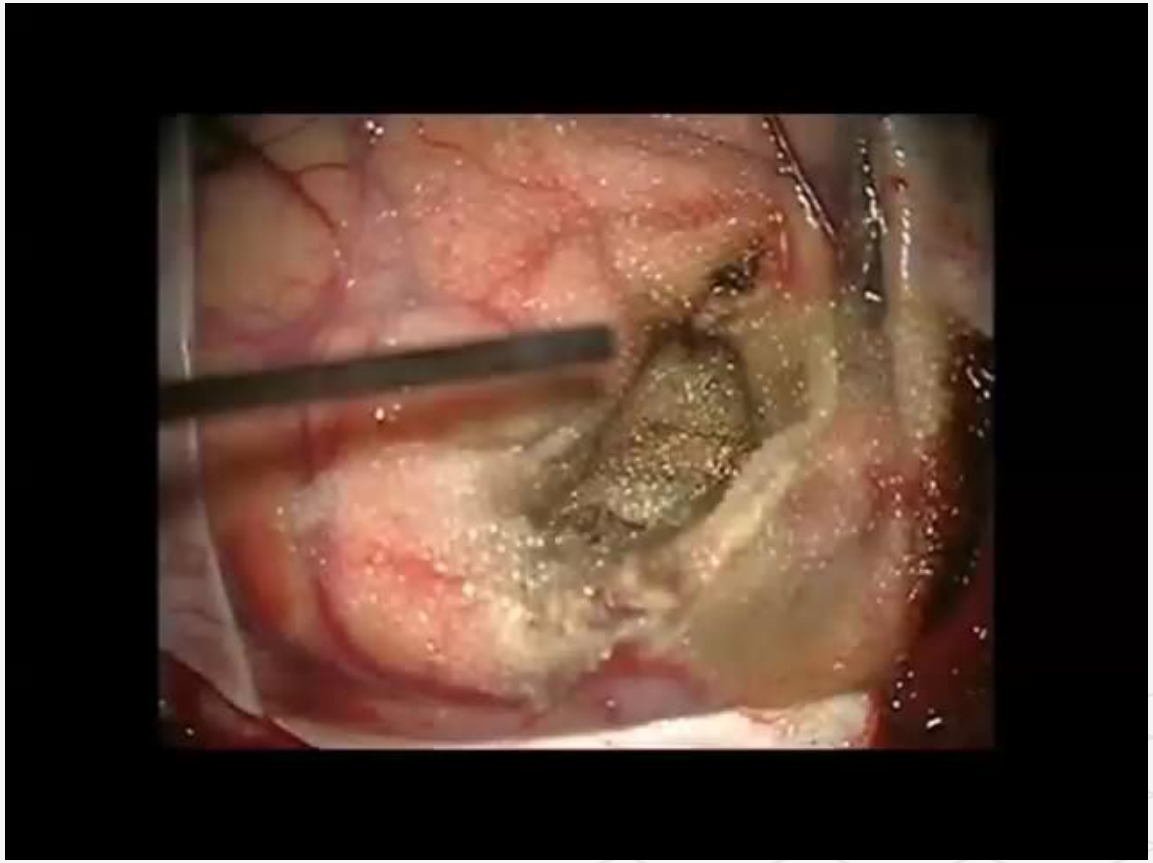


Representative images of single-layered (A), L/H/L (B), and core-in-shell PLGA films (C, D)

Films	*Half-time (days)
Low (Rapamycin)	75
High (Paclitaxel)	57
L/H/L (Paclitaxel)	63
L/H/L (Rapamycin)	80
H/L/H (Paclitaxel)	56
H/L/H (Rapamycin)	74
Core-in-Shell (Paclitaxel)	54
Core-in-Shell (Rapamycin)	75

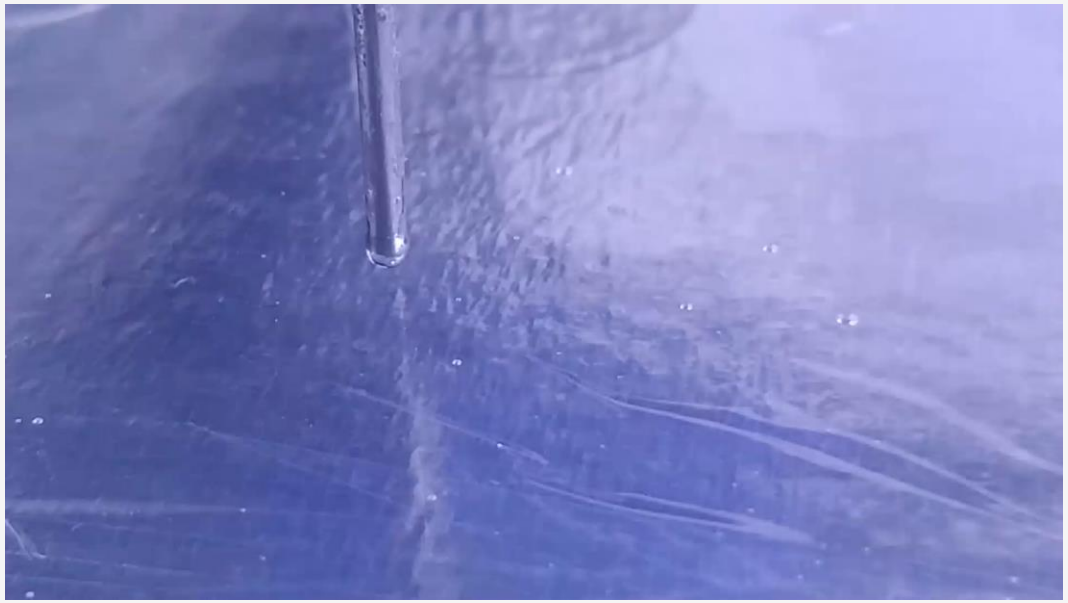
Ioannis Serris, Panagiostis Serris, Kathleen M. Frey, Hyunah Cho, Development of 3D-printed layered PLGA films for drug delivery and evaluation of drug release behaviors. 21(7):256. AAPS PharmSci Tech. doi: 10.1208/s12249-020-01790-1

Application 1: Regional chemotherapy (e.g., ovarian, breast, and brain cancer)

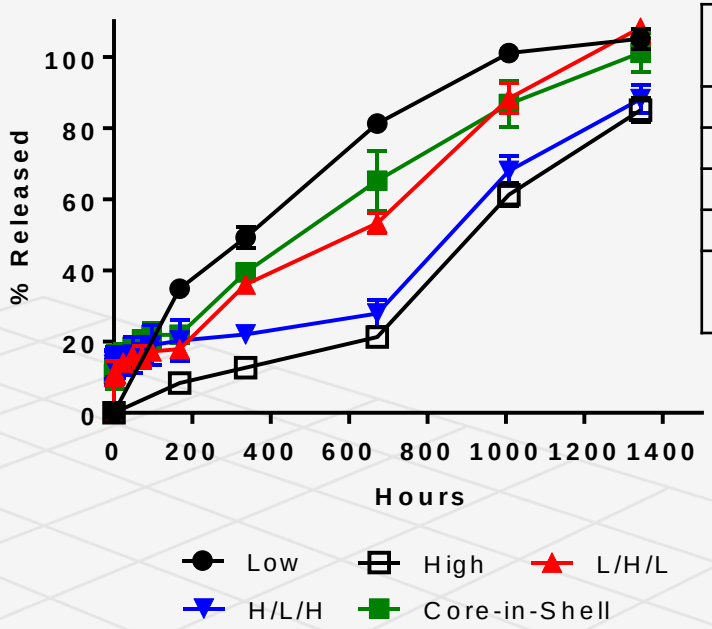


- Chemotherapeutic agents generally have low BBB penetration
  - Local drug delivery needed
  - Accurate dosing needed
- Surgery often includes local implantation of Gliadel® wafers, biodegradable polymers containing 3.85% carmustine
  - Wafers are solid and inflexible
- Spatial constraints
  - Neurological tissue is sensitive increasing side-effects if not correctly shaped

Application 2: Pain relief (controlled of lidocaine)



	Diameter (mm)	Weight (mg)	Lidocaine (mcg)
Low	16 ± 0.1	16 ± 1	802 ± 12
High	16 ± 0.2	18 ± 1	800 ± 14
L/H/L	18 ± 0.5	52 ± 1	2408 ± 29
H/L/H	17 ± 0.8	50 ± 1	2309 ± 29
Core-in-Shell	17 ± 0.5	54 ± 1	2484 ± 28



Model	*Half-time (days)
Low (Lidocaine)	13
High (Lidocaine)	36
L/H/L (Lidocaine)	23
H/L/H (Lidocaine)	32
Core-in-Shell (Lidocaine)	22

Ioannis Serris, Panagiostis Serris, Kathleen M. Frey, Hyunah Cho, Development of 3D-printed layered PLGA films for drug delivery and evaluation of drug release behaviors. 21(7):256. AAPS PharmSci Tech. doi: 10.1208/s12249-020-01790-1

Ongoing: Making our own “INK” using recycled polymer (**Sustainable science**)

Women in Science

1. Be prepared, persistent, and resilient
2. Think strategically: find a niche
3. Pick your battles and do not be intimidated
4. Looking back and projecting ahead
5. Believe in yourself and your science: be confident and optimistic
6. **Enjoy what you do!**

Acknowledgement

School of Pharmacy and Health Sciences, Fairleigh Dickinson University

FDU University Provost Seed Grant Program

Maryland Technology Development Corporation (TEDCO) Grant

OncoGone, LLC

FDU Student Researchers (Ioannis Serris, Panagiotis Serris, Suzanne Persaud, Sandra Eid, Natalia Swiderski, John Henaen)

Other FDU Student Researchers (Loyde Almirola, Serena Shammas, Kayla Paz, Jenna Sandomenico, Tyler Scgacger, Brielle Stawicki)

Newark Academy High school STEM Internship Program (Vikram Bala, Lillian Wu, Kaya Patel, Benjamin Chaddha,and Michael Wang)

Samuel Achilefu, Washington University in St. Louis

Udayabhanu Jammalamadaka, Washington University in St. Louis

Karthik Tappa, Washington University in St. Louis

Glen Kwon, University of Wisconsin-Madison

THANK YOU!

Questions? Interested in Joining us or Collaborations?

hyunahc@fdu.edu

Hyunah Cho, Ph.D
Assistant Professor
Pharmaceutical Sciences
School of Pharmacy and Health Sciences
Fairleigh Dickinson University