Poster # 475

Design and Characterization of Long-acting Subcutaneous Implants Developed Using Hot-Melt Extrusion

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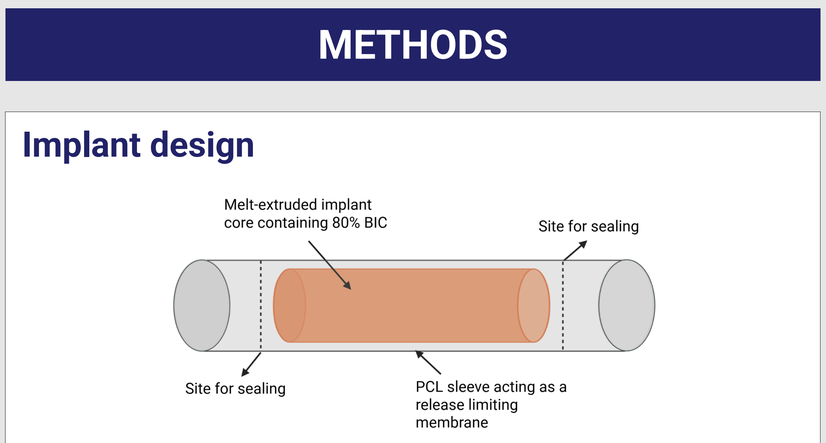
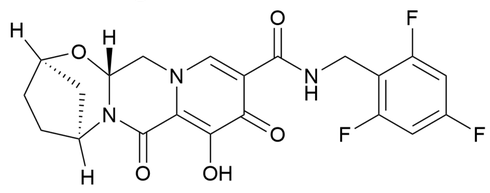
PURPOSE & BACKGROUND

- Pre-exposure prophylaxis (PrEP) is a promising strategy for the prevention of Human Immunodeficiency Virus (HIV).
- Currently, 41% of oral daily PrEP users discontinue it within 6 months of initiation[1].
- A long-acting delivery system that releases the drug in a controlled manner can help overcome challenges, including poor adherence and burdensome daily regimens associated with oral PrEP[2].



- **Study Goal** - Develop a **high-drug loaded** subcutaneous implant containing bictegravir (BIC), and screen it for physical properties and in vitro performance. BIC is a second-generation integrase inhibitor[3].



BIC

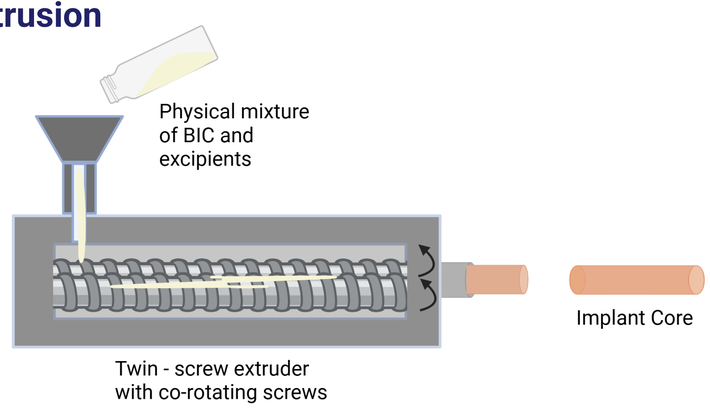
- Mol Weight - 449.39 g/mol
- BCS class - II
- Solubility in 1x PBS (25°C) – 0.1 mg/mL

METHODS

Implant design

Polycaprolactone (PCL) sleeves of 200 or 70 µm thickness, with 2.5 mm outer diameter, were used as release-rate limiting membranes.

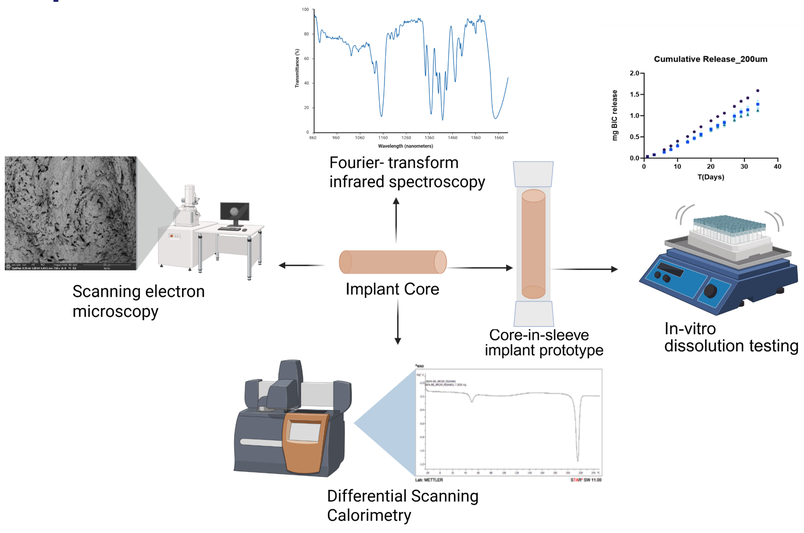
Implant core manufacturing using hot-melt extrusion



Explored drug loads and extrusion parameters

% BIC loading	Loading temperature (°c)	Loading screw speed (rpm)	Mixing temperature (°C)	Mixing screw speed (rpm)	Appearance
70%	150°C	20	150°C	50-100	white, rough surface
75%	150°C	20	150°C	50-100	white, rough surface
80%	150°C	20	150°C	50-100	white, smooth surface with slight unevenness
80%	150°C	20	180°C	50-100	off-white, smooth
80%	180°C	20	180°C	50-100	brownish, smooth

Implant characterization



RESULTS

Thermal evaluation shows presence of crystalline BIC

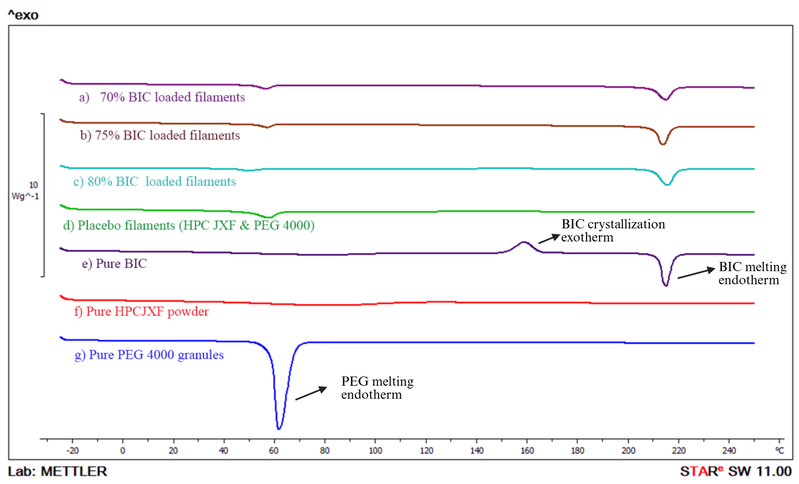


Figure 1: DSC thermograms of melt-extruded BIC implant cores compared to pure BIC and pure excipients, showing the presence of BIC melting endotherm, indicative of crystalline nature.

SEM evaluation shows improvement in surface morphology with increase in temperature

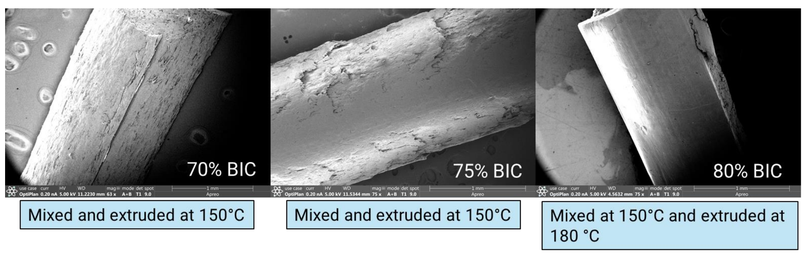


Figure 2: SEM images of outer surface of implant cores showing improvement in surface morphology with an increase in extrusion temperature.

ATR-FTIR evaluation shows O-H group isolation in extruded core

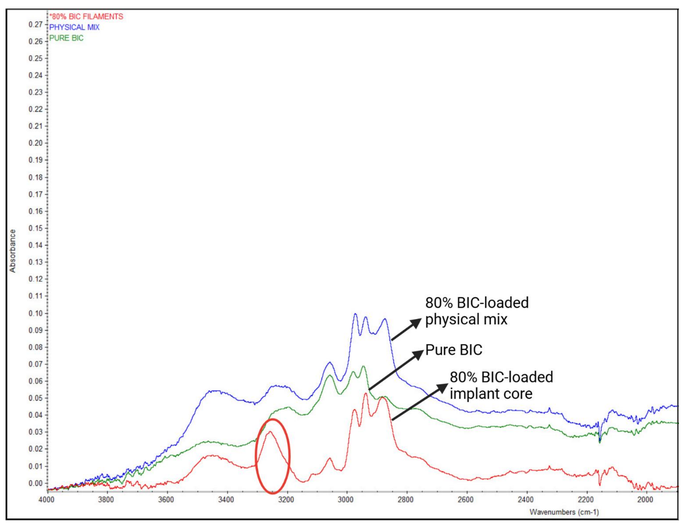
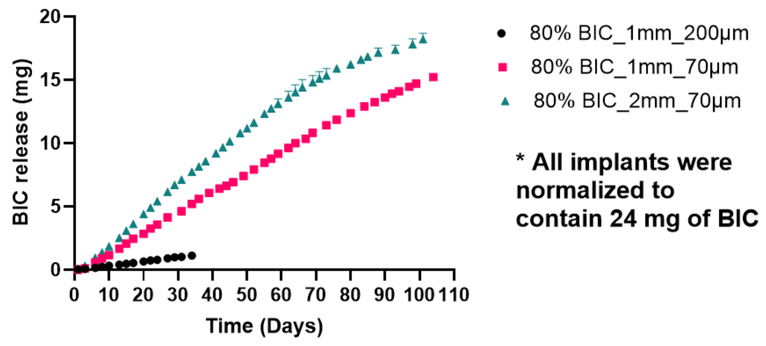


Figure 3: ATR-FTIR spectra overlay comparing pure drug, physical mixture of 80% BIC with excipients, and melt-extruded core formulation showing sharpening of OH stretch at 3250 cm^{-1}.

In vitro evaluation of smaller implant prototypes shows tunability of BIC release



Implant Dimensions				
Implant core length	Implant core thinkness	Implant sleeve thickness	Time Range	Release (mg/day)
1.3 cm	1 mm	200 µm	0-34 days	0.034
1.3 cm	1 mm	70 µm	0-100 days	0.15
0.8 cm	2 mm	70 µm	0-100 days	0.2

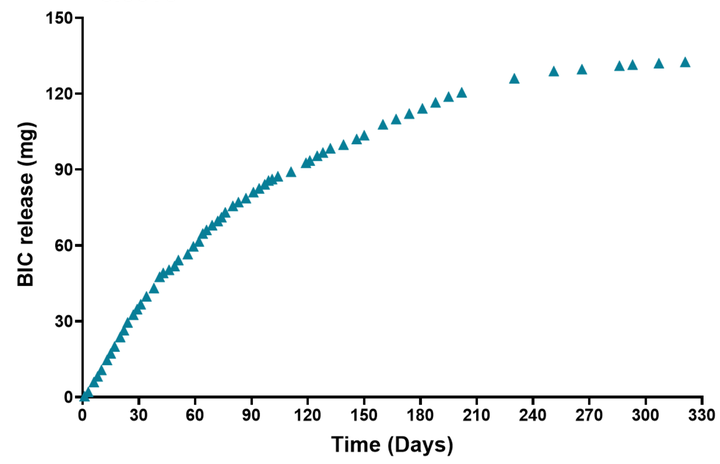
Figure 4: Cumulative release profiles of smaller implant prototypes showing tunability of release rate with the change in implant core and sleeve dimensions. All implants were normalized to contain 24 mg BIC.

In vitro evaluation of clinically suitable-sized implants (4 cm long and 2 mm thick core) shows controlled BIC release

Time Interval (days)	Release (mg/day)
First 30 days	1.27
30-60 days	0.79
60-100 days	0.59
100-130 days	0.39
130-160 days	0.34
160-200 days	0.31
200-321 days	0.07

RESULTS CONT'D

Implant core with dimensions **4 cm x 2 mm** containing **130 mg** of BIC in a **70 µm thick PCL sleeve**



Model	Time Range	R^2 Value
Zero-Order	0–60 days	0.9856
Zero-Order	0–321 days (overall)	0.8646
First-Order	0–321 days (overall)	0.9978

Figure 5: Cumulative BIC release over 321 days with table showing segmented zero-order rates. A strong linear fit was observed in the first 60 days (R^2 = 0.9856), indicating controlled release. Overall, the first-order model showed the best fit (R^2 = 0.9978), suggesting concentration-dependent kinetics.

Storage stability evaluation shows good BIC content even 6 months after storage

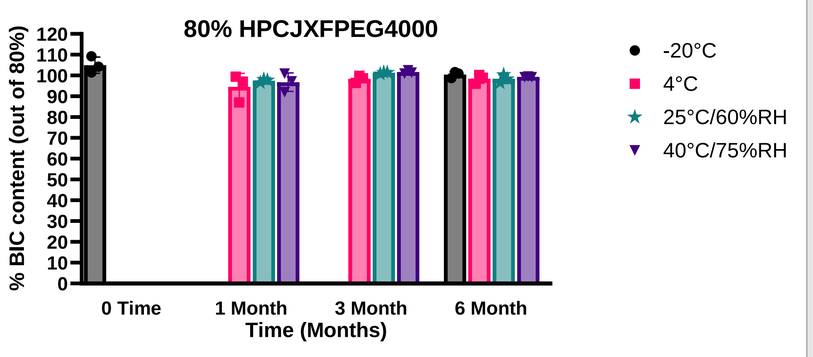


Figure 6: Percentage drug content of the melt-extruded core formulation before and after storage for up to 6 months. Drug content remained within acceptable limits, indicating chemical stability.

CONCLUSIONS

- The extruded core-in-sleeve approach successfully yielded an implant with **high-BIC load (80% BIC)** for HIV PrEP using a **two-step manufacturing and fabrication process**.
- Implant dimensions were varied to tune drug release rate.
- Importantly, implants were fabricated using dimensions (4 cm x 2 mm) that align with approved trocars currently used clinically and could incorporate a **high BIC amount of 130 mg.**
- These clinically-suitable sized implants showed **controlled release of BIC for 60 days** and a sustained BIC release for more than 300 days.

FUTURE DIRECTIONS

- Maximizing the BIC amount within the implant may necessitate an increase in implant size and adoption of alternative fabrication methods, like dip coating.

REFERENCES / FUNDING

1. Zhang J et al. Lancet HIV. 2022:254-268.
2. Wang W et al. JMIR Public Health Surveill. 2023:1-22.
3. Tsiang M et al. Antimicrob Agents Chemother. 2016:7086-7097.

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