Anchoring the Next Wave of HIV Treatments: Preclinical Evaluations of Long-Acting Implantable Formulations

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HIV Treatment Options

- Highly active antiretroviral therapies (HAART) have reduced significantly HIV-related morbidity and mortality
- HIV and AIDS still poses a significant global health care challenge
  - *In 2021*
    - *85% of people living with HIV knew their status*
    - *75% were accessing treatment*
    - *68% were virally suppressed*
- Patient Adherence remains a major challenge

- Extended duration dosing regimens are highly desired by both patients and physicians
  - Treatment
    - Cabenuva (monthly IM injection)
    - Sunlenca (6-week SC injection)

UNAIDS_FactSheet_en.pdf

Long-acting antiretrovirals and HIV treatment adherence
https://doi.org/10.1016/S2352-3018(23)00051-6

Polymeric Implants

General

- **API/polymer construct**
- Dose: <1 mg/day, 50-400 mg total
- Q6M-Q3Y duration

API

- **Can be adapted to fit molecules with diverse physchem properties**
- Highest potency requirements

Formulation

- **High complexity**
- Highly controlled release rates possible
- Administered by injection device
- Can be removed

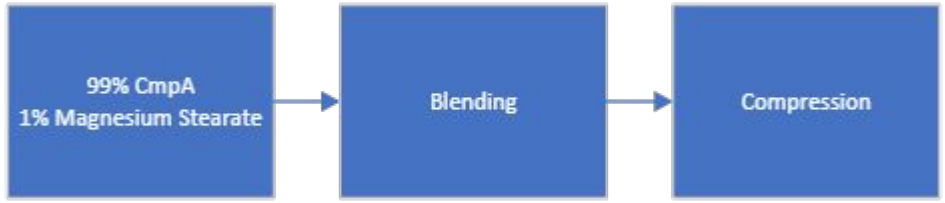
	Reservoir Implant	Matrix Implant
		
Polymer Material	Generally nondegrading (eg, polyurethanes)	Degrading or nondegrading (eg, PLA, PLGA, EVA)
Drug Load Operating Range	50-150 mg	50-70 mg
Release Kinetics	Zero and 1st order	1st order
Removable	Yes, with nondegrading polymers and biodegradable polymers at early time points	
Duration of Therapy	Up to 3 yr (eg, Implanon)	Up to 1 yr

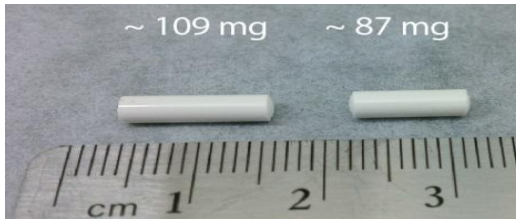
Drug eluting implants in pharmaceutical development and clinical practice
https://doi.org/10.1080/17425247.2021.1856072

API Sparing Approaches for Polymeric Implants in Preclinical Studies

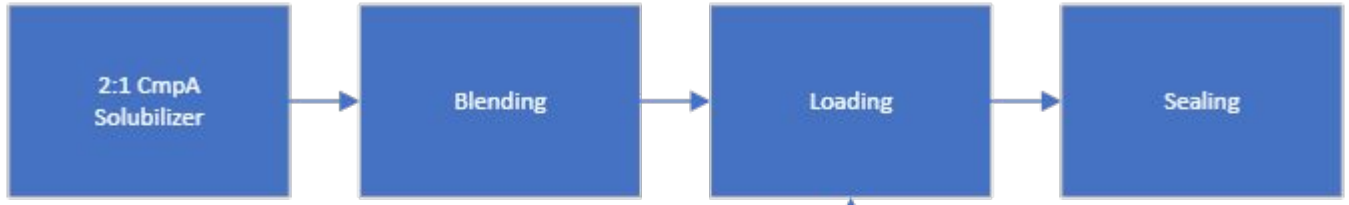
- Miniaturized prototype options needed for discovery or early development studies
- API is often limiting
- Need for a formulation that can mimic or have line of site to pilot or commercial scale

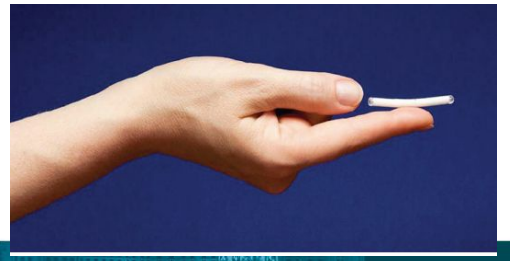
Matrix Implants: 99% DL compressed tablet





Reservoir Implants: 66.6% DL paste in a polyurethane tube

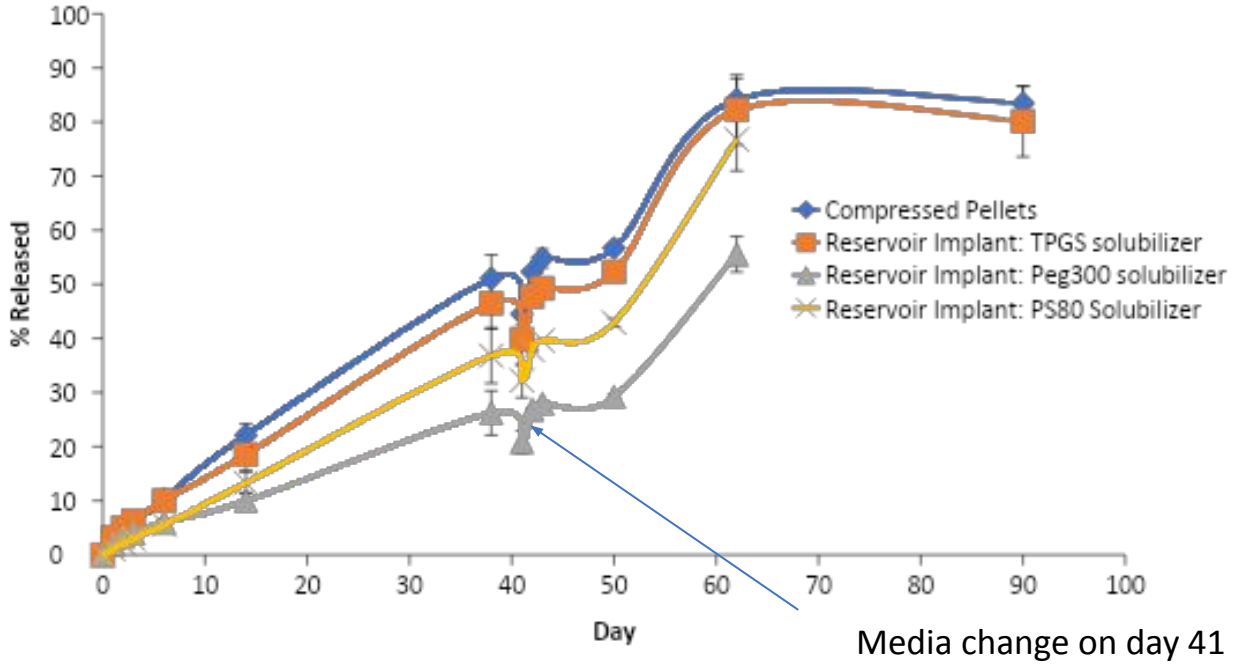




Compound A was identified by Merck team with potential for 6 month implant

In Vitro Dissolution Studies

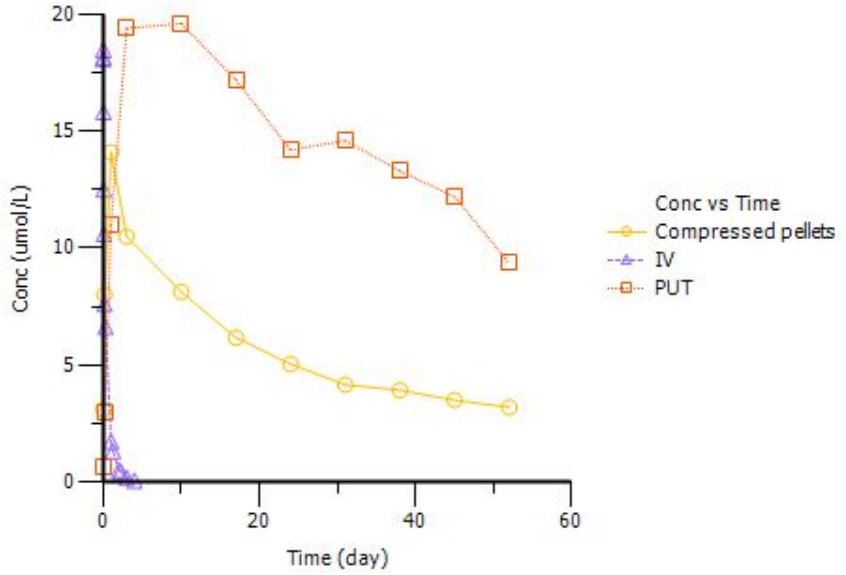
- In vitro release was studied at 37°C on an orbital shaker for up to 90 days.
- Dissolution volume is equivalent to 0.66x the equilibrium solubility of CmpA in this media. The media was completed switched on day 41 to avoid saturation.

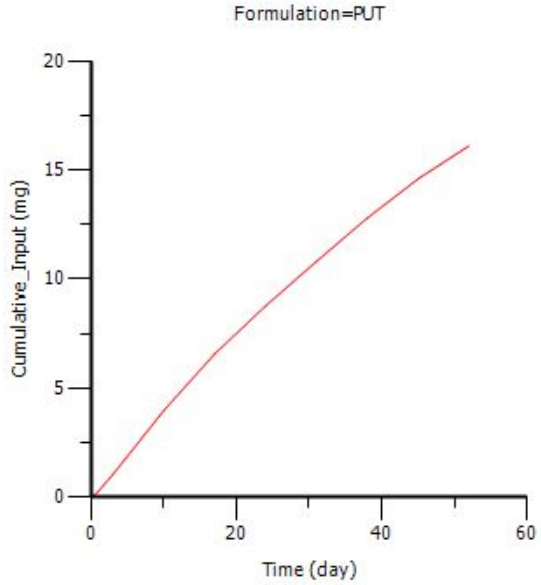


- All formulations showed gradual release with minimal burst release
- The solubilizer in the reservoir implant impacted release TPGS>PS80>Peg300
- Compressed pellet and TPGS implant were progressed into rat PK studies

Rat PK Results

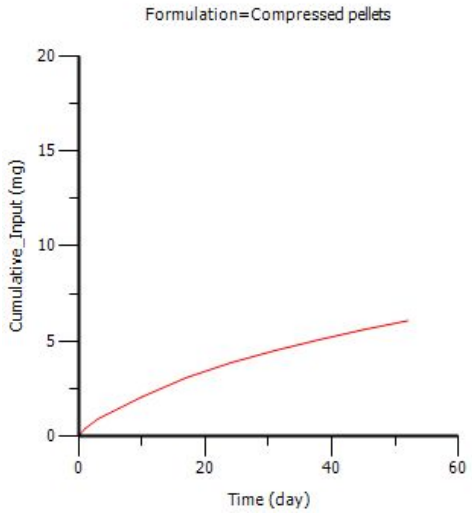
- A rat PK study was performed after SC implantation of reservoir (42 mg dose,) or compressed pellet matrix (50mg dose)
- Reservoir Implant (PUT) showed higher cumulative release compared to reservoir compressed pellets.
- The cumulative percent released for the reservoir implant closely matched the dissolution performance while the compressed pellet formulation was several fold lower.





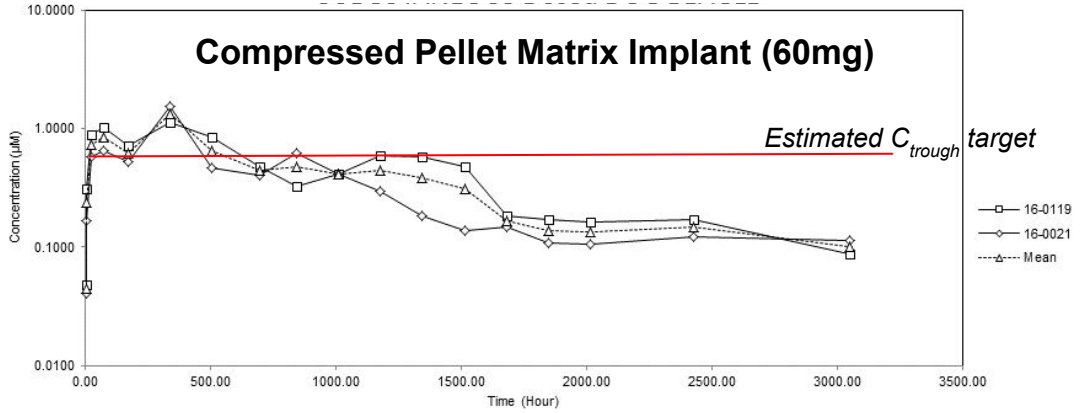
Reservoir Implant Release Rates

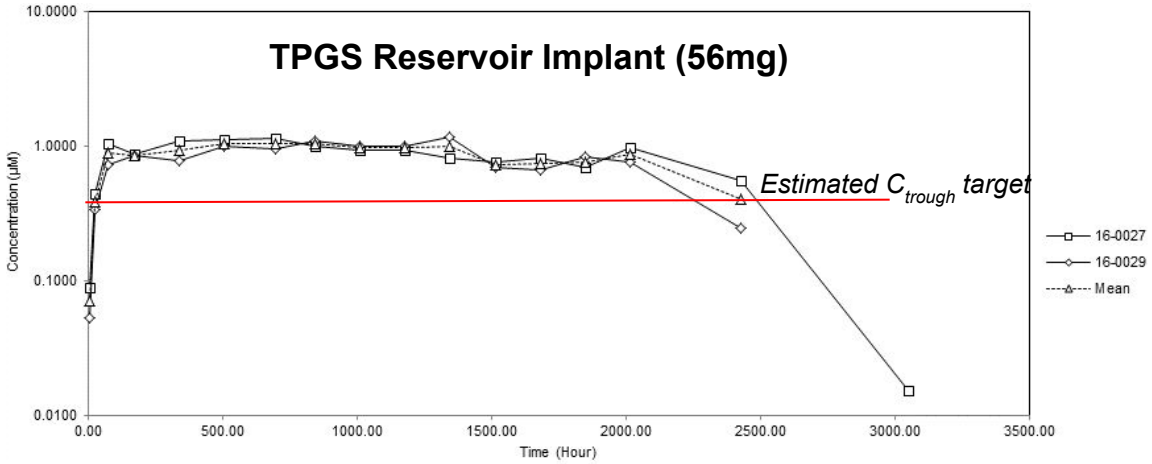
In Vitro Day	% Released	In Vivo Day	% Released
6	10.05	10	12.08
38	46.5	31	32.9
50	52.3	52	48.9



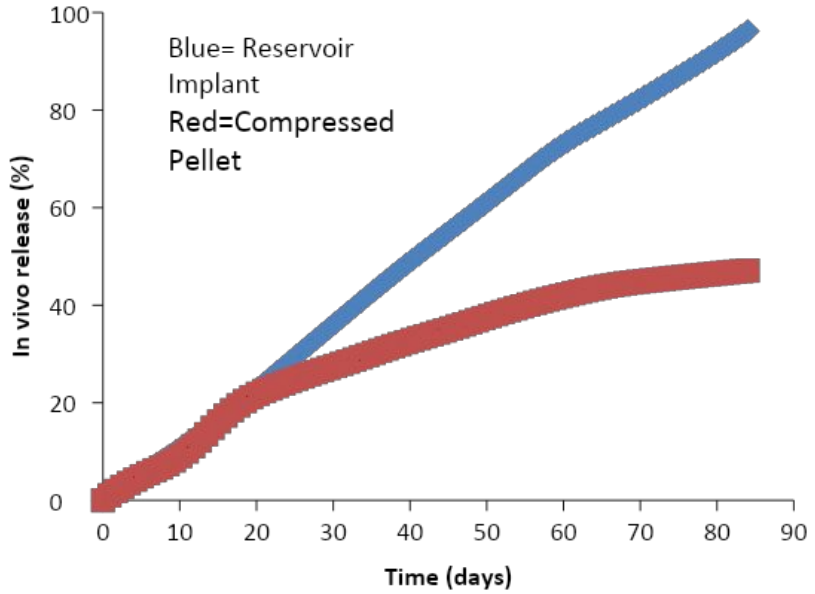
Dog PK Studies

- Compressed pellet implant displays moderate release rate at SS and moderate cumulative release over 3 months
- TPGS PU tube implant displays near 0-order release with good release rate at SS and high cumulative release over 3 months
- Compressed pellet implant provides plasma exposures above estimated target C_{trough} in dog for ~3 weeks
- TPGS PU tube implant provides plasma exposures above estimated target C_{trough} in dog for 3 months
- **~2x increase in implant duration required to hit 6-month target**





Deconvolution of Dog PK Data

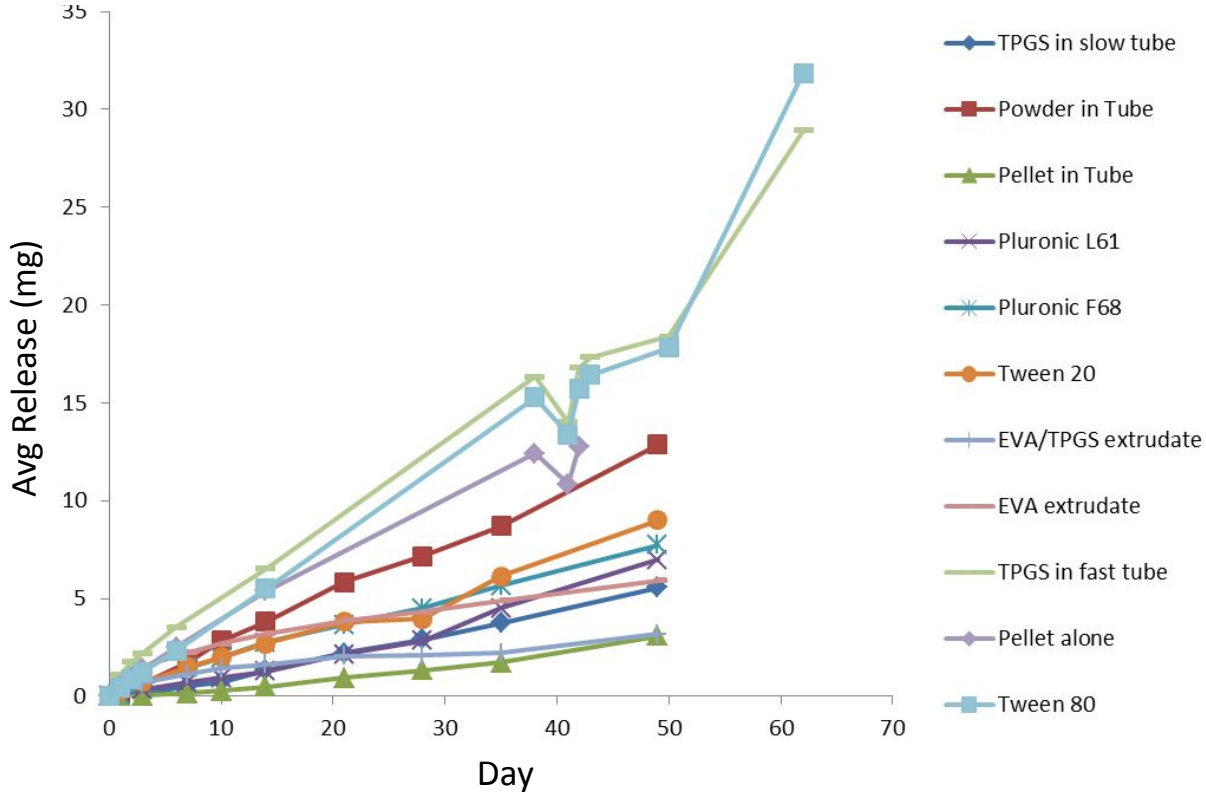


- Reservoir Implants displayed release rates and durations consistent with target profile
- Release rates vary by species, with release rates in dog higher than rat for comparable formulations

Formulation	Average release rate (mg/day)	Cumulative Release (%)
CP Matrix	0.33	47
TPGS Reservoir	0.63	96

Further Implant Evaluation for CmpA

- The impact of solubilizer, polyurethane tube type and API densification was studied on a series of reservoir implants
  - Solubilizer may negatively impact release rate
  - Reducing tube hydrophilicity and densifying API slowed release rate
- EVA matrix implants were also produced and showed similar release rates



Conclusions

- Polyurethane reservoir implants of CmpA demonstrated rodent in vivo release rates comparable to in vitro dissolution results. In dogs, the formulations displayed release rates consistent with the target profile of CmpA with ~3months of efficacious coverage
- Compressed pellet matrix implants of CmpA demonstrated more variable release rates and shorter duration coverage
- These approaches can be extended to early implant evaluations for alternate indications

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