Feasibility of Subcutaneous Entecavir Implants for Chronic Hepatitis B Treatment

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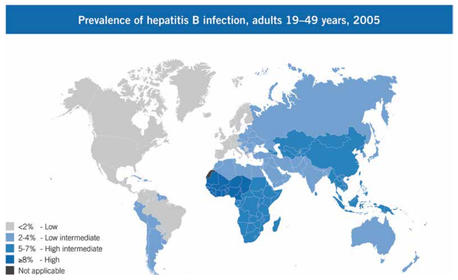
Abstract

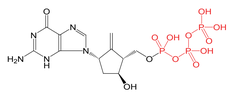
Patient compliance in the treatment of chronic infectious diseases is critical in preventing disease progression but often hampered by the burden of a lifelong pill regimen.[1] Entecavir (ETV) is a first-line antiretroviral agent for the treatment of chronic hepatitis B administered as a once-daily oral pill or solution.[2] The aim of our work was to evaluate the feasibility of long-acting implantable formulations of ETV to reduce the compliance burden on patients. To this end, we engineered hot melt extrudates and coated tablets for sustained ETV release in the subcutaneous (SC) space.

A variety of pharmacokinetic release profiles were achieved in rats by tuning the rate-controlling properties within a given modality. While 6-month SC delivery of ETV was demonstrated, local inflammation and necrotic tissue were observed proximal to the implant. Although SC ETV was not well tolerated at high input rates, the demonstrated implant longevity was a substantial increase over previous efforts reported in the literature.[3] The modalities employed herein may have applicability to other therapeutic agents for long-acting hepatitis B treatment.

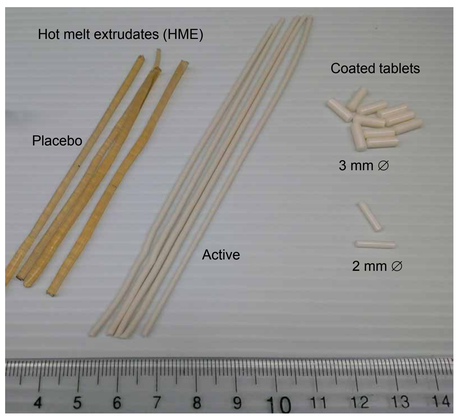
A Problem of Global Proportions: 240-360 Million Individuals With CHB[2,4]



Entecavir (ETV) is an off-patent first-line nucleotide reverse transcriptase inhibitor taken at 0.5 mg/day orally for a patient's lifetime. The molecule is shown in its intracellular triphosphorylated form to the right.



Hot Melt Extrudates and Coated Tablets



Polymers Evaluated

Hot melt extrudates (HME)

- 1X DL poly(D,L-lactide) (PLA)
- 1X DL polycaprolactone (PCL)

Polymer coated tablets (Tab)

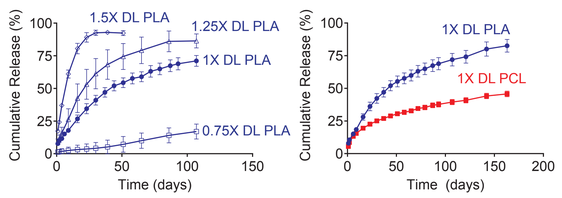
- 2.3X DL uncoated (bare)
- 2.3X DL polyurethane† (PU)
- 2.3X DL poly(D,L-lactide-co-glycolide) (PLGA)
- 2.3X DL poly(D,L-lactide-co-caprolactone) (PLCL)

†All polymers evaluated were bioerodible with exception of PU.

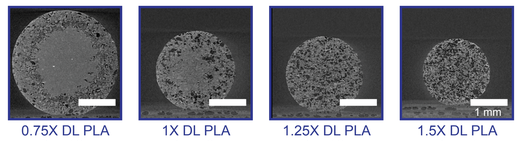
References

1. Buell KG, et al. *AIDS Care*. 2016;28(2):242-246. DOI: 10.1080/09540121.2015.1074653
2. World Health Organization. Guidelines for … chronic hepatitis B infection. 2015. ISBN: 9789241549059
3. Lim JL, et al. *Int J Pharm*. 2015;490(1-2):265-272. DOI: 10.1016/j.ijpharm.2015.05.049
4. Shepard CW, et al. *Epidemiol Rev*. 2006;28:112-125. DOI: 10.1093/epirev/mxj009

Tuning HME *In Vitro* Release

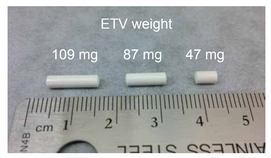


Error bars = ± SD (n = 3 replicates per condition)

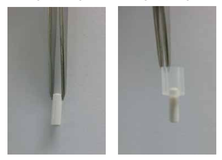


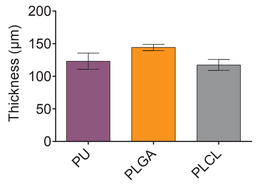
0.75X DL PLA Day 107 | 1X DL PLA Day 107 | 1.25X DL PLA Day 107 | 1.5X DL PLA Day 51

Manual Tablet Coating: Dip-Flip-Dip



Intrinsic ETV compressibility enables high drug load (DL) tablets by direct compression.

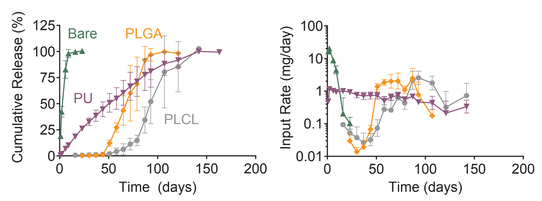




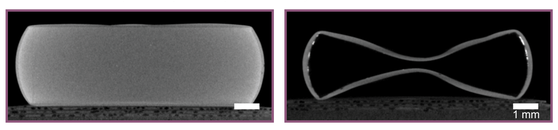
Drying rack

Error bars = ± SD
(n = 3 replicates per condition)

Tuning Coated Tablet *In Vitro* Release

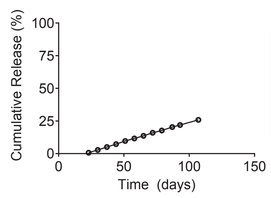


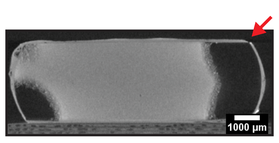
Error bars = ± SD (n = 3 replicates per condition)



PU Tab, Day 0 | PU Tab, Day 163

Defect-Enabled Release From PCL Tablet Suggests Utility of a Fixed-Orifice Design



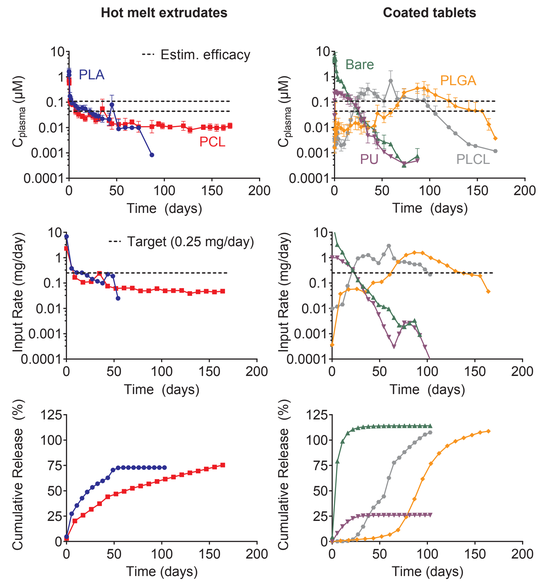


PCL Tab, Day 121

1/6 replicates: Defect-enabled release (see XRCT cross section above)
5/6 replicates: No detectable release through 121 days

The defect-enabled release of ETV from PCL-coated tablets suggests that the predominate mechanism of ETV escape from PCL HMEs is through pores and channels, not via diffusion through the polymer matrix itself.

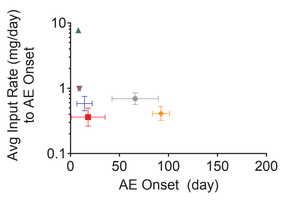
A Variety of ETV PK Profiles Were Achieved in Rats Using HMEs and Coated Tablets



Error bars = ± SD (n = 2-4 rats per condition)

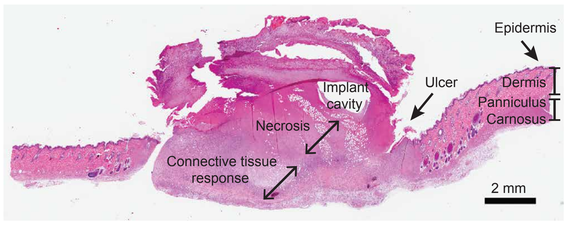
Note: Input rate and cumulative release were result of deconvolution analysis using measured clearance rate of ETV from rats.

Chronic Subcutaneous ETV Exposure-Induced Local Inflammation



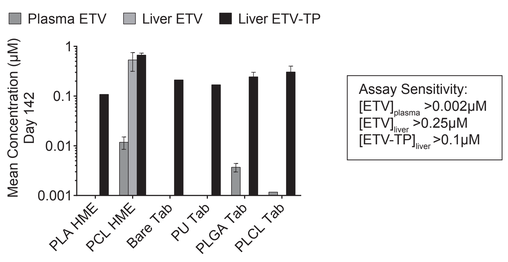
Solid mass/protrusion surrounding implant

Local inflammation



Hematoxylin- and Eosin-stained tissue around PU-coated tablet. Locally extensive necrosis proximal to the implant cavity is shown, along with a connective tissue response in the subdermal layers. The severity of the adverse event was proportional to the average ETV input rate of the implant.

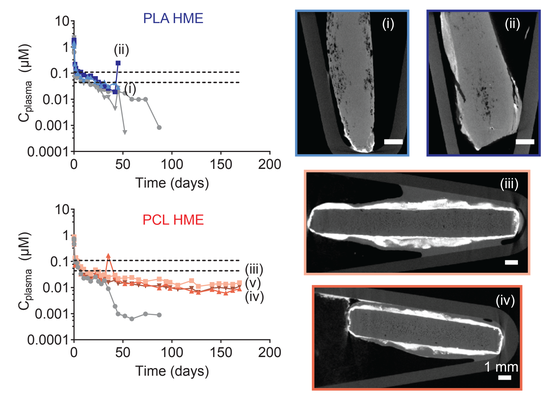
Liver Entecavir-Triphosphate (ETV-TP) Detected at Day 142 or Longer in All Groups



Assay Sensitivity:
$[ETV]_{plasma}$ >0.002μM
$[ETV]_{liver}$ >0.25μM
$[ETV\text{-}TP]_{liver}$ >0.1μM

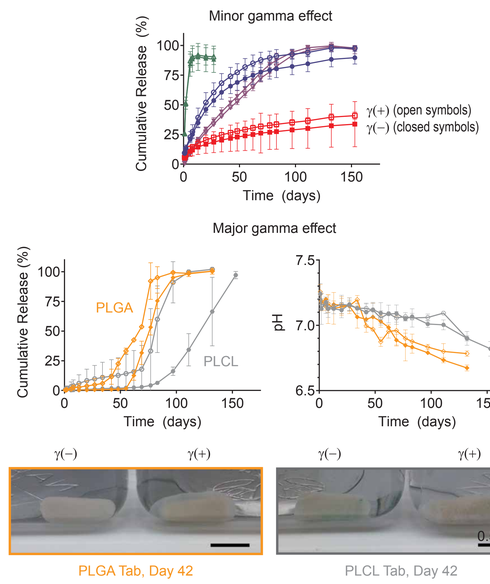
If column is absent, concentration was below limit of quantitation at Day 142.
If error bars are absent, only a single replicate was measured at Day 142.

XRCT of Recovered Implants Reveals That Tissue Adhesion Alters HME Erosion Pathway



PCL HME replicate (v) illustrates how extent of surface tissue adhesion correlates with erosion pathway. Single-headed arrow shows surface erosion in region with thin tissue adhesion. Double-headed arrows show core erosion in region with thick tissue.

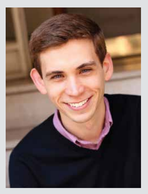
Gamma Irradiation (25 kGy) Accelerates Release in Lactide-Containing Polymers



PLGA Tab, Day 42 | PLCL Tab, Day 42

Conclusions

- Achieved an unprecedented 169 days of parenteral ETV release
- Of polymers tested, PCL HMEs provided most stable *in vivo* ETV blood plasma content
- Liver ETV-TP levels appear long-lived relative to plasma ETV. However, it is unclear if these ETV-TP levels are efficacious
- Local AEs at implantation site appear ETV specific, suggesting that polymer modalities may be applicable to better-tolerated drugs
- Differential erosion pathway of HMEs appears to correlate with tissue adhesion, but PK profiles were not differentiated
- Gamma irradiation accelerated *in vitro* release of lactide-containing polymers



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