Delivery of Hepatitis B vaccine via a Self-Boosted System

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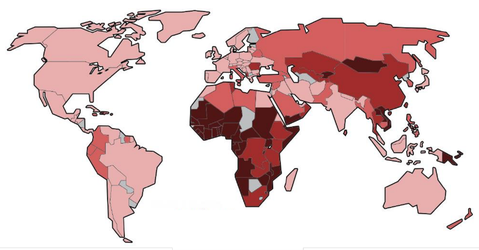
Introduction

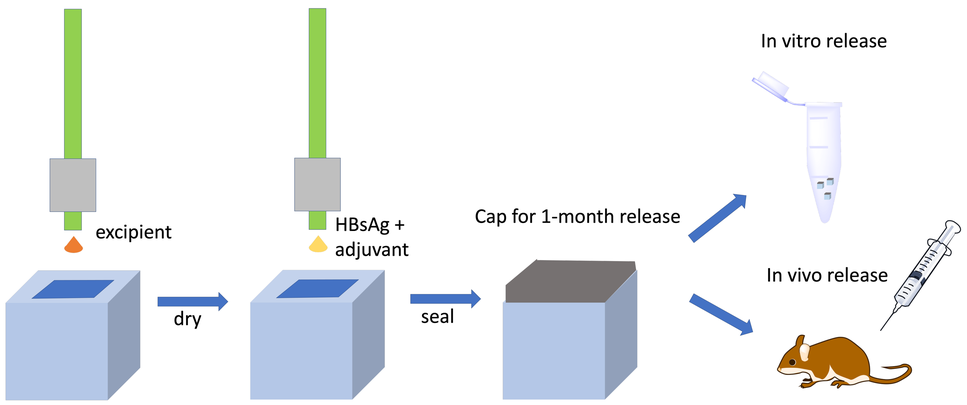
Vaccination in the developing world is challenging due to limited patient access and compliance, resulting in patients missing booster shots necessary for protective immunity. Herein, a single-injected fully biodegradable system is described based on core-shell microparticles fabricated via the novel Stamp Assembly of Polymer Layers (SEAL) process[1] and optimized to release booster dose for Hepatitis B vaccine in a pulsatile manner. Hepatitis B affects 325 million people globally and presents high prevalence in Asia and sub-Saharan Africa. The particles are co-delivered with the prime dose via single injection and the booster dose is released 1 month apart, adhering to the accelerated vaccination schedule for individuals ≥18 years approved by CDC. This system could help alleviate issues of under-vaccination due to missed appointments pertaining to patient adherence or poor vaccination records in low-resource settings.

Hepatitis B prevalence [2]



Materials and methods

from filling to administration



- PLGA core-shell microparticles were fabricated through the SEAL process[1].
- Base-cap structure allows filling with excipients, antigen and TLR9 CpG sequence as adjuvant[3] using a BioJet Ultra picoliter dispensing instrument (BioDot). The aqueous solutions of cargos were dispensed for multiple 15-drop cycles of 180- to 230-pl drops.
- Filled particles were aligned and sintered with PLGA caps using a microscope.
- Sealed particles were separated from glass slides and used to perform antigen stability and release tests in vitro or evaluation of the humoral response with the elicitation of anti-Hep B antibodies in vivo through ELISA.

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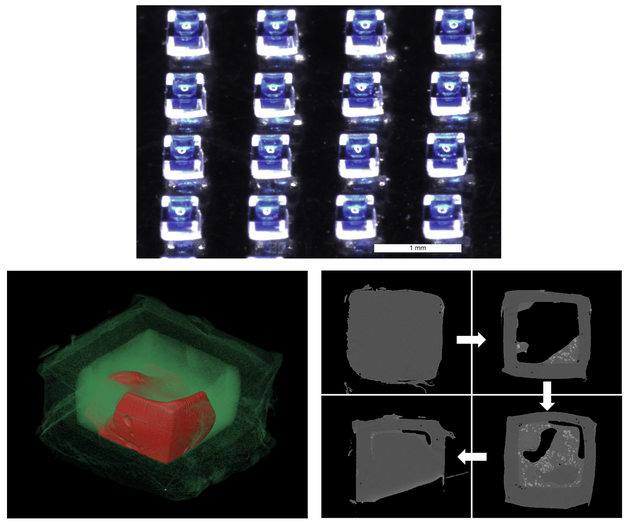
Results and Discussion

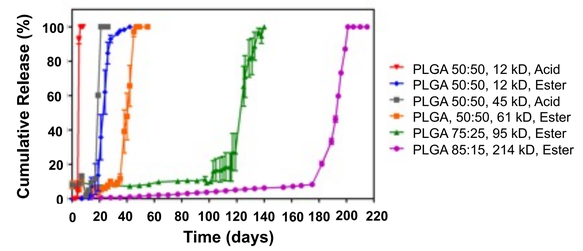
Optical and CT Imaging of Microparticles and Cross-sections



- PLGA microparticles present a **core-shell** structure and the excipients, vaccine and adjuvant are dispensed in the core of the base. The base is subsequently capped.

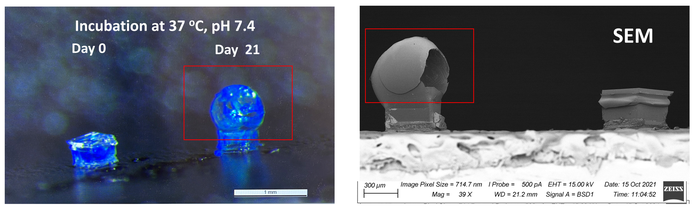
In vivo Release Profile and Release Mechanism

***In Vivo* Release Kinetics**



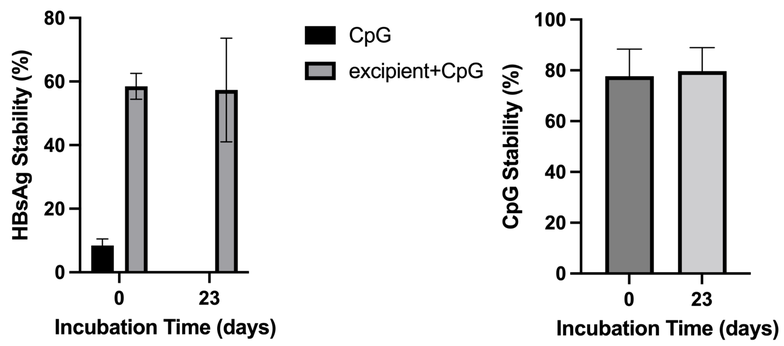
- The release profile is dictated by the polymer used to fabricate the microparticles.

***In Vitro* Release Mechanism**



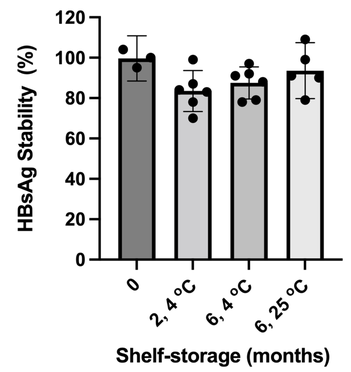
- PLGA cap swells due to hydration and eventually bursts releasing the cargo in pulsatile manner.

HBsAg and CpG stability *in vitro*



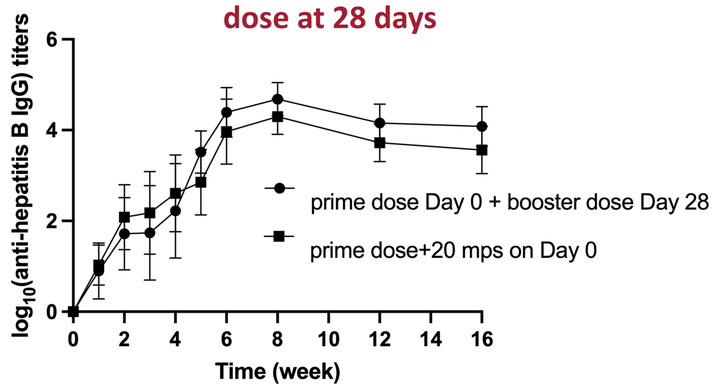
- Excipients are necessary to stabilize vaccine in the presence of CpG.
- Hep B antigen retains 60 % of its stability after incubation for 23 days at 37 °C, pH 7.4.
- CpG retains 78 % of its stability after incubation for 23 days, at 37 °C, pH 7.4.

Microparticles shelf-life



- Hep B antigen encapsulated in PLGA microparticles retains 90 % stability for at least 6-month storage at 4 °C and 25 °C.

Log10 anti-Hep B titers produced after prime and booster dose at 28 days



- Prime dose and 20 microparticles loaded with excipients blend, HBsAg and CpG adjuvant (4.5 μg, 0.15 and 11.2 μg per particle) were injected subcutaneously in mice on day 0 and the produced antibodies were comparable to fresh prime and booster dose administered with 28-day interval.

Acknowledgements

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References

[1]McHugh KJ et al. Science.2017;357, 1138–1142
[2]Shweitzer A. The Lancet. 2015; 386(10003), 1546-1555
[3]Lee GH et al. Expert Rev Vaccines. 2021;20(5):487-495