

# CONTROLLED, PULSATILE RELEASE OF THERMOSTABILIZED INACTIVATED POLIO VACCINE FROM PLGA-BASED MICROSPHERES

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Many vaccines, such as the inactivated polio vaccine (IPV), must be administered in several doses for full efficacy. Because patient access is a major challenge for vaccination efforts in developing countries, administering multiple doses per patient is impractical in those areas. Single-administration vaccines would greatly improve efforts to vaccinate populations in Third World countries, and the World Health Organization (WHO) Expanded Program for Immunization describes an ideal vaccine as one that is heat-stable, requires only one shot, and is easy to administer. Although already existing technologies, such as microspheres composed of poly(lactic-co-glycolic acid) (PLGA), are able to encapsulate vaccines and release them over an extended period of time up to several weeks, they are not able to maintain antigen stability over the longer time intervals *in vivo*. Vaccines such as IPV, however, are known to be unstable at elevated temperature, such as the 37°C environment of the body, as well as in the acidic environment of the degrading PLGA microspheres.

We identified excipients that stabilize IPV at elevated temperature over time as well as against other stresses that the vaccine would face during encapsulation in PLGA microspheres. We then showed that PLGA-based microsphere formulations can co-encapsulate IPV along with stabilizing excipients and release D-antigen active IPV over the course of weeks *in vitro*. The pH-sensitive material Eudragit E PO was doped into the microsphere formulation and controlled the PLGA degradation rate in a concentration-dependent, easily tailored manner while also protecting IPV from acid damage. The best formulations released IPV in two separate bursts, with the total release equivalent to two standard clinical doses (Figure 1), mimicking the delivery of two boluses approximately one month apart.

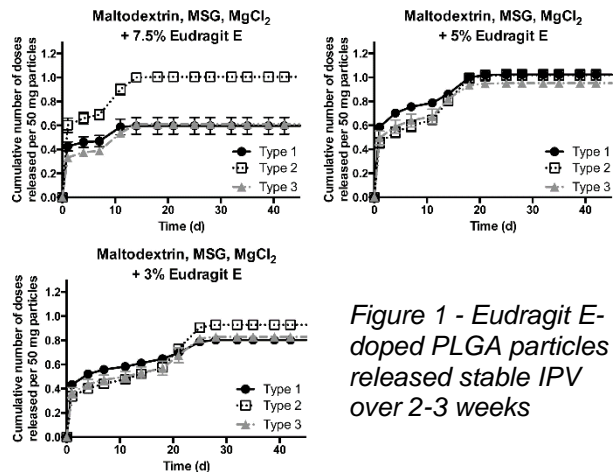


Figure 1 - Eudragit E-doped PLGA particles released stable IPV over 2-3 weeks

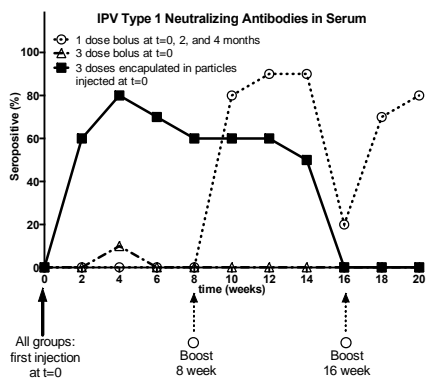


Figure 2 - Encapsulated IPV elicits a more robust neutralizing response than a bolus of IPV.

Leading formulations from the *in vitro* release studies were administered intramuscularly (IM) to rats, and antibody titers were measured over time. A single bolus was not sufficient to generate any measurable neutralizing antibody response against poliovirus serotype 1, the least stable of the three serotypes, and only with multiple bolus doses spread over 2-4 months did we detect protective levels of antibodies in the animals, with a peak of 90% protection (Figure 2). In contrast, only one injection of IPV encapsulated in microspheres was enough for 80% seroprotection within 4 weeks. In addition, while protective levels after bolus IPV injections fall to 20% within 8 weeks of the last administration, encapsulated IPV required only a single administration and conferred protection of >50% for at least 14 weeks. By reducing the number of necessary administrations to elicit a more long-lasting and robust protective response, this technology could be a tool to aid in the eradication of polio and could serve as a platform technology applicable to other infectious diseases for the improvement of global health.