**Methods:** Prompt a mucosal immune response. Small intestine for uptake by M cells of Peyer’s Patches to PNPs enable transport of a depot of nanoparticles to the system is a Polyanhydride-Releasing Oral Microparticle formulation and antigen release kinetics. Be included during microgel synthesis to optimize vaccine protection in a noninvasive manner. Subunit vaccines by eliciting both mucosal and systemic immune upon traditional injection-based administration strategies by elicits both mucosal and systemic immune protection in a noninvasive manner. Subunit vaccines (e.g. protein antigens) can improve vaccine safety. However, they are often poorly immunogenic, requiring adjuvants to achieve protection. In order to effectively induce immunity, an oral vaccine must overcome the challenges of maintaining antigen stability in the harsh conditions of the gastrointestinal tract, including acidic pH and proteolytic enzymes in the stomach, to reach the antigen-sampling cells of the small intestine. As a solution, we propose combining the unique properties of two promising biomaterial platforms into a solution for vaccination with protein antigens. First, the use of pH-responsive hydrogel enables safe transport of an antigenic payload through the stomach and delivery into the small intestine. Second, polyanhydride nanoparticles (PNPs) with tunable polymer chemistry possess innate adjuvant properties that enable a modulated immune response and tailored antigen release kinetics, as well as activation of antigen presenting cells in a pathogen-mimicking manner. PNPs serve as both a delivery vehicle for protein antigens and adjuvant to direct immune response. The proposed system is a Polyanhydride-Releasing Oral Microparticle Technology (PROMPT), in which microencapsulation of PNPs enable transport of a depot of nanoparticles to the small intestine for uptake by M cells of Peyer’s Patches to prompt a mucosal immune response.

**Results:** Hydrolysis: Mass loss of hydrogels with varying crosslinking density demonstrates hydrogel degradation is tunable by modifying DMHA crosslinking density, and is confirmed by turbidity measurement. P(MAA-g-EG) gels degrade more rapidly than P(MAA-co-NVP) counterparts. Enzymolysis: Peptide-crosslinked P(MAA-co-NVP) microgels selectively degrade in intestinal conditions (trypsin, intestinal fluid isolated from rats) within hours. Turbidity remains constant in gastric fluid. PNPs have been successfully incorporated into both systems, and are readily taken up by macrophages.

**Conclusions:** In this study, pH-responsive hydrogels were adapted to incorporate two biodegradable crosslinking strategies and optimized for delivery of nanoparticles. Degradation studies indicate therapeutic release at physiologically relevant conditions, and in vitro assessment indicates no cytotoxicity and substantial internalization, indicating PROMPT has potential as an adaptable platform for oral vaccine administration.

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