Design of a Polyanhydride-Releasing Oral MicroParticle Technology (PROMPT) for Oral Vaccine Delivery

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Statement of Purpose: Vaccines administered via injection result in robust systemic immune response but no mucosal immunity. Mucosal tissues serve as a first line of defense. As such, they are the route of access for the majority of viral or bacterial pathogens of infectious diseases. Oral vaccination has the potential to stimulate both systemic and mucosal immunity, generating protection via both cellular (T cell) and humoral (B cell) immune responses.[1] Additionally, oral administration specifically addresses shortcomings of mass-vaccination in developing nations that pose a higher risk of pathogen exposure, improving ease of distribution, administration, and safety via elimination of needle-prick injuries. Anionic hydrogel microparticles based on pH-sensitive poly(methacrylic acid-grafted polyethylene glycol), P(MAA-g-EG), have been successfully used for oral delivery of therapeutic proteins (e.g., insulin) due to pH-sensitivity that results in protein protection in the stomach and release in the small intestine.[2] Modification of the P(MAA-g-EG) system with a biodegradable crosslinker allows for release of larger encapsulated agents, such as polyanhydride (PA) nanoadjuvants. PAs, specifically the copolymer of poly(1,6-bis-(*p*-carboxyphenoxy)hexane (CPH) and poly(1,8-bis(p-carboxyphenoxy)-3,6-dioxaoctane) (CPTEG) provide significant advantages for vaccine delivery. Tunable polymer chemistry generates 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.[3] This work focuses on development and optimization of a Polyanhydride-Releasing Oral MicroParticle Technology (**PROMPT**) platform, combining the two biomaterial-based technologies, for a potential solution to achieving single dose oral vaccines.

Methods: *Hydrogel Synthesis.* The network used in this work is P(MAA-g-EG), comprised of a poly(methacrylic acid) backbone and grafted poly(ethylene glycol) tethers. Microparticles were synthesized by UV-initiated free radical solution polymerization of PEG monomethylether monomethacrylate (PEGMMA), MAA, and dimethacryloyl hydroxylamine (DMHA) crosslinking agent, with Irgacure® 184 photoinitiator.[2] DMHA is a biodegradable crosslinker, stable at pH<5 and hydrolytically cleavable in an alkaline environment, coinciding with particle swelling in the small intestine. Films were made with varying crosslinking density to allow temporal control of nanoparticle release, while varying the amount of nanoparticles incorporated into the monomer mixture will ultimately allow differing payloads to be delivered to tailor dosage. For preliminary studies, PA nanoparticles containing quantum dots were incorporated into the monomer mixture for encapsulation during polymerization. After purification, the polymer film was dried and then crushed into microparticle carriers 75-90μm in size. *PROMPT Characterization*. Degradation studies were performed to determine hydrogel behavior at gastric and intestinal pH conditions on both a macroscale, using discs from polymer film, and microscale, using laser diffraction. Percent incorporation and subsequent release of nanoparticles from the P(MAA-g-EG) was verified and assessed by fluorescence microscopy and intensity measurements, respectively.

Results: Microscale assessment of degradation by laser diffraction indicates partial degradation in PBS buffer (pH 7.4) within 6 hours (Figure 1C), indicated by reduced light transmission and a broader distribution of small particles in comparison to measurements taken upon initial exposure PBS buffer (Figure 1A). Macroscale studies with blank discs (6mm diameter, no PA nanoparticles – Figures 1B,D) demonstrated that gels remained stable for several weeks at acidic pH. Hydrogels discs with greater crosslinking density degraded more rapidly, as assessed by visual inspection. Hydrogels with 2% crosslinker degraded completely within 18 hours, while their 1.5% counterparts did not.

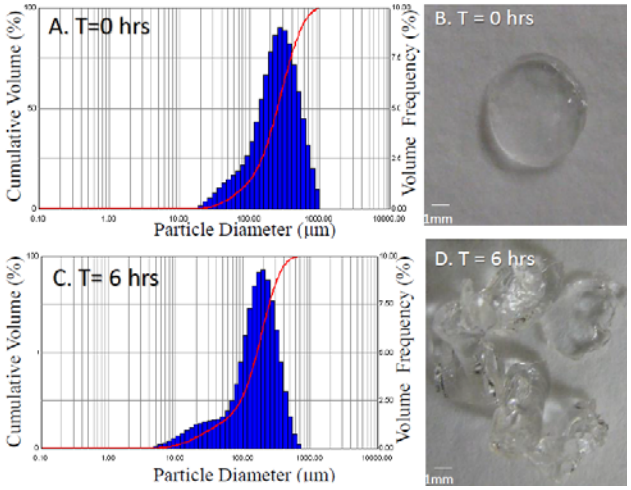

Figure 1. Degradation studies of P(MAA-g-EG) with 2% DMHA microparticles by laser diffraction (A, C) and discs by visual inspection (B, D)

Conclusions: In this study, P(MAA-g-EG) hydrogels were adapted to incorporate a biodegradable crosslinker and optimized for delivery of nanoparticles. Degradation studies indicate therapeutic release at physiologically relevant pH, with tunable rate by varying crosslinking density. These studies indicate PROMPT has potential as an adaptable platform for oral vaccine administration.

References: This work was supported by a grant from the National Institutes of Health (5-R01-EB-000246-20) and the Fletcher S. Pratt Foundation. [1]Russel-Jones. *J. Controlled Release,* 2000; 65: 49-54. [2]Besheer A. et al. *J. Controlled Release*, 2006; 11: 73-80. [3]Ulery B. et al. *Sci Rep.* 2011, 1-9