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Development of an Oral Polymersome Formulation for Ammonia Detoxification

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Introduction: In hepatic encephalopathy (HE), a highly prevalent complication in patients with liver cirrhosis, systemic ammonia levels are chronically elevated due to a reduced hepatic ammonia clearance, which can lead to potentially life-threatening neuropsychiatric symptoms [1]. As systemic ammonia mainly originates from bacterial urease activity in the gut, sequestering gut ammonia is a promising strategy to reduce systemic ammonia levels [1]. Recently, we developed a transmembrane pH-gradient liposome formulation for peritoneal dialysis which selectively sequestered ammonia in the peritoneum and decreased systemic ammonia levels [2,3]. Due to its invasiveness, this treatment is reserved for acute hyperammonemic crises.
Aim: We aim to develop an oral ammonia-sequestering formulation based on transmembrane pH-gradient vesicles for use in chronic hyperammonemia. These vesicles should exhibit excellent stability in the harsh environment encountered in the gastro-intestinal (GI) tract (bile slats, variable osmolarity, digestive enzymes [4]).
Methods: Polymersomes made of diblock copolymers with a low or a high glass transition temperature (LGT and HGT, respectively) were prepared with an emulsification-based method in acidic buffer, yielding vesicles with an acidic core. Highly stable PEGylated liposomes composed the unsaturated lipid 1,2-distearoyl-*sn*-glycero-3-phosphocholine and a high cholesterol content (~45 mol%) were prepared by film rehydration in acidic buffer. The polymersomes and liposomes were exposed to ammonia-containing GI tract-simulating media with high bile salt concentrations at pH 6.8 and compared in terms of ammonia uptake capacity. The ammonia uptake capacity of HGT polymersomes was further assessed in severely hypo- and hyperosmolar bile salt-containing solutions and in intestinal enzyme-containing buffer (trypsin and alpha-chymotrypsin each at 1 mg/mL, lipase 3 mg/mL). Finally, the HGT polymersomes were incubated in a buffer containing the caecal content from healthy rats.
Results: While transmembrane pH-gradient liposomes and LGT polymersomes efficiently captured ammonia in phosphate buffer after 6 h (860.8 ± 2.4 µM and 260.2 ± 5.3, respectively), their capture capacity was reduced in a cholate- and deoxycholate-containing (each at 25 mM) solution (135.2 ± 26.8 µM and 7.4 ± 3.6, resp.). In contrast, HGT polymersomes sequestered ammonia in bile salt concentrations largely exceeding those found under physiological conditions (307.3 ± 52.4 µM, cholate, deoxycholate, and taurocholate, each at 30 mM), at extreme hypo- (283.5 ± 76.9 µM, 160 mOsmol/kg) and hyperosmolal conditions (331.5 ± 27.1 µM, 620 mOsmol/kg) after 24 h, and in pancreatin-containing simulated intestinal fluid (361.4 ± 41.6 µM) after 4 h. Upon incubation in buffered caecal fluid for 6 h, the HGT polymersomes showed a similar uptake capacity as in simple buffers.
Conclusion: We developed a transmembrane pH-gradient-based HGT polymersome formulation which strongly sequesters ammonia in simulated GI fluids. LGT polymersomes and liposomes, on the other hand, were not stable in bile salt-containing solutions. These findings underline that the HGT polymersome formulation warrants preclinical testing in bile duct-ligated rats, an animal model of hyperammonemia.

Keywords: Polymersomes, liposomes, gastrointestinal tract, hyperammonemia, liver cirrhosis

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