Gamma Irradiation-Controlled Burst Release Of Curcumin From Chitosan to Counteract Radiation Damage

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Statement of Purpose: A major challenge to enabling long-range space travel is the threat of astronaut exposure to ionizing radiation leading to debilitating cell and tissue damage. It is therefore desirable to develop new drug delivery strategies that can distribute therapuetic agents to counter the effects of ionizing radiation in a dose dependent manner using radiation exposure levels to determine the effective dose of agent provided to the astronaut. Curcumin, a major component of turmeric powder, is a potent antioxidant and pharmacon against the deleterious effects of ionizing radiation exposure. Curcumin mitigates radiation effects such as DNA damage and oxidative stress by directly counteracting reactive oxygen species (ROS) produced *in vivo* via ionizing radiation exposure, and also triggers signaling pathways to facilitate DNA repair mechanisms. Clinical use of curcumin, however, has been limited due to poor aqueous solubility and limited bioavailability. In order to create a radiation-controlled curcumin release system, curcumin has been covalently tethered to chitosan polymer, Figure 1, and spray dried to produce hybrid curcumin-chitosan particles. The release of curcumin from the particles with differing doses of gamma radiation has been characterized.

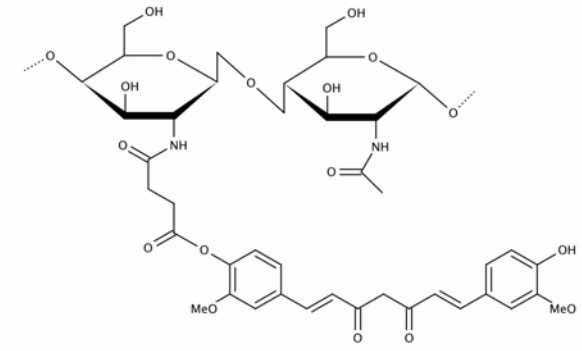

Figure 2. Curcumin covalently bound to chitosan.

Methods: Chitosan 90/200 was purchased from Heppe Medical Chitosan, GmbH (Halle, Germany). Curcumin, ascorbic acid, glutaric anhydride, 4-dimethylaminopyridine (DMAP), triethylamine, *N*-hydroxysulfosuccinimide (sulfo-NHS), 1-Ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC), diethylether, and polyethylene glycol sorbitan monolaurate (Tween 20), were purchased from Sigma Aldrich (St. Louis, MO, USA) and used as received unless otherwise noted. Curcumin was modified according with a pendant carboxylic acid tether according to published protocols[1] and conjugated to chitosan at 1% molar ratio using standard EDC/sulfo-NHS amide bond-forming chemistry. Sub-micron chitosan-curcumin particles were produced using a Buchi B-90 Nanospray dryer. A solution of 0.05 w/v% curcumin-chitosan polymer (CCP) and 0.025% Tween 20 was placed on a mixing plate overnight before spray-drying. Spray dryer inlet temperature: 120°C; internal pressure: 45 hPa; Spray mesh: 4 µm. These parameters were previously determined in an optimization study[2]. Dry particles were collected from the collecting drum using a particle scraper and stored at 4°C. CCP was irradiated in a Gammacell 40 Cesium Irradiator (Nordion, Ottawa, ON, Canada). Release studies were conducted by extracting an aqueous solution of CCP fortified with 1% ascorbic acid as preservative with ethyl acetate to extract released curcumin. The ethyl acetate layer was fortified with 0.1% BHT. Curcumin concentration was measured using UV-visible spectroscopy at 420 nm and compared to known standards.

Results: Pure unmodified CCP released curcumin over a period of 19 days and maintained a concentration of 0.23 ± 0.12 µM curcumin/mg polymer/mL solution based on 1% curcumin loading on the polymer. Spray dried particles of CCP (Diameter = 330 ± 114 nm) released only minute traces of curcumin over 2 days, after which release was undetectable. Exposing CCP particles to varying doses of gamma irradiation caused accelerated release of curcumin for CCP particles in a dose-dependent manner, Figure 2. Curcumin release from the chitosan polymer was found to increase linearly with radiation doses between 0 and 3 Gy.

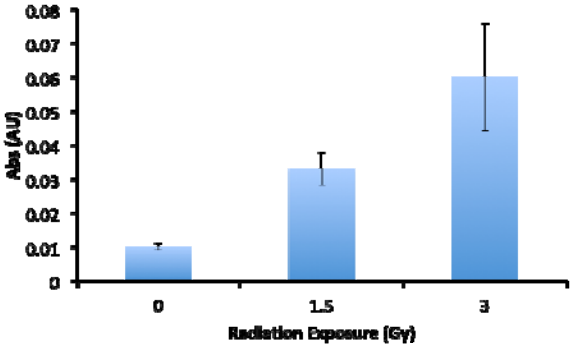

Figure 1: Curcumin release from chitosan after radiation exposure

Conclusions: Accelerated release of covalently bound curcumin from a chitosan scaffold upon gamma irradiation was found to occur in a radiation-dose dependent manner. This offers a promising approach to protect astronauts from cosmic radiation-induced injuries with a drug delivery mechanism that holds the active agent in reserve and introduces medication only when needed to counteract radiation damage.

References:

1. Shi, et. al. *Org. Lett.*, **2007**, 9(26), 5461-5464.
2. O'Toole, et. al., *Biomacromolecules*, **2012**, 13 (8), 2309-2314.