

AN INTRA-PERITONEAL DELIVERY OF NANOCAPSULE LOADED HYDROGEL TO TREAT ADVANCED OVARIAN CANCER

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Background: The standard treatment for ovarian cancer (OC) is cytoreductive surgery, performed either in between or followed by intravenous. The difficulty in excising all the disease leads to recurrence in many patients. Hence, there is an urgent need for treatment options that can remove microscopic or macroscopic disease effectively. Poor tolerability limits the usage of many therapies for OC. However, loco-regional delivery is being used for the therapeutic index improvement. Nevertheless, intraperitoneal (IP) chemotherapy has not yet been widely adopted for OC treatment due to the risk of local toxicity, catheter-associated infections, bowel perforations and obstructions, and lack of products specifically approved. Nanoparticles (NPs) have been investigated for IP delivery of chemotherapeutics because of their potential to offer higher tumour penetration. However, in general, NPs are rapidly cleared from the peritoneal cavity. Hence, to maximise this NPs loco-regional effect, we have proposed the incorporation of nanocapsules (NCs) within a hydrogel for IP delivery and to provide a more sustained release profile. The first part of this work involves the NCs formulation optimization and incorporation of paclitaxel (PCX), a first-line drug for OC and the focus herein. The second part will be the development and evaluation of a cross-linked polyethylene glycol (PEG) NCs loaded hydrogel for IP drug delivery, for use at the point of surgical resection, and will be the focus of future studies.

Methods: Polymeric NCs were prepared with hyaluronic acid 40 KDa (HA), Tween[®] 80, Cremophor[®] RH 40 and Labrafac in an ethanolic solution by a self-emulsifying method. The physico-chemical properties and stability were characterized in terms of size (Z-Ave) and polydispersity index (PDI), by Dynamic Light scattering (DLS), and zeta potential (ZP), by Laser Doppler Electrophoresis. The NC formulation optimization was supported by Design of Experiments (DoE) to obtain monodisperse and stable NCs around 400-600 nm. Blank NCs were prepared, stored at 2-8 °C and in physiological conditions (37 °C) and then their stability evaluated after 6 days (size, PDI and ZP). After NCs optimization, PCX was encapsulated in the NCs (PCX-NCs).

Results: The DoE screening showed a major influence of the oil Labrafac on the size, PDI and ZP. Blank NCs were optimized to a proportion of 20:10:20 (% w/w) of Tween[®] 80, Cremophor[®] RH 40 and Labrafac, respectively. These NCs gave a size, PDI and ZP of 357 ± 8 nm, 0.2 ± 0.01 and -20 ± 0.2 mV, respectively. Furthermore, they were stable for at least 6 days under storage conditions (2-8 °C). Incorporation of PCX into NC (PCX-NCs) presented a slight increase in size to 391 nm, and a PDI and ZP of 0.2 and -18 mV, respectively. The drug loading and encapsulation efficiency are expected to be at least 3 mg/mL and 45%, based on previous data for a drug with similar physicochemical properties to PCX. PCX-NCs will then be loaded in a PEG-based hydrogel, developed by chemical crosslinking of a multi-arm PEG-maleimide (PEG-MAL) with a PEG-dithiol.

Conclusions: The Paclitaxel loaded NCs were optimized by using a DoE approach to a maximum size that is also stable. A larger size will increase the sustained release time course from the hydrogel and reduce clearance from the IP cavity. Future studies will incorporate PCX-NCs into a hydrogel formulation.