Loading and coating of microcontainers for oral drug delivery - DTU Orbit (03/11/2019)

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Oral delivery is the most preferred route of administration of drugs by the patients. When a drug is taken orally, its absorption will occur in the small intestine as it provides a high surface area. For example, low gastric pH, enzymes and mucus layer can have a negative impact on the administered active pharmaceutical compound (API). Excipients, mucoadhesive and enteric coatings, and permeation enhancers are all common strategies to facilitate the delivery of the API. Nevertheless, these approaches are not always enough making necessary the development of new oral drug delivery systems.

Recently, microfabricated devices have been explored as alternative oral drug delivery systems to enhance release and absorption of drugs. One of these systems is microcontainers which are polymeric cylindrical microdevices fabricated in epoxy-based photoresist SU-8. They have an external diameter and height of approximately 300 µm. Contrary to the omni-directional release that is characteristic of loaded formulation tablets, capsules and particulate systems, the unidirectional release provided by microcontainers avoids loss of the API in the lumen.

In this project, the work focused on two main aspects i) loading techniques for enhancing oral delivery of poorly water soluble drugs and ii) coating the cavity of microcontainers in order to functionalize these for increasing the oral absorption of proteins. In order to enhance the release and absorption of poorly soluble drugs, they were loaded into microcontainers with either polyvinylpyrrolidone (PVP) or polycaprolactone (PCL). It has been showed in vitro that the loading technique influences the release of the poorly soluble model drug ketoprofen even when loaded with the same polymer (PCL). In particular, the distribution of the ketoprofen or naproxen loaded into the PVP matrix using supercritical scCO2 (scscCO2) impregnation was evaluated. This was possible using a custom-made Raman system, where volumetric Raman maps of a whole microcontainer were obtained. These analyses showed that the drug was on top of the polymer even when the area exposed to the scscCO2 was changed. Such results confirmed and explained the fast release profiles obtained by in vitro analyses. These studies were followed by in vivo experiments in rats to fully understand the behavior of the microcontainers in vivo. These studies showed an enhanced relative oral bioavailability compared to control samples. For oral protein delivery, microcontainers were loaded with the model protein, lysozyme together with a permeation enhancer (sodium decanoate). The loaded microcontainers were functionalized by applying on their cavity two polymeric coatings. The idea was to enhance the protein delivery and mucoadhesion of the microcontainers. For these reasons, the first coating was poly(lactic-co-glycolic acid) (PLGA) and on top of this either chitosan or polyethylene glycol (PEG) was applied. The functionalization was evaluated in vitro for morphology, drug release and mucoadhesive properties. These were coupled with in vitro and ex vivo studies using cell models and porcine intestinal tissue. This showed that microcontainers can be functionalized with bi-layer lids facilitating tunable protein release as well as improved mucoadhesion of the microcontainers.

In conclusion, techniques for loading microcontainers with poorly water soluble drugs were compared and characterized. Moreover, microcontainers were functionalized for oral delivery of protein. These results showed a promising potential for microcontainers as oral delivery system for poorly soluble drugs and proteins. Further optimization of the microcontainers and their characterization techniques are however still required in order to improve their efficacy and flexibility.

**General information**

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