Cellulose based aerogel microfibers for biomedical applications

Summary

The treatment of wounds, in particular chronic types, is an unresolved challenge due to its complicated healing process, which can adversely impact the patient's quality of life. The design and fabrication of new wound dressing materials with enhanced performance from renewable biobased resources such as cellulose is a continuous demand from healthcare services. Bioaerogels fabricated from biopolymers can simultaneously provide high porosity, low density, large specific surface area, biocompatibility, biodegradability, and the possibility to load and locally release single or multiple drugs and bioactive agents at the wound site. Therefore, they are considered as promising materials to address the limitations of currently existing wound dressings.

In this PhD project, cellulose was used to fabricate aerogel microfibers for biomedical applications of drug delivery and wound dressing. Three main objectives were achieved:

I. Evaluating the effect of the cellulose properties and the preparation conditions on the internal structure of the aerogel and its physicochemical properties.

II. Optimizing and designing the fiber processing conditions and textile fabrication techniques for cellulose aerogel microfibers (CAFs) production.

III. Investigating the feasibility of using cellulose aerogels as advanced biomaterials for the two different applications of drug delivery and wound dressing.

Various cellulose types, dissolving agents, precursor concentration, and the nature of regeneration solvent were indicated to play a vital role in aerogel morphology and properties. Solvent exchange and post-treatment supercritical CO_2 ($scCO_2$) impregnation were investigated for CAFs drug impregnation. When used as drug delivery matrices, the profile and kinetics of drug release were correlated with the textural properties of cellulose aerogels such as specific surface area and pore volume. CAFs were proven to be a promising material for wound dressing application since they were able to uptake large amounts of moist, water, and wound exudate due to their nanoporous texture. Drug-loaded CAFs can be used to control the release of the encapsulated drug to the wound site while enhancing the healing process. Upon cellulose blending with chitosan, the wound dressing also showed bactericidal properties. Overall, a high potential of CAFs to be used as biomaterials with highly tunable properties and functionalities was demonstrated, which is briefly explained in the following summary of the chapters.

In **chapter 1** an introduction on wound healing, wound dressing, and aerogel fabrication with an emphasis on the bioaerogels and the importance of the production of aerogels in the fibrous format has been provided. Furthermore, the chapter has reviewed advances in drug-eluting medical textiles including different fiber production methods, such as melt-, wet-, and electro-spinning, and textile fabrication techniques, such as knitting and weaving. Various loading processes of bioactive agents to obtain drug-loaded fibrous structures with required physicochemical and morphological properties, drug delivery mechanisms, and drug release kinetics were also discussed. Finally, the current applications of drug-eluting textiles in wound care, tissue engineering, and transdermal drug delivery were highlighted. From this chapter, the technical requirements for fiber production and the ultimate biomedical application were finally derived and further developed into the overall concept of the thesis.

Chapter 2 aimed at evaluating the correlations between the initial cellulose characteristics, aerogel's internal structure, and its prospective biomedical application. Wet-spun cellulose aerogel fibers were obtained by $scCO_2$ drying from low and high molecular weight microcrystalline cellulose. The CAFs from high molecular weight cellulose (Mw ~ 565 kg/mol) proved to have a higher surface area (~197 m^2/g), denser structure, and finer nanofibrils (~20 nm) with better thermal stability in comparison with the fibers produced from low molecular weight cellulose (Mw ~ 163 kg/mol). The fibers were nontoxic, and cell proliferation was observed over time. Both low and high molecular weight CAFs showed promising results to be developed further for biomedical applications such as drug delivery and wound care.

In **chapter 3**, CAFs were explored and evaluated as drug delivery systems using three different drug models of methyl blue, rhodamine B, and fluorescein. It was proven that the solvent exchange $scCO_2$ impregnation was an effective single-step techniques for drug loading and aerogel formation. Loaded and non-loaded CAFs proved to have a macro-porous outer shell and a nano-porous inner core with interconnected pore structure and a specific area in the range of 100–180 m^2/g. The CAFs were able to form knitted mesh and needle punched nonwoven textiles. Humidity and water uptake assessments indicated that the fibrous structures were highly moisture absorbable and non-toxic with immediate drug release profiles due to the highly open interconnected porous structure of the fibers. In conclusion, CAFs are propitious to be further developed for biomedical textile applications such as wound care; however, some drawbacks such as immediate drug release profile and not possessing antibacterial properties require additional modifications of the fibers.

Chapter 4 addresses the potential of chitosan-cellulose aerogel fibers (CHCLAF) for the development of antibacterial wound dressings. Wet spun CHCLAF in two ratios of 1:5 and 1:10 have been produced by $scCO_2$ drying for wound dressing application. The fibers were also loaded with ibuprofen through post-treatment $scCO_2$ impregnation. CHCLAF characteristics in terms of morphology, textural properties, thermal stability, mechanical properties, and *in vitro* assessment such as drug release, antibacterial properties, cytotoxicity, and wound exudate uptake were analyzed and compared to pure CAFs. Blended CHCLAF showed a low density (~ 0.2 g/cm^3), high porosity (~ 85%), and large specific surface area (~ 300 m^2/g) with a macro-porous outer shell and a nano-porous inner core. The fibers could be fabricated to braided meshes that were highly water absorbable (~ 400 wt. %) and bactericidal against *escherichia coli* and *staphylococcus aureus*. Furthermore, the fibrous structure was biocompatible with fibroblast cells and was able to release ibuprofen over 48 hours in a sustained manner. The results showed that the CHCLAF have better functionalities compared to the CAFs and thus could be used as a promising antibacterial candidate for wound dressing applications.

In **chapter 5**, solution blowing spinning, an innovative technique for spinning micro-/nano-fibers from polymer solutions, has been combined with $scCO_2$ drying to develop highly porous cellulose aerogel nonwovens (CANs). In order to tune the hydrophobicity and drug release profile of the CANs , the meshes were surface treated through gas-phase esterification with palmitoyl chloride. The nonwoven aerogels benefited from both inter- and intra-fiber porosity, and the majority of the fiber diameters were between 3-9 µm. The CANs possessed a large specific surface area (~ 450 m^2/g), pore volume (~ 3.37 cm^3/g), and high humidity absorption (~ 15 wt. %). The palmitoyl chloride gas-phase reaction enhanced the contact angle drastically (from 0 to ~ 130°) for the surface modified samples and resulted in a more sustained thymol release profile in comparison to the non-modified samples. All samples exhibited cell viability, and the thymol loaded CANs were bactericides against *E. coli* and *S. aureus*. In conclusion, the surface treated CANs loaded with thymol are highly promising materials for wound dressing applications.