

Development and Characterization of Drug Delivery Systems for Oral and Intravaginal Applications

Fabio Tentor, PhD Thesis November 2018



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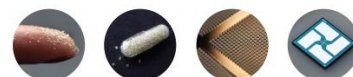
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To my loved ones

To my family,

To my friends,

To my girlfriend

“Everyone sees what you appear to be, few experience what you really are.”

- Niccolò di Bernardo dei Machiavelli -

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Preface

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Abstract

Drug delivery systems are important medical tools that can effectively improve therapeutic outcomes. Establishing new drug delivery systems, to enhance the effectiveness of active pharmaceutical ingredients, is extremely important. It is moreover essential to consider the benefits of using a specific material for providing the drug delivery system with desired properties taking into account the route of administration that has to be used. Among the various routes of administration, the oral one is the preferred by the patients and with the highest compliance. Oral drug delivery is however limited by physiological barriers that determine a reduction in bioavailability. Nowadays, oral administration is performed using tablets and capsules. The interest towards new oral drug delivery systems based on micro-fabricated devices is, however, increasing.

Within the frame of this PhD project, microcontainers were deployed as an alternative oral drug delivery system. Microcontainers have been extensively studied in the past years, some question have, however, yet to be answered.

As a first goal of the PhD project, the addition of a water soluble sacrificial layer, included during the microcontainers fabrication, has been explored to improve the handling of the microcontainers. The compatibility of this layer with the loading and coating of microcontainers was also assessed. The resulting formulation has been tested *in vivo* and *ex vivo*. The effect of tuning the loading method in terms of different release profiles was also assessed. Finally, the 3D distribution of the active pharmaceutical ingredients within the microcontainers was visualized by Raman spectroscopy, evaluating the effect of changing the microcontainers sizes.

A second goal of the PhD project was to develop an intravaginal drug delivery system able to exploit the intravaginal environment for improving the retention time of the formulation. To reach this objective, an AL and CH mucoadhesive and biocompatible membrane was fabricated and tested *in vitro*. The membrane demonstrated to possess good mechanical properties and to slowly degrade in a simulated vaginal medium, remaining intact for up to one month.

The third goal of the PhD project involved the fabrication of polymeric nanoparticles. Polymeric nanoparticles have been extensively studied and used for several applications by many research groups. The focus of this study was to evaluate the possibility of using an ultrasonic spray coater as a novel technique for continuously producing polymeric nanoparticles in a controlled fashion. In this work, the parameters controlling the ultrasonic spray coater were also modulated to elucidate their influence upon the nanoparticles size distribution.

Resumé på Dansk

Drug delivery systemer er vigtige medicinske redskaber der effektivt forbedrer resultatet af medicinske behandlinger. Etableringen af nye drug delivery systemer er vigtig i forhold til at forøge effekten af aktive farmaceutiske ingredienser. Derudover er det essentielt, at overveje hvilke fordele specifikke materialer kan have på drug delivery systemet i forhold til at opnå de ønskede egenskaber og med tanke på administrationsvejen. Af samtlige administrationsveje, er oral indtagelse den fortrukne hos patienter og samtidig den administrationsvej med størst compliance. Oral drug delivery er dog forbundet med fysiologiske barrierer som giver en reduceret biologisk tilgængelighed. For tiden er tabletter og kapsler de fortrukne orale drug delivery systemer, men interessen for nye mikro-fabrikerede enheder er stigende.

I dette PhD projekt testes mikrocontainere som et alternativt oral drug delivery system. Mikrocontainere er blevet udførligt beskrevet de seneste år, men der er stadig ubesvarede spørgsmål.

Det første mål for dette PhD projekt var, at undersøge om tilføjelsen af et vandopløseligt aftageligt lag, under fabrikationen af mikrocontainerne, kunne forbedre håndteringen af mikrocontainerne. Kompatibiliteten med loading og coating af mikrocontainerne blev vurderet. Det endelige design blev testet både in vivo og ex vivo. Effekten af forskellige loading metoder på stofferens release-profiler blev bestemt. Slutteligt blev 3D distributionen af de aktive farmaceutiske ingredienser visualiseret med Raman spektroskopi for at evaluere effekten af varierende mikrocontainer størrelse.

Dernæst var målet at udvikle et intravaginalt drug delivery system, i stand til at udnytte det intravaginale miljø og derigennem forbedre retentionstiden for formuleringen. En alginat og chitosan mucoadhesive og biokompatibel membran blev derfor fabrikeret og testet in vitro. Membranen demonstrerede gode mekaniske egenskaber samt en langsom nedbrydning i et simuleret vaginalt miljø, varende op mod en måned.

Det tredje og sidste mål for dette PhD projekt var fabrikationen af polymeriske nanopartikler. Polymeriske nanopartikler er vel undersøgt og bruges til mange formål af flere forskellige forskningsgrupper. Fokus i dette studie var at evaluere muligheden for brugen af en ultrasonisk spray coater som en ny teknik til kontrolleret kontinuerlig produktion af polymeriske nanopartikler. Derigennem blev de kontrollerende parametre for den ultrasoniske spray coater også moduleret for, at synliggøre parametrenes indflydelse på nanopartiklernes størrelsesfordeling.

Drug delivery is defined as the method used to administer a pharmaceutical to obtain the desired effect. Drug delivery systems represent the carriers the active pharmaceutical ingredient is delivered with. In this project with developed drug delivery systems to be used for oral and intravaginal administration.

In regards of oral delivery, we made use of microcontainers: cylindrical microdevices able to be loaded with a drug formulation and to be protected from the harsh gastric environment. By optimizing our microcontainers-based drug delivery system, the relative oral bioavailability of ketoprofen, chosen as a model drug, was significantly increased in vivo.

As concerns for the intravaginal administration, we developed a polysaccharide based membrane that resulted able to withstand a simulated vaginal environment for one month, improving the intravaginal retention time. Aimed at addressing bacterial vaginosis, the membrane demonstrated viable for killing bacteria such as *Gardnerella vaginalis* and *Staphylococcus aureus* while resulting biocompatible towards a cervix epithelial cell line.

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