Microfluidic Templated Multistage Porous Silicon Based Platform for Enhanced Enteric Cancer Drug Delivery

H. Zhang1*, D. Liu1, M. Shahbazi1, E. Mäkilä2, J. Salonen2, J. Hirvonen1 and H.A. Santos1

1Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Helsinki, FI-00014, Finland; 2Laboratory of Industrial Physics, Department of Physics and Astronomy, University of Turku, FI-20014, Turku, Finland.

hongbo.zhang@helsinki.fi

ABSTRACT
A multistage pH-triggered and mucosadhesive drug delivery system is developed for enteric cancer drug delivery. The undecylenic acid functionalized thermally hydrocarbonized porous silicon nanoparticles (UNCHCPSi-Nano) were covalently conjugated with polyethyleneimine (PEI) and poly(methyl vinyl ether-co-maleic acid) (PMVEMA) and subsequently encapsulated with pH-responsive hydroxypropyl cellulose acetate succinate based polymers (ASHF) by microfluidic flow-focusing device. The fabricated microcomposites (UN-P-P-A) showed monodisperse size distribution, precisely radiometric drug loading degree, pH-responsive drug release profiles, highly mucosadhesion and enhanced drug permeability through Caco-2/HT-29 monolayer.

INTRODUCTION
Droplet-based microfluidic devices are developed to produce nano/microparticles. Polymer solutions or melts are introduced in along with immiscible carrier phases in different channels and the devices will precisely disperse these solutions into equally sized nano/microdroplets, subsequently the droplets can be solidified and become solid, monodisperse nano/microparticles.1

Porous silicon (PSi) has been intensively investigated in drug delivery applications. These materials are biocompatible and they can be used as promising vehicle for imaging and cancer therapy. PSi-based materials can be chemically modified with functional groups, such as –COOH in UNTHCPSi.2

Herein, we conjugated UNTHCPSi with PEI and PMVEMA polymers, which have potential on mucosadhesion, and then applied droplet-based microfluidic techniques to encapsulate the modified particles with pH-responsive enteric coating to fabricate an advanced drug delivery system for lower intestinal and colonic cancer drug delivery.

EXPERIMENTAL METHODS
PEI and PMVEMA were conjugated to UNTHCPSi NPs with a two round EDC/NHS chemical reaction to form UN-P-P.3

The UN-P-P was subsequently encapsulated with ASHF, in a flow focusing microfluidic chip with oil in water (O/W) emulsions. The inner fluid contained 5-FU loaded UN-P-P, ASHF and celecoxib dissolved in ethyl acetate (EA) and outer fluid was 2% amphiphilic Poloxamer 407 (P-407, w/v), pH 5.5 (Fig. 1).

Figure 1. Microscopic image of the droplet formation in a microfluidic device.

RESULTS AND DISCUSSIONS
The UNPPA microcomposite showed a clear pH-responsive behavior, maintaining its structural integrity at pH values below 6.5 (Fig. 2A), and dissolving fast at pH 7.4 (Fig. 2B). 5-FU and celecoxib were encapsulated within the microcomposite with no drug release at pH below 6.5 (Fig. 3).

At pH 7.4, the released UNPP from UNPPA showed strong mucosadhesion properties due to the surface modification with PEI and PMVEMA. In addition, the drug permeabilities of both 5-FU and celecoxib were enhanced by the presence of UNPPA (Fig. 4).
Figure 2. Dissolution and drug release profile of UNPPA at different pH-values. (A) SEM images of UNPPA at different pH-values. (B) Confocal of the UNPPA dissolving profile at pH 7.4 by time, the UNPP nanoparticles inside was conjugated with Rhodamine 123 (green) and outer layer ASHF was labeled with TRITC (red).

Figure 3. (A) 5-FU and (B) Celecoxib release profile from UNPPA in continuous pH buffers. Data represent mean ± S.D. (n = 3).

Figure 4. (A) TEM images of the mucosadhesion properties of the released UNPP from UNPPA at pH 7.4 across Caco-2/HT-29 monolayer. (B) Effect on 5-FU and celecoxib permeation across Caco-2/HT-29 monolayer of the UNPPA at pH 7.4. Data represent mean ± S.D.

CONCLUSION

The fabricated UNPPA microcomposite provides promising properties for lower intestinal and colonic cancer drug delivery. The payloads can be efficiently encapsulated and the release profiles can be precisely controlled by pH-responsive polymers. In addition, the microcomposite shows multistage properties, which will release the functional nanoparticles at pH 7.4 and achieve high mucosadhesion and enhanced drug permeability at the targeted sites. Thus, this multistage multifunctional system represents a promising new platform for controlled and targeted oral drug delivery and enhanced gastro-intestinal cancer therapy.

REFERENCES


ACKNOWLEDGMENTS

Financial support from the Academy of Finland (decision numbers 252215 and 256394), the University of Helsinki and the European Research Council under the European Union’s Seventh Framework Programme (FP/2007-2013, Grant No. 310892) are acknowledged.