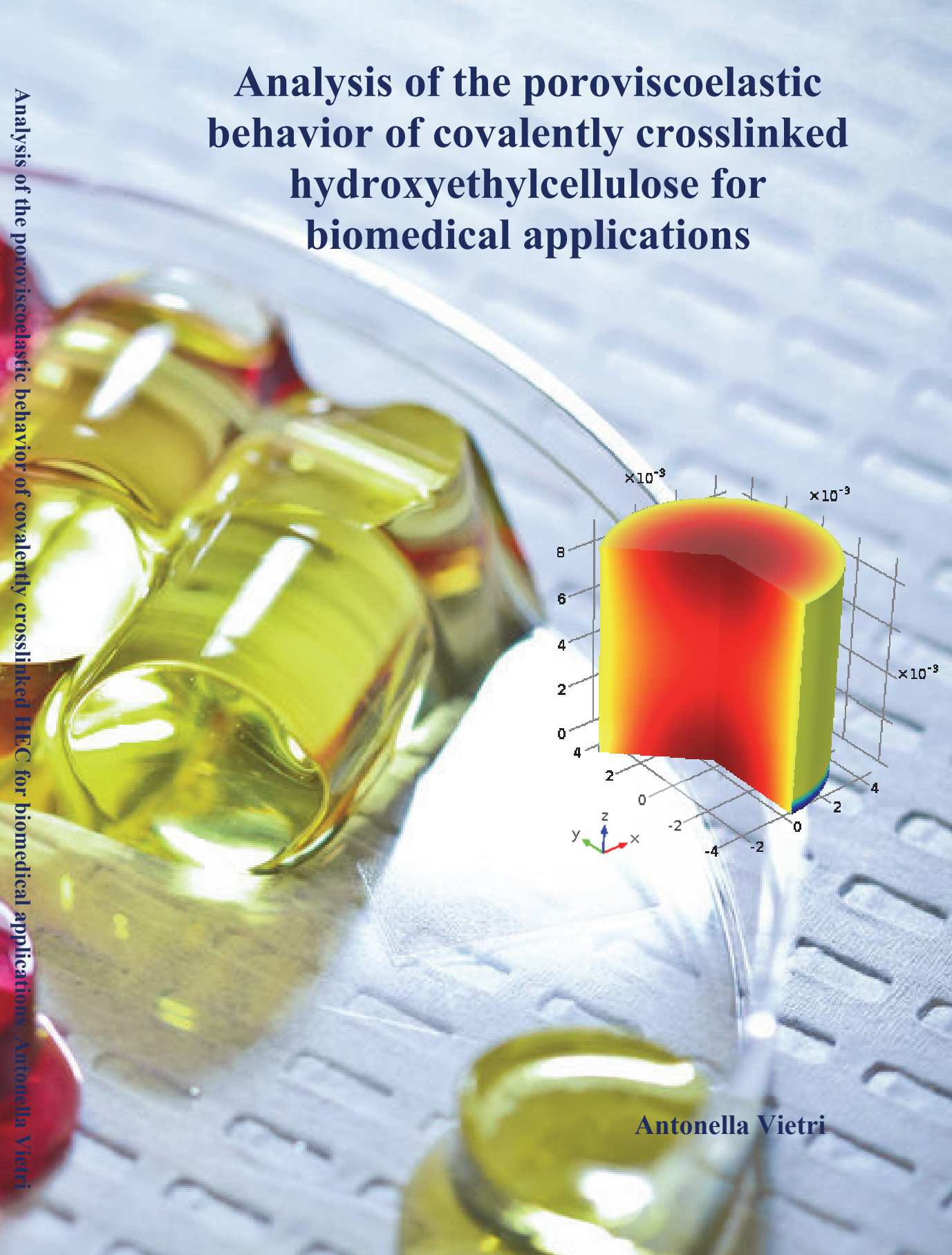
Analysis of the poroviscoelastic behavior of covalently crosslinked hydroxyethylcellulose for biomedical applications



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Analysis of the poroviscoelastic behavior of covalently crosslinked HEC for biomedical applications Antonella Vietri

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Corso di Laurea in Ingegneria Chimica

Analysis of the poroviscoelastic behavior of covalently crosslinked hydroxyethylcellulose for biomedical applications

Tesi in

Fenomeni di trasporto

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Anno Accademico 2016/2017

CHALMERS

Part of this thesis work has been developed during the Erasmus project at Chalmers University of Technology, Göteborg, Sweden. In particular it has been performed at the Department of Chemistry and Chemical engineering, in the Pharmaceutical Technology, under the supervision of Prof. Anette Larsson and Dr. Anna Ström.

CHALMERS

Parte del lavoro di tesi è stata realizzata nell'ambito del progetto Erasmus presso la Chalmers University of Technology, Göteborg, Svezia. In particolare le attività di ricerca sono state svolte presso il Dipartimento di Chimica e Ingegneria Chimica, in Tecnologie Farmaceutiche, sotto la supervisione della Prof.ssa Anette Larsson e della Dott.ssa Anna Ström.

To my parents
Giuseppe and Maria Grazia

Questo testo è stato stampato in proprio, in Times New Roman

La data prevista per la discussione della tesi è il 14 dicembre 2016
Fisciano, 4 dicembre 2016

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Sommario

Gli idrogel sono network polimerici tridimensionali capaci di assorbire elevate quantità di acqua. Essi sono costituiti da lunghe catene polimeriche idrofile interconnesse da punti di reticolazione (*cross-links*), che impediscono la dissoluzione del network. Sono impiegati in diversi campi di applicazione, quali rilascio controllato, ingegneria tissutale ecc. In particolare questo lavoro di tesi è connesso all'utilizzo di idrogel nel trattamento del dolore lombare, dove l'obiettivo è quello di sostituire la parte degradata dei dischi invertebrali, detta "Nucleus Pulposus" con un idrogel.

Al fine di approfondire il comportamento degli idrogel, in questo lavoro è stata effettuata la caratterizzazione meccanica di idrossietilcellulosa (HEC) reticolata chimicamente ed è stato sviluppato, implementato e testato un modello monofasico 3D capace di descrivere la diffusione combinata con la viscoelasticità degli idrogel (comportamento poroviscoelastico).

L'HEC è stata reticolata con Divinilsolfone (DVS) attraverso una reazione di Michael. Sono stati realizzati e testati gel con tre diversi rapporti massici HEC/DVS (2:1, 4:1, 10:1). Le proprietà meccaniche dei gel a base di idrossietilcellulosa sono state determinate attraverso test di *stress-relaxation* e *frequency sweep*.

Il modello matematico è stato sviluppato nel campo della meccanica dei solidi non lineare, considerando il gel come un materiale iper-viscoelastico, dove le equazioni costitutive possono essere derivate dall'energia libera di Helmholtz del sistema. Quest'ultima è stata considerata come la somma del contributo elastico del network (basato sulla teoria del modello affine) e sul contributo di *mixing* (basato sulla teoria di Flory-Huggins). Il bilancio di massa relativo all'acqua, il bilancio di quantità di moto relativo all'idrogel combinato con un vincolo volumetrico sono state riformulate nella forma debole

(*weak form*) 2D-assialsimmetrica e implementate nel software COMSOL Multiphysics 5.0.

Dal test di frequency sweep è stato visto che lo *storage modulus*, G' era indipendente dalla frequenza e sempre maggiore del *loss modulus* G'', per tutti i rapporti HEC/DVS utilizzati. Questo ha dimostrato un comportamento prevalentemente elastico e poco viscoso dei gel a base di idrossietilcellulosa. Il modulo di rilassamento G(t) è stato ottenuto da G' e G'' e poi confrontato con il valore di G(t) ottenuto usando un modello SLS (*Standard Linear Solid model*), al fine di ricavare valori di primo tentativo di G_1, G_2 e τ per inizializzare la procedura di ottimizzazione all'interno del modello poroviscoelastico.

Test non confinati sono stati eseguiti per un tempo di 600 secondi fissato il diametro dei gel (9.5 mm) al fine di valutare l'effetto di differenti quantità di reticolante, e per tempi più lunghi (10000 secondi), per un dato rapporto HEC/DVS (2:1), allo scopo di ricavare una stima dell'effetto di diversi diametri dei campioni (d=5, 12, e 20 mm). I risultati hanno mostrato che aumentando il grado di reticolazione dell'HEC, lo stress raggiunge valori più elevati (per una determinata deformazione). Per i test di lunga durata, le curve di *stress-relaxation* sono risultate inizialmente indipendenti dal diametro dei campioni mentre si sono distinte per tempi più lunghi, confermando che il rilassamento di gel a base di HEC è dovuto alla viscoelasticità intrinseca del network polimerico nella prima fase e alla migrazione di solvente nella fase finale degli esperimenti.

I test confinati sono stati effettuati per un tempo di 600 secondi, su gel di diametro pari a 9.5 mm variando il rapporto HEC/DVS, e anche su gel di differente diametro (9.5 e 5 mm) per un determinato grado di reticolazione dell'HEC (HEC/DVS = 2:1). L'andamento ottenuto è risultato simile alla compressione non confinata: aumentando la quantità di reticolante utilizzata, anche lo stress registrato è più elevato, per una data deformazione. Inoltre lo stress è risultato indipendente dal diametro del campione assumendo valori simili per ambedue le dimensioni analizzate. Tuttavia, i risultati confinati non sono discostati da quelli confinati in modo pronunciato.

Per quanto riguarda i risultati modellistici, la procedura di ottimizzazione è stata eseguita sui test a breve termine al fine di determinare i moduli elastici G_1, G_2 e il tempo di rilassamento τ. Una stimati questi parametri, il modello è stato capace di predire il comportamento dei gel per diversi valori di deformazione applicata.

Nel caso di test a lungo termine, uno studio parametrico sulla diffusività D_1 è stato eseguito in modo da descrivere il rilassamento poroelastico. L'ordine di grandezza del coefficiente di diffusione ottenuto dallo *sweep* parametrico che meglio prevedeva il rilascio di acqua e il rilassamento del sistema è risultato pari a $1 \times 10^{-6} m^2/s$. Le predizioni del modello per gli esperimenti confinati non sono state soddisfacenti, tuttavia hanno sottolineato l'importanza della cinetica del trasporto di acqua sul comportamento di *stress-relaxation*.

Abstract

Hydrogels are three-dimensional polymeric network capable of absorb large amount of water. They are composed of long hydrophilic polymer chains interconnected by cross-links, which prevent the network dissolution. They are used in several frontier fields, such as in drug delivery applications, tissue engineering applications, etc. In particular this thesis is connected to the use of hydrogels for the treatment of low back pain, where the purpose is to replace degraded "Nucleus Pulposus" with a hydrogel.

With the aim of further investigate the hydrogels' behavior, in this work the mechanical characterization of covalently crosslinked HydroxyEthylCellulose (HEC) was carried out and a 3D monophasic model capable of describing the diffusion coupled with the viscoelasticity of hydrogels (poroviscoelastic behavior) was developed, implemented and tested.

The HEC was crosslinked by the Divinyl Sulfone (DVS) according to a Michael addition reaction. Gels with three different HEC/DVS weight ratios (2:1, 4:1 and 10:1) were produced and tested. The mechanical properties of the HEC gels were determined through stress relaxation tests and frequency sweeps.

The mathematical model was developed within the field of nonlinear solid mechanics, considering the gel as a hyper viscoelastic material where the constitutive equations could be derived from the system Helmholtz free energy. This last was derived as the sum of the network elastic contribution (based on the affine network model) and the mixing contribution (based on the Flory-Huggins theory). The water mass balance and the hydrogel linear momentum balance, coupled with a volumetric constraint were recast in the 2D-axisymmetric weak form and implemented in COMSOL Multiphysics 5.0.

The frequency sweep test gave frequency independent storage moduli G' and always greater than the loss moduli G'', for all the three HEC/DVS ratios. This demonstrated a predominant elastic character and low viscous properties of the prepared HEC gels. The linear relaxation modulus G(t) was derived from G' and G'' and then compared to the value of G(t) obtained by using a Standard Linear Solid model (SLS) in order to get the starting values of G_1, G_2 and τ to initialize the optimization procedure into the poroviscoelastic model.

Unconfined tests were performed in a short time range (600 seconds), on gels of a given diameter (9.5 mm) in order to evaluate the effect of different amount of crosslinker, and in a long time range (10000 seconds), on gels of a given HEC/DVS ratio (2:1), in order to estimate the effect of different diameters of the samples (d= 5, 12, and 20 mm). The results showed that increasing the degree of crosslinking of the HEC, the stress reaches higher values (for a given strain). In the long time range, the stress relaxation curves resulted to be size independent at the beginning whereas they separated for longer times, confirming that the HEC gels' relaxation was due to the intrinsic viscoelasticity of the network in the first part and due to migration of solvent in last part of the experiments.

The confined experiments were performed for 600 seconds, on gels of a given diameter (9.5 mm) varying the HEC/DVS ratio, and also on different gel's diameters (9.5 and 5 mm) for a fixed degree of crosslinking of the HEC (HEC/DVS = 2:1). The trend was the same of the unconfined compression: the stress increased as the amount of crosslinker used increased, for a fixed strain. In the short time range, the stress for both the diameters assumed similar values and the relaxation recorded, in the case analyzed, was independent of the size of the gel. However, the confined results were not dramatically different from the unconfined ones.

Regarding the modeling results, an optimization procedure was performed on a short time test in order to determine the elastic moduli G_1, G_2 and the relaxation time τ. Once the parameters were estimated the model was able to predict the gel behavior at different strains. For the long time tests, a parametric study on the diffusivity D_1 was carried out in order to describe the poroelastic relaxation. The order of magnitude of the diffusion coefficient obtained from the parametric sweep study that better predicted the water expelled and the system relaxation was $1 \times 10^{-6}\ m^2/s$. The model predictions for the confined

experiments were not satisfying, however they pointed out the importance of the kinetic of water transport on the stress-relaxation behavior.

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Aknowledgements

I could not have written this thesis without all the support and encouragement I've got during this period. So I would like to mention and thank a few people.

First of all, Prof. Anette Larsson, for being more than a Supervisor with me. Your enthusiasm, your devotion to science and your determination inspired me during my experience in Sweden. I will never forget each time you endorsed my ideas and incited me to carry on with my project. Thank you for welcoming me in your group ad for teaching me how important is to collaborate and share the knowledge with other people.

I want to thank Prof. Gaetano Lamberti, for giving me the opportunity to take part in the Erasmus project. It was a long way before I chose to enjoy your group but you have always been helpful in answering my curiosity and dispensing me useful advice. Thank you for providing me a second chance : I have learned a lot from your way of doing research and dealing with new challenges.

I am grateful to Diego for being always present and for supervising my project in Italy and also in Sweden. Your thirst for knowledge and your ambition were the driving force for pursuing my goals, being aware of my limitations and going beyond them. Thanks for your huge patience and for all the debates we had about our loved and hated hydrogels, it was instructive and fun at the same time!

I also want to thank Dr. Anna Ström for answering to my questions and doubts. I loved your enthusiasm, your curiosity and your inquiring mind.

A special thanks goes to all the members of the MasterRoom for giving me the adventure of my life in Sweden. Thank Raphaëlle for helping me the first days in Chalmers, for being always available in the lab when I needed help and for letting me to know new things about France! Thanks to Dominik, the German Boy: with him I discovered a lot of new things about Gothenburg and I got a friend for

life! Finally, I have to express my gratitude to Christer, Johan and Johanna: thanks to you I felt never alone, I knew more about Swedish culture and I tried the Julmust ! Thanks for all the moments that we couldn't stop laughing and thanks Johanna for inviting me to the Spex: It was an honour for me! Tack så mycket !

Thanks to my parents, without your help I would not have lived my experience in Sweden. You supported my during the whole academic path: this thesis is dedicated to you. Thanks to Raffaele, my brother, to share with me the best and worst moments of my life: observe you growing up and taking care of you will always be my task as your sister.

A huge "Grazie" goes to Gaetano: when you say that part of my degree is also thanks to you, you're absolutely right ! Thanks for all the nights you spent by my side, listening to my oral presentations and encouraging me when the tiredness prevailed. Thanks for helping me one year ago, when something really bad upset my life and I almost decided to give up. It's because of you and your endless love if today I'm a stronger person and I'm achieving this important goal.

Finally, I want to thank all my university colleagues and in particular Piera and Martina for all the good moments we spent together and for helping each other in dealing with our exams.

A special thanks to Martina, you were always with me during my adventure in Sweden. Thank you for calling me every time I needed help, for comforting me when I had bad days and for sharing with me all the good things of your life, without envy or ulterior motive.

Antonella Vietri