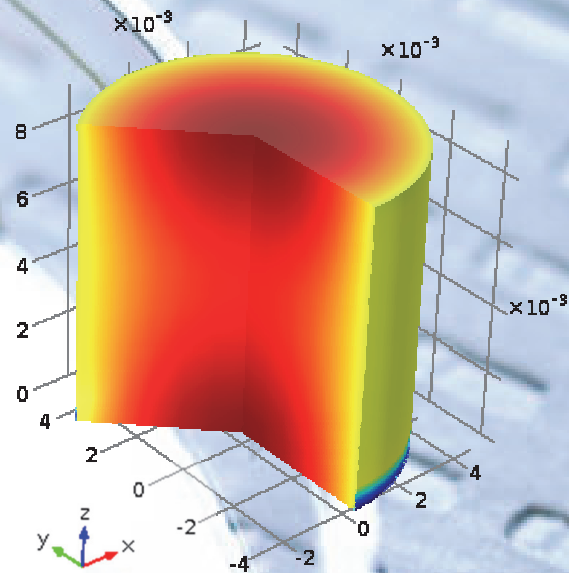


Analysis of the poroviscoelastic behavior of covalently crosslinked hydroxyethylcellulose for biomedical applications



Antonella Vietri



UNIVERSITÀ DEGLI STUDI DI SALERNO

Facoltà di Ingegneria
Dipartimento di Ingegneria Industriale
Corso di Laurea in Ingegneria Chimica

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Relatori:

Prof. Ing. Gaetano Lamberti

Prof. Anette Larsson

Correlatori:

Ing. Diego Caccavo

Dr. Anna Ström

Candidata:

Antonella Vietri

matricola 0622200269

Anno Accademico 2016/2017





CHALMERS

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*To my parents
Giuseppe and Maria Grazia*

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

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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 intervertebrali, 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 $1 \times 10^{-6} \text{m}^2/\text{s}$. 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 ($d= 5, 12, \text{ and } 20 \text{ mm}$). 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 $1 \times 10^{-6} \text{ m}^2/\text{s}$. 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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