化學修飾雙性幾丁聚醣衍生物及其持水特性研究

學生：林怡伶　　　　　　　　　　　　　指導教授：陳三元博士

國立交通大學材料科學與工程研究所

中文摘要

幾丁聚醣只能溶解在稀酸水溶液中，故本論文中希望化學改質幾丁聚醣進而改善其溶解性與增加應用性，得到可完全溶在中性純水中的幾丁聚醣衍生物。利用在幾丁聚醣上的羥基與胺基接上親水性羧甲基酸(carboxymethyl)，得到可完全溶在中性純水中的 N，O-carboxymethyl chitosan (NOCC)。為了能夠包覆雙性藥物達到控制藥物釋放效果，所以我們在 NOCC 上殘留的胺基接枝上疏水性己醯基，合成出同時具有 hydrophilic/hydrophobic 的水溶性幾丁聚醣衍生物(HNOCC)。此外還另外合成出可完全溶解於 CH_2Cl_2、$CHCl_3$ 等有機溶劑的 O-hexanoyl chitosan 及 N,O-hexanoyl chitosan，可用來包覆高親油性的藥物。

本研究由不同羧甲基酸接枝率(DS)和己醯基接枝率(DH)組成八種兩性衍生物。幾丁聚醣本身具細微結晶區域，由 XRD 知道 NOCC 因 NaOH 及接枝羧甲基酸，會破壞其結晶性；當 HNOCC 因導入己醯基後又稍增加結晶度。由 FTIR-ATR 研究衍生物分子內部的氫鍵強度，推測隨提高羧甲基酸化程度，因為-COOH 產生的 conjugative H-bond 會導致分子間氫鍵增加相對結

構越緊密；但 HNOCC 接枝長碳鏈己醯基後卻會破壞氫鍵強度，撐開分子間間距，因此能有更多氫鍵與水形成鍵結，而提高保濕能力。配合 DSC 掃描濕膜內含鍵結水量，同時進行材料吸濕率、持水率實驗，其中以 HNOCC-3A (DS=0.5，DH=0.441)的保濕能力最好。在膨潤度試驗中，相較幾丁聚醣在中性時分子會緊縮，以 genipin 交聯後 HNOCC 膜的在中性環境下仍有膨潤態。HNOCC 水膠在中性環境下的膨潤度可是 NOCC 的四倍，所以 HNOCC 可說是含水率材料。

另外還以兩性幾丁聚醣衍生物包覆雙性藥物 ibuprofen，進行藥物釋放。發現因 HNOCC 的雙性化學結構可以平衡 IBU 產生的 hydrophilic/ hydrophobic 界面，即 HNOCC 能夠和 IBU 較為互溶，在包覆藥物成膜後也比較無明顯 IBU 結晶現象。HNOCC-3 系列因羧甲基酸接枝率高，所以分子結構較緊密又呈現較高雙性特徵，所以釋放速率是最低的。

水溶性 NOCC 材料被研究已久，兩性幾丁聚醣 HNOCC 則是新開發材料，且仍保有原 NOCC 的 pH 敏感性，HNOCC 又有更加顯著的 pH 敏感，可作為智慧型生醫材料。同時具驚人保水能力，又可完全溶解於中性純水。經過細胞毒性試驗，知道雙性幾丁聚醣是低細胞毒性材料。基於我們上述驗證實驗雙性幾丁聚醣衍生物可以說具有高潛力的生醫材料。

Chemical modified amphiphilic chitosan derivative and moisture-retention ability

Student：Yi-Ling Lin Advisors：Dr. San-Yuan Chen

Department of Materials Science and Engineering

National Chiao Tung University

Abstract

Carboxymethyl-hexanoyl chitosan (HNOCC) amphiphilic hydrogel with excellent water-retention ability and pH-sensitivity were synthesized as a carrier for hydrophilic-hydrophobic bioactive agent. Cytotoxicity, water absorption ability (Ra%), water-retention ability, pH sensitivity and subsequent release behaviors of the carboxymethyl-hexanoyl chitosan hydrogel were investigated in terms of the degree of COOH substitution and hexanoyl substitution. It was found that the absorption ability became more sensitive to humidity change when OH group and NH_2 group were partially substituted by COOH group (NOCC-1). However, Ra% became less sensitive to humidity change as COOH substitution was further increased. On the other hand, water retention ability was decreased when OH group and NH_2 group were substituted by COOH group. As for the influence of hexanoyl substitution on water-absorption and water-retention, due to hexanoyl group substitution could retard the formation of

intermolecular hydrogen bonding, Ra% value at relative humidity of 40% and water-retention ability increased drastically as NOCC was acylated by hexanoyl group. However, as the degree of hexanoyl substitution was further increased over 0.25, water-retention ability was decreased. Moreover, for the samples with the same degree of hexanoyl substitution, the water-retention ability increased with an increasing COOH substitution degree because COOH could provide more water bonding sites. Deswelling kinetics study shows that (M_t/M_o)-$t^{1/2}$ curve of sample HNOCC-2A exhibited two distinct stages. The first stage in the range 0-20 $hr^{1/2}$ fitted Higuchi model, which was associated with the release of free water. The other stage in the range 20-25 $hr^{1/2}$ was probably associated with the release of the water tightly bonded with polymer chain. On the other hand, the (M_t/M_0)-$t^{1/2}$ curve of sample NOCC-2 also fitted Higuchi model with a higher diffusion coefficient compared to sample NOCC-2A.

It was found that ibuprofen encapsulation efficiency was enhanced as parts of amino groups in NOCC were substituted by hexanoyl groups. Additionally, for the sample with medium degree of COOH substitution, the encapsulation efficiency increased with increasing the degree of hexanoyl substitution. However, for the sample with high degree of COOH substitution, hexanoyl group did not affect drug encapsulation efficiency significantly. Moreover, the ibuprofen release study shows that sample HNOCC-2A and HNOCC-2B exhibited a one-stage bursting release behavior. In contrast, the release profile of HNOCC-3A and HNOCC-3B exhibited a two-stage release behavior. Besides, the bursting behavior was more prominent for the sample HNOCC-2A and HNOCC-2B compared to HNOCC-3A and HNOCC-3B, respectively.

In summary, the amphiphilic and pH sensitive hydrogel derived from chitosan is feasible to be employed as amphiphilic carrier to load hydrophilic-hydrophobic drug as injectable drug-loaded implants or as wound dressing material with excellent water-retention ability and pre-designed drug release function for particular therapeutic effect.

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