

# 幾丁聚醣對藥物之影響

易延陵、王三郎;?;耀國

E-mail: 9318452@mail.dyu.edu.tw

## 摘要

本研究主要係以幾丁聚醣探討對於藥物釋放的影響，比較不同的比例，不同造粒製程，不同幾丁聚醣加入方式，進行比較錠劑的溶離試驗(Dissolution Profile)的差異進而可推知於人體內藥物釋放的情形。並了解當有幾丁聚醣存在時，其打錠製程所得參數ex:硬度、厚度、崩散試驗等是否有顯著差異，實驗主題選擇2種藥物分別就其藥物本身訴求進行處方設計，研究在控釋劑型幾丁聚醣能扮演的角色，基於文獻上對於幾丁聚醣能促進藥物吸收的特性，故選擇一般習知的普拿疼(Acetaminophen)止痛藥，期使幾丁聚醣能使其藥物迅速發揮，進而推知在人體內時其會快速解決疼痛病人的苦痛，於體外評估實驗結果(測試Dissolution Profile)其與一般市售的樣品比較，可知不同比例的幾丁聚醣會影響溶出的速率。其實驗處方設計原理是利用幾丁聚醣所佔濃度及Acetaminophen在酸性環境下會使溶解度增加且其幾丁聚醣本身有如崩散劑的性質，因而可得一個預期加速溶出的結果。另選擇一個抗暈車藥(Meclizine HCl)，因一般長途旅遊的旅者，若服用一般止暈藥僅能維持3~4小時，於途中需再服藥，否則旅遊將受暈車影響因其引起身體不適、嘔吐、頭暈等痛苦，故基於幾丁聚醣能有吸水形成膠體的特性，故進行比較不同比例的幾丁聚醣實驗，由其體外溶解試驗結果可知其可使抗暈車藥控制釋放延長，進而可達到存在體內作用的時間。故基於以上結果可知，幾丁聚醣對於不同藥物的訴求及特性時，可經由處方設計將幾丁聚醣的功能發揮適得其所。

關鍵詞：幾丁聚醣；溶離曲線；控制釋放；快速釋放；延遲釋放；乙醯胺酚；鹽酸氯苯& #21537

## 目錄

目錄 封面內頁 簽名頁 授權書.....	iii	中文摘要.....	iii
.....v 英文摘要.....	vii	誌謝.....	vii
.....ix 目錄.....	x	圖目錄.....	x
.....xiii 表目錄.....	xiv	緒論.....	xiv
.....1 第一章 研究目的.....	2	第二章 文獻回顧.....	2
.....3 2.1 幾丁質之開發及分佈.....	3	2.2 幾丁質之簡介.....	3
.....4 2.2.1幾丁質及幾丁聚醣.....	4	2.2.2 幾丁質及幾丁聚醣之結構.....	5
.....7 2.2.3幾丁質及幾丁聚醣之物化特性.....	7	2.2.4 幾丁質物質在生醫材料上的應用.....	9
.....12 2.3 藥物型式.....	12	2.3.1 以幾丁聚醣製成之藥品型式.....	13
.....22 2.3.2 幾丁聚醣的應用.....	20	2.4 藥物釋放控制.....	22
.....24 2.4.1 藥物釋放模式.....	23	2.4.2 幾丁聚醣於藥物釋放控制應用.....	24
.....29 第三章、Chitosan於Acetaminophen控制釋放之應用.....	29	3.1 研究目的.....	29
.....29 3.2 Acetaminophen(乙醯胺酚)物理化學物質.....	29	3.3 實驗使用的儀器.....	31
.....32 3.4 實驗材料明細.....	32	3.5 實驗內容.....	32
.....32 3.5.1 製備方法.....	32	3.5.2 操作步驟.....	33
.....35 3.6 實驗配方.....	35	3.7 打錠結果.....	35
.....35 3.8 成品檢驗方法.....	35	3.9 檢驗項目.....	36
.....51 3.10 結果與討論.....	51	第四章、Chitosan於Meclizine Hydrochloride控制釋放之應用.....	52
.....52 4.1 研究目的.....	52	4.2 Meclizine Hydrochloride物理化學性質.....	52
.....54 4.3 實驗儀器.....	54	4.4 實驗材料.....	55
.....55 4.5 操作步驟.....	56	4.6 實驗配方.....	57
.....58 4.7 打錠結果.....	58	4.8 成品檢驗方法.....	58
.....58 4.9 檢驗項目.....	58	4.10 結果與討論.....	59
.....70 第五章、結論.....	70	參考文獻.....	70
.....71 圖目錄 圖2.1 幾丁質、幾丁聚醣以及纖維素之化學結構.....	6	圖2.2 幾丁質生物體內的排列方式.....	7
.....37 圖3.1 自動溶離試驗器(basket).....	37	圖3.2 自動溶離試驗器(paddle).....	38
.....41 圖3.5自動溶離試驗器(UV).....	41	圖3.6 重量比較表.....	44
.....45 圖3.7 硬度比較表.....	45	圖3.8 厚度比較表.....	46
.....47 圖3.9 崩散比較表.....	47	圖3.10 Acetaminophen在0.1HCl時之溶出比較圖.....	48
.....49 圖3.11 Acetaminophen在pH4.5時之溶出比較圖.....	49	圖3.12 Acetaminophen在pH6.8時之溶出比較圖.....	49

圖.....50	圖4.1重量比較表.....62	圖4.2 硬度比較表.....
.....63	圖4.3厚度比較表.....	圖4.4崩散比較表.....
.....65	圖4.5 Meclizine在0.1HCl時之溶出比較圖.....	圖4.6 Meclizine在pH4.5時之溶出比較圖.....
.....67	圖4.7 Meclizine在pH6.8時之溶出比較圖.....	表目錄 表2.1 來源昆蟲甲殼類真菌軟體動物.....
.....8	表2.2 全世界每年所能回收的幾丁質潛在量.....	表3.1 處方比較表.....
.....42	表3.2 重量厚度硬度崩散比較表.....	表4.1 處方比較表.....
.....60	表4.2 重量厚度硬度崩散比較表.....	61

## 參考文獻

1. 97.Zhao, F., Y. Yin, W. W. Lu, J. C. Leong, W. Zhang, M. Zhan王三郎(2000), 水產資源利用學, 高立圖書公司。
2. 王三郎(1998), 應用微生物學, 高立圖書出版社。
3. 王三郎(1999), 海洋未利用生物資源之回收再利用-幾丁質及幾丁聚醣, 生物資源 生物技術, 1:1-8。
4. 王正一、林峰輝(2000), 生醫材料概論, 教育部醫學工程科技教育改進計劃, 台北, 44-45。
5. 王啟浩(1999), 利用細菌發酵農水產廢棄物生產生物製劑之研究.大葉大學食品工程研究所碩士論文。
6. 田福助(1988), 電化學基本原理與應用, 五洲出版社, 台北, 11-20。
7. 生物技術產業資訊叢書(1989), 藥物控制釋放劑型技術與市場分析, 財團法人生物產業資訊叢書。
8. 呂明洲(1994), *Pseudomonas aeruginosa* K-181 所產幾丁質分解酵素之探討.大葉工學院食品工程研究所碩士論文。
9. 李安榮、鄒台黎(2000), 新編藥物學, 永大書局有限公司, 台北, 38。
10. 邱少華(2000), 幾丁聚醣在藥物控制釋放上的應用以及其微膠囊製備的技術, 生物資源 生物技術, 2(3), 19-23。
11. 林佳姘、張曉婷、吳柏昇、林睿哲(2001), 幾丁聚醣於生醫材料之應用與特性, 化工, 48(2), 84-91。
12. 林錫杰(2000), 幾丁質在環保方面之應用, 食品技術, 32(7), 27-33。
13. 林睿哲、莊文喜(2000), 血液相容性高分子生醫材料, 化工技術, 8(10), 230-240。
14. 吳永志、陳松青、林宥欣、梁祥發、糜福龍、宋信文(2003), 水溶性幾丁聚醣酸鹼應答型水膠之製備及其蛋白質藥物包覆與制放行為探討, 第二十六屆高分子研討會。
15. 吳襄、林坤偉(1994), 生理學大綱, 藝軒圖書出版社, 台北, 44-45。
16. 洪敏元、劉良慧、林育娟、何明聰、賴明華(2000), 當代生理學, 華杏出版股份有限公司, 台北, 41-42。
17. 莊仲揚(2002), 幾丁聚醣於生醫產業上的應用, 化工資訊, 16(4), 46-50。
18. 陳美惠、莊淑惠、吳志津(1999), 幾丁聚醣的物化特性, 食品工業月刊, 31(10), 1-6。
19. 陳美惠(2000), 幾丁聚醣之抑菌作用, 食品工業月刊, 32(4), 29-38。
20. 陳慶鴻圖(2000), 幾丁聚醣在藥物運送系統上之應用, 食品工業月刊, 32(4), 18-28。
21. 楊禎明、林浩慈(2001), 含肝素的改質熱可塑性橡膠在血液相容性的研究, 化工, 48(2), 78-83。
22. 張根源(2001), 智慧型料之生物醫學應用, 化工, 48(2), 53-61。
23. 劉興華、陳思萍(1996), 簡明藥物學, 華杏出版社, 台北, 11-12。
24. 蘇遠志(2001), 幾丁質與幾丁聚醣之機能及其有效利用, 生物資源 生物技術, 3(2), 6-19。
25. 闕山璋(1998), 淺談骨科生醫材料之展望, 工業材料, 4(136), 81-84。
26. Akbuga J. and Durmaz, G.(1994) Preparation and evaluation of crosslinked chitosan microspheres containing furosemide. *Int. J. Pharm.* 100: 257-261.
27. Akbuga J. and Durmaz, G.(1994) Preparation and evaluation of crosslinked chitosan microspheres containing furosemide. *Int. J. Pharm.* 111: 217-222.
28. Allan, G. G.(1985) US patent No. 4,532,267. Vision correction lens made from an aminopolysaccharide compound or an ether or ester thereof. Board of Regents, University of Washington, Seat-tle, Washington.
29. Araki, Y. and Ito, E.(1975) A pathway of chitosan formation in *Mucor rouxii*. Enzymatic deacetylation of chitin. *Eur. J. Biochem.* 56:669-674.
30. Biagini, G., Muzzarelli, R. A. A., Giardino, R., and Castaldini, C. (1992) Biological materials for wound healing. In "Advance in chitin and chitosan". Brine. C. J., Sandford, P. A., and Zikakis, J. P. (eds.). p16-24. Eisevier Applied Science. London and New York.
31. Borah, G., Scott, G. and Wortham, K.(1992) Bone induction by chitosan in endochondral Bones of the extremities. In "Advance in chitin and chitosan". Brine, C. J., Sandford, P. A. and Zikakis, J. P. (eds.), p47-53. Eisevier Applied Science, London and New York.
32. Brine, C. J.(1989) Controlled release pharmaceutical applications of chitosan. In "Chitin and Chitosan". Skjak-Braek, G., Anthonsen, T. and Sandford, P. (eds.), p679-691. Eisevier Applied Science. London and New York.
33. Calvo, P., R.L. Carmen, L. V. J. Jose, and J. A. Maria (1997), Chitosan and Chitosan/Ethylene Oxide-Propylene Oxide Block Copolymer Nanoparticles as Novel Carriers for Proteins and Vaccines, Plenum Publishing Corporation, 14 431-1436.
34. Calvo-Mendze, C. and Ruiz-Herrera, J.(1987) Biosynthesis of chitosan in membrane fraction from *Mucor rouxii* by the concerted action of chitin synthetase and a particulate deacetylase. *Exp. Mycol.* 11:123-140.
35. Chandy, T. and Sharma, C. P.(1992) Chitosan beads and granules for oral sustained delivery of nifedipine: in vitro studies. *Biomaterials.* 13: 949-952.
36. Chandy, T. and Sharma, C. P.(1993) Chitosan matrix for oral sustained delivery of ampicillin. *Biomaterials.* 14: 939-944.
37. Collinge, D. B., Kragh, K. M., Mikkslesen, J. D., Nielsen, K. K., Rasmussen, U. and vad, K. (1993) Plant Chitinase. *J. Plant.* 3:31-40
38. Corrood D. A. and Tom, R. A. (1978) Bioconversion of shellfish chitin waste : process conception and selection of microorganism. *J. Food Sci .*, 43: 1158-1164.
39. Cosio, I. G., Fisher, R. A. and Carrood , D. A. (1982) Bioconversion of shellfish chitin waste: waste pretreatment , enzyme production, process design , and economic analysis. *J. Food Sci .*, 47: 901-905.
40. Eicin, Y. M. Dixit, V., Lewin, K., and Gitnick. G. (1999) Xenotransplantation of fetal porcine hepatocytes in rats using a tissue engineering approach. *Artificial Organs* 23:146-152.
41. Eicin, Y. M.. Dixit, V., Lewin, K., and Gitnick. G. (1999) Xenotransplantation of fetal porcine hepatocytes in rats using a tissue engineering approach. *Artificial Organs* 23:146-152
1999. Xenotransplantation of fetal porcine hepatocytes in rats using a tissue engineering approach. *Artificial Organs* 23:146-152.
42. Eser Elcin, A., Elcin, Y. M., and Pappas. G. D.(1998) Neural tissue engineering: adrenal chromaffin cell attachment and viability on chitosan scaffolds. *Neurological Research* 20:648-654.
43. Felt, O., Furrer, P., mayer, J. M., Plazonner, B., Buri, P., and Gurny, R. (1999) Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention. *International J. Pharmaceutics.* 180:185-193.
44. FRANK S , G. J *Pharm Sci*, (1975), 64(10):1585.
45. Ganza-Gonzalez, A., Anguiano-Igea, S., Otero-Espinar, F. J., and Blanco Mendez, J.(1999) Chitosan and Chondroitin microspheres for

oral-administration controlled release of metoclopramide. *European J. Pharmaceutics & Biopharmaceutics*. 48:149-155. 46. Harada, A., Higashiyama, S., Muranaka H., and Kawase, M. (1997) Effectiveness of fructose-modified Chitosan as a scaffold for hepatocyte. *Biological & Pharmaceutical Bulletin* 20:1290-1294. 47. Hari, P. R., Chandy, T., and Sharma, C. P. (1996) Chitosan/calcium alginate microcapsules for intestinal delivery of nitrofurantoin. *J. Microencapsul.* 13:319-329. 48. Hou, W. M., Miyazaki, S., Takada, M., and Komai T. (1985) Sustained release of indomethacin from chitosan granules. *Chem. Pharm. Bull.* 33:3986-3992. 49. Jumaa, M., and Muller, B. W. (1999) Physicochemical properties of chitosan-lipid emulsions and their stability *International J. Pharmaceutics* 183:175-184. 50. Kawase, M., Michibayashi, N., Nakashima, N., Yagi, K., and Mizoguchi, T. (1997) Application of glutaraldehyde-crosslinked chitosan as a scaffold for hepatocyte attachment. *Biological & Pharmaceutical Bulletin* 20:708-710. 51. Kawashima, Y., Handa, T., Kasai, A., Takenaka, H., and Lin, S. Y. 1985a. The effects of thickness and hardness of the coating film on the drug release rate of theophylline granules coated with chitosan-sodium tripolyphosphate complex. *Chem. Pharm. Bull.* 33:2469-2474. 52. Kawashima, Y., Lin, S. Y., Kasai, A., Handa, T., and Takenaka, H. (1985b) Preparation of a prolonged release tablet of aspirin with chitosan. *Chem. Pharm. Bull.* 33:2107-2113. 53. Kawashima, Y., Yamamoto, H., Takeuchi, H., and Kuno, Y. (2000) Mucoadhesive DL-lactide/glycolide copolymer nanospheres coated with chitosan to improve oral delivery of calcitonin. *Pharm. Dev. Technol.* 5:77-85. 54. Khor, E., and Y. L. Lee (2003), Implantable application of chitin and chitosan, *Biomaterial*, 24, 2339-2349. 55. Kifune, K. (1992) Clinical application of chitin artificial skin (Beschitin W). In *Advances in chitin and chitosan*. Brine, C. J., Sandford, P. A. and Zikakis, J. P. (eds.), p9-13. Elsevier Applied Science, London and New York. 56. Klokkevold, P. R., Vandemark, L., Kenny, E. B., and Bernard, G. W. (1996) Osteogenesis enhanced by chitosan (poly-N-acetylglucosaminoglycan) *In vitro*. *J. Periodontology* 67:1170-1175. 57. Knapczyk, J. (1993) Chitosan hydrogel as a base for semisolid drug forms. *Int. J. Pharm.* 93:233-237. 58. Kratz, G., Arnander, C., Swedenborg, J., Back, M., Falk, C., Gouda, I., and Larm, O. (1997) Heparin-chitosan complexes stimulate wound healing in human skin. *Scandinavian J. Plastic & Reconstructive Surgery & hand Surgery*. 31:119-123. 59. Kratz, G., back, M., Arnander, C., and Larm, O. (1998) Immobilized heparin accelerates the healing of human wounds *in vivo*. *Scandinavian J. Plastic & Reconstructive Surgery & Hand-Surgery* 32:381-385. 60. Kuang, Y., Hou, C., and Gou, S. (1998) Experimental study of the effect on growth of Schwann cell from chitin and chitosan *in vitro*. *Chung-Kuo Hsiu Fu Chung Chien Wai Ko Tsa Chih/Chinese J. Reparative & Reconstructive Surgery* 12:90-93. 61. Kurita, K. (1998), Chemistry and Application of chitin and chitosan, *Polymer Degradation and Stability*, 59, 117-120. 62. LACH JL and PAULI W A, *J Pharm Sci*, (1966), 55(1):32-38. 63. Lee, J. Y., S. H. Nam, S. Y. Im, Y. J. Park, Y. M. Lee, Y. J. Seol, C. P. Chung, and S. J. Lee (2002), Enhanced bone formation by controlled growth factor delivery from chitosan-based biomaterials, *Journal of Controlled Release*, 78, 187-197. 64. Leroix, L., Hatim, Z., Freche, M., and Lacout, J. L. (1999) Effects of various adjuvants (lactic acid, glycerol, and chitosan) on the injectability of a calcium phosphate cement. *Bone* 25 (2Suppl) : 31 S —34S. 65. Markey, M. L., Bowman, L. M., and Bergamini, M. V. W. (1992) Contact lenses made of chitosan. In " *Advance in chitin and chitosan* ". Brine, C. J., Sandford, P. A. and Zikakis, J. P. (eds.), p713-717. Elsevier Applied Science, London and New York. 66. Meyer, S. P., and Chen H. M. 1985. Process for the utilization of shellfish waste. U. S. Patent 4, 505,936. 67. Lorenzo, L. M. L., R. L. Carmen, L. V. J. Jose, and J. A. Maria (1998), Design of microencapsulated chitosan microspheres for colonic drug delivery, *Journal of Controlled Release*, 52, 109-118. 68. Liu, L. S., Liu, S. Q., Ng, S. Y., Froix, M., Ohno, T., and Heller, J. (1997) Controlled release of interleukin-2 for tumor immunotherapy using alginate/chitosan porous microspheres. *J. Control. Rel.* 43: 65-74. 69. Macleod, G. S., Fell, J. T., Collett, J. H., Sharma, H. L., and Smith, A. M. (1999) Selective drug delivery to the colon using pectin: chitosan: hydroxypropyl methylcellulose film coated tablets. *Int. J. Pharm.* 187: 251-257. 70. Majeti, N. V., and R. Kumar (2000), The review of chitin and chitosan applications, *Reactive & Function Polymers*, 46, 1-27. 71. Mi, F. L., S. S. Shyu, Y. B. Wu, S. T. Lee, J. Y. Shyong, and R. N. Huang (2001), Fabrication and characterization of a spong-like asymmetric chitosan membrane as a wound dressing, *Biomaterial*, 22, 165-173. 72. Mi, F. L., Y. B. Wu, S. S. Shyu, A. C. Chao, J. Y. Lai, and C. C. Su (2002), Asymmetric chitosan membrane prepared by dry/wet phase separation: a new type of wound dressing for controlled antibacterial release, *Journal of Membrane Science*, 212, 237-254. 73. Mi, F. L., Wong, T. B., and Shyu, S. S. (1997) Sustained-release of oxytetracycline from chitosan microspheres prepared by interfacial acylation and spray hardening methods. *J. Microencapsulation* 14:577-591. 74. Miwa, A., Ishibe, A., Nakano, M., Yamahira, T., Itai, S., and Kawahara, H. (1998) Development of novel chitosan derivatives as micellar carriers of taxol. *Pharmaceutical Research* 15:1844-1850. 75. Miyazaki, S., Ishii, K., and Nadai, T. (1981) The use of chitin and chitosan as drug carriers. *Chem. Pharm. Bull.* 29:3067-3069. 76. Miyazaki, T., Komuro, T., Yomota, C., and Okada, S. (1990) Usage of chitosan as a Pharmaceutical Material: effectiveness as an additional additive of sodium alginate. *Eisei Shikenjo Hokoku* 108:95-97. 77. Miyazaki, S., Nakayama, A., Oda, M., Takada, M., and Attwood, D. (1994) Chitosan and sodium alginate based bioadhesive tablets for intraoral drug delivery. *Biol. Pharm. Bull.* 17:745-747. 78. Muzzarelli, R. (1992) Role of lysozyme and N-acetyl-β-D-glucosaminidase in the resorption of wound dressings. In " *Advance in chitin and chitosan* ". Brine, C. J., Sandford, P. A. and Zikakis, J. P. (eds.), p25-p33. Elsevier Applied Science, London and New York. 79. Narayani, R. and Panduranga R. K. (1995) pH-Responsive Gelatin Microspheres for Oral Delivery of Anticancer Drug Methotrexate. *J. Appl. Polym. Sci.* 58:1761-1769. 80. Nigalaye, A. G., Adusumilli, P., and Bolton, S. (1990) Investigation of prolonged drug release from matrix formulations of chitosan. *Drug Devel. Ind. Pharm.* 16:449-467. 81. Nishioka, Y., Kyotani, S., Okamura, M., Miyazaki, M., Okazaki, K., Ohnishi, S., Yamamoto, Y., and Ito, K. 1990. Release characteristics of cisplatin chitosan microspheres and effects of containing chitin. *Chem. Pharm. Bull.* 38:2871-2873. 82. Okhamafe, A. O., Amsden, B., Chu, W., and Goosen, M. F. A. (1996) Modulation of protein release from chitosan-alginate microcapsules using the pH-sensitive polymer hydroxypropyl methylcellulose acetate succinate. *J. Microencapsul.* 13:497-508. 83. Park, Y. J., Y. M. Lee, S. N. Park, S. Y. Sheen, C. P. Chung, and S. J. Lee

(2000), Platelet derived growth factor releasing chitosan sponge for periodontal bone regeneration, *Biomaterials*, 21, 153-159. 82.Polk, A., Amsden, B., De Yao, K., Peng, T., and Goosen, F. A.(1994) Controlled release of albumin from chitosan-alginate microcapsules. *J. Pharm. Sci.* 83: 178-185. 83.Ramanathan, S., and L. H. Block(2001), The use of chitosan gels as matrices for electrically-modulated drug delivery, *Journal of Controlled Release*, 70, 109-123. 84.Remunan-Lopez, C. and Bodmeier, R.(1996) Effect of formulation and process variables on the formation of chitosan-gelation coacervates. *Int. J. Pharm.* 135:63-72. 85.Rentel, C. O., Lehr, C. M., Bouwstra, J. A. Luessen, H. L., and Junginger, H.E.(1993)Enhanced peptide absorption by the mucoad- hesive polymers polycarbophil and chitosan. *Proceed Intern. Symp. Control. Rel. Bioact. Mater.* 20:446-447. 86.Ruel, G. E., G. Leclair, P. Hildgen, A, Gupta, J. C. Leroux (2002), Thermosensitive chitosan-based hydrogel containing liposomes for the delivery of hydrophilic molecules,*Journal of Controlled Release* ,82, 373-383. 87.Sawayanagi, Y., Nambu, N., and Nagai, T.(1982a). Directly compressed tablets containing chitin or chitosan in addition to lactose or potato starch.*Chem. Pharm. Bull.* 30:2935-2940. 88.Soane, R. J., M. Frier, A. C. Perkins, N. S. Jones, S. S. Davis, and L. Iium (1999), Evaluation of the clearance characteristics of bioad- hesive systems in humans, *International Journal of Pharmaceutics*, 178, 55-65. 89.Sundararajan V. M., and W. T. M. Howard (1999), Porous chitosan scaffolds for tissue engineering, *Biomaterials*, 20, 1133-1142. 90.Takayama, K., Hirata, M., Machida, Y., Masada, T., Sannac, T., and Nagai, T.(1990) Effect of interpolymer complex formation on bioadhesive property and drug release phenomenon of compressed tablets consisting of chitosan and sodium hyaluronate. *Chem. Pharm. Bull.* 38:1993-1997. 91.Takeuchi, H., Yamamoto, H., Niwa, T. Hino, T., and Kawashima Y. 1996. Enteral absorption of insulin in rats from mucoadhesive chitosan-coated liposomes. *Pharm. Res.*13:896-901. 92.Thanoo, B. C., Sunny, M. C., and Jayakrishnan,A.(1992) Crosslinked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. *J Pharm Pharmacol.* 44:283-286. 93.Tozaki, H., Komoike, J., Tada, C. Maruyama, T., Terabe, A.,Suzuki, T., Yamamoto, A., and Muranishi, S. (1997) Chitosan capsules for colon-specific drug delivery: improvement of insulin absorption from the rat colon. *J. Pharm. Sci.* 86:1016-1021. 94.Upadrashta, S. M., Katikaneni, P. R., and Nuesste, N. O. (1992) Chitosan as a tablets binder. *Drug Devel. Ind. Pharm.* 18:1701-1708. 95.Vandenberg, G. W., C. Drolet, S. L. Scott, and J. D. L. Noue(2001),Factors affecting Protein release from alginate-chitosan coacervate microcapsules during production and gastric/intestinal simulation, *Journal of Controlled Release*,77,297-307. 96.Wang, X, H., W. J. Wang, Q. L. Feng, F. Z. Cui, Y. X. Xu, X. H. Song, and V. D. W. Mark(2003), Crosslinked collagen/chitosan matrix for artificial livers, *Biomaterials* , 24, 3231-3220. g, and K. Yao(2002), Preparation and histological evaluation of biomimetic three-dimensional hydroxyapatite/chitosan-gelatin network composite scaffolds, *Biomaterials*, 23, 3227-3234.