Chitosan-Pectin Composite Gel Spheres: Effect of Some Formulation Variables on Drug Release

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Summary: Chitosan-pectin composite gel spheres were prepared by ionotropic gelation method. Pectin solution containing indomethacin, a model drug, was extruded into a mixture of chitosan and calcium chloride. The release behavior of indomethacin from composite gel spheres was investigated *in-vitro*. The influence of factors affecting release behavior, such as type of pectin, molecular weight of chitosan, cross-linking time and release medium, were discussed in this study. Adding chitosan into gelation medium could retard the release of indomethacin from gel spheres. The different type of pectin used demonstrated slightly different drug release profiles. The higher molecular weight of chitosan showed less indomethacin release than the lower one. The increased cross-linking time slowed the drug release from composite gel spheres. The release of indomethacin from composite gel spheres was also dependent on the release medium. The drug release was slower in tris buffer where no phosphate ions which can induce the precipitation of calcium phosphate. The results suggested that the composite gel spheres of pectin and chitosan could be used as a controlled release drug delivery carrier.

Keywords: chitosan; composite; drug delivery system; gel; pectin; polysaccharides

Introduction

Chitosan is a cationic polysaccharide made from alkaline N-deacetylation of chitin, consists of N-acetylglucosamine and glucosamine residues (Figure 1a). It has biocompatible, biodegradable, nontoxic and mucoadhesive characteristics.[1] Pectin is an anionic polysaccharide that can be used as a carrier for drug delivery to gastrointestinal tract.[2-3] The polymeric chain of pectin contains galacturonic acid and its methyl esters (Figure 1b).

The properties of interpolymeric complex gel beads and films composed of chitosan and pectin have been reported recently.[4-5] The complex formation changed the drug release behavior of

 DOI: 10.1002/masy.200451203

hydrogel beads and modified their swelling behavior of complex particles. However, the effect of factor influencing the release behavior, i.e., type of pectin, molecular weight of chitosan, cross-linking time and release medium, has not been examined in detail. The objective of this study was to investigate the release of indomethacin, a model drug, from composite gel particles made of pectin and chitosan.

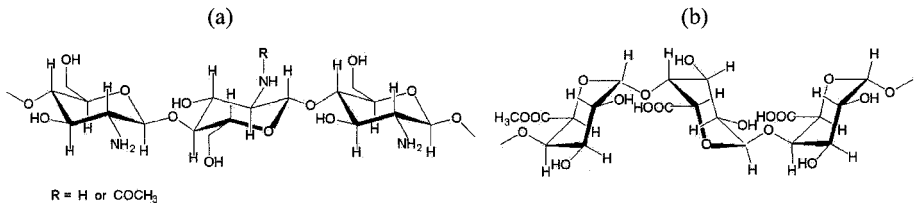

Figure 1. Structure of (a) chitosan and (b) pectin.

Experimental Methods

High (MW 814000) and low (MW 111000) molecular weight chitosans (with degree of N-acetylation of 88% and 95%, respectively) were purchased from Seafresh Chitosan (Lab) Company (Thailand). GENUpectin type LM-101 (degree of esterification, DE 36%) and LM-104 AS-FS (DE 28%) were the generous gift of CP Kelco (Denmark) and are referred to as P36 and P28 respectively. Indomethacin and calcium chloride ($CaCl_2$) were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Pectin gel spheres were prepared by ionotropic gelation method.[2-3] Pectin was dissolved (5% w/w) in water with gentle agitation and indomethacin was dispersed to aqueous solution. The dispersions were dropped using a nozzle of 0.80 mm inner diameter into a 5% (w/v) $CaCl_2$ with gentle agitation. The spheres formed were allowed to stand in the solution for 30 min or 24 h, separated and washed with distilled water, then filtered and dried at 37 °C for 12 h. Pectin-chitosan composite gel spheres were prepared by the same method except the mixture of chitosan (0.2% w/v of C-H or C-L) and $CaCl_2$ (5% w/v) was used instead of $CaCl_2$ alone.

The scanning electron microscope (Model Maxim 2000S, CamScan Analytical, England) equipped with back-scattered electron detector and x-ray detector (Model Econ-4, EDAX, USA)

was used to examine the surface and cross-section of gel spheres. Drug release kinetics from the gel spheres were evaluated using the rotating basket dissolution method (USP dissolution apparatus 1, Erweka, Germany). The baskets were rotated at 100 rpm at 37 °C. The dissolution medium used was pH 7.4 Tris buffer or pH 7.4 phosphate buffer. All dissolution runs were performed in triplicate.

Results and Discussion

Aqueous solution of pectin containing indomethacin was dropped into either $CaCl_2$ solution or chitosan-$CaCl_2$ mixture and gelled spheres were formed instantaneously by ionotropic gelation in which intermolecular cross-links were formed between the divalent calcium ions and the negatively charged carboxyl groups of the pectin molecules. In case of chitosan-$CaCl_2$ mixture was used, the positively charged ammonium groups of chitosan may also interact with carboxyl groups of the pectin molecules.

Back-scattered electron images revealed the more intense calcium signal from calcium pectinate structure, which appeared brighter than drug particles (Figure 2). On the contrary, the image of chitosan-pectin composite gel sphere (Figure 3) did not show difference in color, suggested that the calcium atoms in the pectin chain have been replaced by positively charged atoms of chitosan. The images of composite gel spheres made of different chitosans showed similar results.

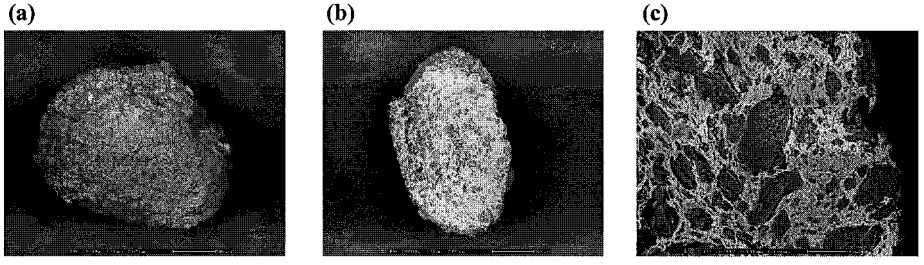

Figure 2. Images of (a) external and (b-c) internal structure of drug-loaded calcium pectinate gel sphere. Magnifications and scale bars are shown on the individual photographs.

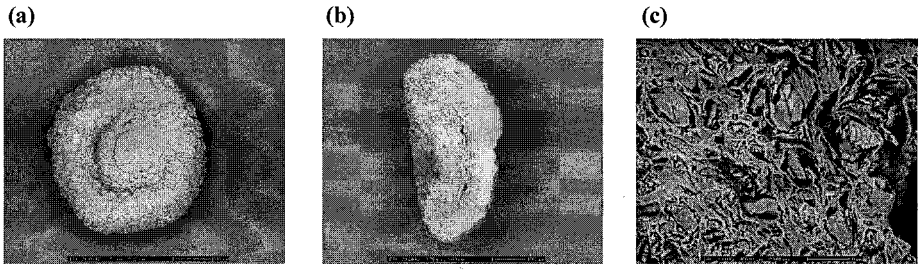

Figure 3. Images of (a) external and (b-c) internal structure of drug-loaded composite gel sphere of chitosan and pectin. Magnifications and scale bars are shown on the individual photographs.

The release behavior of indomethacin from composite gel spheres was investigated *in-vitro*. The influence of factors affecting release behavior, such as type of pectin, molecular weight of chitosan, cross-linking time and release medium, were investigated. Adding chitosan into gelation medium sligthly retarded the release of indomethacin from gel spheres (Figure 4). The different type of pectin used demonstrated different drug release profiles. The lower the DE of pectin showed the slower drug release (Table 1).

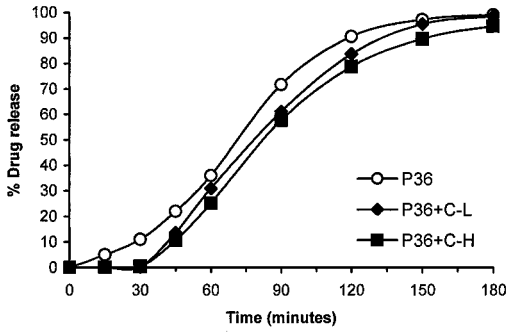

Figure 4. Release (in Tris buffer) of indomethacin from gel spheres. The chitosan used was 0.2% and the cross-linking time was 30 minutes. Note: P36 = calcium pectinate gel spheres using pectin (P36); P36+C-L = composite gel spheres of pectin (P36) and chitosan (low molecular weight); P36+C-H = composite gel spheres of pectin (P36) and chitosan (high molecular weight).

Table 1. Mean percentage of drug release at time of 90 minutes (n=3).

Chitosan	Cross-linking time	pH 7.4 phosphate buffer		pH 7.4 Tris buffer	
		P28	P36	P28	P36
No chitosan	30 min	76.7%	92.9%	25.5%	71.7%
	24 h	80.1%	91.8%	23.2%	45.3%
Chitosan C-L	30 min	60.1%	90.0%	45.5%	61.1%
	24 h	58.2%	80.7%	41.9%	65.6%
Chitosan C-H	30 min	70.6%	90.0%	40.5%	57.6%
	24 h	68.4%	77.5%	32.8%	54.5%

The higher molecular weight of chitosan showed less indomethacin release than the lower one. The increased cross-linking time slowed the drug release from composite gel spheres. The release of indomethacin from composite gel spheres was also dependent on the release medium. The drug release was slower in Tris buffer where no phosphate ions which can induce the precipitation of calcium phosphate. The results suggested that the chitosan-pectin composite gel spheres could be used as controlled release drug delivery carrier.

Acknowledgements

The authors gratefully acknowledge Mr Witoon Sae-Ngow from SUSTREC (Silpakorn University Scientific and Technological Research Equipment Centre) for technical assistance on SEM imaging. Thanks also go to Food & Cosmetic System Co., Ltd. (Thailand) for supplying pectin samples.

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