Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2018, 10(8):161-167

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of Pectin Derivatives by Chain of Carboxylic Acids Esters Using Cross Esterification and Comparing the Pharmaceutical Properties as a Drug Delivery

Mohammad Keshe[1*], Rushdi Madwar[1] and Joumaa Merza[2]

[1]*Department of Chemistry, Faculty of Sciences, Al-Baath University, Homs, Syria*
[2]*Chemistry of Natural Products, Department of Chemistry, Faculty of Science, Al-Baath University, Homs, Syria*

ABSTRACT

In this research, the chemical structure of the pectin was modified by reacted of carboxylic group in pectin with Fatty acid esters to change the hydrophilic properties of pectin by adding alkyl hydrophobic chains. Then, the effectiveness of drug release was studied by loading aspirin to forming beads for both of pectin and modified pectin containing the substance "aspirin" and comparing the time of release between pectin and modified pectin beads. The result showed an increase in the release time of drug substance by increasing the hydrophobic properties of alkylated The structures have been determined by spectroscopic methods: FT-IR, 1H-NMR.

Keywords: Pectin; Cross esterification reaction, Beads; Drug Delivery

---

INTRODUCTION

Pectins are a group of polysaccharides ubiquitously found in plants. They are present in the cell walls located in the middle lamella and primary and secondary cell walls [1]. The chemical structure of pectin is heterogenic, based on the origin, location in the plant, and extraction method, the main residue is galacturonic acid (GalA), α-1,4-glycosidically linked. Beyond this standard structural feature, different pectic structures have been described in the literature: homogalacturonan and rhamnogalacturonan I are the most cited ones. Homogalacturonan is a simple linear α-1,4-linked galacturonic acid polysaccharide, whereas in the backbone of rhamnogalacturonan I the galacturonic acid is partly substitutedwith α-1,2-linked rhamnose, In addition, several side chains containing sugars such as xylose, arabinose, glucose, fucose, mannose, or galactose have been found to be linked to the backbone structure. Pectin (Figure 1) can be furthermore methylesterified on the galacturonic acid carboxylic acid moiety acetyl-esterified at the O2/O3-position, or, less commonly, ferulyl-esterified on side chains Ferulylated pectin has been reported in sugar beet[2] spinach [3] and glasswort [4].

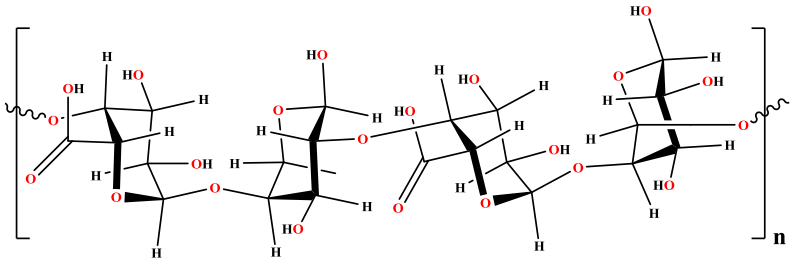


Figure 1: Structure of Pectin

Pectins are a family of complex polysaccharides that contain 1,4-linked α-Dgalactosyluronic residues. Three pectic polysaccharides, homogalacturonan, rhamnogalacturonan-I and substituted galacturonans, have been isolated from primary plant cell walls. Homogalacturonan (HG) is a linear chain of 1,4-linked α-D-galactosyluronic residues, in which some of the carboxyl groups are methyl esterified. They may also be Oacetylated at the C-2 and C-3 positions. Homogalacturonans have been isolated from sunflower heads and apple pectin but were obtained by extraction treatments likely to cleave covalent bonds so they may have been released from a heterogeneous pectic polysaccharide [5], there are hydrophilic polysaccharides derived from plant cell walls. They contain linear chains of (1→4) linked α-Dgalacturonic acid residues [6], these uronic acids have carboxyl groups, some of which are naturally presented as methyl esters. The degree of esterification (DE), which is expressed as a percentage of the esterified carboxyl groups, is an important means to classify pectins.

High methoxy (HM) pectins (with DE >50%) require a relatively high concentration of soluble solids and a low pH for gel formation. Low methoxy (LM) pectins (with DE <50%) form rigid gels by the action of calcium or multivalent cations, which cross-link the galacturonic acid chains [7] the nontoxicity and the low production costs of pectins make them of great interest for the formulation of controlled-release dosage forms [8].

pectin has broad applications in both the food and pharmaceutical industries, where it acts as gelling and thickening agents, prevents the formation of cheesy milk layer in gelled milk dessert, and regulates the thickness and mouth-feel of fruit drink powder when the powder is dissolved in cold water [9]. In addition, pectin has proven to have beneficial effects on human health [10-15].

EXPERIMENTAL SECTION

Apparatus

All materials are commercial reagent grade and were obtained from Merck Co. FT-IR spectra were recorded on a Jasco FT-IR 4100/tybe obtained by KBr disk method using computer-mediated Fourier transformed infrared spectroscopy. 1H NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer and D2O was used as NMR solvent.

Thermogravimetric Analysis (TGA) thermograms were obtained on a Du Pont 910 Thermogravimetric Analysis connected to a DuPont 9900 computer/thermal analyzer (TA Instruments, Delaware, DE). Approximately 9 mg of samples was sealed in the aluminum pan, and measurement was performed at a heating rate of 10°C/min. The temperature was calibrated with pure indium, with a melting point of 156.60°C. An empty pan was used as a reference.

All chemicals including Pectin, octanoic acid, decanoic acid, dodecanoic acid, monopotassium phosphate, tetrabutylammonium hydroxide, Sodium hydroxide and other organic solvents were purchased from Merck Laboratories and were analytical grade materials

Experimental Procedure

First phase: preparation of methyl esters for each of the following acids: "Octaneic acid, Dicanoic acid, Dodecanic acid": In addition, a 100 mL filter with a magnetic motor and an inverted radiator will be added a corresponding amount of acid according to Table 1. Two drops of methan sulfonic acid as a catalyst will be added with stirring for 5 minutes at 70 ° C. after that added about 2ml (ten times) of the methanol "plays as a solvent and reactive material at once" and then stirred the reaction mixture at 70 ° C with follow the reaction output via TLC. The eraction lasted for four hours. The direct ester product was observed using a (25 % n-hexane: 75% ethylacetate).

Table 1: Quantity of fatty acids to preparation of methyl esters

Entry	Fatty acid	The formula	Waight "gr"	Quantity "mol"
1	Octaneic acid	C7H15COOH	1	69 X 10-4
2	Dicanoic acid	C9H19COOH	1	58 X 10-4
3	Dodecanic acid	C11H23COOH	1	50 X 10-4

Second phase: Preparation of Esters Corresponding to Pectin

A. Modification of pectin structure using tetrabutylammonium hydroxide [TBA-OH]: A 100 mL filter with a magnetic motor and an inverted radiator will be added a (0.5gr, 0.0028mol) of pectin and then add 50mL of distilled water with stirring at 40°C. After that, tetrabutyl ammonium (TBA-OH) is added drop by drop with stirring until the decomposition is complete, a bright yellow solution was obtained, in pH ("8-9"). The solution is then extracted using a freezer for 72 hours to obtain a flexible yellow polymer, which is highly soluble in sodium sulfoxide. The weight of the deposit is 1.087gr and the yield 91.73%, substitution degree 67.94%.

B. Preparation of tetra-butyl ammonium pactin esters [Pec-TBA]: In addition to the reaction of the A. phase (0.6 gr, 14.4 X 10-4 mol) of tetbutyl ammonium pectin [Pec-TBA] with stirring and then add 10 ml of potassium carbonate as a catalyest "0.4gr / 10ml" at 70 ° C, for Six hours, and finally the product is separated by 100 ml acetate ethyl acetate and then filtered and washed several times. The product is purified by re-dissolving it in methanol "about 5ml" and deposited with ethyl acetate to remove the effects of reaction. The product is filtered and dried under vacuum at 40 ° C for 24 hours.

Finally the product added to the a 100 mL filter with a magnetic motor containing 10 mL water and then add potassium carbonate 0.1N drop by drop until the decomposition is complete, The solution is then extracted using a freezer for 72 hours to obtain the product, The yield and the substitution degree shown in Table 2.

Table 2: The yield and substitution degree of tetra-butyl ammonium pactin esters

Entry	Fatty acid esters	Quantity of tetra-butyl ammonium pactin	The yield %	substitution degree "Ds"
1	C7H15COOCH3	(0.6 gr, 14.4 X 10-4 mol)	78	11.086
2	C9H19COOCH3	(0.6 gr, 14.4 X 10-4 mol)	75	9.084
3	C11H23COOCH3	(0.6 gr, 14.4 X 10-4 mol)	77	4.180

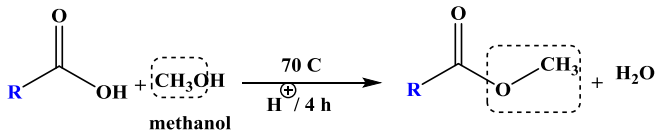
Third phase: Loading the drug substance "aspirin" in the beads of Pectin and pactin esters: A 100 mL filter with a magnetic motor will be added a 0.3gr product and add 10mL of water with stirring for half an hour at 30 ° C. The viscous solution was formed, and then 0.2gr of the aspirin is added with stirring for two hours. The beads were formed with drops by syringe "as shown in Figure 2" in a water solution of 10% W "zinc chloride to be deposited in the shape of the" beads "of the gels were separated from the water solution by filtration washed with distilled water and dried at 40 ° C for 24 hours.

Figure 2: Preparation of beads drops by syringe

Fourth Phase: Study of the release of the drug substance: A 100 mL filter with a magnetic motor will be added a (10) Granules "beads" and then add 50mL of 1N monopotassium phosphate solution with stirring, The concentration of aspirin is measured by measuring the UV-VIS absorption spectra at 234 nm at times of (10, 20, 30, 40, 50, 60, 70, 80, 90, 100) Min.

RESULTS AND DISCUSSION

In the first phase, the esters of octaneic acid, dicanoic acid and dodecanic acid were prepared using methane sulfonic acid as an acid catalyst as shown in Figure 3:



R: C_7H_{15}- , C_9H_{19}- , $C_{11}H_{23}$- .

Figure 3 : Reaction of fatty acids and methanol

The structure of the resulting esters was confirmed using spectroscopy methods and compared with fatty acids, a shift in the absorption value of both the carbonyl and ester groups that of the carbonyl group in the acid is observed as shown in Table 3, indicating the composition of the compound.

Table 3: Amount of absorption bands for carbonyl group and ester groups and their displacements

Entry	Fatty acid esters	Absorption "cm-1"		Fatty acid	Absorption "cm-1"		carbonyl group displacement
1	C7H15COOCH3	CSP3-H C=O C-O	2955 1742 1168	octaneic acid	CSP3-H C=O	2918 1711	31
2	C9H19COOCH3	CSP3-H C=O C-O	2954 1743 1168	dicanoic acid	CSP3-H C=O	2926 1710	33
3	C11H23COOCH3	CSP3-H C=O C-O	2954 1742 1165	dodecanic acid	CSP3-H C=O	2922 1700	42

In the second phase, tetrahybutylammonium pectin was prepared using tetrabutyl ammonium hydroxide according to the following figure (Figure 4):

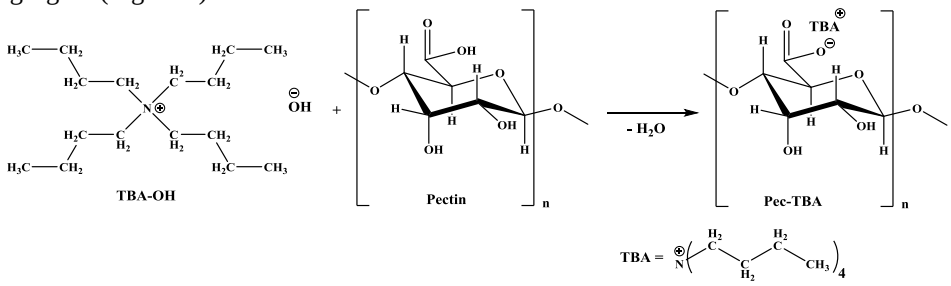


Figure 4: Modification of pectin structure using tetrabutyl ammonium hydroxide

The tetrabutyl ammonium hydroxide compound was added to the water solution of pectin with drip and stirring at 40 ° C where pH ranged from 8-9. Finally, tetrahybutylammonium pectin was separated using a freezer and the structure of the results compound was studied using spectroscopy methods. After that Pectin Ester is prepared by cross esterefication reaction of the fatty acid esters with tetrabutylammonium pectin using potassium carbonate K2CO3 as a catalyst at 70 ° C and 6 hours finally the reaction output is converted from ammonium to sodium form using sodium carbonate, according to the following Figure 5:

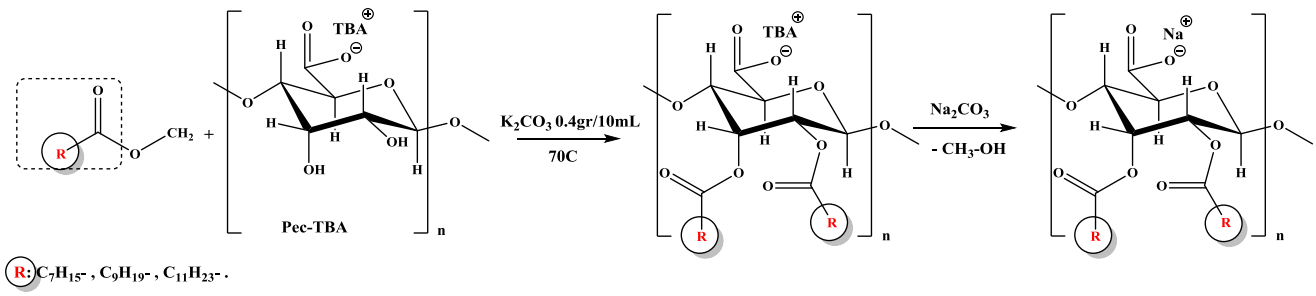


Figure 5: Cross esterefication reaction of tetrabutylammonium pectin using fatty acid esters

The thermodynamic analysis curves "TGA" for pectin and its derivatives were recorded using a weighted thermal analysis device, The thermodynamic analysis curves "TGA" of the prepared compounds were used to determine their thermal stability and compare them with the raw material.

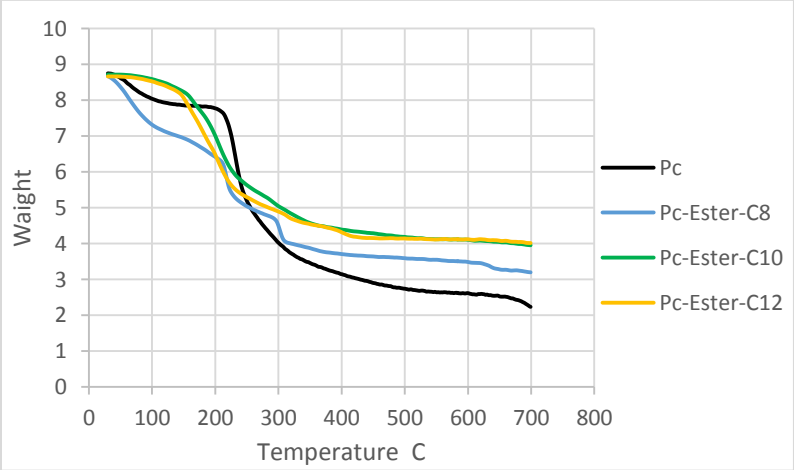


Figure 6: curved quantitative thermal analysis for pectin and its derivatives

Figure 6 shows the curved quantitative thermal analysis of pectin, where three areas for losing weight are shown in this curve. The first area: at a temperature of about 70 °C where the losing weight of the sample about 10% and returns Due to moisture sample. The second area: at a temperature of about 255 °C where a significant loss in the sample weight about 50% corresponds to the disintegration of pectin due to heat. The third area: above 400 ° C, where this degree coincides with the roasting of the compound and its combustion, thus losing the remaining weight of the polymer as shown in Table 4.

Table 4: Thermal aging values of prepared compounds

Entry	compound	Start disintegration temperature	Amount of losing waight %
1	[Pec]	254C˚	50%
2	[Pec -Ester-C8]	217C˚	44.16%
3	[Pec -Ester-C10]	206C˚	54.1%
4	[Pec -Ester-C12]	189.08C˚	42.18%

The effectiveness of drug release was studied by loading aspirin to forming beads for both of pectin and modified pectin containing the substance "aspirin", the beads were formed with drops by syringe in a water solution of 10% W "zinc chloride, the mechanism of placement of drug within the formed beads shown in Figure 7:

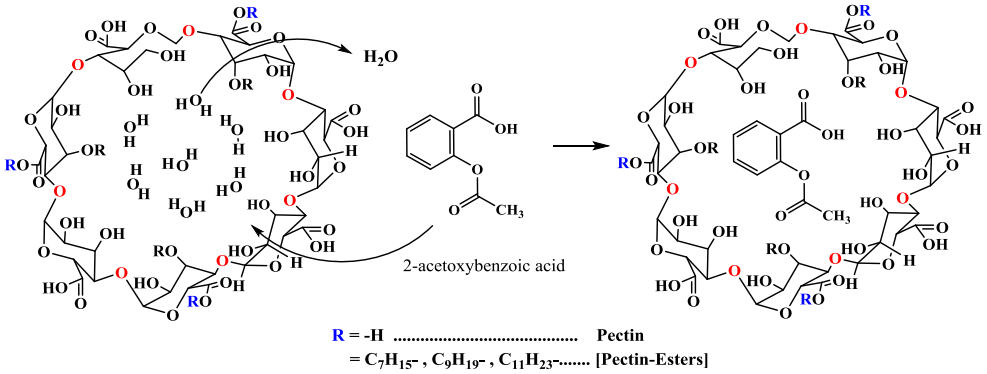


Figure 7: the mechanism of placement of drug within the formed beads

As shown in Figure 8 images beads of pectin and pectin esters after loading the drug "aspirin" and drying.

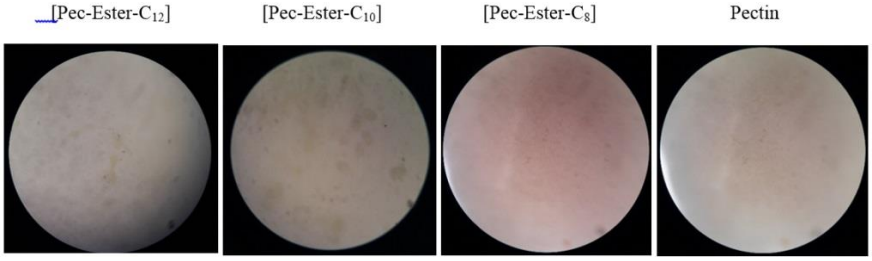


Figure 7: Optical microscopy images of beads after loading and drying of the drug substance

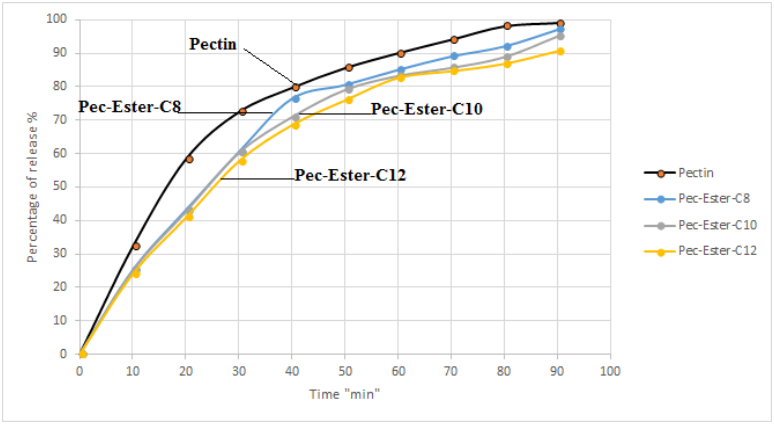


Figure 8: Curved release of the drug substance "Aspirin" In both pectin and pectin esters

Figure 8 shows the release of aspirin in both pectin and pectin esters in terms of time, It is noted from the curves that the drug is released in the modified pectin at a longer time than the pectin. The difference in the release time of the recorded product is due to the effect of the alkyl chains, which impede the penetration of the water molecules between the polymer chains, thus gaining hydrophobic properties. The alkyl chain, which shows the increase in the release time of the drug substance loaded on the modified pectin compared to the raw pectin.

Spectral Data

[Pec-TBA]: was obtained as a solid status. FT-IR spectrum (v, cm^{-1}): 3428 (-OH), 2960 ($C_{SP}{}^3$-H), 1636 (C=O Ester), 1384 (CH_2 Bent), 1106-1024 (Glycoside binding). ^{1}H-NMR (400MHz, D_2O, δ, ppm): 5.25 (m, 1H), 3.20-3.24 (m, 3H), 5.19 (m, 1H), 0.95-0.99 (t, 3H, J^3=8Hz) -CH_3 alkyl, 1.36-1.41 (m, 2H) -CH_2-, 1.66-169 (m, 2H)) -CH_2-, 1.98-1.99 (t, 2H, J^3=4Hz) -CH_2-.

[Pec-Ester-C_8]: (78%) was obtained as a solid status. FT-IR spectrum (v, cm^{-1}): 3421 (-OH), 2924 ($C_{SP}{}^3$-H), 1606 (C=O Ester), 1408 (CH_2 Bent), 1102-1008 (Glycoside binding). ^{1}H-NMR (400MHz, D_2O, δ, ppm): 5.4 (m, 2H),

3.75-3.98 (m, 3H), 2.79 (S, 3H), 0.83-0.86 (t, 3H, J^3=8Hz) -CH_3 alkyl, 1.27 (m, 6H) -C_3H_6-, 1.52-1.53 (m, 2H) -CH_2-, 1.89-1.91 (m, 2H) -CH_2-, 2.13-2.18 (m, 2H) -CH_2-.

[Pec-Ester-C_{10}]: (75%) was obtained as a solid status. FT-IR spectrum (v, cm^{-1}): 3419 (-OH), 2924 ($C_{SP}{}^3$-H), 1636 (C=O Ester), 1405 (CH_2 Bent), 1192-1100 (Glycoside binding). ^{1}H-NMR (400MHz, D_2O, δ, ppm): 5.38 (m, 2H), 3.73-3.97 (m, 3H), 2.75 (S, 3H), 0.79-0.84 (t, 3H, J^3=7.8Hz) -CH_3 alkyl, 1.25 (m, 10H) –C_5H_{10}-, 1.50-1.52 (m, 2H) -CH_2-, 1.86-1.89 (m, 2H) -CH_2-, 2.10-2.15 (m, 2H) -CH_2-.

[Pec-Ester-C_{12}]: (77%) was obtained as a solid status. FT-IR spectrum (v, cm^{-1}): 3438 (-OH), 2925 ($C_{SP}{}^3$-H), 1637 (C=O Ester), 1420 (CH_2 Bent), 1192-1088 (Glycoside binding). ^{1}H-NMR (400MHz, D_2O, δ, ppm): 5.35 (m, 2H), 3.70-3.95 (m, 3H), 2.74 (S, 3H), 0.77-0.88 (t, 3H, J^3=7.6Hz) -CH_3 alkyl, 1.24(m, 12H) –C_7H_{14}-, 1.48-1.50 (m, 2H) -CH_2-, 1.85-1.87 (m, 2H) -CH_2-, 2.08-2.14 (m, 2H) -CH_2-.

CONCLUSION

In conclusion, The chemical structure of the pectin was modified using Simple and efficient method for preparing pectin esters via cross esterification by addition of alkyl hydrophobic chains through reacted with methyl esters of fatty acids then the compounds were characterized using spectral methods, thin The effectiveness of drug release was studied by loading aspirin to forming beads for both of pectin and modified pectin containing the substance "aspirin"

The release time of drug was compared in both pectin and pectin modified it shows that the time was increace with pectin modified, because the alkyl chain impede the penetration of the water molecules between the polymer chains, which shows the increase in the release time of the drug substance loaded on the modified pectin compared to the raw pectin. So it is make preparing compounds a promising pharmaceutical drug in the pharmaceutical chemical industry.

ACKNOWLEDGEMENTS

The authors express their thanks to central organic laboratory in department of chemistry, AL Baath University, faculty of sciences, for their assistance during the work.

REFERENCES

[1] Ridley BL; O'Neill MA; Mohnen D. *Phytochemistry*. **2001**, 57(6), 929-967.
[2] Voragen AG; Coenen GJ; Verhoef RP; Schols HA. *J Struct Chem*. **2009**, 20(2), 263.
[3] Saulnier L; Thibault JF. *J Sci Food Agric*. **1999**, 79(3), 396-402.
[4] Fry SC. *Biochem J*. **1982**, 203(2), 493-504.
[5] Renard CMGC; Champenois Y; Thibault JF. *Carbohydr Polym.* **1993**, 22(4), 239-245.
[6] Voragen A. Pectins. Food polysaccharides and their applications. 2nd edition, Taylor & Francis, London. **1995.**
[7] Sungthongjeen S; Sriamornsak P; Pitaksuteepong T; Somsiri A; Puttipipatkhachorn S. *Aaps Pharmscitech*. **2004,** 5(1), 50.
[8] Oakenfull DG. The chemistry and technology of pectin, Elsevier. **1991,** 87-108.
[9] Nunthanid PSJ. *J Microencapsul*. **1999,** 16(3), 303-313.
[10] Sungthongjeen S; Pitaksuteepong T; Somsiri A; Sriamornsak P. *Drug Dev Ind Pharm*. **1999,** 25(12), 1271-1276.
[11] Glicksman M. Gelling hydrocolloids in product applications. In JVM Blanshard, JR Mitchell (Ed.). Polysaccharides in Foods. Butterworths, London. **1979**, 185- 204
[12] Pedersen JK. Textural ingredients for food. Business Briefing. Innovative Food Ingredients. **2002**, 1-4.
[13] Yamaguchi F; Shimizu N; Hatanaka C. *Biosci Biotechnol Biochem.* **1994,** 58(4), 679-682.
[14] Tian C; Wang G. *J Biotechnol*. **2008**, 136, S351.
[15] Inngjerdingen M; Inngjerdingen KT; Patel TR; Allen S; Chen X; Rolstad B; Morris GA; Harding SE; Michaelsen TE; Diallo D; Paulsen BS. *Glycobiology*. **2008,** 18(12), 1074-1084.