Pectin Grafted Poly(*N*-vinylpyrrolidone): Optimization and *In Vitro* Controllable Theophylline Drug Release

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ABSTRACT: The present article describes preparation, optimization, and characterization of pectin grafted polyvinylpyrrolidone hydrogels followed by controllable theophylline drug release. The gels were prepared in the presence of *N,N′*–methylenebisacrylamide (MBAA) crosslinker and ceric ammonium nitrate (CAN) initiator under N_2 atmosphere. Optimum conditions, in terms of percent of grafting (%G), were determined as follows: Pectin = 1.0 g, [NVP] = 2.81 m*M*, [MBAA] = 0.65 m*M*, [CAN] = 0.073 m*M*, polymerization temperature = 30°C and time = 4.0 hrs. Hydrogels were characterized by FTIR, TGA, DSC, XRD, and SEM. *In vitro* controllable release of theophylline model drug was studied using different *N*-vinylpyrrolidone monomer to MBAA crosslinker ratio (i.e., *[NVP]/[MBAA]* ratios) and different polymerization temperatures at two pH values, namely 5.5 and 7.4. The optimum conditions for colon-targeted vehicles that could provide the least theophylline release at pH 5.5, and the most theophylline release at pH 7.4, were as follows: *[NVP]/[MBAA]* = 4.33, polymerization temperature = 10°C and %G = 62.2. Such promising hydrogel characteristics may play the key role in many future drug release implementations. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 1945–1954, 2010

Key words: pectin grafted poly(vinylpyrrolidone); hydrogel; *in vitro* controllable release; theophylline

INTRODUCTION

Pectin is a heterogeneous polysaccharide which contains large amount of poly(D-galacturonic acid) bonded via α-1, 4-glycosidic linkage, where the carboxyl groups are partially in the methyl ester form. It is inexpensive, naturally occurring and abundantly available carbohydrate. The degree of esterification (DE), which is expressed as percentage of the esterified carboxyl groups, is an important mean to classify pectin. When the DE is more than 50%, pectin is said to be high methoxy, HM, pectin. The large applicability of pectin in food industry as gelling or thickening agent and in pharmaceutical industry as an excipient is mainly due to nontoxicity, low production costs and gelling activity properties.[1] The factors that influence the gel characteristics of pectin are the DE,[2–4] the change in chemical structure (i.e.,via grafting)[5,6] and the presence of cations.[7,8] Furthermore, it has been reported that aqueous mixtures of pectin-chitosan can permit formation of thermoreversible gelation properties.[9]

The formation of modified natural polymers via grafting copolymerization does not only form nontoxic and low price hydrogel copolymers but also show interesting biocompatibility and biodegradability properties. The highly porous structure of these hydrogels can easily be tuned by controlling the density of crosslinks and the degree of hydrophilicity in the gel matrix. This phenomenon of hydrogel porosity permits loading of drug into the gel matrix and subsequent drug release.[10] Different natural polymers such as pullulan,[11] cellulose,[12] starch,[13,14] chitosan,[14–16] amylopectin,[12] amylase[12,17] and sodium alginate[18] have been utilized to be used as drug delivery systems.

Oral drug delivery is still the most popular and preferred route of drug administration, especially for chronic therapies where repeated administration is required.[1] Colon–specific delivery systems has been widely investigated,[19] where it remain intact in the upper gastrointestinal (GI) tract and consequently, release the incorporated drug immediately upon reaching the colon. Pectin is considered as a potential oral drug delivery system for colon as it remains intact in the upper GI tract and then digested by colonic microflora.[20] In physiological conditions the inclusion of a more hydrophobic

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polymer via grafting into pectin, forming networks, may suppress the %release of drug, forming typical controlled drug system. Pectin–based formulations provide promising potential formulations for colon–specific drug delivery.[20]

The aim of this investigation was the modification of pectin, via grafting, to form an effective hydrogel copolymer that can make effective colon-targeted drug delivery. To this end, we have synthesized poly(*N*-vinylpyrrolidone) grafted pectin (Pectin-*g*-PVP) copolymers. The choice of poly(*N*-vinylpyrrolidone) was due to its biocompatibility with human body as approved by FDA,[21] where it had been used as local dressings on wound treatments[22,23] and as controller of drug release systems.[24–26] Furthermore, oral dosage form developed with our copolymers was tested to observe controlled dissolution behavior of theophylline model drug, where theophylline is an effective drug used in the treatment of nocturnal asthma and pulmonary disease.[27,28] The release data had been measured at pH 5.5 and pH 7.4 buffer solutions representing small intestines and colon respectively.

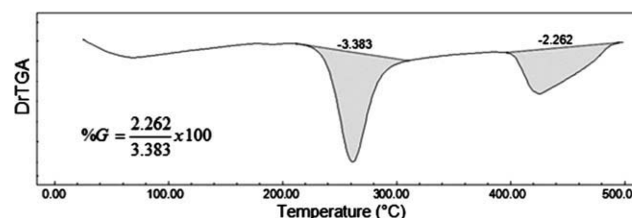
MATERIALS AND METHODS

Materials

Pectin from citrus peel (average molecular weight 30,000–100,000 g/mol, DE 60%) (Fluka). *N*-vinylpyrrolidone (NVP) monomer (99%, Across), *N,N′*-methylenebisacrylamide (97%, Lancaster). Anhydrous theophylline (QC No. 991,153) was kindly donated by United Pharmaceuticals, Jordan. Ceric ammonium nitrate (CAN) (Scharlau) was used as 0.1 *M* solution in molar nitric acid. Phosphate buffer (pH 7.4): monobasic potassium phosphate (Sigma-Aldrich) and sodium hydroxide (Sigma-Aldrich). Acetate buffer (pH 5.5): sodium acetate trihydrate (Sigma-Aldrich) and acetic acid (Sigma-Aldrich). Water used in all experiments was deionized and double distillated. All other reagents were analytical grade. All chemicals were used as supplied without further purification.

Synthesis of (pectin-*g*-PVP) hydrogel copolymers

An amount of 1.0 g of pectin was dissolved in 200 mL of deionized water and was stirred magnetically under N_2 atmosphere, then treated with a predetermined amount of CAN for 10 min to facilitate free radical formation on pectin. This treatment was followed by drop wise addition of NVP monomer and *N,N′*–methylenebisacrylamide (MBAA) as crosslinker. The total volume was made up to 250 mL by deionized water and then polymerization was continued at 30°C for 4 h unless mentioned elsewhere, where different monomer concentrations, crosslinker concentrations, and different temperatures were used. After polymerization time was over, the solution was allowed to cool and 250 mL of methanol as a nonsolvent was used to precipitate the copolymer. Then the copolymers were collected by filtration and macerated in methanol for 24 h to dissolve poly(*N*-vinylpyrrolidone) (PVP) homopolymers and then refiltrated. Excess PVP in the filtrate were checked by precipitation using dimethylether. Continuous methanol washing were persist until no precipitation of PVP homopolymers were observed. The washing process included removal of unreacted suspended pectin particles incubated between copolymer chains. Finally, the formed hydrogel copolymer (Scheme 2) was dried to constant weight and kept in desiccator under zero humidity for further investigation.



Scheme 1 Percent of grafting (%G) as determined using TGA derivative curve.

The percent of grafting (%G) was evaluated using the below mentioned formula;

$$\%G = \frac{W_1}{W_2} x100 \qquad (1)$$

where W_1 is the peak area of poly(vinylpyrrolidone) in the copolymer (i.e., fraction of PVP in the copolymer) located at 425°C, which is derived from the derivative of the TGA thermogram, whereas the W_2 is the peak area of pectin in the copolymer (i.e., fraction of pectin in the copolymer) located at 261°C as depicted in Scheme 1.

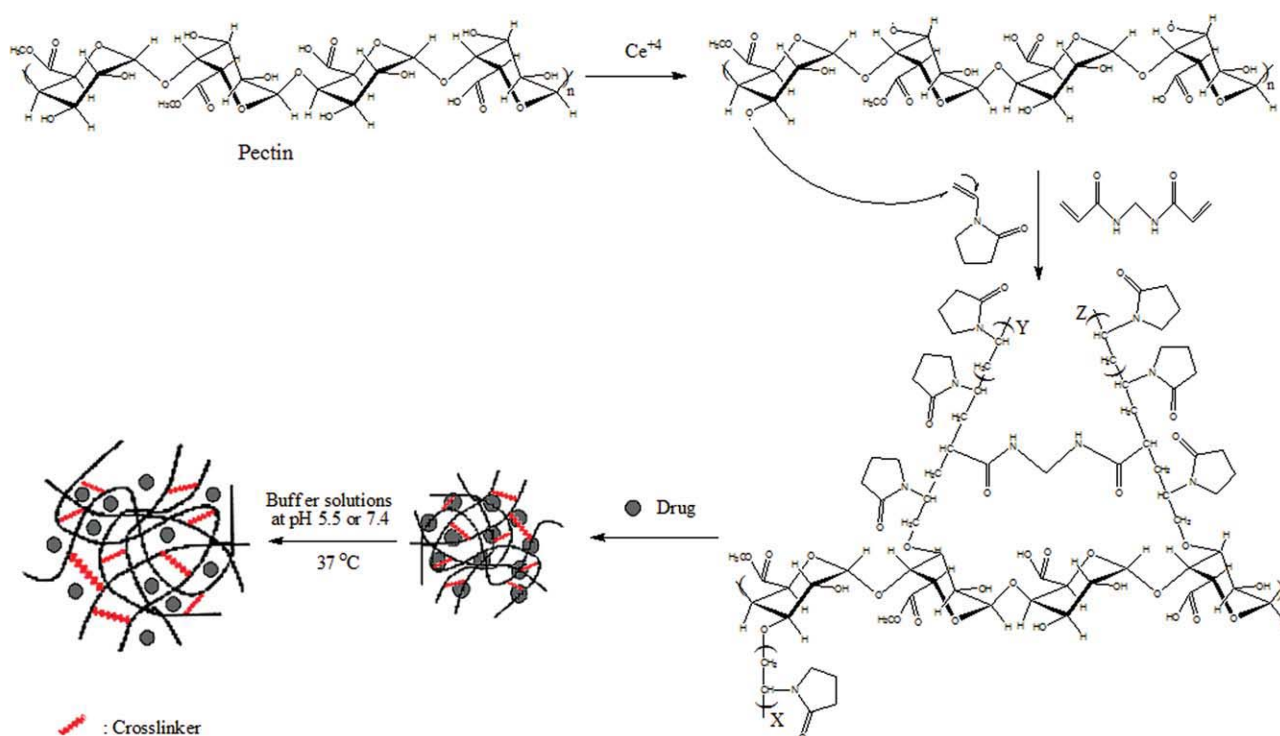
Thermal analysis

Thermogravimetric analysis (TGA)

All samples were studied using Shimadzu TA-50 (Japan) Thermogravimetric analysis (TGA), under N_2 atmosphere at a heating rate of 10°C/min and 25 −500°C temperature range.

Differential scanning calorimetry (DSC)

Shimadzu DSC-50Q quick cooling differential scanning calorimeter under a N_2 atmosphere was used at a heating rate of 5°C/min. The values of glass transition temperature (T_g) for polymers were detected



Scheme 2 Schematic presentation of pectin-*g*-PVP formation and its use in drug release system. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

after the second run as the midpoint between the onset and end-set of the thermogram curve.

Spectroscopic and optical analysis: FTIR

FTIR spectra were recorded via Thermo Nicolet (avator-360) FTIR spectrophotometer in the range of $4000-400\ cm^{-1}$using KBr pellets.

XRD

The X-ray diffraction samples were scanned between 5° and 100° using Philips Diffractometer (model PW 1729, Holland) equipped with copper as target material under the operational conditions of 30 kV, 40 mA and wavelength between 1.54060 and 1.54438 Å.

Scanning Electron Microscope (SEM)

Images were taken with Polaroid film. The samples in film form were mounted on specimen stubs and coated with gold ions by sputtering method with a Zeiss (United States) DSM 950 and a Polaron E6100. Electronic absorption spectroscopy was performed with a Unican Helios Alpha apparatus.

In vitro drug release of theophylline using (pectin-*g*-PVP) hydrogels

An amount of 100.0 mg of theophylline model drug was dissolved in 5 mL buffered solution (pH 5.5 or pH 7.4) then 300.0 mg of hydrogel formulation was added into the solution. Then the solution composites were allowed to stir magnetically over night, to incorporate the drug into the hydrogel matrix, where theophylline was found to be stable under such conditions. The mixture was conducted into 7 cm membrane dialysis bag (cellulose, cut-off $\mathbf{M_r}$ 12–14 kD) allowing 2 cm for tying up. The bag was closed and transferred to paddles equipped USP dissolution apparatus II (Vankel VK 750 D) containing 900 mL of the same buffer solution maintained at physiological temperature 37.0°C ± 0.1. The external solution was continuously stirred at 50 rpm. At predetermined time intervals 2.0 mL sample aliquots were withdrawn, filtered by a cellulose membrane filter (pore size 0.45 μm) and then replaced by fresh buffer solution. The different hydrogel formulations prepared in this work were investigated for *in vitro* theophylline release. Enteric-coated dosage forms are often used in colon-targeted drug delivery to avoid variations in gastric emptying.[29] Therefore, dissolution studies were conducted at pH 5.5 and pH 7.4 representing that of small intestines and colon respectively. Sink conditions were assured. All experiments were conducted in triplicates ($n = 3$). The amount of released drug was analyzed by means of HPLC as described later. The average percent cumulative drug released was then calculated. Results were expressed as mean values ± standard deviation (SD).

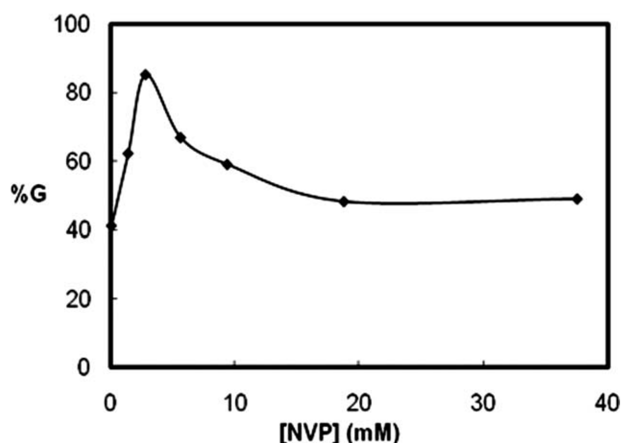


Figure 1 The change of %G as a function of NVP monomer concentration, using pectin = 1.0 g, [MBAA] = 0.65 mM, [CAN] = 0.073 mM at 30°C in 250 mL solution.

HPLC analysis of theophylline

Concentrations of theophylline in release media were determined by HPLC method in accordance with USP guidelines (USP 30/NF 25, 2007) with slight modifications. The analytical HPLC system consisted of an LC system (LC- 10 AD vp, Shimadzu, Japan), UV- visible detector (SPD- 10 AD vp, Shimadzu, Japan) and degasser (DG 12 AD, Shimadzu, Japan), a system controller (SCL- 10 AD vp, Shimadzu, Japan), and was connected to a computer furnished with the appropriate software (Class VP, V 6.2, Shimadzu, Japan). The chromatographic separation was carried on a C18 column (Reprosil 100®, 5 μm, 250 × 4.6 mm, Maisch, Germany). The injection volume was 25 μL at detection wavelength of 280 nm. The flow rate was 1.2 mL/min. The mobile phase used was acetate buffer/acetonitrile = 88/12 v/v.

RESULTS AND DISCUSSION

Optimization conditions

Monomer concentration

Figure 1 shows the change of %G as a function of increasing monomer concentration. The increase of %G from [NVP] = 0 to 2.82 mM was expected due to the availability of NVP monomers surrounding pectin macroradicals, which subsequently led to larger grafting. Further increase in monomer concentration led to exponential decline of %G. This decline could be attributed to the probable formation of PVP homopolymers as a result of using larger NVP concentration, and consequently the rate of consumption of monomers toward homopolymers could, as a result, hinder the interaction of monomers with pectin macroradicals which result with exponential decrease of %G.

Crosslinker concentration

The concentration of the crosslinker used plays a very crucial role in the control of release of drugs. Thus the optimization of crosslinker concentration, [MBAA], becomes crucial too. Figure 2 shows the optimum crosslinker concentration which shows the maximum %G at [MBAA] = 0.65 mM. The increase in crosslinker concentration led to larger %G due to availability and thus large incorporation of crosslinker molecules into the backbone. The sudden decline of %G at 1.2 mM and higher crosslinker concentrations suggest faster terminations through loop and cyclic structures formation leaving the leftover unreacted crosslinker molecules in the solution, which then were removed by washing process.

Polymerization temperature

Figure 3 illustrates the change of percent grafting (%G) as a result of increase of polymerization temperature. It could be clearly seen that the %G increased linearly with temperature up to 30°C then decline down. This increase is owed to possibility of increase of rate of diffusion of NVP molecules into pectin macroradicals, which opened up as a result of temperature increase. This behavior led to higher grafting. However, at higher temperatures pectin may undergo some modification like partial hydrolysis through C—O—C bond breakage in the presence of nitric acid or partial dissolution of some fractions in pectin, which could lead to decrease in grafting possibility and consequently increase in rate of homopolymerization.

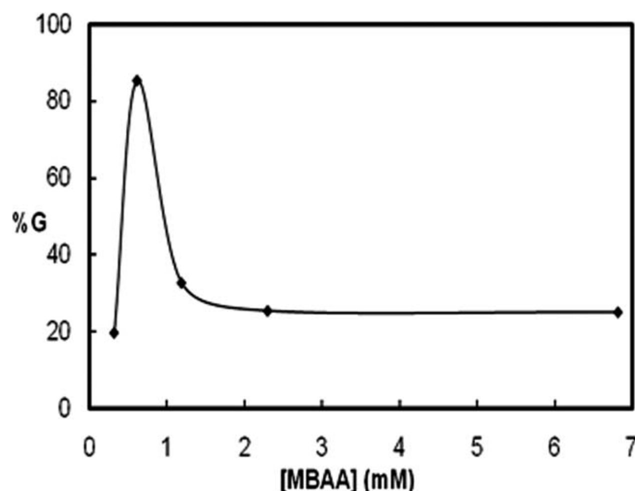


Figure 2 The change of %G as a function of MBAA crosslinker concentration using pectin = 1.0 g, [NVP] = 2.81 mM, [CAN] = 0.073 mM at 30°C in 250 mL solution.

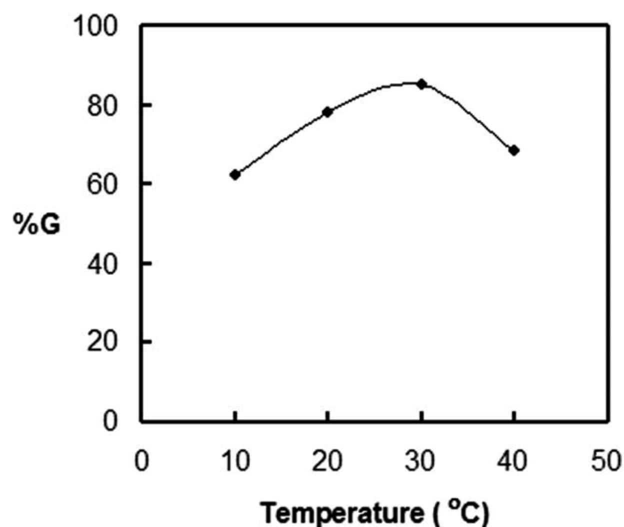


Figure 3 The change of %G as a function of polymerization temperature using pectin = 1.0 g, [NVP] = 2.81 m*M*, [MBAA] = 0.65 m*M*, [CAN] = 0.073 m*M* in 250 mL solution.

Characterization of (pectin-*g*-PVP) copolymers

Thermal analysis

Figure 4(A) shows the derivative of TGA thermogram of pectin, pure PVP, and different %G copolymers. It could be seen that pectin and pure PVP showed decomposition temperatures at 261 and 425°C, respectively. Whereas in pectin-*g*-PVP copolymers, shift toward higher decomposition temperature of pectin fraction, and shift toward lower decomposition temperature of PVP were monitored. The higher temperature shift confirmed the presence of stronger intermolecular forces between pectin and grafted PVP chains, mainly H-bonding which led to larger thermal stability and consequently higher temperature shift, whereas the lower decomposition temperature shift could be explained on the basis that pure PVP contains larger fraction of crystalline regions caused from packing of chains on each other. These crystalline regions were quite lowered in the pectin grafted PVP chains due to different grafting positions and thus the volume between chains per unit area became larger, which lowered the consistency of chains and resulted with lower decomposition temperatures. The ratio of peak areas of pectin and grafted PVP can resemble the fraction of pectin and grafted PVP in the copolymer and thus were used in determination of percent grafting (%G).

DSC thermograms in Figure 4(B) show the T_g of pectin, pure PVP and pectin-*g*-PVP. It could be clearly seen that one T_g of pectin-*g*-PVP located at 123°C was determined, which strongly confirmed that PVP chains were chemically bounded and grafted onto pectin. No T_g values of pure PVP located at 138°C and pectin located at 85°C were found in pectin-*g*-PVP copolymer. The high $T_g$value of pure PVP at 138°C indicated good orientation of intermolecular forces and packing of chains above each other which led to larger consistency and

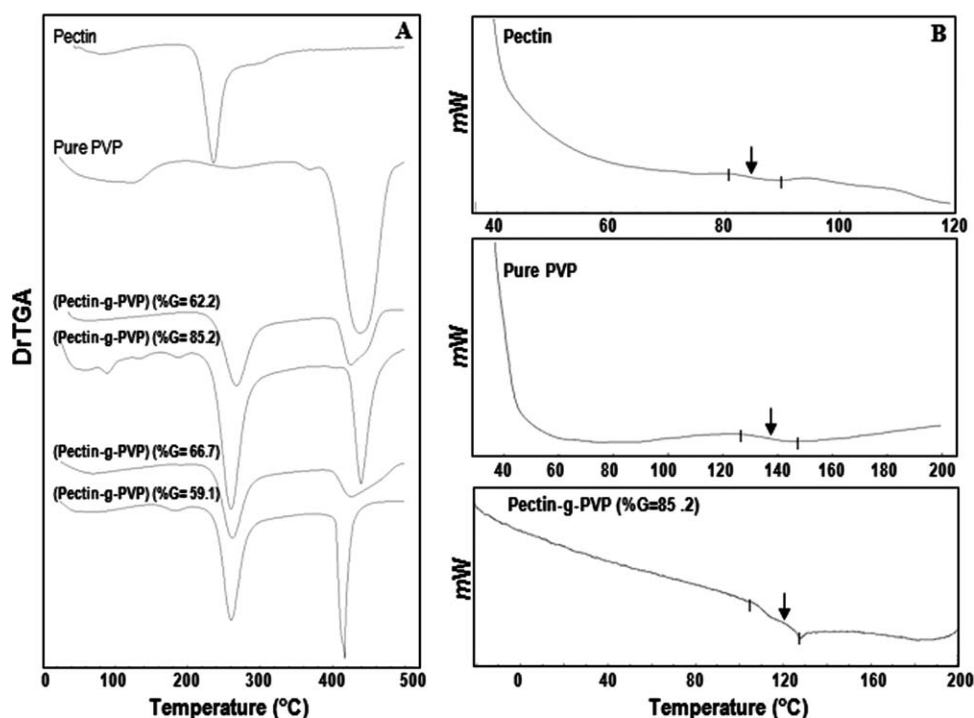


Figure 4 (A) Derivative of TGA thermograms of pectin, pure PVP and different %G pectin-*g*-PVP samples. (B) DSC thermograms of pectin, pure PVP and pectin-*g*-PVP (%G = 85.2).

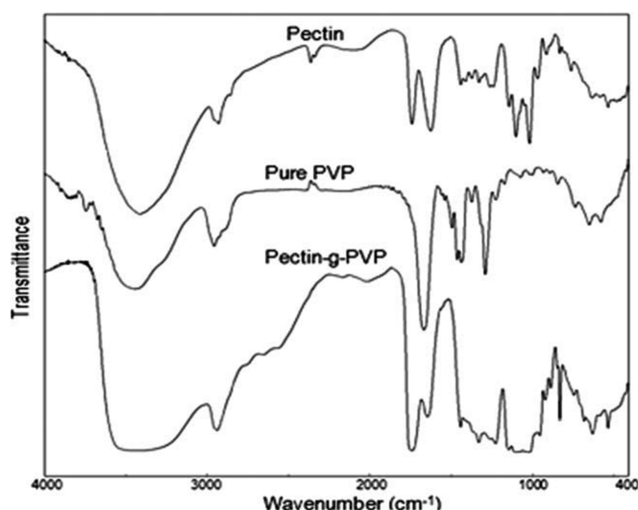


Figure 5 FTIR spectra of pectin, pure PVP and Pectin-*g*-PVP (%G = 85.2) copolymer.

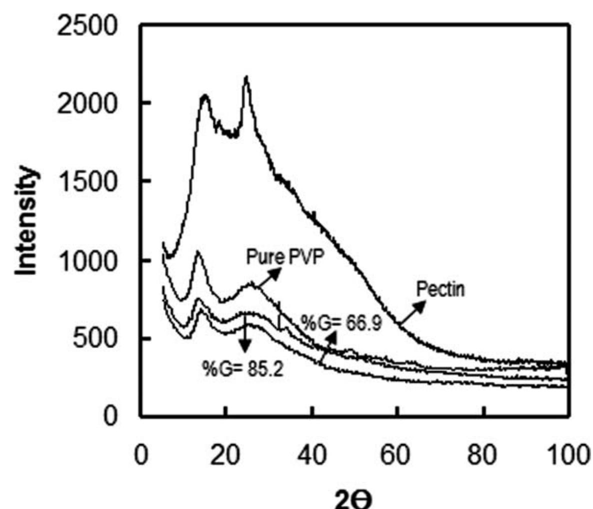


Figure 6 XRD pattern of pectin, pure PVP and different %G of pectin-*g*-PVP.

toughness. Despite the presence of H-bonding between pectin and PVP chains in pectin-*g*-PVP, the $T_g$value was lowered (i.e., 123°C). This lowering was owed to presence of un-packed pectin chains together with distributed PVP chains that were reflected on consistency and toughness of the copolymer.

Spectroscopic and optical analysis

FTIR. The corresponding functional groups of pectin, pure PVP and pectin-*g*-PVP are illustrated in Figure 5 and Table I.

It could be seen that symmetric and asymmetric carbonyl stretchings of acid and ester groups were existed in pectin and pectin-*g*-PVP, and carbonyl stretching of the amide in the vinylpyrrolidone group was also existed in pectin-*g*-PVP, which is another clue of formation of grafted copolymer. In further, the C—O—C stretching was found in pectin and pectin-*g*-PVP. The symmetric C=O of the ester and C=O of the amide were very close to each other, overlapped and appeared as one broader band. The ratio of absorbance of amide C=O stretching to the absorbance of ester C=O stretching were found to be 0.804, (i.e., $\frac{A_{CO-\text{amide}}}{A_{CO-\text{ester}}} = 0.804$), which was very close to percent grafting (%G) determined using equation (1) (i.e., %G = 85.2). This provides an evidence of the consistency of measurements determined through TGA or FTIR techniques.

XRD. The X-ray diffraction pattern used for determination of %Crystallinity is illustrated in Figure 6 and Table II.

%crystallinity were determined from the peaks area at 18 and 24° divided by the background area multiplied by 100. It could be seen that %Crystallinity of pectin was 8.4%, which means that 91.6% was amorphous, whereas pure PVP was largely crystalline (around 50%). The large %Crystallinity indicated a large amount of chain packing on each other, which happen as a result of relatively inter- and intramolecular forces such as H-bonding between

TABLE I
FTIR Characteristic Peaks of Pectin, Pure PVP and Pectin-*g*-PVP

Polymer	Characteristic peaks		Remarks
	cm^{-1}	% Transmittance	
Pectin	2928	71.0	CH_2 str.
	1739	69.9	Asymmetric C=O str. of acid and ester
	1624	68.0	Symmetric C=O str. of acid and ester
	1016	63.3	C—O—C str.
Pure PVP	2954	80.8	CH_2 str.
	1670	45.0	C=O str. of amide
Pectin-*g*-PVP	2941	71.5	CH_2 str.
	1740	60.7	Asymmetric C=O str. of acid and ester
	1625	71.4	Symmetric C=O str. of acid and ester
	1669	75.5	C=O str. of amide
	1018	62.7	C—O—C str.

TABLE II
Change of %Crystallinity with Percent Grafting (%G) Deduced From XRD Pattern Data

Polymer	%G	%Crystallinity
Pectin	–	8.4
Pure PVP	–	46.6
Pectin-*g*-PVP	62.3	15.6
Pectin-*g*-PVP	66.9	21.6
Pectin-*g*-PVP	85.2	38.4

pendant groups (i.e., pyrrolidone groups). In pectin-*g*-PVP copolymer the %Crystallinity increased linearly with increasing %G (i.e., increasing the fraction of grafted PVP in the copolymer), which suggested that the content of PVP played the crucial role in increasing %Crystallinity of the formed copolymers.

SEM.. The study of morphological changes of polymers through scanning electron microscopy (SEM) gains large interest in the nano region. In our case the micro region could show the flakes shape of pectin agglomerated on each other [Fig. 7(A)], the layers of pure PVP packed on each other forming crystalline regions [Fig. 7(B)] and consequently the different crystalline regions formed after grafting of PVP onto pectin, where similar layers packed on each other to that of pure PVP [Fig. 7(C,D)], whereas a rod like structure that contained parallel grooves aligned allover the rod [Fig. 7(E)]. These findings confirmed the %Crystallinity determinations through XRD pattern and gave an insight image of structures of pectin-*g*-PVP on the micro level.

In vitro release studies

Drug release was carried out from pectin and from different liquid hydrogel matrix systems at pH 5.5 and 7.4. The *in vitro* release profiles of theophylline into acetate buffer (pH 5.5) at different %G and different polymerization temperatures conducted at 37°C were presented in Figure 8(A) and 8-B, respectively. The optimum conditions of the Pectin-*g*-PVP hydrogel used were Pectin = 1.0 g, [NVP] = 2.81 m*M*, [MBAA] = 0.65 m*M*, [CAN] = 0.073 m*M*, polymerization temperature = 30°C and time = 4.0 hrs. unless mentioned elsewhere.

The *in vitro* release profile of theophylline into phosphate buffer (pH 7.4) at different %G and different polymerization temperatures conducted at 37°C were presented in Figure 9(A,B), respectively.

To understand the mode of theophylline drug release from the different polymeric hydrogels, the release data were fitted to the following power law equation.[30]

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

Where M_t/M_∞ is the fraction of drug released at time t, k is proportionality constant which accounts

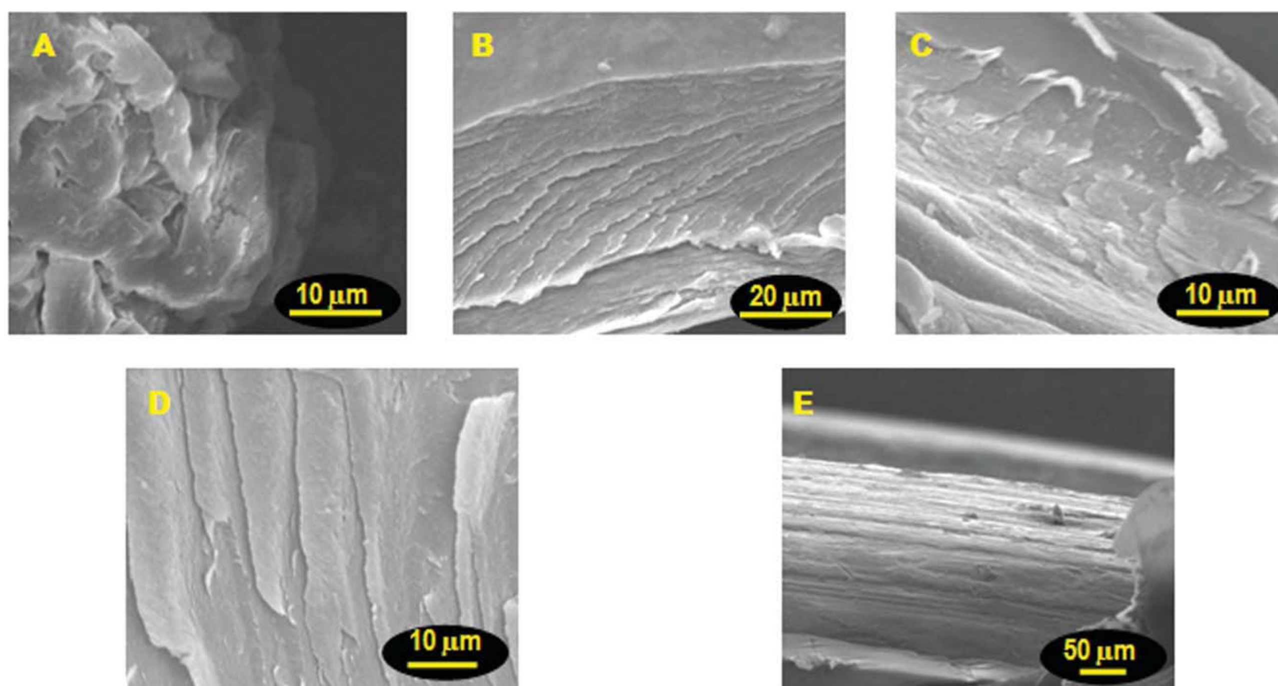


Figure 7 SEM micrographs of (A) Pectin, (B) Pure PVP, (C) Pectin-*g*-PVP (%G = 62.2), (D) Pectin-*g*-PVP (%G = 85.2), (E) Pectin-*g*-PVP (%G = 66.9). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

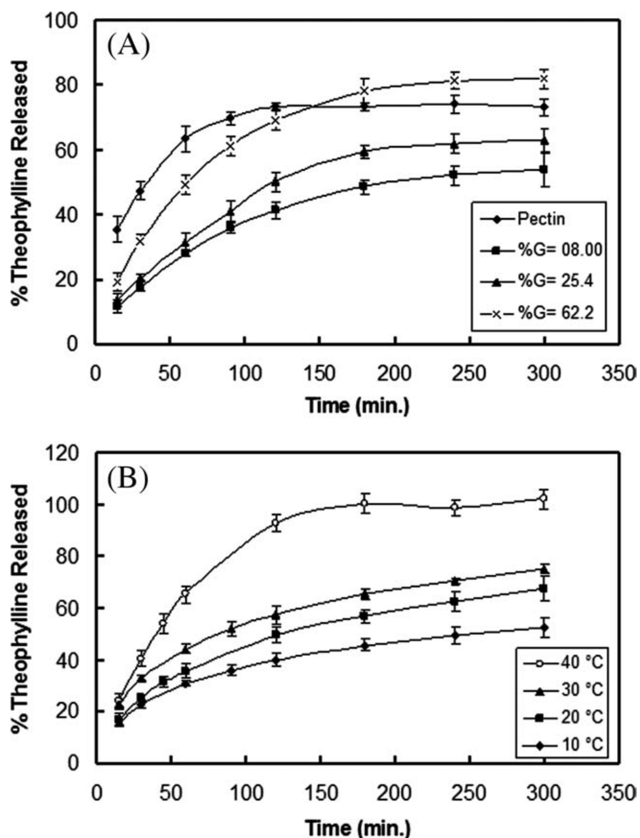


Figure 8 (A) *In vitro* drug release profile, into acetate buffer (pH 5.5) conducted at 37°C from Pectin-*g*-PVP hydrogel with different %G. Each point represents the mean ± SD ($n = 3$). (B) *In vitro* drug release profile, into acetate buffer (pH 5.5) at 37°C from Pectin-*g*-PVP hydrogel prepared at different temperatures. Each point represents the mean ± SD ($n = 3$).

for consistency, structural and geometrical properties of polymeric matrix, and n is the diffusional exponent indicative of release rate. Dissolution data are summarized in Table III [statistical correlation coefficient ($\boldsymbol{R}^2$) $\geq$ 0.95].

According to Miyazaki et al.[31] a value of the exponent, $n \leq 0.5$, $0.5 < n < 1.0$, $n = 1.0$ indicates diffusion controlled (Fickian diffusion), anomalous diffusion (non-Fickian) and zero-order transport mechanisms, respectively.

From Table III pectin showed similar drug release regardless of pH value (i.e., 5.5 or 7.4), though at pH 7.4 formation of negatively charged ions of COO^- were expected. Higher and similar calculated release rates at pH 5.5 and 7.4 indicated that mesh size of pectin was large enough to inlet and outlet the drug very easily. In addition, drug release from pectin approached zero-order with good correlation ($\boldsymbol{R}^2 \geq 0.99$).

For pectin-*g*-PVP hydrogels, at pH 5.5 the elevated polymerization temperatures showed increase in release rate (higher *n*-value) due to lower consistency of polymeric structure (lower *k*-value), whereas at pH 7.4 it showed decrease in release rate (lower *n*-value) due to higher consistency (higher *k*-value). The preparation temperature had significant influence on the coiling of polymeric chains, which is pH dependent. At pH 5.5 using higher preparation temperatures more uncoiling of polymeric chains was expected, which consequently was reflected on the ease of drug release (higher *n*-value). Exceptionally, at 30°C the *n*-value was reduced and larger *k*-value was observed, which confirms more coiling of polymeric chains due to larger %G value (i.e., %G = 85.2).

On the contrary, at pH 7.4 the larger release rate (higher *n*-value), due to in-consistent polymeric chains (lower *k*-value), were seen at lower preparation temperatures. The formation of negatively charged ions, COO^- ions, led to uncoiling of polymeric chains due to repulsive forces, which resulted in larger release rate, and approached zero-order mechanism. Furthermore, increasing preparation temperatures decreased release rate, due to formation of more consistent polymeric matrix system, as

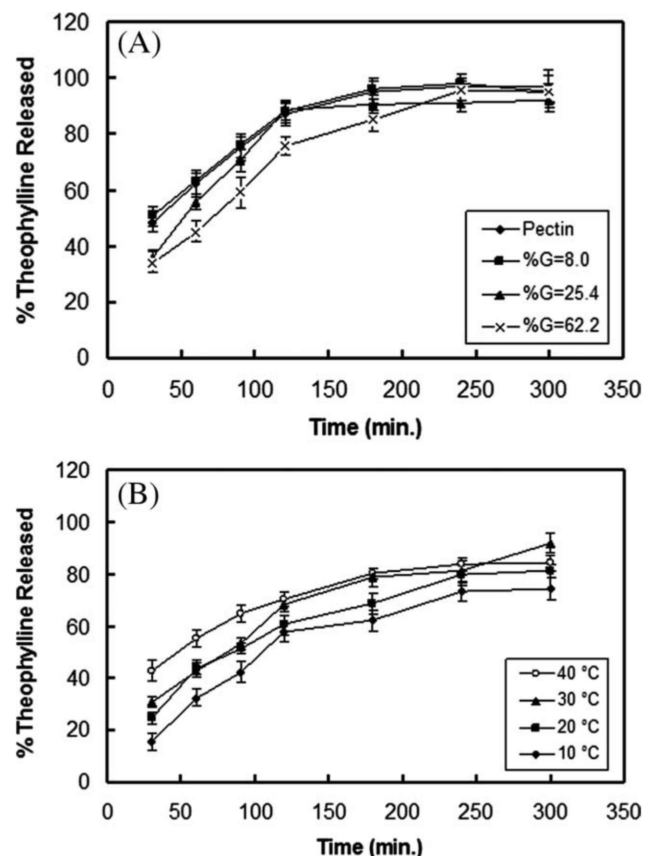


Figure 9 (A) *In vitro* drug release profile, into phosphate buffer (pH 7.4) conducted at 37°C from Pectin-*g*-PVP hydrogel with different %G. Each point represents the mean ± SD ($n = 3$). (B) *In vitro* drug release profile, into phosphate buffer (pH 7.4) at 37°C from Pectin-*g*-PVP hydrogel (%G = 85.2) prepared at different temperatures. Each point represents the mean ± SD ($n = 3$).

TABLE III
Different Synthetic Parameters of Pectin-*g*-PVP Hydrogel with Apparent *In Vitro* Drug Release Parameters [Coefficient Parameter (*k*), Diffusional Exponent (*n*)]

Polymer	$\frac{[NVP]}{[MBAA]}$	T (°C)	%G	pH 5.5		pH 7.4	
				n	*k*	*n*	*k*
Pectin	–	–	–	1.044	1.67	1.200	1.59
Pectin-*g*-PVP	4.33	10	62.2	0.408	5.69	0.938	1.54
	4.33	20	77.9	0.520	4.08	0.652	2.76
	4.33	30	85.2	0.476	6.70	0.562	4.43
	4.33	40	68.3	0.720	3.50	0.366	12.35
	0.27	30	8.0	0.594	2.35	0.418	11.52
	1.08	30	25.4	0.624	2.45	0.565	4.78
	2.17	30	62.2	0.688	3.30	0.646	3.96

a result of formation of inter- and intramolecular interactions between partially hydrolyzed pectin macromolecules with themselves and with PVP networks.

When $\frac{[NVP]}{[MBAA]}$ ratio increased from 0.27 to 2.17 at fixed preparation temperature, 30°C, and pH 5.5, the release was non-Fickian as indicated by the *n* values (0.59–0.69). Further increase in $\frac{[NVP]}{[MBAA]}$ ratio to 4.33 showed Fickian diffusion release ($n = 0.48$). This lowering of drug release at 4.33 ratio was explained on the basis of formation of more compact, well-organized and controllable mesh size structure, that controlled the drug release efficiently (i.e., $k = 6.7$). Furthermore, at pH 7.4 no effect of negatively charged ions on the release rate due to expected larger mesh sizes, with Fickian behavior at ratio of 0.27 and non-Fickian behavior from 1.08 to 4.33.

Conclusively, since colon–targeted vehicles should remain intact in the upper GI tract and release the incorporated drug immediately upon reaching the colon. The expected successful hydrogel properties that fit to the above goal is as follows: $\frac{[NVP]}{[MBAA]} = 4.33$, polymerization temperature = 10°C and %G = 62.2. Such conditions could provide the least theophylline release at pH 5.5, and the most theophylline release at pH 7.4, which is the main theme of colon-oriented studies.

CONCLUSIONS

Optimization of pectin grafted with poly(*N*-vinylpyrrolidone) formed hydrogels had been accomplished as prestep toward implementing such gels in controllable theophylline drug release at pH's 5.5 and 7.4. Different conclusive remarks could be deduced;

- The optimum conditions, in terms of percent of grafting (%G), were as follows: Pectin = 1.0 g, [NVP] = 2.81 m*M*, [MBAA] = 0.65 m*M*, [CAN] = 0.073 m*M*, polymerization temperature = 30°C and time = 4.0 hrs.
- At pH 5.5, the elevated preparation temperatures showed increase in theophylline release rate due to lower consistent polymeric structure (higher porosity), whereas at pH 7.4 elevated preparation temperatures showed decrease in theophylline release rate due to higher consistency (lower porosity) and formation of inter- and intramolecular interactions between partially hydrolyzed pectin macromolecules with themselves and with PVP networks.
- Theophylline release showed non-Fickian behavior for $\frac{[NVP]}{[MBAA]}$ ratio from 0.27 to 2.17 at fixed preparation temperature, 30°C, and pH 5.5, and Fickian diffusion release for $\frac{[NVP]}{[MBAA]}$ ratio = 4.33. Furthermore, at pH 7.4 no effect of negatively charged ions on the release rate due to expected larger mesh sizes, with Fickian behavior at ratio of 0.27 and non-Fickian behavior range from 1.08 to 4.33.
- The optimum conditions for colon-targeted vehicles, that could provide the least theophylline release at pH 5.5, and the most theophylline release at pH 7.4, are as follows: $\frac{[NVP]}{[MBAA]} = 4.33$, polymerization temperature = 10°C and %G = 62.2.

References

1. Liu, L.; Fishman, M. L.; Kost, J.; Hicks, K. B. Biomaterials 2003, 24, 3333.
2. Thakur, B. R.; Singh, R. K.; Handa, A. K. Crit Rev Food Sci Nutr 1997, 37, 47.
3. Rolin, C. P. Industrial Gums: Polysaccharides and Their Derivatives; Whistler, R. L.; Bemiller, J. N., Eds.; Academic Press: California, 1993; 257–293.
4. Oakenfull, D. G. The Chemistry and Technology of Pectin; Walter, R. H., Ed. Academic Press: New York, 1991; 88–108.
5. Sutar, P. B.; Mishra, R. K.; Pal, K.; Banthia, A. K. J Mater Sci: Mater Med 2008, 19, 2247.
6. Chauhan, G. S.; Kumari, A.; Sharma, R. J Appl Polym Sci 2007, 106, 2158.
7. Lofgren, C.; Guillotin, S.; Evenbratt, H.; Schols, H.; Hermansson, A. Biomacromolecules 2005, 6, 646.
8. Mcconaughy, S. D.; Kirkland, S. E.; Treat, N. J.; Stroud, P. A.; Mccormick, C. L. Biomacromolecules 2008, 9, 3277.

9. Nordby, M. H.; Kjøniksen, A.; Nystrom, B.; Roots, J. Biomacromolecules 2003, 4, 337.
10. Hoare, T. R.; Kohane, D. S. Polymer 2008, 49, 1993.
11. Fundueanu, G.; Constantin, M.; Ascenzi, P. Biomaterials 2008, 29, 2767.
12. Cai, H.; Zhang, Z. P.; Sun, P. C.; He, B. L.; Zhu, X. X. Radiat Phys Chem 2005, 74, 26.
13. Prashanth, K. V.; Lakshman, K.; Shamala, T. R.; Tharanathan, R. N. Int Biodeterioration Biodegrad 2005, 56, 115.
14. Singh, V.; Tripathi, D. N.; Tiwari, A.; Sanghi, R. Carbohydr Polym 2006, 65, 35.
15. Rath, S. K.; Singh, R. P. J Appl Polym Sci 1997, 66, 1721.
16. Rokhade, A. P.; Patil, S. A.; Aminabhavi, T. M. Carbohydr Polym 2007, 69, 678.
17. Alias, J.; Silva, I.; Goni, I.; Gurruchaga, M. Carbohydr Polym 2008, 74, 31.
18. Isiklan, N.; Inal, M.; Yigitoglu, M. J Appl Polym Sci 2008, 110, 481.
19. Libo, Y.; Chu, J. S.; Fix, J. A. Int J Pharmaceuticals 2002, 235, 1.
20. Sinha, V. R.; Kumira, R. Int J Pharm 2001, 224, 19.
21. Robinson, B. V.; Sullivan, F. M.; Borzelleca, J. F.; Schwartz, S. L. PVP: A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone); Lewis publisher: Michigan, 1990.
22. Miranda, L. F.; Lugao, A. B.; Machado, L. D. B.; Ramanathan, L. V. Radiat Phys Chem 1999, 55, 709.
23. Razzak, M. T.; Darwis, D.; Zainuddin, S. Radiat Phys Chem 2001, 62, 107.
24. Risbud, M. V.; Hardikar, A. A.; Bhat, S. V.; Bhonde, R. R. J Controlled Release 2000, 68, 23.
25. Am Enda, M. T.; Peppas, N. A. J Appl Polym Sci 1996, 59, 673.
26. Ravichandran, P.; Shantha, K. L.; Panduranga, R. K. Inter J Pharm 1997, 154, 89.
27. Ferrero, C.; Bravo, I.; Jimenez-Castellanos, M. R. J Controlled Release 2003, 92, 69.
28. Geresh, S.; Gdalevsky, G. Y.; Gilboa, I.; Voorspoels, J.; Remon, J. P.; Kost, J. J Controlled Release 2004, 94, 391.
29. Karrout, Y.; Neut, C.; Wils, D.; Siepmann, F.; Deremaux, L.; Desreumaux, P.; Siepmann, J. Int J Pharm 2009, 371, 64.
30. Ritger, P. L.; Peppas, N. A. J Control Release 1987, 5, 37.
31. Miyazaki, Y.; Yakou, S.; Takayama, K. Int J Pharm 2004, 287, 39.