# Chemoenzymatic Synthesis, Characterization, and Controlled Release of Functional Polymeric Prodrugs with Acyclovir as Pendant

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**ABSTRACT:** An efficient protocol for the synthesis of functional polymeric prodrugs of acyclovir with variable copolymer composition and potential liver-targeting delivery was achieved by combining enzymatic selective synthesis of polymerizable acyclovir derivatives with radical copolymerization of properly selected comonomers. Vinyl D-galactose ester (VAG), acrylic acid (AA), and methyl methacrylate (MMA) were chosen as comonomers and three novel polymeric prodrugs with acyclovir as pendant were synthesized using 2,2′-azo-bis-iso-butyronitrile (AIBN) as initiator in *N*,*N*-dimethylformamide (DMF). The resulting polymers were characterized by FTIR, NMR, and GPC. The influence of the concentration of initiator and the molar ratio of comonomers on the polymerization was investigated. *In vitro* drug release studies showed that acyclovir could be released from poly(2-*N*-vinylsebacyl-acyclovir-*co*-methyl methacrylate) (poly(VSA-*co*-MMA)), and the total released acyclovir after 7 days in buffer solution at pH 1.2 and 7.4 was $\sim$ 35% and 29%, respectively. Also, homopolymers of vinyl acyclovir derivatives with high drug payload (>50 wt %) were obtained and characterized by the same methods. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 108: 431–437, 2008

**Key words:** drug delivery systems; enzymes; copolymerization; acyclovir

## INTRODUCTION

Recently, research at the interface of polymer chemistry and the biomedical sciences has given rise to the polymer therapeutics, among which, polymer-drug conjugates have attracted increasing attention since these systems offer numerous advantages compared to conventional low-molecular-weight drugs including prolonged drug release, improved site-specificity, reduced toxicity, and increased patient acceptance.[1–6] Especially, the introduction of targeting moieties, such as antibodies, galactose, lectin, folic acid, or their fragments, effectively achieves the specific recognition of polymeric prodrugs to such tissue or organ as human ovary, liver, lung, colon, and so on, and thus enhances the pharmacological effect of given drugs.[7–17]

Acyclovir (9-(2-hydroxyethoxymethyl)guanine) is an acyclic nucleoside analogue that has shown a potent antiviral activity, and it is known to inhibit the replication of herpes viruses and hepatitis B virus.[18–20] However, acyclovir has rather short plasma half-life (about 2–3 h in adults without renal impairment) and limited selectivity.[21,22] Only small amounts of the drug reach the target site following administration, and therapy is associated with side effects. To circumvent these limitations and improve the pharmacokinetics of acyclovir, some drug delivery systems of acyclovir have been under investigation. These systems could be generally classified as nanoparticulate drug delivery systems, in which acyclovir is physically incorporated into microparticles, or as polymer-drug conjugates where drugs are covalently linked to polymer carriers through cleavable linkers.[23–26] In comparison with nanoparticulate drug delivery systems, polymer-acyclovir conjugates had longer half-life. Several polymer-acyclovir conjugates have been synthesized by coupling acyclovir to such polymers as α,β-poly[*N*-2-(hydroxyethyl)-DL-aspartamide] (PHEA), PEG, and dextran.[20,21,27] However, so many modification steps to acyclovir or polymer precursors before conjugating acyclovir to polymers made the entire synthesis of these polymer-drug conjugates tedious and difficult to be controlled. Therefore, it is significant to seek more facile protocol for the synthesis of polymeric prodrugs of acyclovir with such important properties as high drug loading, targeting, electriferous property, and so on.[28]

Enzymes play an important role in selective synthesis of polymerizable multifunctional substrate derivatives because of high selectivity and mild reac-

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tion conditions.[29,30] Polymerizable acyclovir esters or amides could be respectively obtained by enzymatic transesterification.[31] The radical copolymerization of vinyl acyclovir derivatives with properly selected comonomers could provide an enormous variability in composition and properties of the resulting polymeric prodrugs. It is possible to tailor-make the anticipant structure to endow these polymeric prodrugs with important properties. Also, the two-step synthetic route of functional polymeric prodrugs was very facile.

In this study, the facile synthesis of functional polymeric prodrugs of acyclovir with different moieties, D-galactose, acrylic acid (AA), and methyl methacrylate (MMA), was achieved by combining enzymatic synthesis with radical polymerization. First, polymerizable acyclovir amides, 2-*N*-vinyladipyl-acyclovir (VAA) and 2-*N*-vinylsebacyl-acyclovir (VSA), were prepared by enzymatic transesterification according to our previous description.[31] Then the homopolymers of VAA and VSA, and the copolymers of VSA with 6-*O*-vinyladipyl-D-galactose (VAG) or AA or MMA were synthesized and characterized. The influence of the concentration of initiator and the molar ratio of comonomers on the polymerization was investigated. Furthermore, in comparison with the acyclovir microcapsules prepared with self-assembly technique, *in vitro* release of acyclovir from poly(VSA-*co*-MMA) was studied in buffer solutions at different pH values.

## EXPERIMENTAL

### Materials and instruments

Lipase PS ''Amano'' (PS), poly(sodium 4-styrenesulfonate) (PSS, $M_w$ = 70,000 Da) and poly(allylamine hydrochloride) (PAH, $M_w$ = 70,000 Da) were purchased from Aldrich. Acyclovir (raw drug) was obtained from Xinxiang Tuoxin Biochemical Technology & Science (Xinxiang, P. R. China). 6-*O*-vinyladipyl-D-galactose (VAG) was synthesized according to the description of literature.[32] 2,2′-azo-bis-iso-butyronitrile (AIBN) was purified by recrystallization in ethanol and dried at room temperature under vacuum. *N*,*N*-dimethylformamide (DMF) was HPLC grade. D-galactose, MMA, AA, and all other chemicals were analytical grade.

All reactions were monitored by TLC on silica gel plates. FTIR spectra were measured using a Nicolet Nexus FTIR 670 spectrophotometer at room temperature in the range between 4000 and 400 $cm^{-1}$. $^1H$ NMR and $^{13}C$ NMR spectra were recorded with TMS as internal standard using a Bruker AMX-500 MHz spectrometer. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz. Gel permeation chromatography (GPC) was performed with a system equipped with refractive-index detector and Pre-Packed Column RT. The GPC columns were standardized with near-monodisperse polystyrene in molecular weights ranging from $7.0 \times 10^5$ to 1920. DMF was used as the mobile phase and the flow rate was 1.0 mL/min. The qualitative analysis of the product released from polymeric prodrugs was carried out by Shimadzu SPD-10Avp HPLC with a reversed-phase Shim-Pack VP-ODS column (150 mm × 4.6 mm). A mixture of water, acetic acid, and methanol (v/v/v = 70/0.07/30) was employed as the mobile phase, and the detection wavelength was 254 nm. The concentration of the acyclovir released in buffer solution was determined by an Analytikjena SPECORD 200 UV–vis spectrophotometer at 254 nm.

### Enzymatic synthesis of vinyl acyclovir amides (VAA and VSA): General procedure

The reaction was initiated by adding PS (15 mg/mL) to DMSO (20 mL) containing acyclovir (0.225 g, 1 mmol) and divinyl dicarboxylate (6 mmol).[31] The suspension was kept at 50°C and stirred under 250 rpm for 3 days. Formation of vinyl acyclovir amide was monitored by TLC. The reaction was terminated by filtering the enzyme, and DMSO was evaporated under reduced pressure. The product was separated by silica gel chromatography with an eluent consisting of ethyl acetate/methanol/ammonia (v/v/v = 50/8/1).

### Synthesis of poly(VAA) (PVAA, 4a)

The homopolymerization of VAA was carried out as follows: VAA (500 mg, 1.3 mmol) was dissolved in DMF (0.8 mL), and AIBN (10 mg) was added as initiator. The mixture was sealed in a 10-mL polymerization tube and stirred at 70°C under nitrogen for 24 h. The resulting product was repeatedly precipitated in methanol and dried under vacuum to give a light yellow solid PVAA (368 mg, 74%), $M_n$ = 23,000, $M_w/M_n$ = 2.65. IR (KBr, $cm^{-1}$): 2940, 2876, 1680, 1613, 1561. $^1H$ NMR (DMSO-$d_6$, δ, ppm): 12.09 (NH of acyclovir), 11.70 (NH of acyclovir), 8.13 (8-H of acyclovir), 5.45 (1′-H of acyclovir), 4.66 (CHO; OH of acyclovir), 3.46 (3′-H and 4′-H of acyclovir), 2.47–1.57 ($CH_2$). $^{13}C$ NMR (DMSO-$d_6$, δ, ppm): 176.7, 170.9 (C=O), 155.5 (C-6 of acyclovir), 149.4 (C-4 of acyclovir), 148.7 (C-2 of acyclovir), 140.7 (C-8 of acyclovir), 120.7 (C-5 of acyclovir), 73.2 (C-1′ of acyclovir), 73.2 (CHO), 71.1 (C-3′ of acyclovir), 60.6 (C-4′ of acyclovir), 36.2, 33.9, 33.6, 24.4 ($CH_2$).

### Synthesis of poly(VSA) (PVSA, 4b)

The homopolymerization of VSA was achieved by the same method as the synthesis of PVAA. The resulting PVSA was a light yellow solid (224 mg, 45%), $M_n$ = 29000, $M_w/M_n$ = 2.21. IR (KBr, $cm^{-1}$):

2930, 2856, 1678, 1612, 1561. $^1$H NMR (DMSO-$d_6$, δ, ppm): 12.02 (NH of acyclovir), 11.68 (NH of acyclovir), 8.06 (8-H of acyclovir), 5.42 (1′-H of acyclovir), 4.66 (CHO; OH of acyclovir), 3.46 (3′-H and 4′-H of acyclovir), 2.42–1.24 ($CH_2$). $^{13}$C NMR (DMSO-$d_6$, δ, ppm): 176.9, 172.8 (C=O), 155.4 (C-6 of acyclovir), 149.4 (C-4 of acyclovir), 148.7 (C-2 of acyclovir), 140.6 (C-8 of acyclovir), 120.7 (C-5 of acyclovir), 73.2 (C-1′ of acyclovir), 73.2 (CHO), 71.1 (C-3′ of acyclovir), 60.5 (C-4′ of acyclovir), 36.5, 34.2, 33.9, 29.2, 25.0 ($CH_2$).

### Synthesis of poly(VSA-*co*-MMA) (5b)

In a 10-mL sealed polymerization tube, a mixture containing VSA (350 mg, 0.8 mmol), MMA (800 mg, 8 mmol), AIBN (12 mg), and DMF (0.8 mL) was stirred at 70°C under nitrogen for 24 h. The resulting product was repeatedly precipitated in methanol and then dried under reduced pressure to give a light yellow solid poly(VSA-*co*-MMA) (322 mg, 28%), $M_n$ = 24000, $M_w/M_n$ = 1.91. IR (KBr, cm$^{-1}$): 1729, 1678, 1612, 1560, 1269, 1242, 1194, 1149. $^1$H NMR (DMSO-$d_6$, δ, ppm): 12.04 (NH of acyclovir), 11.69 (NH of acyclovir), 8.07 (8-H of acyclovir), 5.43 (1′-H of acyclovir), 4.66 (CHO; OH of acyclovir), 3.55 ($CH_3O$ of MMA), 3.47 (3′-H and 4′-H of acyclovir), 2.43-1.14 ($CH_2$), 1.10–0.74 ($CH_3$ of MMA). $^{13}$C NMR (DMSO-$d_6$, δ, ppm): 177.8, 176.8, 172.7 (C=O), 155.4 (C-6 of acyclovir), 149.4 (C-4 of acyclovir), 148.7 (C-2 of acyclovir), 140.6 (C-8 of acyclovir), 120.6 (C-5 of acyclovir), 73.1 (C-1′ of acyclovir), 73.1 (CHO), 71.0 (C-3′ of acyclovir), 60.4 (C-4′ of acyclovir), 52.2 ($CH_3O$ of MMA), 44.8, 44.4, 37.8, 36.4, 33.9, 29.1, 28.9, 24.9, 24.5, 19.0, 16.6 ($CH_3$, $CH_2$, C). By the same method, a series of poly(VSA-*co*-MMA) with different acyclovir loading capacity were synthesized by changing the molar ratio of VSA to MMA.

### Synthesis of poly(VSA-*co*-AA) (5c)

The copolymerization of VSA and AA was achieved according to the earlier method. The reactive comonomers (VSA and AA) were mixed in a molar ratio of 1 : 2 and 0.5 wt % AIBN was added as initiator. The resulting prodrug was a light yellow solid poly (VSA-*co*-AA) (440 mg, 76%), $M_n$ = 210000, $M_w/M_n$ = 2.11. IR (KBr, cm$^{-1}$): 3431, 2931, 2857, 1701, 1681, 1612, 1561. $^1$H NMR (DMSO-$d_6$, δ, ppm): 12.06 (NH of acyclovir), 11.70 (NH of acyclovir), 8.08 (8-H of acyclovir), 5.45 (1′-H of acyclovir), 4.67 (CHO; OH of acyclovir), 3.46 (3′-H and 4′-H of acyclovir), 2.89–1.25 (CH of AA; $CH_2$). $^{13}$C NMR (DMSO-$d_6$, δ, ppm): 176.9, 176.4, 172.8 (C=O), 155.4 (C-6 of acyclovir), 149.4 (C-4 of acyclovir), 148.7 (C-2 of acyclovir), 140.6 (C-8 of acyclovir), 120.6 (C-5 of acyclovir), 73.1 (C-1′ of acyclovir), 73.1 (CHO), 71.0 (C-3′ of acyclovir), 60.4 (C-4′ of acyclovir), 40.3, 37.1, 36.4, 34.0, 33.5, 29.0, 24.9, 24.6 ($CH_2$, CH).

### Synthesis of poly(VSA-*co*-VAG) (5d)

Poly(VSA-*co*-VAG) was synthesized by the same method as the preparation of poly(VSA-*co*-MMA) and the molar ratio of VSA to VAG was 1 : 4. The resulting copolymer was a light yellow solid (384 mg, 48%), $M_n$ = 11,000, $M_w/M_n$ = 2.63. IR (KBr, cm$^{-1}$): 3431, 2934, 1735, 1678, 1610, 1561, 1414, 1378, 1144, 1073. $^1$H NMR (DMSO-$d_6$, δ, ppm): 12.09 (NH of acyclovir), 11.72 (NH of acyclovir), 8.11 (8-H of acyclovir), 6.57, 6.20 (1-OH of D-galactose), 5.46 (1′-H of acyclovir), 5.31–3.46 (CHO; 3′-H, 4′-H, and OH of acyclovir; 1-H, 2-H, 3-H, 4-H, 5-H, 6-H, 2-OH, 3-OH, and 4-OH of D-galactose), 2.44–1.25 ($CH_2$). $^{13}$C NMR (DMSO-$d_6$, δ, ppm): 176.9, 173.2, 172.6, 172.3 (C=O), 155.5 (C-6 of acyclovir), 149.4 (C-4 of acyclovir), 148.6 (C-2 of acyclovir), 140.6 (C-8 of acyclovir), 120.6 (C-5 of acyclovir), 97.8, 93.1 (C-1 of D-galactose), 73.1 (C-1′ of acyclovir), 71.0 (C-3′ of acyclovir), 69.0, 69.2, 69.5, 69.8, 70.0, 72.3, 73.2, 73.6 (C-2, C-3, C-4, and C-5 of D-galactose), 64.6 (C-6 of D-galactose), 60.4 (C-4′ of acyclovir), 36.5, 33.6, 33.2, 31.2, 29.0, 24.9, 24.3, 24.1 ($CH_2$).

### Preparation of acyclovir microcapsules

Acyclovir (raw drug) was chosen as a template and the layer-by-layer assembly of polyelectrolytes onto acyclovir microcrystals was carried out as follows: Acyclovir microcrystals were alternately dispersed in PSS and PAH solutions. Following an adsorption time of 15 min for PSS or PAH adsorption, the suspension was centrifuged at a speed of 10,000 rpm for 5 min. The supernatant was then removed, and three cycles of water washing and redispersion were applied to remove the excess unadsorbed polyelectrolytes in solution. The assembly procedure described earlier was repeated until 5 bilayers-coated microcapsules ($(ACV)_5$) were obtained.[28,33]

### *In vitro* drug release studies

Poly(VSA-*co*-MMA) (entry 2 in Table I) was chosen as a model polymeric prodrug of acyclovir for *in vitro* drug release studies in pH 1.2, 0.2*M* HCl/NaCl/glycine and pH 7.4, 0.1*M* phosphate buffer solution. The experiment was carried out as follows: poly (VSA-*co*-MMA) (15 mg) was added to 1 mL buffer solution and subsequently placed into a dialysis membrane (MWCO = 3500) for release study. The dialysis membrane was then placed into a 10-mL bottle with 5 mL corresponding buffer solution and the medium was stirred under 100 rpm at 37°C. At set time intervals, the whole medium (5 mL) was

**TABLE I**
**The Influence of the Concentration of Initiator and the Molar Ratio of VSA to MMA on the Copolymer**

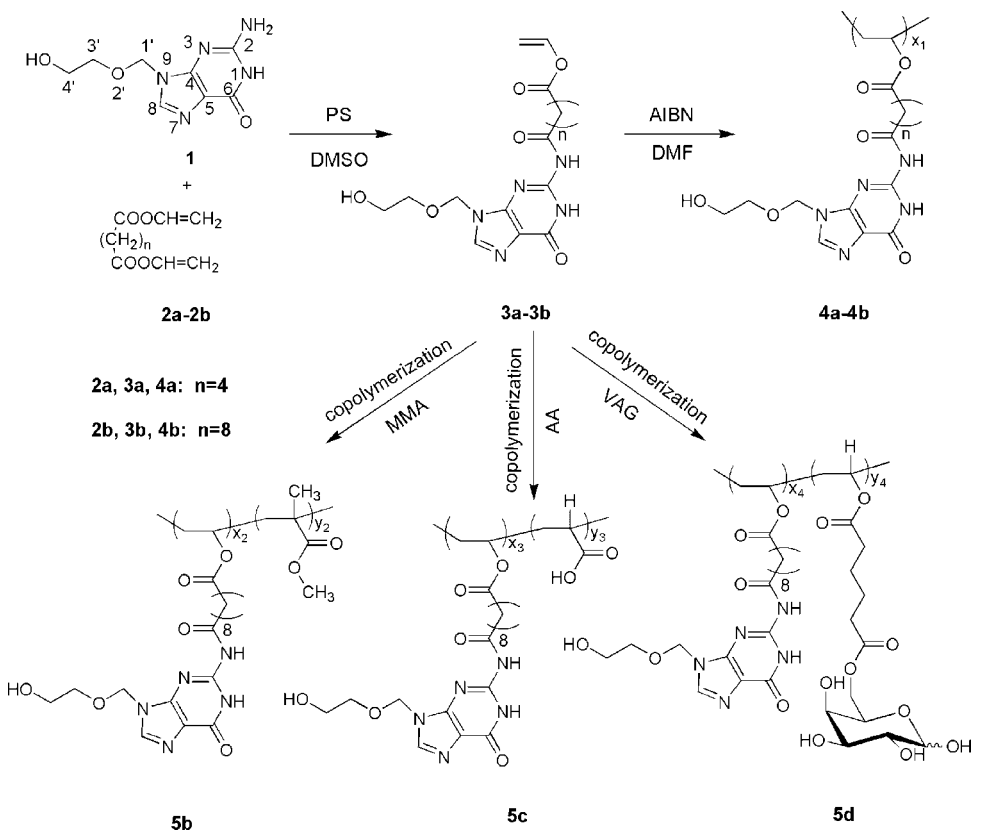
| Entry | VSA/MMA in the Feed (mol %) | Initiator (%) | Conversion (%) | ACV in the copolymer[a] (wt %) | $M_n$[b] $\times 10^{-4}$ | $M_w/M_n$[b] |
|---|---|---|---|---|---|---|
| 1 | 1/10 | 10 | 56 | 15.7 | 2.0 | 2.40 |
| 2 | 1/10 | 5 | 52 | 15.7 | 2.1 | 2.40 |
| 3 | 1/10 | 1 | 28 | 16.5 | 2.4 | 1.91 |
| 4 | 1/5 | 1 | 25 | 18.9 | 2.1 | 2.21 |
| 5 | 1/20 | 1 | 61 | 9.6 | 20 | 1.68 |

[a] Determined by the integration ratios of $^1$H NMR spectra.
[b] Determined by GPC analysis.

taken and replaced with the same volume of fresh buffer solution. HPLC was used for the qualitative analysis of the product released. The concentration of acyclovir released in buffer solution was determined by UV at 254 nm. The small-molecular-weight acyclovir (raw drug) and the acyclovir microcapsules ($(ACV)_5$) prepared by self-assembly technique were chosen as control.

## RESULTS AND DISCUSSION

A facile protocol for the synthesis of functional polymeric prodrugs of acyclovir was achieved by combining selective enzymatic synthesis with radical polymerization, and a series of polymer-acyclovir conjugates were obtained. The entire synthetic route was shown in Scheme 1. Acyclovir was first converted to polymerizable monomers, which were then homopolymerized or copolymerized with a series of suitable comonomers to produce polymeric prodrugs of acyclovir. Polymerizable acyclovir esters and amides could be respectively synthesized through selective enzymatic transesterification of acyclovir with divinyl dicarboxylates.[31] As it was easier to obtain the homopolymers of vinyl acyclovir amides and the cleavage of an amide bond was slower than that of an ester bond in acid medium, two vinyl acyclovir amides (VAA and VSA) were chosen as mono-




**Scheme 1** Synthesis of polymeric prodrugs of acyclovir.

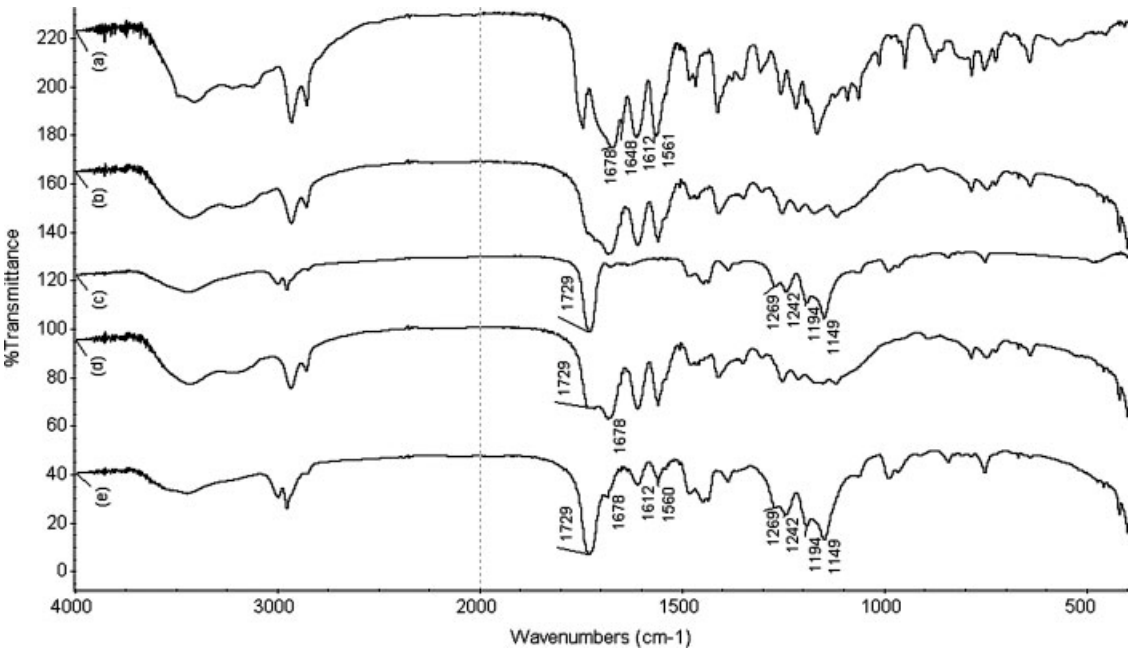



**Figure 1** IR spectra of (a) VSA, (b) PVSA, (c) PMMA, (d) poly(VSA-*co*-MMA) (VSA:MMA = 1 : 2, by mol), and (e) poly (VSA-*co*-MMA) (VSA:MMA = 1 : 10, by mol).

mers for the further synthesis of polymeric prodrugs.

The homopolymerization of vinyl acyclovir amides was achieved by radical polymerization using AIBN as initiator in DMF and two corresponding polymeric prodrugs with acyclovir as pendant (PVAA and PVSA) were obtained (Scheme 1). The resulting polymeric prodrugs were characterized by FTIR and NMR, and the molecular weights were determined by GPC. Taking PVSA for example, IR spectrum of the polymeric prodrug revealed that vinyl group absorption (1648 $cm^{-1}$) present in the vinyl acyclovir amide monomer was absent in the corresponding polymer (Fig. 1). $^1H$ NMR of the homopolymer showed that the peak of poly(vinyl alcohol) main chain ($^1H$ NMR: δ 4.66) appeared, while the peaks of vinyl group existing in monomer ($^1H$ NMR: δ 7.20, 4.87, 4.63) were absent (Fig. 2). Both the resulting homopolymers have high acyclovir loading capacity (>50 wt %).

The radical copolymerization of vinyl acyclovir amide VSA with different comonomers was also carried out to endow the polymeric prodrugs with more variability in their composition and properties. VAG, MMA, and AA were chosen as comonomers to synthesize poly(VSA-*co*-VAG), poly(VSA-*co*-MMA), and poly(VSA-*co*-AA), respectively. The resulting copolymers were characterized by FTIR, NMR, and GPC. IR spectrum of poly(VSA-*co*-VAG) showed that vinyl group absorption disappeared, and the characteristic absorption assigned to D-galactose ester moiety (3431, 1735, 1073 $cm^{-1}$) and that assigned to acyclovir amide moiety (1678, 1610, 1561 $cm^{-1}$) appeared. Also, $^1H$ NMR and $^{13}C$ NMR of poly(VSA-*co*-VAG) revealed the absence of vinyl group and existence of acyclovir, D-galactose groups, and poly(vinyl alcohol) main chain. In IR spectrum of poly(VSA-*co*-MMA), 1729, 1269, 1242, 1194, and 1149 $cm^{-1}$ were attributed to MMA and 1678, 1612, and 1560 $cm^{-1}$ showed the existence of acyclovir (Fig. 1). From $^1H$ NMR of poly(VSA-*co*-MMA), the molar ratio of VSA to MMA on the copolymer could be calculated according to the ratio between the integral of ethoxyl protons of acyclovir (δ 5.43) and the integral of methoxyl protons of MMA (δ 3.55) or that of methyl protons of MMA (δ 1.14–0.74). As expected, the double bonds present in VSA and AA were absent in poly(VSA-*co*-AA). Moreover, the other bonds assigned to vinyl acyclovir derivative and AA still appeared in the IR and NMR of the copolymer.

The influence of the concentration of initiator and the molar ratio of VSA to MMA on the copolymerization was investigated. The results were shown in Table I. From this Table, we found that the molecular weight and conversion of the polymeric prodrug were in connection with the concentration of initiator and the molar ratio of VSA to MMA. Also, the composition of polymeric prodrugs and the loading capacity of acyclovir in polymeric prodrugs could be easily controlled by changing the molar ratio of comonomers. In this article, polymeric prodrugs with different composition were prepared and acyclovir loading capacity in these prodrugs was between 9.6 and 18.9 wt %.

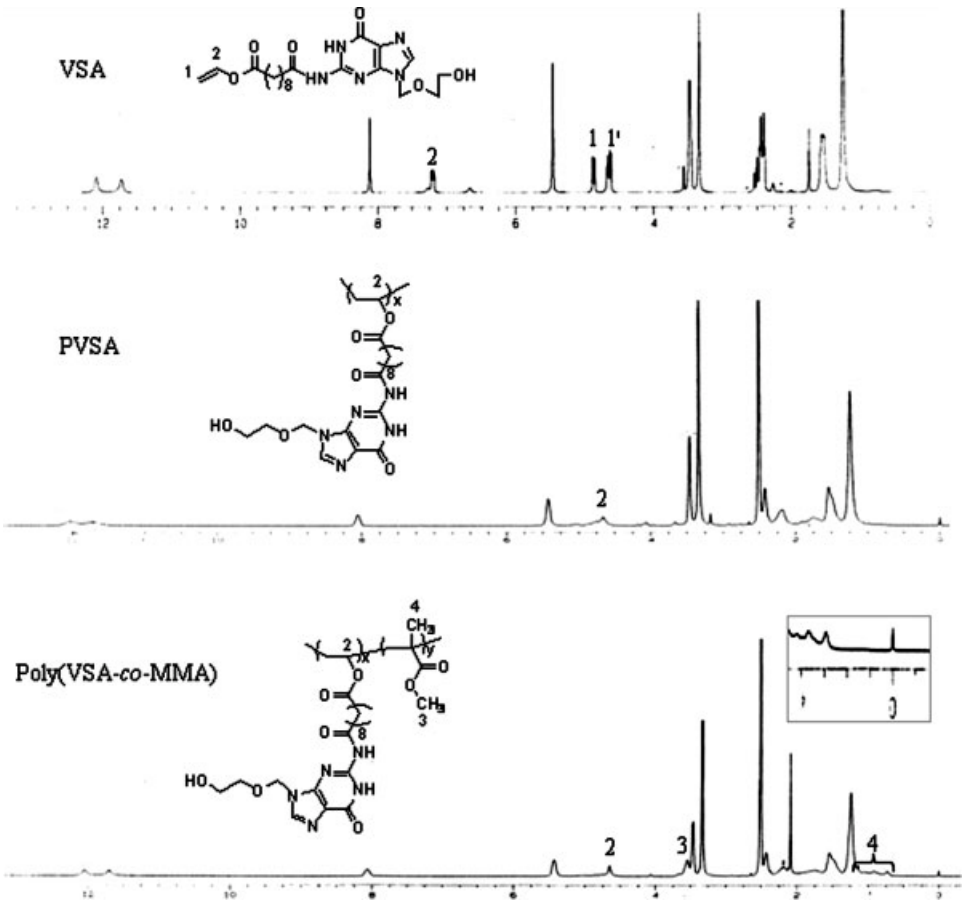



**Figure 2** $^1$H NMR spectra of vinyl acyclovir amide, its homopolymer and its methyl methacrylate copolymer.

*In vitro* release of acyclovir from poly(VSA-*co*-MMA) was studied in different buffer solutions at pH 1.2 (simulated gastric juice) and at pH 7.4 (extracellular fluids) by HPLC and UV. First, HPLC was used for the qualitative analysis of the product released. When a mixture of water, acetic acid, and methanol (v/v/v = 70/0.07/30) was employed as the mobile phase, the retention time of acyclovir was 3.09 min at a flow rate of 1.0 mL/min. The HPLC profile of the product released from the polymeric prodrug at pH 7.4 bluffer solution after 2 days was shown in Figure 3. It could be determined that product released from poly(VSA-*co*-MMA) was acyclovir. The curves of the total amount of acyclovir released (determined by UV) against time in buffer solutions at different pH values were shown in Figure 4(a). Acyclovir released from poly(VSA-*co*-MMA) after 7 days was $\sim$ 35 and 29% in buffer solution at pH 1.2 and 7.4, respectively. Also, we compared the release curves of acyclovir (raw drug), 5 bilayers-coated acyclovir microcapsules ($(ACV)_5$), and poly(VSA-*co*-MMA) at pH 1.2 [Fig. 4(b)]. Herein, low-molecular-weight acyclovir (raw drug) was fast released and the cumulative release amount was $\sim$ 85% after 2 h. The release rate of acyclovir from $(ACV)_5$ was slower than that of low-molecular-weight acyclovir and the released acyclovir was $\sim$ 45% after 2 h. Only 8% acyclovir was released from the polymeric prodrug after

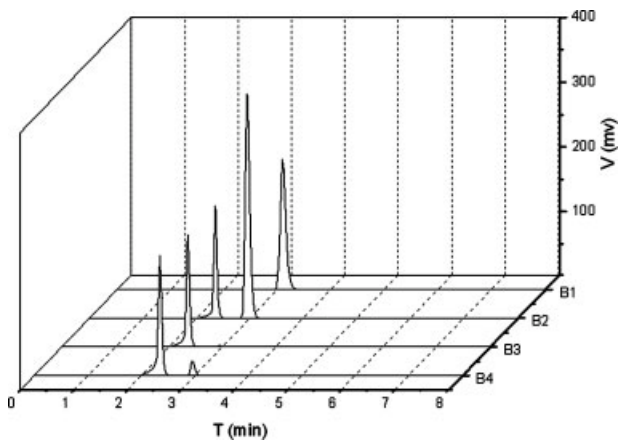



**Figure 3** Determination of product released from poly (VSA-*co*-MMA) in buffer solution at pH 7.4. B1. HPLC profile of acyclovir dissolved in methanol; B2. HPLC profile of acyclovir dissolved in pH 7.4 phosphate buffer solution; B3. HPLC profile of phosphate buffer solution (pH 7.4); B4. HPLC profile of product released from poly(VSA-*co*-MMA) in pH 7.4 phosphate buffer solution.

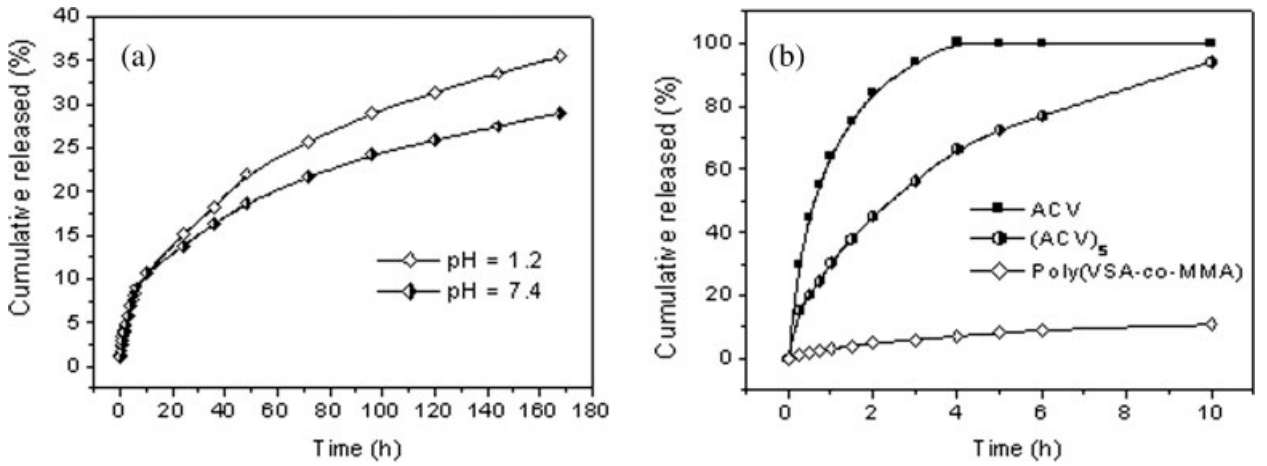



**Figure 4** *In vitro* release of acyclovir. (a) the release of acyclovir from poly(VSA-*co*-MMA) in buffer solutions at different pH values; (b) the release curves of acyclovir (ACV, raw drug), 5 bilayers-coated acyclovir microcapsules ($(ACV)_5$) and poly(VSA-*co*-MMA) in pH 1.2 buffer solution.

2 h. It was evident that the resulting polymeric prodrug, in which acyclovir was covalently linked to polymer carrier, showed the best effect of prolonged release.

## CONCLUSIONS

By combining enzymatic selective transesterification with radical polymerization, a facile route for the synthesis of functional polymeric prodrugs with acyclovir as pendant was achieved. Five novel polymeric prodrugs of acyclovir were synthesized and characterized. The loading capacity of acyclovir in polymeric prodrug could be easily controlled by changing the molar ratio of comonomers. *In vitro* drug release studies showed that acyclovir was slowly released from the polymeric prodrug poly (VSA-*co*-MMA). The galactose-functionalized polymeric prodrug of acyclovir, poly(VSA-*co*-VAG), was potential liver-targeting drug delivery system. Further research about high affinity of poly(VSA-*co*-VAG) to HepG2 cells is in progress.

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