Biodegradable Amphiphiles of Grafted Poly(lactide) onto 2-Hydroxyethyl Methacrylate-*co*-*N*-Vinylpyrrolidone Copolymers as Drug Carriers

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ABSTRACT: This article describes the synthesis and characterization of 2-hydroxylethyl methacrylate-*co*-*N*-vinylpyrrolidone copolymers, (HEMA-*co*-NVP), via free radical polymerization followed by grafting of poly(lactide) onto (HEMA-*co*-NVP) copolymers, via ring opening polymerization using tin octoate as a catalyst. The copolymers and the grafted copolymers (i.e., amphiphiles) were subjected to sustained release studies using salicylic acid, as a model drug. Characterization of the formed copolymers was performed using ^{1}H-NMR, ^{13}C-NMR, FTIR, TGA, DSC, and SEM techniques. Derivative of TGA thermogram was used to determine %hydrophilicity and %hydrophobicity in the grafted and ungrafted copolymers. The SEM morphology revealed porous layers with crispy structure that were most likely due to the presence of poly(lactide) chains. At lower content of poly(lactide) moiety, grafted copolymers showed non-Fickian diffusion release rate, whereas Fickian diffusion release rate at higher content of poly(lactide) was observed. The increase of poly(lactide) content (i.e., larger %hydrophobicity) in the copolymer increased the drug-sustainability, due to the consistent but porous amphiphilic degradable structures that allow controllable release of drug in time interval. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 840–848, 2011

Key words: grafting; poly(lactide); amphiphiles; sustained drug release

INTRODUCTION

Biomimetic polymers that control the interactions between the material and its environment in certain biological systems are gaining too much interest especially in designing polymeric vehicles for drug targeting or tissue engineering.[1–4] This class of biodegradable polymers is known to have various biomedical implementations due to their biodegradability and biocompatibility with human tissues. Their main applications include drug delivery systems, artificial organs, surgical devices, temporary implants for tissue regeneration, carriers of immobilized enzymes and cells, and biosensors.[5–9] Among the vast applications of biodegradable polymers, drug delivery systems emerge as successful solution for targeting selected organs or tissues. The use of biodegradable polymers in drug delivery systems may have various advantages such as possible control of drug release rate at the desired position and/or time, stability of the polymer in blood stream and capability of the polymer to protect the drug against *in vivo* decomposition.

Poly(lactide), PLA, has been widely applied as surgical suture, drug carrier, and temporary scaffold for tissue engineering due to its good mechanical properties.[10–16] On the other hand, PLA has high crystallinity, strong hydrophobicity, and no clear bioactive function, which necessarily result in uncontrollable biodegradation rate and unexpected biological response to cells and/or tissues.[17] Therefore, the introduction of more hydrophilic moieties, through copolymerization, into the structure of PLA containing polymeric matrix may end up with large development on the properties of the drug delivery systems through formation of balanced hydrophilic/hydrophobic amphiphiles.

Poly(*N*-vinylpyrrolidone), PNVP, is a hydrophilic water-soluble and biocompatible polymer that has been extensively used in pharmaceuticals, cosmetics, food, printing inks, textiles, and many more diverse applications. Because of its versatility, PNVP and its copolymers have also found numerous applications in modern biological and material sciences and

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technologies.[18–23] Whereas poly(2-Hydroxyethyl methacrylate), PHEMA, is a well known amphiphilic thermo- and pH-sensitive, molecularly imprinted material, and biocompatible structure drug delivery vehicle.[24–29]

The aim of this study was to synthesize balanced hydrophilic/hydrophobic (HEMA-*co*-NVP) copolymers grafted with PLA, via ring opening polymerization, to obtain various %hydrophobic forms of biodegradable biocompatible amphiphiles. Later on, the formed grafted copolymers (i.e., amphiphiles) were tested and evaluated as successful candidatures to sustain and control the release of salicylic acid, as a model drug, from tablets prepared by direct compression.

EXPERIMENTAL

Materials

2-hydroxyethyl methacrylate, HEMA, (96%, Sigma), *N*-vinylpyrrolidone, NVP, (98%, Acros), 3,6-dimethyl-1,4-dioxane-2,5-dione, lactide (100%, Sigma), benzoylperoxide (moistened with 25%, Merk), tin(II)2-ethylhexanoate [$Sn(Oct)_2$] (95%, Sigma) were used as received. All organic solvents used were of solvent grade. Buffer solutions of pH 5.5 and 7.4 were prepared from mono and dibasic sodium phosphates (JHD) in purified deionized double distilled water.

Synthesis of (HEMA-*co*-NVP) copolymers

Two molar feed ratios of 0.66 and 1.00 HEMA and NVP (i.e., [HEMA]/[NVP]) were used in the formation of (HEMA-*co*-NVP) copolymers. The corresponding monomer amount of each HEMA and NVP were weighed and mixed in 50-mL conical flasks, degassed, and flushed for 5 min with dry N_2 stream. A 1.0 mol % of benzoylperoxide with respect to total monomers was dissolved in each flask under N_2 atmosphere and polymerization was conducted at 60°C for 4 h. After polymerization was over, the samples were left to cool to room temperature. Four-folds of methanol solvent were then added, sonicated for 2 h, and each sample was continuously washed with diethyl ether. Products were collected in gel form and dried in vacuum-oven at 70°C for 24 h. All collected products were reserved in a desiccator over silica-blue until being used elsewhere.

Synthesis of grafted PLA onto (HEMA-*co*-NVP) copolymers

Corresponding amount of 0.66 and 1.00*M* feed ratios of (HEMA-*co*-NVP) copolymers were weighed in separate predried 100-mL round-bottomed flasks equipped with magnetic stirrers and outer stopcocks, then flushed with N_2-stream for 5 min while stirring, and dried in vacuum line at 75°C for 1 h. After cooling to room temperature, a corresponding lactide weight with respect to HEMA content was added (Table I), mixed under N_2 stream, and redried in the same manner. Thereafter, each flask was refilled with N_2 gas and sealed with rubber valve and eventually inserted in oil-bath fixed at 160°C. After 30 min, 2.0 mol % of $Sn(Oct)_2$ catalyst with respect to the HEMA content was added under N_2 stream, resealed and kept for 4 h at the same temperature. After cooling, each flask was filled with methanol and sonicated for 2 h. Products were then collected by precipitation with ethyl acetate : hexane : diethyl ether (1 : 1 : 0.25) mixture, to remove possible unreacted lactide and its homopolymers. Products were dried in vacuum-oven at 50°C for 24 h. All products were collected and reserved in desiccators over silica-blue until being used elsewhere (Scheme 2).

TABLE I
Copolymer/Lactide Ratio Together with Sample ID's

$\left(\frac{HEMA}{NVP_{feed}}\right)$	HEMA : Lactide[a] molar ratio	Sample ID
0.66	1 : 1	0.66–1
	1 : 3	0.66–3
	1 : 5	0.66–5
1.00	1 : 1	1.00–1
	1 : 3	1.00–3
	1 : 5	1.00–5

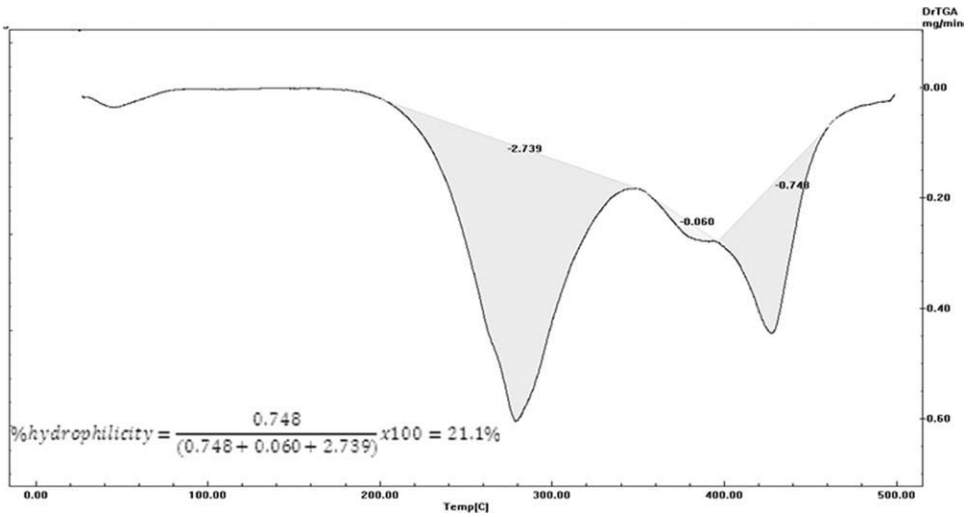
[a] Ratio of lactide to the copolymer was taken with respect to HEMA content in copolymer.

Using the derivative of TGA thermogram, the area under curve presents the change of degradable mass loss% in temperature interval, in mg/min/K. Therefore, this change could present the fraction of a certain moiety in the copolymer. Since PNVP moiety has hydrophilic character whereas both PHEMA and PLA moieties have hydrophobic character, then the area under PNVP moiety curve divided by the total area under curves would present the %hydrophilicity in the copolymer and likewise, the area under PLA and PHEMA divided by the total area under curves would present the %hydrophobicity in the copolymer. According to Scheme 1 and relations (1) and (2), the decomposition temperatures of PLA, PHEMA, and PNVP moieties were 280, 385, and 435°C, respectively.

$$\%\ \text{hydrophilicity} = (A_{PNVP}/A_T) \times 100 \quad (1)$$

$$\%\ \text{hydrophobicity} = [(A_{PHEMA} + A_{PLA})/A_T] \times 100 \quad (2)$$

where A_{PNVP}, A_{PHEMA}, and A_{PLA}, are the area under PNVP, PHEMA, and PLA curves respectively, and

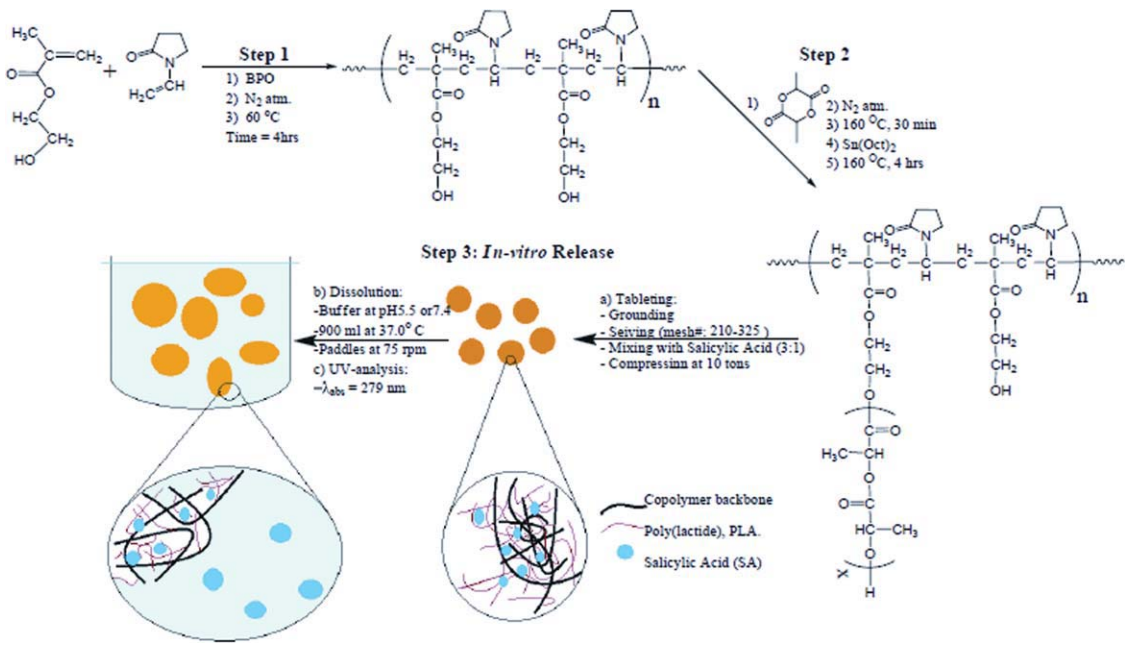


Scheme 1 Derivative of TGA thermogram and corresponding areas of PLA, PHEMA, PNVP moieties, sample 0.66–5, respectively.

A_T is the total area under the curves. If %hydrophilicity equals zero then the copolymer is said to be totally hydrophobic, whereas if %hydrophilicity equals 100 then the copolymer is said to be totally hydrophilic.

Characterization techniques

Nuclear magnetic resonance (NMR): The ^{1}H- and ^{13}C-NMR Spectra were recorded on a Bruker Biospin spectrometer of 400 MHz in CD_3OD for the copolymers and in DMSO-d_6 for the final products; the samples were macerated in solvents for 2 days before analysis. Chemical shifts (δ) were given in ppm. Fourier-Transform infrared spectroscopy (FTIR): FTIR spectra were recorded by KBr disks, using a JASCO (Japan) FTIR spectrophotometer in the range of 4000–400 cm^{-1}. Thermo-Gravimetric Analysis (TGA): samples were studied using a Shimadzu TA-50 (Japan) thermogravimetric analyzer. Samples were heated at a heating rate of 10°C/min from room temperature to 500°C under N_2 atmosphere. Differential scanning calorimetry (DSC): samples were studied using a Metler-Toledo differential scanning calorimeter. Samples were first heated from ambient temperature to 200°C at a heating rate



Scheme 2 Synthesis of grafted PLA onto (HEMA-*alt*-NVP) copolymers and its sustained release drug delivery system. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of 10°C/min under N_2 atmosphere, and then cooled to ambient temperature and reheated to 200°C at the same heating rate. Glass transition temperature (T_g) was taken as the mid-point between onset and end-set points of the transition. Scanning electronic microscopy (SEM): Samples were coated on carbon plates under vacuum using an Emitech K500X coating chamber (England) and imaged by an FEI Inspect F50 scanning electronic microscope (Netherlands) equipped with a Field Emission Gun (FEG).

Model delivery system and *in vitro* drug release

Salicylic Acid, SA, (*o*-hydroxybenzoic acid) is a water-soluble anti-inflammatory agent known for its ability to ease aches and pains and reduce fevers, especially in bowel and intestine. Grafted copolymers were grounded, sieved to the range of 210–325 mesh# and physically mixed with SA in a weight ratio of 3 : 1, respectively, in closed glass tubes using vortex. Tablets were made by direct compression under a 10 ton piston. *In vitro* drug release was conducted using a VanKel Dissolution Testing Station, VK 700, assembled with VK 750D electrical heater, at 37.0°C ± 0.5°C, and rotating paddles, at 75 rpm of chosen speed. Each dissolution vessel was filled with 900 mL of phosphate buffer solution (pH 5.5 or 7.4) and thermostated at 37.0 ± 0.5°C for 30 min. Tablets were then placed in separate vessels and sink conditions were assured. Samples were withdrawn from the receiver solutions at different time intervals and analyzed for drug content. The withdrawn samples were replaced with equivalent volumes of fresh phosphate buffer solution of appropriate pH. All runs were repeated in triplicates and the average accumulated drug release was calculated in terms of percentage. *In vitro* drug release versus time profiles were constructed. Linear profiles were taken and reanalyzed using Steady-State J_{SS}-Model as diffusion developed assumption.[30]

Method of drug analysis

Drug content was measured using a Cintra 5 double beam UV-vis Spectrophotometer, GBC Scientific Equipment, USA, at $\lambda_{max} = 279$ nm. The method of analysis was fully validated.

RESULTS AND DISCUSSION

^{1}H- and ^{13}C-NMR

The ^{1}H-NMR spectrum of grafted PLA onto (HEMA-*co*-NVP) copolymer presented in Figure 1 showed the different moieties in the copolymer. For NVP moiety, the methylene group in the backbone was located at 1.92 ppm (b′), the methyne group at 4.20

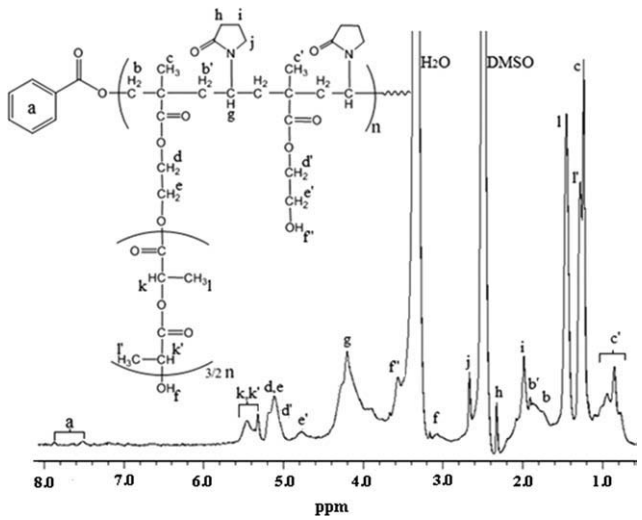


Figure 1 ^{1}H-NMR spectrum of grafted PLA onto (HEMA-*co*-NVP) copolymers, sample 0.66–3, in DMSO-d_6.

ppm (g), and the pyrrolidone ring protons α-H at 2.35 ppm, β-H at 1.95 ppm, while γ-H at 2.71 ppm (h, i, and j, respectively). For ungrafted HEMA moiety; methyl group at 0.83 ppm (c′), methylene next to the ester at 5.08 ppm (d′) overlapped with (d) and (e) peaks, alcoholic methylene (e′) at 4.78 ppm, and OH group at 3.62 ppm (f′). For grafted HEMA moiety; methylene group in the backbone located at 1.72 ppm (b), methyl group was at 1.21 ppm (c), methylene groups (d) and (e) next to the ester was positioned at the same δ = 5.10 ppm, and OH group was located at 3.02 ppm (f). For PLA moiety; the presence of intensed methyl groups located at 1.28 and 1.45 ppm (l, l′), and methyne groups at 5.32 and 5.46 ppm (k and k′) were the clue to the grafting process. Hence, the presence of methyl groups l and l′, and methyne groups k and k′, together with chemical shifts of HEMA groups, upon grafting, were the evidence of the grafting process of PLA moiety on the hydroxyl group of HEMA moiety.

Furthermore, to ensure the structural confirmation of grafted copolymers, a clearer ^{13}C-NMR spectrum for the sample 0.66–3 was obtained in Figure 2. Obvious distinction between grafted and ungrafted carbonyl groups (x, x′, y, y′, and z) and methyl groups (l, l′, c, and c′) were considered clue for the grafting process.

FTIR

The FTIR spectra of ungrafted and different PLA grafted (HEMA-*alt*-NVP) copolymers is shown in Figure 3. The HEMA carbonyl stretching band was located at 1724 cm^{-1}, whereas the NVP carbonyl stretching band was located at 1664 cm^{-1}. Similarly, the COC bending band at 1168 cm^{-1} and the C—N stretching band at 1460 cm^{-1} of the HEMA moiety

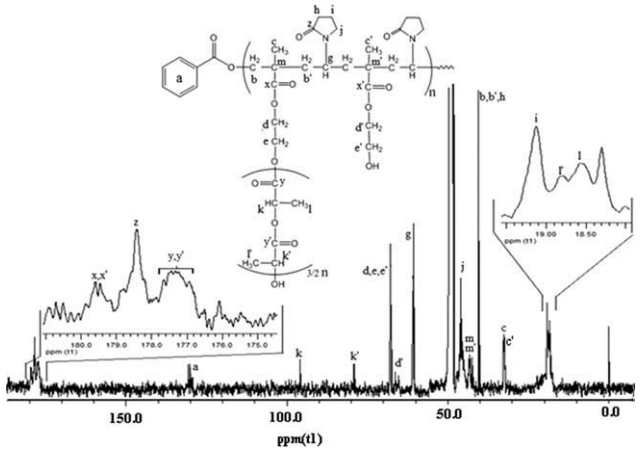


Figure 2 ^{13}C-NMR spectrum of grafted lactide onto (HEMA-*co*-NVP) copolymers, sample 0.66–3.

were also distinguishable. Furthermore; upon grafting of lactide onto the copolymer, a new carbonyl stretching band of PLA ester group appeared at 1729 cm^{-1}, which was overlapped with the carbonyl band of HEMA moiety. It could be clearly seen (Fig. 3) that the carbonyl band of PLA located at 1729 cm^{-1} strongly increased upon the increase of PLA content in the grafted copolymer. Moreover, a new C—H stretching band corresponding to the PLA methyl group has emerged at 2984 cm^{-1}.

One interesting feature must also be included; the broadening of OH band at 3400 cm^{-1} decreased until it almost disappeared in sample 0.66–5. This decrease was attributed to the increase in PLA content (i.e., increase in %hydrophobicity) which retarded moisture and water absorbency, compared with the ungrafted copolymer, which was in jelly form with high capability for water absorbency. Hence, it was deduced that the inclusion of a hydrophobic moiety (i.e., PLA) into the copolymer would result in a more hydrophobic copolymer that would retard water absorbency and hence become less hygroscopic.

Thermal analysis

The derivative of TGA thermograms shown in Figure 4(a) illustrated the thermal decomposition temperatures (T_d) of PHEMA, PNVP, and ungrafted (sample 0.66) and PLA grafted copolymers (arrows indicate the T_d of PLA moiety). Furthermore, the area under curve corresponds with the change of %mass loss at certain temperature interval (i.e., decomposition range). The decomposition temperatures of PHEMA and PNVP moieties were 365 and 435°C, respectively. Upon grafting, the area under PLA curve has increased due to expected larger content of lactide incorporated onto the copolymer. On the other hand, the area under PHEMA curve has decreased and an up-shift in its T_d value of about 30°C was observed. This large up-shift in T_d of PHEMA moiety confirmed that degradable PLA moiety has removed further the ester group of HEMA moiety. This removal of HEMA pendent groups could encourage hydrophobic interactions, formation of expected crystalline regions, and moreover consistent structure reformation, which then would result in larger decomposition temperatures.

Table II summarizes the %hydrophilicity and %hydrophobicity determined using the derivative of TGA thermogram and relations (1) and (2).

It could be seen that as the PLA in the feed increased, a simultaneous increase in the %hydrophobicity and a decrease in the %hydrophilicity had occurred. The increase in %hydrophobicity values of samples 0.66–5 and 1.00–5 confirmed their dominantly hydrophobic nature, which came in accordance with the lesser water absorbency deduced from the FTIR spectra. Furthermore, the significance of the %hydrophobicity will be discussed in sustained drug release, where it could play a dominant role in the rate of drug release.

The DSC thermograms presented in Figure 4(b) showed the glass transitions of different 0.66 grafted copolymer samples (arrows indicate T_g values). The reported glass transition temperature values for PLA and its functional derivatives are in the range between 15 and 45°C.[31] All grafted copolymer showed glass transitions between 42 and 70°C,

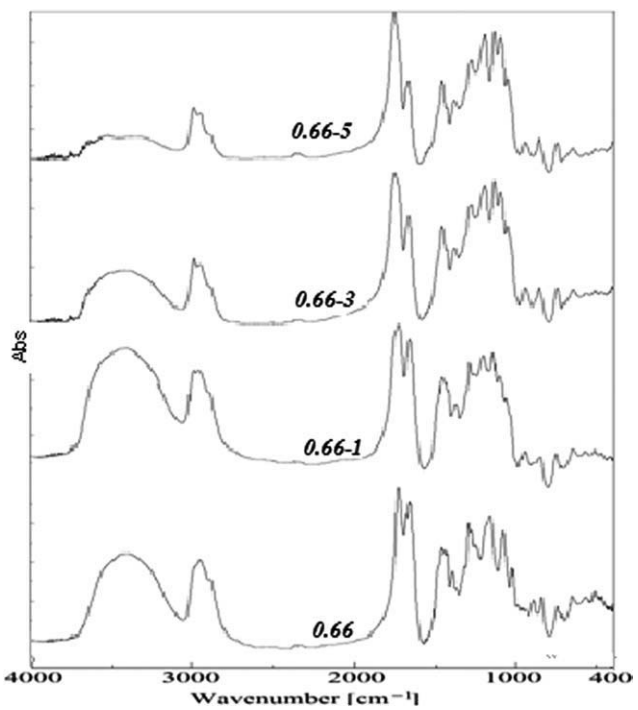


Figure 3 FTIR spectra for the grafted copolymers (0.66–1, 0.66–3, and 0.66–5) together with ungrafted copolymer (0.66).

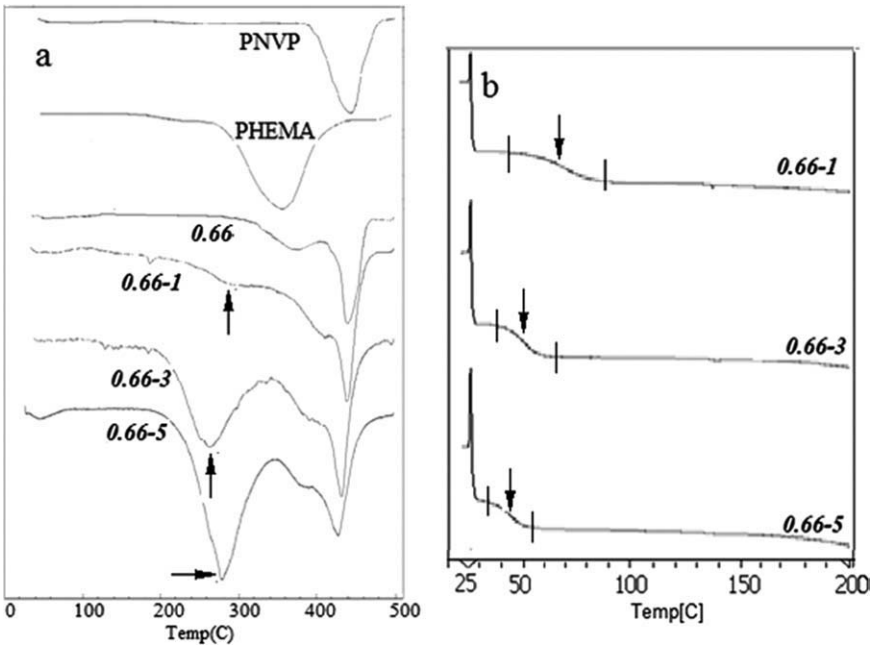


Figure 4 (a) Derivative of TGA thermogram of ungrafted and different 0.66 samples, (b) DSC thermogram of different 0.66 samples with its T_g values.

decreasing as the content of PLA increased. This decrease in T_g values upon the introduction of larger PLA moiety implicitly indicated that the introduction of PLA chains into the copolymer may have reduced intermolecular and intramolecular forces between chains, and thus reduced chain alignment and increased the free volume between chains. As a result, consequent larger end-to-end distance in these amorphous copolymers could have occurred.

SEM morphology

SEM images (Fig. 5) of ungrafted (HEMA-*alt*-NVP) copolymers showed separable flattered flakes accumulated above each other with almost 7.0 × 3.0 μm area. Such flakes were penetrated and diffused through melt lactide, upon grafting at 160°C, and formed PLA unoriented amorphous structures with melt phase shape (0.66–1 and 1.00–1). Accordingly, upon increasing the PLA content in the copolymer the flaky shapes increasingly disappeared and more likely became more flattered with pealed-like crunchy layers observed. These pealed-off layers were most likely due to the presence of PLA chains. Experimentally, it was noticed that as the content of PLA increased, grafted copolymers became crunchier, crispier, and more easily handled, especially in tablet formation. On the other hand, ungrafted copolymers were more flexible and more difficult to deal with during tablet formation. In addition to the crunchier appearance of grafted copolymers, two dimensional porous-like structures were observed (0.66–3, 0.66–5, 1.00–3, and 1.00–5). The appearance of porous system would occur as a result of the increase in the free volume between chains and expected larger end-to-end distance, as deduced from DSC thermograms. Furthermore, the porosity of the formed grafted copolymers would be very useful in explaining the controlled release of salicylic acid in the following section.

TABLE II
%Hydrophilicity and %Hydrophobicity as Determined from Relations (1) and (2) Using TGA Thermogram Derivative

Sample ID	%Hydrophilicity	%Hydrophobicity
0.66	76.9	23.1
0.66–1	75.9	24.1
0.66–3	26.2	73.8
0.66–5	21.1	78.9
1.00	69.8	30.2
1.00–1	86.7	13.3
1.00–3	55.8	44.2
1.00–5	6.9	93.1

In vitro drug release

Figures 6 and 7 show the *in vitro* release profiles of salicylic acid (SA) at pH 7.4 and 5.5 respectively, recorded by plotting %accumulated drug released versus time using grafted and ungrafted copolymers in buffer solution at 37°C ± 0.5, where ungrafted copolymer was used as control experiments. The ungrafted copolymer tablets were completely disintegrated and the entire SA content was released within 45 min, whereas the grafted copolymers

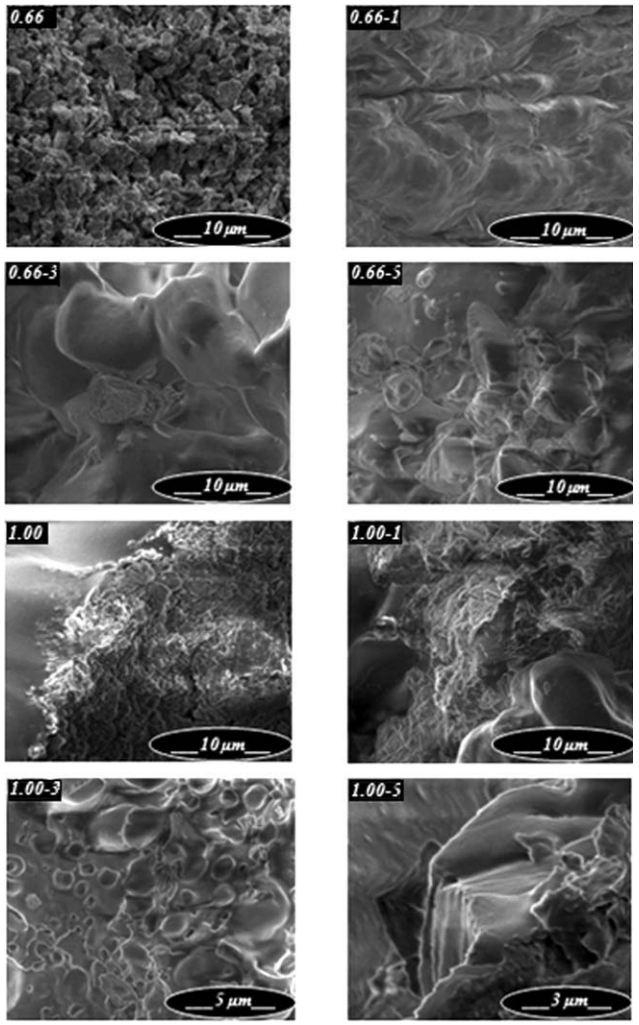


Figure 5 SEM images of ungrafted and PLA grafted (HEMA-*alt*-NVP) copolymers.

tablets (i.e., amphiphiles) showed differentiable and more sustained release profiles depending on pH and copolymer/PLA ratio. Inspecting the release profiles, it was obvious that the increase of PLA content in the copolymer increases the drug-sustaining in the matrix due to more consistent but porous amphiphilic degradable systems that allow controlled release of drug in time interval.

For sample 0.66–1 it took 290 min until 100% SA content were released at pH 7.4, whereas it took 225 min for the same sample to release at pH 5.5. This could be due to ionized carbonyl groups that repel each other, cause uncoiling, larger free volume and more porous system between polymeric chains, and hence larger release rate would be expected. Although faster SA release from 1.00–1 tablets (100% within 175 min) was observed, 1.00–3 and 1.00–5 showed more sustaining in their profiles; 1.00–3 released only 78.9% in the first 6 h and get slower release next to this point (99.8% in 24 h), whereas 1.00–5 showed almost linear trend that didn't exceed 80.5% in 24 h. In the

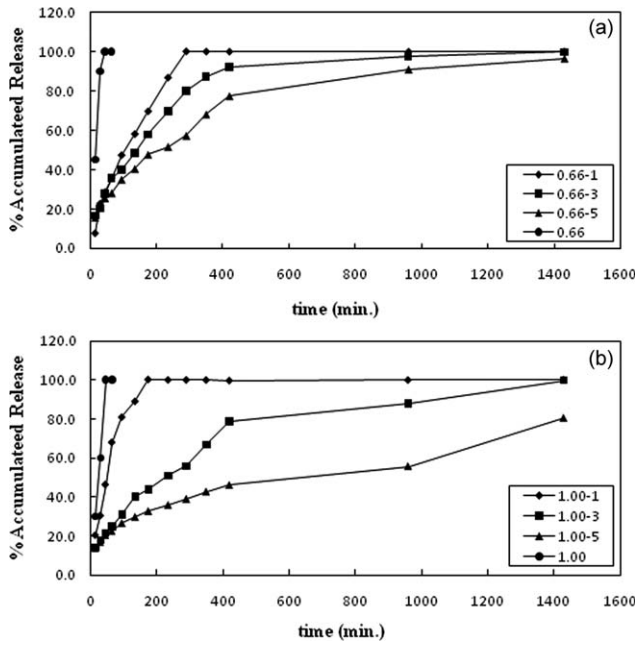


Figure 6 (a) *In vitro* release profile of salicylic acid using copolymer molar ratio = 0.66 and its increasing grafted content of PLA performed at pH 7.4. (b) *In vitro* release profile of salicylic acid using copolymer molar ratio = 1.00 and its increasing grafted content of PLA performed at pH 7.4

presence of increasing PLA content, more coherent and more consistent systems were formed due to the formation of inter- and intramolecular interactions

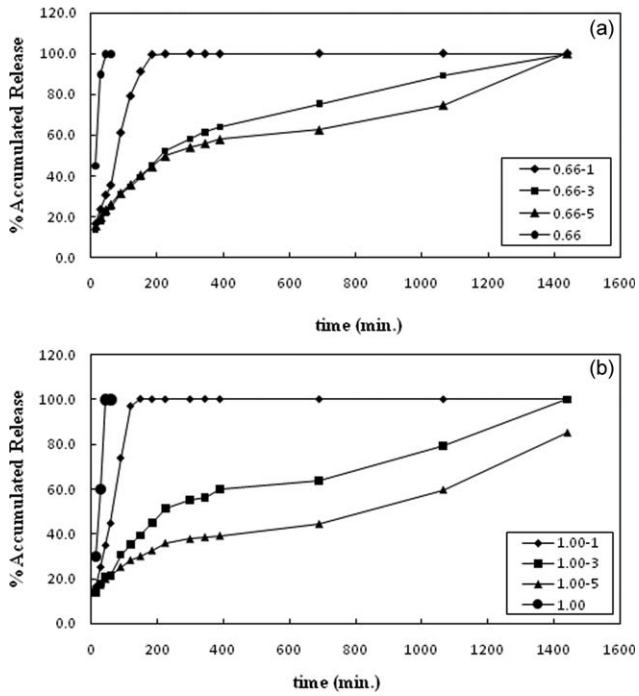


Figure 7 (a) *In vitro* release profile of salicylic acid using copolymer molar ratio = 0.66 and its increasing grafted content of PLA performed at pH 5.5. (b) *In vitro* release profile of salicylic acid using copolymer molar ratio = 1.00 and its increasing grafted content of PLA performed at pH 5.5.

TABLE III
***k* and *n* Values for Grafted PLA onto (HEMA-*co*-NVP) Copolymer Performed at pH 7.4 and 5.5, Respectively**

	pH 7.4			pH 5.5		
Polymer	R^2	n	k	R^2	n	k
0.66	–	0.756	6.317	–	0.756	6.317
0.66–1	0.9988	0.661	2.316	0.9745	0.771	1.805
0.66–3	0.9918	0.547	3.473	0.9944	0.497	3.324
0.66–5	0.9949	0.456	4.421	0.9940	0.430	4.660
1.00	–	1.00	2.680	–	1.00	2.680
1.00–1	0.9685	0.682	3.307	0.9801	0.860	1.459
1.00–3	0.9888	0.499	3.354	0.9758	0.493	3.340
1.00–5	0.9982	0.367	4.917	0.9982	0.353	5.183

(i.e., dipole-dipole and Van der Waals forces). At higher PLA content samples (i.e., 0.66–5 and 1.00–5 samples) the release rate was similar at different pH values (i.e., 5.5 and 7.4), which indicates that the release rate was not influenced by the acidic environment at pH 5.5 (Table III).

Release profile by steady state flux model

The use of steady state flux model[30] as a diffusion developed assumption reveals the matrix physical properties such as k and n through the following relation:

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t and M_∞ are the concentrations of the drug released to the medium at time t and time ∞, respectively. k is the proportionality constant which accounts for consistency, structural, and geometrical properties of the polymeric matrix, and n is the diffusional exponent that indicates the release rate. Plotting $\ln(M_t/M_\infty)$ versus $\ln(t)$ will give a linear curve with a slope value equals n and an intercept value equals $\ln(k)$. Statistical correlation coefficient, R^2, was larger than 0.97. The release parameters k and n are summarized in Table III.

At lower content of PLA moiety (0.66–1 and 1.00–1), grafted copolymers showed a non-Fickian diffusion release rate (i.e., $0.5<n<1.0$), whereas, at higher content of PLA (0.66–5 and 1.00–5), Fickian diffusion release rate (i.e., $n \leq 0.5$) was observed. In addition, since k value resembles the consistency of the polymer used, it could be seen that the k value became larger at larger PLA content, which could mean that the hydrophobic character of the polyester could possibly prevent water penetration through the copolymer and hence more sustained lower release rate (i.e., lower n-value) have occurred. Furthermore, it is known that significant change in pH value have an adverse effect on the polyester structure, where it may undergo decomposition reaction under acidic or basic conditions, to yield acid and alcohol, which would show different drug release rate. But since the pH values used were slightly acidic or neutral (i.e., 5.5 and 7.4), and the obtained k and n values show similar results especially at higher content of PLA moiety. Then, no expected degradation of either PLA or PHEMA moieties would have occurred through the release process and the drug was said to be released by diffusion only.

CONCLUSIONS

Synthesis and characterization of (HEMA-*co*-NVP) copolymers via free radical polymerization followed by grafting of PLA, onto (HEMA-*co*-NVP) copolymers, via ring opening polymerization using Tin octoate catalyst was performed. The ungrafted and grafted copolymers were fully characterized using ^{1}H-NMR, ^{13}C-NMR, FTIR, TGA, DSC, and SEM techniques. Derivative of TGA thermogram was successfully used to determine the %hydrophilicity and the %hydrophobicity of the ungrafted and grafted copolymers. The SEM images revealed pealed-off, crunchy, and porous layers that were most likely due to the presence of PLA chains. Grafted copolymers (i.e., amphiphiles) showed non-Fickian diffusion release rate at lower content of PLA in the copolymer, whereas, at higher content of PLA, a Fickian diffusion release rate was observed. It was obvious that the increase in the PLA content in the copolymers resulted in more sustained drug release profiles from matrix tablets, due to the formation of consistent but porous amphiphilic degradable structures that permitted controlled release of salicylic acid, as model drug, in time interval.

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