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Release of Dexamethasone from Poly(*N*-vinyl pyrrolidone-*co*-*n*-hexyl methacrylate) Copolymers of Controlled Hydrophilicity

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ABSTRACT: A copolymer system with controlled hydrophilicity has been prepared through copolymerization technique and its capability as controlled drug release carrier is investigated. The effect of copolymer composition on water uptake, thermal properties, and morphology is reported. The water uptake increases with increasing *N*-vinyl pyrrolidone content and diffusion of water molecules appears to be non-Fickian. Dexamethasone has been selected as model drug and its controlled release from selected water stable copolymers follows for more than 1 month. Initial burst release of more than 50% occurs in 7 days. The remaining drug is released in a sustained way upto 37 days. Initial 10 h drug release pattern involves first-order kinetics (NH73) and zero-order kinetics (NH55), whereas initial 60% drug release mechanism appears to be non-Fickian for NH73 ($n = 0.71$) and Case II transport ($n = 1.24$) for NH55. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

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INTRODUCTION

N-vinyl pyrrolidone (NVP) is the monomer being used to prepare homopolymer poly(vinyl pyrrolidone) (PVP) and copolymers with different vinyl monomers. NVP is amphiphilic in nature and can be polymerized by a variety of techniques such as free radical and solution polymerizations.[1] PVP has long history of use in controlled drug delivery due to its biocompatibility, chemical stability, and excellent aqueous solubility.[2,3] A downside for its application is higher water solubility.

NVP is used in conjuncture with some hydrophobic segments to copolymers and/or blends to overcome the problem of hydrosolubility. Vinyl pyrrolidone-*co*-(meth) acrylic acid inserts have been studied for ocular drug delivery.[4] Biocompatible and biodegradable copolymeric hydrogels based on PVP and poly (ethylene glycol diacrylate) have been prepared for *in vitro* release of anticancer drug 5-fluorouracil.[5] Copolymers and terpolymers containing n-butyl methacrylate (nBMA) and *n*-hexyl methacrylate (nHMA) monomers besides NVP and vinyl acetate have been used for biocompatible coatings for medical devices.[6,7] Alkyl methacrylates have a long history of use in drug delivery. In a recent literature, multifunctional poly(alkyl methacrylate) films have been reported for dental care application.[8] Shalaby et al.[9] have reported the tissue protecting spray on copolymer film composition based on NVP and nHMA.

Dexamethasone (Dx) is a glucocorticoid with a relevant clinical use mainly due to its anti-inflammatory and immunosuppressive effects.[10] A comprehensive literature is available on the study of dexamethasone release from various polymeric matrices.[11–13] However, the release of Dx from poly(*N*-vinyl pyrrolidone-*co*-*n*-hexyl methacrylate) P(NVP-*co*-nHMA) copolymer system of controlled hydrophilicity has not been investigated for extended period of time.

In this study, P(NVP-*co*-nHMA) copolymers with varying weight % ratios has been synthesized to find out a copolymer composition with optimum water uptake, better hydrostability at body temperature and capable of releasing dexamethasone for extended period of time. FTIR, elemental analysis, thermal analyses, wide angle X-ray diffraction (WAXD), and swelling of the synthesized copolymers are reported. Dx loaded P(NVP-*co*-nHMA) copolymer films exhibit controlled drug release for extended period of time, a characteristic feature required for medical implant coatings.

EXPERIMENTAL

Materials

NVP, nHMA, and PVP(K-30 M_w 40,000) were purchased from Tokyo Chemical Industry (TCI), Tokyo, Japan. NVP and nHMA

were vaccum distilled and stored below 5°C before use. 2-propanol, methanol, petroleum ether (boiling point 40–60°C), and chloroform received from Panreac, Barcelona, Spain were used without further purification. Benzoyl peroxide was obtained from ACROS organics, Geel, Belgium, dried at 45°C for several hours till constant weight and used as radical initiator. All chemicals were of analytical reagent grade. Dexamethasone micronized was generously donated by Tabros Pharmaceuticals. (Karachi, Pakistan).

Copolymer Synthesis

The mixtures of NVP and nHMA monomers were prepared in percentage weight ratios of NVP : nHMA = 90 : 10, 70 : 30, 50 : 50, 30 : 70, and 10 : 90, which will be designated hereafter as NH91, NH73, NH55, NH37, and NH19, respectively. To avoid oxygen inhibition, the monomer mixtures were purged with nitrogen gas for 30 min. Then, initiator (0.1% by weight of the monomers) and 20 mL 2-propanol solvent were added to the reaction mixture. The polymerization was carried out at 70°C in nitrogen atmosphere. The viscosity of solution was increased with time and after 7 hours, the reaction was terminated. The product obtained was dissolved in chloroform and precipitated in petroleum ether/methanol. The copolymers NH91, NH73, NH55 were purified with petroleum ether, whereas the copolymers NH37 and NH19 were purified with methanol. Poly(*n*-hexyl methacrylate), PnHMA, was also prepared under similar conditions.

Characterization

Elemental Analysis. Elemental analyses of dried samples were done using CHNS analyzer model CHNS-932 from Leco, USA (St Joseph, Michigan). The percentage of nitrogen in the copolymer was used to establish copolymer composition.

FTIR Spectroscopic Analysis. FTIR spectra of copolymer films were recorded on FTIR spectrophotometer (Model 6700 Nicolet, Thermo Scientific, USA (Waltham, Massachusetts)) fitted with ATR accessory. The spectra were scanned from 4000 to 400 cm^{-1} with resolution of 4 cm^{-1} and averaged over 120 scans. The crystal type used in ATR was diamond. Preweighed copolymers were dissolved in chloroform and the solutions were poured in Teflon coated petri dishes. The films were then obtained by the vacuum evaporation of the solvent.

^{1}H NMR Spectroscopy. ^{1}H NMR spectra were obtained on BRUKER 300 MHz NMR Spectrometer (BRUKER, USA, Billerica, Massachusetts) in $CDCl_3$ solvent using tetramethylsilane as internal reference.

Thermal Analysis. Thermogravimetric analyses were carried out on a TGA-7 by Perkin Elmer, USA (San Jose, California) under argon atmosphere (50 cm^3 min^{-1}). The samples were first isothermally heated at 100°C for 15 min for the complete removal of absorbed water and then heating was done from 100 to 700°C at 20°C min^{-1} heating rate. The activation energies for all the samples were calculated by Horowitz method.[14]

Glass transition temperature (Tg) measurements were performed on DSC-7 by Perkin Elmer, USA (San Jose, California) under argon (30 cm^3 min^{-1}). The DSC scans were carried out by heating the sample to 200°C, then cooling back to 20°C to remove all thermal history. The samples were then reheated to 200°C at heating rate of 20°C min^{-1}. For each sample run, Tg was taken as the midpoint of the transition appearing in the second heating scan.

Gel Permeation Chromatography. Molecular weights and polydispersity index of the synthesized polymers were determined on gel permeation chromatography (GPC) using refractive index detector model RID-6A by Schimadzu, Tokyo, Japan and styragel columns (HR1, HR2, HR3) by Waters, USA (Milford, Massachusetts). Tetrahydrofuran was used as the eluting solvent at the flow rate of 1 mL min^{-1} and polybutadiene standards were used for calibration. The GPC data were processed using Empower software.

X-Ray Diffraction Analysis. Wide-angled X-ray diffractograms were obtained in transmission mode with Ni-filtered Cu Kα radiation on an X-ray diffractometer model X'Pert PRO by PANalytical (Almelo, Netherlands) in the range of diffraction angle 2θ = 5–40° and the scan rate 0.04° 2θ per second.

Water Uptake at 37°C. All the P(NVP-*co*-nHMA) copolymers were dried for several hours at 80°C till constant weight. The completely dried sample films (2 × 2 cm) were weighed and then immersed in distilled water maintained at 37°C. The films were withdrawn from the distilled water at selected time intervals, blotted gently on the surface to remove surface water, and weighed on the microbalance. The water uptake studies were continued for 30 h till equilibrium was established. Equations (1) and (2) were used to determine water uptake (W) and equilibrium water content (EWC %):

$$W(\%) = \frac{W_s - W_d}{W_d} \times 100 \quad (1)$$

$$\mathrm{EWC}(\%) = \frac{W_e - W_d}{W_e} \times 100 \quad (2)$$

Where W_d is the weight of dry sample, W_s is the weight of the swollen sample at time t, and W_e is the weight of equilibrium swollen sample.

Preparation of Dx Loaded Copolymer Films. Polymer casting solution was prepared by dissolving 0.9 g of P(NVP-*co*-nHMA) copolymer (NH73 and NH55) in 10 mL chloroform and mixing 0.1 g/5 mL dexamethasone solution in methanol. The mixture was stirred at room temperature for 24 h. The polymer solution was transferred in teflon coated petri dish and was allowed to evaporate at room temperature to form dry polymer film. Samples of 20 × 20 mm^2 dimensions were cut for drug release studies and stored in dark in vacuum desiccator.

***In Vitro* Drug Release Studies.** *In vitro* drug release studies were carried out in phosphate buffer saline (PBS) having pH 7.4 and maintained at physiological temperature (37°C). The preweighed drug loaded films were placed in 100 mL of release medium. At selected time intervals, 10 mL of the sample was taken and an equal amount of complementary PBS was added. The amount of drug released was determined by UV-visible spectrophotometer at a wavelength of 241 nm using standard calibration plots.

Dexamethasone concentration in each sample was calculated according to the equation (3) [15]:

$$C_n = C_{\mathrm{nmass}} + \frac{V}{V_t}\sum_{s=1}^{n-1} C_{\mathrm{mass}} \quad (3)$$

Where C_n = true concentration of sample, C_{nmass} = apparent concentration of sample, V = volume of sample, and V_t = total volume of release medium

Table I. Composition of NVP and nHMA in the Feed and in the Copolymers

Sample ID	% Weight ratios of monomers NVP/nHMA	Mole fraction of monomers in feed		Elemental analysis data			Mole fraction of monomers in copolymer	
		f_{NVP}	f_{nHMA}	Nitrogen (%)	Carbon (%)	Hydrogen (%)	F_{NVP}	F_{nHMA}
PVP	100/0 (100/0)	–	–	[a]12.59 (11.55)	64.78 (58.32)	8.09 (8.37)	–	–
NH91	90/10 (86.99/13.01)	0.932	0.068	11.34 (10.96)	65.36 (60.42)	8.35 (8.41)	0.911	0.089
NH73	70/30 (73.70/26.30)	0.781	0.218	8.82 (9.28)	66.52 (62.78)	8.84 (9.27)	0.811	0.189
NH55	50/50 (50.42/49.58)	0.600	0.399	6.29 (6.35)	67.68 (64.19)	9.34 (9.34)	0.609	0.391
NH37	30/70 (12.69/87.31)	0.396	0.603	3.78 (1.60)	68.84 (69.13)	9.84 (10.67)	0.182	0.818
NH19	10/90 (1.12/98.88)	0.145	0.855	1.26 (0.15)	70.01 (70.31)	10.34 (10.68)	0.017	0.983
PnHMA	0/100 (0/100)	–	–	–	70.59 (69.21)	10.59 (10.83)	–	–

[a]Calculated (Actual)

RESULTS AND DISCUSSION

Elemental Analysis

Elemental analyses data for the homopolymers and copolymers are presented in Table I. The percentage of nitrogen in PVP homopolymer was found to be 11.55%. For the P(NVP-*co*-nHMA) copolymers, the measured percentage of nitrogen by elemental analyses was used to determine the copolymer composition according to the equation (4)[16]:

$$F_{NVP} = \frac{M_{nHMA}N}{M_{nHMA}N + 1400 - M_{NVP}N} \quad (4)$$

where F_{NVP} is the mole fraction of NVP in the copolymer, M_{nHMA} and M_{NVP} are the molecular weights of nHMA and NVP, respectively, and N is the percentage of nitrogen in the copolymer. The mole fraction of nHMA in the copolymer F_{nHMA} was calculated using equation (5):

$$F_{nHMA} = 1 - F_{NVP} \quad (5)$$

The mole fractions of monomers in the copolymer were calculated by the above method and results are shown in Table I. This table shows that the mole fractions of monomers in the copolymers are different from feed and a copolymer rich in nHMA is being produced. This behavior might be due to difference in the reactivity of two monomers. The reactivity ratios for the two monomers were calculated using Alfrey Price equation.[17] The reactivity ratios were found to be r_1 (NVP) = 0.065 and r_2 (nHMA) = 20.20, which indicated that rate of consumption of nHMA is faster than that of NVP, thus a copolymer rich in nHMA could be expected.

FTIR Spectroscopy

FTIR spectroscopy was used to characterize the homopolymers and copolymers. The representative spectra are shown in Figure 1. The IR spectrum of NH73 copolymer shows CO stretching of ester at 1714 cm^{-1} and that of amide at 1681 cm^{-1} with peak intensities corresponding to amount of corresponding monomers. The CO stretching of amide in PVP appears at 1645 cm^{-1} and that of ester in PnHMA appears at 1724 cm^{-1}. The C—H stretching at 2953, 2927, and 2858 cm^{-1}, C—H deformation vibration of CH_2 at 1461 cm^{-1}, and C—O—C antisymmetric stretching at 1165 cm^{-1} are characteristic peaks of nHMA monomer and also present in the IR spectrum of PnHMA. The incorporation of NVP unit is also reflected by the appearance of C—N stretching at 1283 cm^{-1} and CH_2 scissoring at 1421 cm^{-1}.[18] The disappearance of C = C absorption of NVP (1630 cm^{-1}) and nHMA (1635 cm^{-1}) monomers and appearance of the C=O absorptions of amide and ester units indicate copolymerization.

^{1}H NMR Spectroscopic Studies

The ^{1}H NMR spectra of the homopolymers PVP, PnHMA, and the copolymer NH73 are shown in Figure 2(a–c), respectively. The ^{1}H NMR spectrum of NH73 copolymer indicates the incorporation of both NVP and nHMA units. The resonance signals for the methine protons (^{1}CH) of NVP and side chain methylene protons (^{a}CH_2) of nHMA appear in the range 4.1–3.4 ppm. The methylene protons of nHMA (^{f}CH_2), (^{b}CH_2) and main

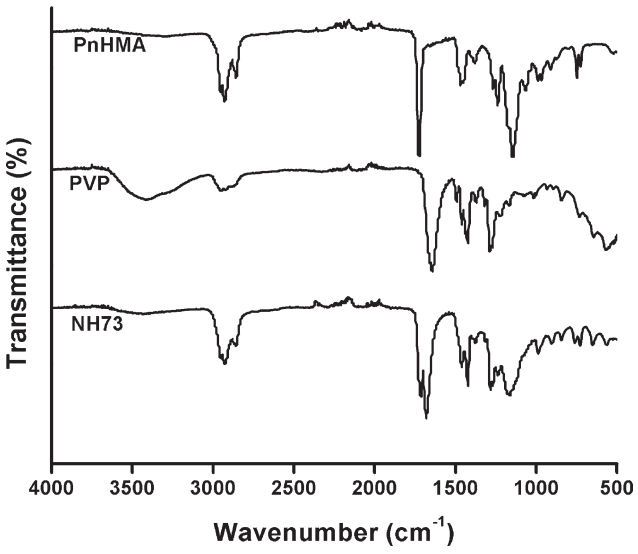

Figure 1. FTIR spectra of homopolymers PVP, PnHMA, and NH73 copolymer.

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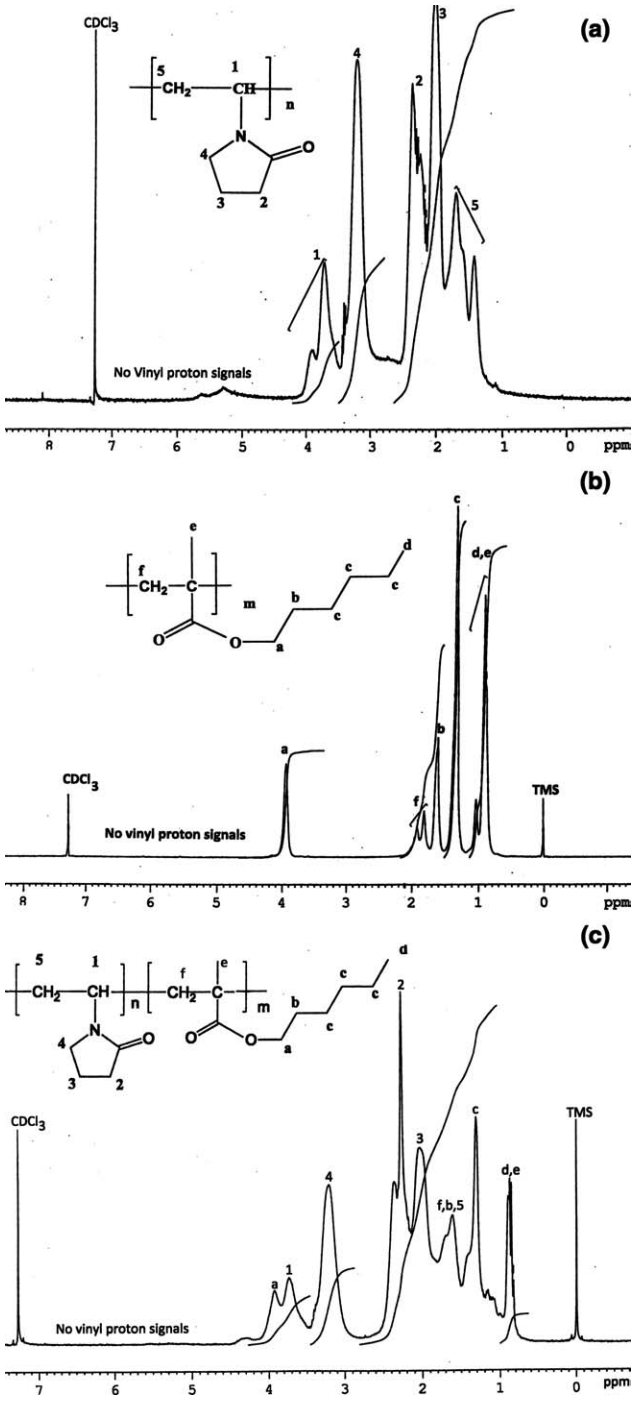

Figure 2. (a) ^{1}H NMR spectrum of PVP. (b) ^{1}H NMR spectrum of PnHMA. (c) ^{1}H NMR spectrum of NH73 copolymer.

chain methylene protons ($^{5}CH_2$) of NVP give overlapping signals in the range 1.9–1.4 ppm. The incorporation of NVP monomer is further confirmed by the appearance of resonance signals of side chain methylene protons at 3.5–3.0 ppm ($^{4}CH_2$), 2.1–1.9 ppm ($^{3}CH_2$), and around 2.5–2.1 ppm ($^{2}CH_2$).[19] The side chain protons of nHMA (^{c} CH_2 equivalent protons from three methylene groups) resonate at 1.3 ppm. The protons from two methyl groups (d and e) show overlapping signals appearing around 1.0–0.8 ppm.[20] The disappearance of vinyl proton resonances in the range 4.5–7.0 ppm and appearance of NVP, nHMA protons resonances in the ^{1}H NMR spectrum of the copolymer NH73 clearly confirm the copolymerization.

Thermal Analyses

Thermogravimetric Analysis. Thermal stability of the pure homopolymers and copolymers was investigated by thermogravimetric analysis (TGA) and results are shown in Figure 3. It can be seen from this figure that all samples undergo single stage thermal degradation. The PnHMA is least stable and PVP shows maximum stability, whereas thermal stability of the copolymers lies in between the two extremes. This is related to the chemical structure and strength of chemical bonds. PVP is more stable to thermal degradation, whereas PnHMA with long pendant alkyl chain is more prone to thermal degradation resulting in low thermal stability.

TG and derivative thermogravimetric (dTG) analyses data are presented in Table II. This table shows that the onset temperature of degradation (T_{onset}) increases as the percentage of NVP increases in the copolymer. The peak temperature "*T*" obtained from the dTG curve and "*M*" is the corresponding mass loss. The data indicates that the addition of NVP in NH19 copolymer increases T_{onset} from 179.4°C for PnHMA to 194.5°C. Further addition of NVP in the P(NVP-*co*-nHMA) copolymers results in corresponding increase in thermal stabilities. The increasingly high thermal stability of copolymers having greater number of NVP units is due to the reason that the presence of NVP moiety imparts the greater possibility of hydrogen bonding.

The TG data was also used to calculate the activation energy (E_a) and results are presented in Table II. Activation energies of 73.24 and 19.74 kJ mol^{-1} were calculated for the homopolymers PVP and PnHMA, respectively. The E_a values of the copolymers lie in the range of 63.32 to 24.13 kJ mol^{-1} and support the above mentioned results.

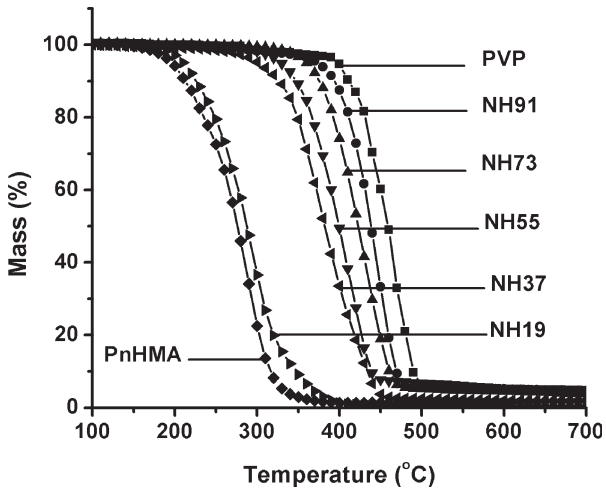

Figure 3. TGA overlap of the P(NVP-*co*-nHMA) copolymers and homopolymers PVP, PnHMA.

Table II. Thermal Analyses Data of PVP, PnHMA Homopolymers, and P(NVP-*co*-nHMA) Copolymers

Sample ID	T_{onset} (°C)	T(°C)	M (%)	M^r (%)	E_a (kJ mol^{-1})	Tg (°C)
PnHMA	179.39	289.72	65.53	1.59	19.74	−5.00
NH19	194.49	294.07	56.94	0.55	24.13	[a]−1.06 (−2.00)
NH37	287.99	384.23	51.95	2.56	49.23	26.55 (27.05)
NH55	319.45	402.69	53.45	6.82	54.44	100.11 (102.26)
NH73	352.06	434.07	63.17	5.18	61.32	136.87 (137.83)
NH91	377.25	447.84	63.49	5.65	63.32	152.98 (155.44)
PVP	401.08	458.19	64.03	4.77	73.24	171.12

[a]Actual (calculated)T = dTG peak temperature; M = mass loss at dTG peak temperature; M^r = Residue at 500°C; E_a = activation energy

Glass Transition Temperature

The glass transition temperatures (Tg) of the dried homopolymers and the copolymers were measured by DSC and shown in Table II. The Tg values of the copolymers are related to the mole fractions of the monomers according to Gibbs-DiMarzio equation (6): [21]

$$\text{Tg of the copolymer} = \Phi_1 \text{Tg}_1 + \Phi_2 \text{Tg}_2 \quad (6)$$

Φ_1 and Φ_2 are the mole fractions of the two monomers and Tg_1, Tg_2 are the glass transition temperatures of their respective homopolymers. Tg values of PVP and PnHMA were measured to be 171.12°C and −5°C, respectively. The measured value of Tg of PVP and PnHMA are consistent with the literature reported values.[22], [20] Tg values of the copolymers are inversely related to nHMA content, that is, low Tg is achieved with high nHMA content. There is a good agreement between the measured and calculated Tg values of copolymers.

Gel Permeation Chromatography. The GPC data of the synthesized copolymers and PnHMA are given in Table III. The number average molecular weights (M_n) of the copolymers are in the range of 13,465–18,634 g mol^{-1}, whereas the polydispersity index ranges from 1.27–1.35. The molecular weights of the copolymers and PnHMA are expected to be controlled by the polymerization conditions (reaction temperature, reaction time, and initiator concentration).

Wide Angle X-ray Diffraction Analysis. The homopolymers and copolymers were characterized by WAXD technique. The XRD diffractogram of PVP shows two broad peaks at 2θ = 10.72 and 21.55° which represents the amorphous nature of PVP. Abou-Taleb[23] reported the similar amorphous features with 2θ positions of 11.5 and 22.5°

Table III. GPC Data of Synthesized Polymers

Sample ID	M_w (g mol^{-1})	M_n (g mol^{-1})	Polydispersity index
NH91	22,022	17,205	1.28
NH73	19,780	15,215	1.30
NH55	18,201	13,465	1.35
NH37	23,754	18,634	1.27
NH19	21,657	16,919	1.28
PnHMA	23,394	18,407	1.27

The diffraction patterns of copolymers NH73, NH37, and homopolymers PVP, PnHMA are shown in Figure 4. The broad diffraction patterns of the homopolymers and copolymers revealed the amorphous nature of these materials.

Water Uptake at 37°C. The PVP is completely soluble in water at room temperature, whereas the PnHMA do not uptake water and is completely hydrophobic. The synthesized copolymers show varying degree of water uptake related to the percentage of hydrophilic vinyl pyrrolidone content. The NH91 copolymer dissolves in water and the resulting solution becomes milky. As the NVP content decreases, the copolymers become stable in water. The copolymeric films become white and opaque and show stability in their structure on prolonged dipping in water. The change of copolymer films from transparent to white and opaque on water uptake indicates the phenomenon of phase segregation. Similar behavior was observed in self-reinforcing hydrogels obtained by copolymerization of methyl methacrylate with 2-hydroxyethyl acrylate.[24]

The water uptake (W) behavior of the copolymer films NH73, NH55, NH37, and NH19 is presented in Figure 5. The results of

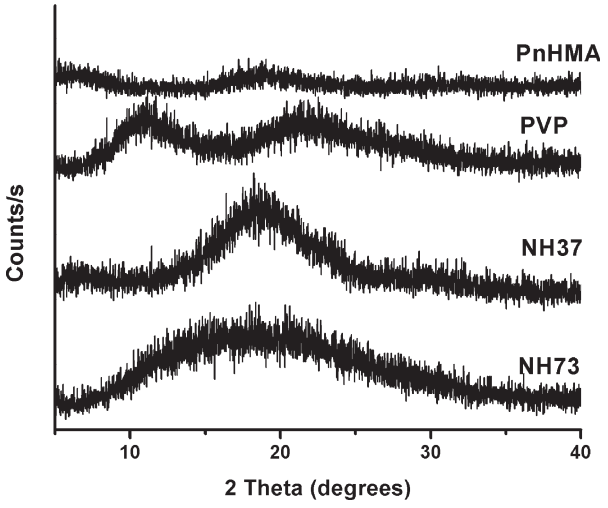

Figure 4. Wide-angle X-ray diffractograms of the homopolymers PVP, PnHMA, and P(NVP-*co*-nHMA) copolymers.

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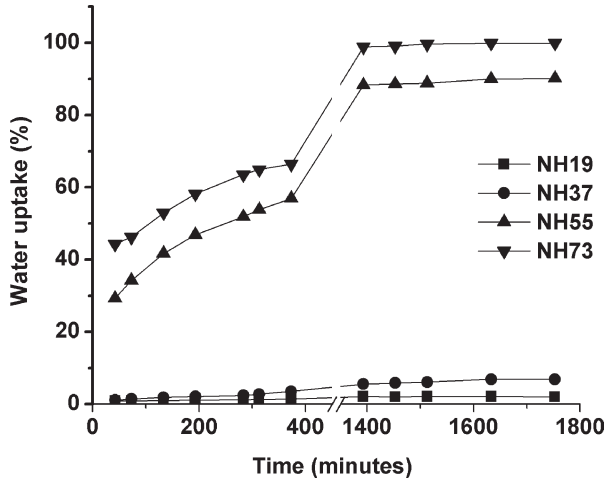

Figure 5. Water uptake behavior of P(NVP-*co*-nHMA) copolymers at 37°C.

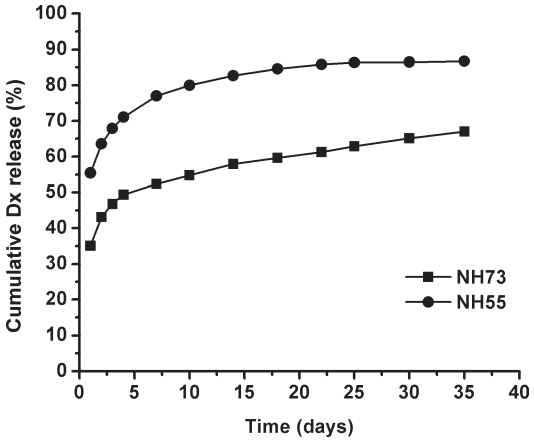

Figure 6. Dexamethasone release profiles of P(NVP-*co*-nHMA) copolymer films in PBS (pH 7.4) at 37°C.

water uptake studies show that the amount of hydrophilic NVP controls water uptake (W) and EWC of P(NVP-*co*-nHMA) copolymers. The EWC decreases with decreasing NVP contents: NH73 (63.02%) > NH55 (48.85%) > NH37 (8.25%) > NH19 (5.83%). The mechanism of diffusion of water molecules into NH73 and NH55 copolymers was determined by the following equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{7}$$

M_t and M_∞ represent amount of water uptake at time t and ∞, respectively; "k" is rate constant and "n" is characteristic exponent of transport of penetrating molecule. The values of "n" were found to be 0.11 (NH73) and 0.10 (NH55) indicating non-fickian diffusion mechanism.

In Vitro Drug Release Studies

The copolymer films NH73 and NH55 were selected for the release studies of dexamethasone. These films were selected due to their prolonged stability in water. The dexamethasone release profiles of 10% drug loaded films in PBS (pH 7.4) release medium are shown in Figure 6. The cumulative drug release pattern of NH73 copolymer film shows an initial burst release of 35% in 24 h and more than 50% drug is released in 7 days followed by a slow and sustained release of remaining amount over a period of more than 1 month. The initial burst release of dexamethasone from the polymeric matrix is probably attributed to the greater hydrophilicity of copolymer to swell in aqueous medium and permit greater water penetration. The swollen structure facilitates the release of incorporated drug. Whereas, in NH55, initial burst release of 55% occurs in 24 h and about 77% drug is released in 7 days followed by slow and sustained release for more than 1 month. From the cumulative drug release patterns of NH73 and NH55, it is clear that faster drug release is observed from NH55 with approximately 87% Dx released in 37 days, which is contrary to the swelling trend (Figure 5) of these copolymer systems. Several factors such as polarity of the polymer segments, glass transition temperature of the polymers, flexibility of the polymer backbone, chain interactions, molecular weight of the polymers, and presence of bulky comonomer pendant groups control the diffusion of drug from the polymer matrix. In present case, NH73 is more hydrophilic than NH55 but the molecular weights of the two copolymers are quite different as reflected in GPC data (Table III). The previous studies demonstrated the effect of molecular weight on drug release. The results showed that drug release rates decrease with increasing molecular weights,[25] as the molecular weight increases, the higher chain entanglements retard the diffusion of drug molecules through polymer matrix. Similarly, NH73 despite of being more hydrophilic, it exhibited slow release profiles of dexamethasone as compared to NH55 which is less hydrophilic but has comparatively low molecular weight.

Analyses of Release Patterns

The initial 10 h drug release data were used to study release kinetics. The release constants were calculated from the slope of the appropriate plots and the correlation coefficient (R^2) by linear regression analysis using software.[26] The comparison of R^2 (Table IV) identified that the *in vitro* drug release from NH73

Table IV. Release Kinetics of P(NVP-*co*-nHMA) Copolymers

	Zero-order kinetics		First-order kinetics		Higuchi kinetics		Korsmeyer-Peppas kinetics		
Sample ID	K_0 (h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H	R^2	R^2	n	SD
NH73	3.247	0.990	0.037	0.994	12.012	0.993	0.906	0.707	0.005
NH55	3.712	0.992	0.051	0.987	13.513	0.962	0.972	1.236	0.006

was best explained by first-order kinetics equation, as the corresponding plot show highest linearity. Here, the drug release rate is dependent on its concentration.

In NH55 drug release profile, the higher value of R^2 was obtained for zero-order kinetics as compared to first-order and Higuchi kinetics suggesting the release of drug from insoluble matrix is independent of its concentration.

The mechanism of drug release was determined by incorporating the data of first 60% drug release; according to Korsmeyer-Peppas model, where "*n*" is the release exponent, indicative of the mechanism of drug release.[27] The values of "*n*" for NH73 and NH55 were 0.71 and 1.24, respectively, indicating non-Fickian and super Case II transport, respectively.

CONCLUSIONS

The P(NVP-*co*-nHMA) copolymers were successfully synthesized and their hydrophilicity was controlled by incorporating different amounts of NVP. FTIR and ^{1}H NMR characterizations confirmed the incorporation of two monomers. Thermal stability, activation energy, and the glass transition temperatures of the copolymers increased with increasing NVP content. The XRD patterns of the copolymers indicated the amorphous nature of copolymer structure. The mechanism of diffusion of water molecules in NH73 and NH55 copolymers was non-Fickian. The water-stable copolymers NH73 and NH55 were loaded with dexamethasone and its release in PBS release medium showed a controlled release pattern for more than 1 month via non-Fickian (NH73) and Case II transport (NH55) mechanisms. Comparatively, slow drug release was observed from NH73 than NH55 due to high molecular weight.

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