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Stimuli-responsive DOX release behavior of cross-linked poly(acrylic acid) nanoparticles

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Abstract: Cross-linked poly(acrylic acid) nanoparticles were synthesized *via* distillation precipitation polymerization of acrylic acid and ethylene glycol dimethacrylate with different molar ratios. Spherical nanoparticles with diameters between 75 and 122 nm were synthesized and exhibited temperature and pH-responsive behaviors. However, this behavior was less pronounced for samples with higher cross-linking degrees. The potential of all nanoparticles as carriers for controlled release of doxorubicin (DOX) anti-cancer drug was examined at pH values of 1.2, 5.3 and 7.4. An obvious alleviation in burst release behavior and the amount of cumulative drug release was seen for all nanoparticles as the pH of the medium and the cross-linking degree of nanoparticle increased. Also kinetics of drug release was studied using mathematical models of zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell, where Higuchi and Korsmeyer-Peppas models best defined the kinetics of drug release.

Keywords: cross-linked poly(acrylic acid); distillation precipitation polymerization; stimuli-responsive behavior; drug release, DOX

1 Introduction

Synthetic polymer nanoparticles in the field of nanomedicines can act either as just drug carriers, hence

they need to be water-soluble and safe to body, or they can actively cooperate to the drug release process, hence they should be stimuli-responsive (1-4). Applying external stimuli including changes in pH, temperature, ionic strength, oxidation/reduction potential, light and electric or magnetic fields, responses may occur as changes in conformation, swelling/collapsing, dissolution/precipitation, etc. (5-8). However, the most attention has been given to temperature- and pH-responsive polymers such as poly(*N*-isopropylacrylamide) (PNIPAM) (9,10) and poly(2-hydroxyethyl methacrylate) (PHEMA) (11,12), poly(acrylic acid) (PAA) (13,14) and poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA) (15,16). PAA as a hydrophilic biocompatible polyacid has distinguished pH-responsive properties due to its ionizable carboxyl groups which make it a suitable choice as a carrier in drug delivery systems (17,18). Although acid dissociation constant of PAA has been reported in the literature ($pK_a = 4.2$) (19), the pH-responsive behavior of PAA needs to be studied for its cross-linked particulate form. Moreover, no mentionable report exists on the temperature-sensitivity of cross-linked PAA as an individual nanoparticle. PAA shows a response to temperature, even not necessarily sharp, because of change in hydrogen bonding, dispersive forces, etc. resulted in agglomeration of polymer chains and so on (20,21). Disruption of hydrogen bonding by temperature is not of importance for linear PAA which is a water-soluble polyanion, while it becomes important when segments of a hydrophobic cross-linker as comonomer are present in the PAA nanoparticle structure. This temperature-sensitivity is therefore expected to be affected by the amount of hydrophobicity of the cross-linker comonomer, degree of cross-linking and also pH of the medium.

Distillation precipitation polymerization (DPP) is a time-saving colloidal polymerization method which yields micro/nanospheres with a uniform size distribution without using surfactants or stabilizers (22,23). This favors the polymerization of many common monomers as reported in the literature, especially for drug release applications where the monodispersity of carriers and absence of toxic additional chemicals

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are important (24,25). In the present work, cross-linked PAA nanoparticles with uniform size distributions are fabricated *via* DPP. Ethylene glycol dimethacrylate (EGDMA) is used as cross-linker and different monomer to cross-linker molar ratios are chosen to study the effect of degree of cross-linking on stimuli-responsive properties of synthesized nanoparticles. Synthesized nanoparticles are used as carriers of DOX as anti-cancer drug and release behaviors are investigated in different conditions. Finally, mathematical release models including zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell are fitted to the drug release data to explain release mechanism.

2 Experimental section

2.1 Materials

Acrylic acid (AA, Merck, 99%) and ethylene glycol dimethacrylate (EGDMA, Merck, 98%) as monomers were passed through alumina column to remove inhibitor before use. Acetonitrile (Merck, 99.9%) was used without further purification. 2,2'-azobisisobutyronitrile (AIBN, Acros, 99%) as initiator in distillation precipitation polymerization, was recrystallized from ethanol. Sodium chloride (NaCl) (Merck, 99.5%), potassium chloride (KCl) (Merck, 99.5%), potassium dihydrogen phosphate (KH_2PO_4) (Merck, 99.5%) and di-sodium hydrogen phosphate dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) (Merck, 99%) were used to prepare phosphate buffer saline (PBS) with distilled water for drug loading and release experiments. Doxorubicin hydrochloride (Adrimycin®CS, Pfizer, 2mg/mL solution) was used as model drug. Cellulose membrane dialysis tube with molecular weight cut-off of 14,000 (Sigma-Aldrich, D9652) was used after careful washing to remove glycerol and sulfur compounds to carry out the drug release experiments.

2.2 Synthesis of cross-linked PAA nanoparticles

Cross-linked PAA nanoparticles were fabricated *via* DPP of AA and EGDMA with different molar ratios of monomer and cross-linker (90:10, 80:20, 70:30 and 60:40). As an example, a 100-mL two-necked flask containing 80 mL acetonitrile equipped with a Liebig condenser and a receiver was heated to 50°C. The monomers were added to the flask in appropriate ratios (2.5 vol% with respect to

total volume of the mixture) under N_2 atmosphere. AIBN (1 mol% of total monomer content) was added and the reaction started to progress by heating to boiling point of acetonitrile. When half of the solvent was collected in the receiver, the reaction was stopped by adding a trace amount of hydroquinone solution. The product was separated and washed with acetonitrile by several times of centrifugation and re-dispersion. It was dried in vacuum oven at 100 mbar and 50°C overnight. Total monomer conversions were measured by gravimetry as 41.7, 52.3, 45.4 and 44.7% for 90:10, 80:20, 70:30 and 60:40 samples respectively.

2.3 Investigation of stimuli-responsive behavior of nanoparticles

pH- and temperature-responsive behaviors of the nanoparticles were investigated using UV-visible spectrometer at 600 nm. A 0.1 mg/mL aqueous dispersion of each nanoparticle was prepared at pH values between 2 and 10 for pH-sensitive studies at 24°C. Same dispersions at pH = 1.2, 7.4 and 10 were heated from 15 to 51°C with 3°C steps and 20 min time of equilibrium at each step for temperature-responsive studies.

2.4 DOX loading and release experiments

Loading of DOX into nanoparticles was carried out for 20 mg samples in 6 mL aqueous drug solutions with concentration of 1 mg/mL. pH was adjusted to 8 to ensure that DOX is not charged regarding its isoelectric point ($\text{pI} = 8.25$) (26). Loading was accomplished by stirring at room temperature and dark for 48 h. Drug loading capacity (DLC) was calculated according to Eq. 1 (27) at $\lambda = 480$ nm to measure the concentration of DOX solution after the separation of nanoparticles by centrifugation at 6000 rpm for 30 min.

$$\text{DLC (mg/g)} = \frac{\text{Weight of drug in nanoparticles (mg)}}{\text{Weight of nanoparticles (g)}} \quad (1)$$

An absorbance-concentration calibration curve was prepared in advance. To remove the surface adsorbed DOX molecules, the loaded nanoparticles were washed once before drying in vacuum oven at room temperature.

In vitro drug release behaviors were investigated in different pH conditions at 37°C. 1 mL of a 4 mg/mL dispersion of each nanoparticle was poured into dialysis tubes and immersed into 80 mL buffer solutions at

pH = 1.2, 5.3 and 7.4. As a comparison, a same release experiment was performed for free drug. Concentration of the dialysate was measured at pre-determined time intervals using UV-visible spectrometer.

2.5 Characterizations

Morphology of nanoparticles was characterized with a TESCAN MIRA3 FE-SEM at 15 kV. All the samples were prepared by drop-dry method either on a simple glass lamellae. The specimens were prepared by coating a thin layer on a mica surface using a spin coater. UV-visible absorption at $\lambda_{\max} = 480$ nm for doxorubicin hydrochloride was measured with Perkin-Elmer Lambda 45 UV/VIS spectrophotometer. ^1H NMR (400 MHz) spectra were recorded on a Bruker Avance 400 spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as an internal standard.

3 Results and discussion

3.1 Characterization of synthesized nanoparticles

Chemical structure of the crosslinked PAA samples was studied using ^1H -NMR spectra (Figures S1-S4). Chemical shifts at 0.99-1.05, 1.67 and 4.35 belong to the protons of PEGDMA (a: $-\text{CH}_3$, b: $-\text{CH}_2-$ and c: $-\text{O}-\text{CH}_2-$ respectively) (28) and those at 1.67, and 1.87 represent the protons of PAA (d: $-\text{CH}_2-$ and e: $-\text{CH}-$) (29). The spectra prove the existence of both monomers in the structure of all products revealing that the copolymerization has been done successfully. The amount of cross-linker in each sample can be calculated by Eq. 2 based on the peak area of protons individually represent monomers in polymer structure.

$$\text{Crosslinker (mol. \%)} = \frac{(\text{peak area of c})/4}{(\text{peak area of c})/4 + (\text{peak area of e})} \quad (2)$$

Obtained cross-linker contents in terms of mol% are given in Table 1 where higher amount of EGDMA in feed results in higher amount of crosslinker in particle structure. However, due to the decrease in activity ratio of EGDMA with conversion against AA, for which the activity ratio remains almost constant, the cross-linker contents are lower in the products compared to those in the feeds

Table 1: Characteristics of the synthesized PAA nanoparticles.

PAA nanoparticle	Cross-linker content (mol. %)	Number average diameter (nm)	PDI	DLC (mg drug/g nanoparticle)
90:10	11.3	122.4	0.114	217
80:20	13.5	110.2	0.120	220
70:30	13.7	113.6	0.125	222
60:40	14.0	75.4	0.119	224

(30). Also, lower boiling point of EGDMA (98-100°C) than AA (141°C) can be another reason to explain such a phenomenon where partially evaporation of EGDMA along with acetonitrile during DPP process decreases its concentration in polymerization medium.

FE-SEM images of PAA nanoparticles are shown in Figure 1. According to the results, well-shaped spherical nanoparticles with a uniform size distribution were fabricated where increase in cross-linker ratio resulted in a decrease in particle size. Results of image analysis based on at least 100 particles are shown in Table 1 (calculations are described in section S4). The relatively small PDI values for all nanoparticles revealed the successful application of DPP method as mentioned before. The fact that the smallest particle size was obtained for the sample with the highest cross-linker amount is explained based on the rigidity of the newly-formed particles in the mid stages of the polymerization process where little amount of monomer can enter the particles and instead more number of particles are formed (higher nucleation) and grow thereafter (31).

3.2 Stimuli-responsive behavior of PAA nanoparticles

pH-responsive behavior of PAA nanoparticles with different cross-linker contents is illustrated in Scheme 1 which shows that less pH-sensitivity, i.e., change in hydrodynamic diameter of the particle as response to pH variations is expected from the PAA nanoparticle with higher cross-linker content.

Responses of the PAA nanoparticles to pH and temperature are investigated separately and results are given in Figure 2. Since pH-responsive behaviors for nanoparticles with different monomer to cross-linker ratios are studied at room temperature, the magnitude of hydrogen bonding and dispersion forces remains the same for all samples while the electrostatic repulsions originating from the negatively-charged hydrophilic carboxyl anions of PAA after deprotonation become

Figure 1: FE-SEM images of PAA nanoparticles with different AA:EGDMA molar ratios.

stronger because of increasing pH (32). Therefore, a continuous decrease in UV absorbance correlated with increase in hydrodynamic diameter of the nanoparticles versus increase in pH is observed in Figure 2a for all samples. However, the magnitude of hydrophobic forces originating from hydrophobic EGDMA segments in the copolymer structure is not similar for all the samples;

the sample with the highest cross-linker content, namely 60:40, shows a weaker response to pH which means that the sharp decrease in pH happens at higher pH values. Besides, UV-visible absorbance is the highest for this sample. Also, the sample with the lowest cross-linker content, 90:10, shows the strongest response to pH variations; the sharp decrease in pH happens at lower pH.

Scheme 1: pH-responsive behavior of PAA nanoparticles with high and low AA:EGDMA molar ratios and its effect on drug release behavior at 37°C.

These could be attributed to the more rigid structure of the nanoparticle with higher cross-linker content for which the access of medium to carboxyl groups of PAA segments is restricted and consequently, the deprotonation becomes more difficult (33). Even if sufficient deprotonation takes place, there would be a prohibition against electrostatic repulsions exerted by cross-linkages. For all PAA samples, a thermo-responsive behavior, in the form of gradual increase in absorbance versus temperature was also observed, as seen in Figures 2b-d. This is attributed to the disappearance of hydrogen bonding by increasing in temperature (34). Decreasing cross-linker content at a specific pH led to shifting the volume phase transition temperature (VPTT) to higher values. This difference was actually less pronounced at pH = 1.2 where all the nanoparticles were already sufficiently hydrophobic. Similarly, at a specific cross-linker content, increase in pH led to more hydrophilic nature of the nanoparticles

and therefore, the VPTT was expectedly shifted to higher values.

3.3 Drug loading and drug release studies

Stimuli-responsive PAA nanoparticles were examined as carriers of DOX as a anti-cancer (35) model drug. A high DLC of about 220 mg g⁻¹ was obtained for all samples as given in Table 1 which is dominated by physical interactions at pH around 8 which is close to its isoelectric point (pI = 8.25) where the drug molecule is not charged. The difference in release behavior of samples with high and low cross-linker contents is schematically shown in Scheme 1. Three different pH values were selected which simulate pH in blood (7.4), slightly acidic pH condition as limit for assimilating vitamins or minerals (5.3) and highly acidic pH condition in stomach (1.2). Since DOX is a basic

Figure 2: pH-responsive behavior at 24°C (a), and temperature-responsive behavior of synthesized nanoparticles at pH values of (b) 1.2, (c) 7.4 and (d) 10.

drug, its solubility in water increases at low pH values (36). Results for *In-vitro* release profile from drug-loaded PAA samples at 37°C are shown in Figure 3. A release experiment was also conducted for pure drug as 1 mg/mL solution for comparison. According to results, an obvious burst release behavior was seen for pure drug at all pH values as expected. This immediate release behavior is modified to different extents for nanoparticles with different cross-linker contents and in media with different pH values. Loading the drug into particles alleviates the burst release, since cavities in the cross-linked nanoparticle act as drug

storage leading to a timed-release behavior (37,38). The lower amount of cumulative release and reduced immediate release for all nanoparticles at all pH values compared to pure drug confirms this expectation. No burst release was seen for PAA samples at pH = 7.4 and more rapid and higher cumulative release was observed at pH = 5.3. This is due to the higher solubility of DOX at lower pH which increases the tendency of drug molecules to leave the nanoparticle toward the aqueous medium (39). Lowering the pH to 1.2 results in a significantly higher cumulative release and a more obvious burst release. This can be ascribed to

Figure 3: Drug release behavior of nanoparticles at 37°C and pH values of 1.2, 5.3 and 7.4.

hydrophilic nature of DOX at low pH values. The other effective factor is the shrinkage of the PAA segments in response to pH reduction. This particle shrinkage exerts a force which further drives the drug molecules outside the nanoparticle (40). In this sense, the degree of cross-linking of the nanoparticles plays a role; as the cross-linker content increases, the drug molecules are faced a greater prevention against diffusion outside the particle due to more rigid structure of the nanoparticle. Moreover, the higher cross-linking degree results in lower degree of pH-responsivity as stated earlier and shown in Scheme 1. Therefore, the 60:40 nanoparticle at pH = 7.4 shows the most controlled release behavior among all nanoparticles and at all pH values.

3.4 Kinetics of drug release

Kinetics of drug release was studied using the most well-known mathematical models such as zero-order,

first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas (41,42). The models were fitted to the data by linear regression with R^2 as correlation coefficient and fitting parameters are shown in Table 2 and Figures 4-8. According to the results, it seems that zero-order, first-order and Hixson-Crowell models are insufficient to define the release kinetics as they do not fit the data properly. Zero-order model is used for slow drug release kinetics as for matrices containing low solubility drugs which is not the case for relatively rapid release of doxorubicin hydrochloride from pH-responsive PAA nanoparticles. First-order model mostly applies to porous matrices and hence cannot describe drug release from our system well. Moreover, Hixson-Crowell model applies to systems where the surface area of drug carrier diminishes gradually as result of dissolution, while the PAA nanoparticles studied in this paper do not dissolve since they are partially cross-linked. In contrast, a relatively good correlation seems to exist between experimental data and regression lines obtained from Higuchi and

Table 2: Drug release kinetic model parameters for nanoparticles with different AA : EGDMA ratios.

pH		Samples	Kinetic models										
			Zero-order		First-order		Hixson-Crowell		Higuchi		Korsmeyer- Peppas		
			$Q_t = Q_0 + K_0 t$		$\log C = \log C_0 + \frac{K}{2.203} t$		$Q_t^{(1/3)} = Q_0^{(1/3)} + kt$		$f_t = K_H t^{1/2}$		$M_t / M_\infty = at^n$		
			R^2	K_0	R^2	K	R^2	k	R^2	K_H	R^2	aM_∞	n
1.2	Free drug	0.859	7.896	0.767	0.121	0.800	0.166	0.949	29.60	0.972	45.53	0.393	
	90:10	0.652	1.050	0.519	0.018	0.564	0.024	0.830	8.966	0.924	34.666	0.266	
	80:20	0.655	0.982	0.519	0.018	0.565	0.023	0.831	8.388	0.922	33.582	0.260	
	70:30	0.625	0.739	0.496	0.014	0.540	0.018	0.809	6.990	0.930	30.960	0.252	
	60:40	0.659	0.720	0.511	0.015	0.562	0.018	0.835	6.740	0.934	28.874	0.255	
5.3	Free drug	0.886	7.095	0.8084	0.117	0.836	0.157	0.964	26.39	0.982	42.49	0.372	
	90:10	0.847	0.624	0.769	0.018	0.798	0.020	0.964	5.047	0.990	20.012	0.229	
	80:20	0.875	0.484	0.8062	0.017	0.832	0.018	0.976	3.875	0.986	16.932	0.211	
	70:30	0.826	0.261	0.756	0.011	0.781	0.011	0.952	2.333	0.992	16.136	0.160	
	60:40	0.871	0.426	0.701	0.022	0.761	0.020	0.975	3.743	0.992	8.837	0.333	
7.4	Free drug	0.923	5.433	0.872	0.101	0.891	0.130	0.982	19.98	0.993	39.093	0.310	
	90:10	0.850	0.488	0.723	0.024	0.770	0.022	0.967	3.943	0.996	10.121	0.311	
	80:20	0.889	0.445	0.781	0.026	0.824	0.023	0.967	3.546	0.992	1.232	0.325	
	70:30	0.837	0.332	0.700	0.021	0.752	0.018	0.958	2.954	0.993	7.637	0.316	
	60:40	0.885	0.396	0.686	0.030	0.768	0.024	0.980	3.463	0.994	4.455	0.460

Figure 4: The curve of zero-order model mechanism of drug release.

Figure 5: The curve of first-order model mechanism of drug release.

Figure 6: The curve of Higuchi model mechanism of drug release.

Figure 7: The curve of Kormseyer-Peppas model mechanism of drug release.

Figure 8: The curve of Hixson-Crowell model mechanism of drug release.

Korsmeyer-Peppas models which can be attributed to the application of the former model to systems with water-soluble drugs and the latter to drug release from polymer matrices (43,44). The value of n parameter in Korsmeyer-Peppas model corresponds to release mechanism; since $n < 0.45$ for almost all nanoparticles at any pH condition, a Fickian diffusion mechanism of drug outward the nanoparticles was suggested.

4 Conclusions

PAA nanoparticles with four different monomer to cross-linker molar ratios, 90:10, 80:20, 70:30 and 60:40 where fabricated *via* DPP method. All nanoparticles showed response to pH and temperature variations; a relatively sharp decrease in UV absorbance as response to pH increase and a gradual increase in UV absorbance with increase in temperature were observed as result of electrostatic repulsion between negatively charged PAA carboxyl anions and disappearance of hydrogen bonds, respectively. Higher cross-linker contents led to weaker pH response and lower VPTT. Profiles of release for DOX as model drug from the nanoparticles were investigated showing a modified release behavior with lowered burst release as the cross-linker content and pH of the release medium increased. The 60:40 sample showed the most desirable controlled release behavior. Kinetics of drug release was studied using mathematical models such as zero-order, first-order, Hixson-Crowell, Higuchi and Korsmeyer-Peppas, where Higuchi and Korsmeyer-Peppas best fitted the release data since the former applies to water-soluble drugs and the latter applies to release from polymer matrices.

Supplementary material: ^1H NMR results; Particle size analysis.

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