

Modeling Diameter Distributions of Poly(*N*-isopropylacrylamide-*co*-methacrylic Acid) Nanoparticles

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ABSTRACT: The Weibull distribution was successfully used to describe the diameter distribution of poly(*N*-isopropylacrylamide-*co*-methacrylic Acid (PNIPAAm-MAA) nanoparticles, whereas the lognormal was deemed not adequate for that purpose. The method of moments was used to predict parameters of the Weibull distribution. In this approach, the Weibull parameters were recovered from the diameter mean and variance, both of which were

predicted from temperature. The distributions predicted from various temperatures for both MAA/NIPAAm ratios of 0.05 and 0.10 showed trends similar to those displayed in the observed data. © 2008 Wiley Periodicals, Inc. *J Appl Polym Sci* 111: 2584–2589, 2009

Key words: PNIPAAm-MAA; goodness-of-fit test; lognormal; maximum likelihood estimation; Weibull

INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNIPAAm) is a thermoresponsive polymer with a low critical solution temperature (LCST) around 32°C.¹ Because of its phase-transition property, PNIPAAm-based nanoparticles have shown great potential applications in drug delivery,^{2,3} sensing,^{4,5} fabrication of photonic crystals,^{6,7} nano templates,^{8,9} and separation and purification technologies.^{10,11} For example, the fast responding property of the PNIPAAm nanoparticles make them useful for developing targeted and regulated drug delivery systems to multiple stimuli within a reasonable time.¹²

The properties of nanoparticles and the performance of the products made with nanosized precursors depend significantly on the shape of the particle-size distribution (PSD). This includes the broadness of the PSD, the modality, and the specific particle size covered by the PSD. The controlled adjustment of particle size is of great interest due to size-dependent physical and chemical properties of nanoparticles. In the pharmaceutical industry, for example, the PSD of the active pharmaceutical ingredients is one of the most important aspects of the dosage form that affect the effectiveness of drug

release.¹³ Besides, PSD may also affect the stability of the dosage and the absorption rate of an active intergradient. As a result, it is essential to control particle-size distribution in development of pharmaceutical dosages.¹⁴

The PSD of many nanoparticles in soil science,¹⁵ environmental science,^{16,17} biology,¹⁸ and medical science¹⁹ is often found to be lognormal. The earliest models of the lognormal distribution were based on Kolmogorov's simple idea of stone cracking, where the relative change of the fragment volumes was taken to be stationary random variables.²⁰ A growth model, based on the same idea in a time-reversed fashion, was used later by Granqvist and Buhrman²⁰ in an attempt to explain the origin of lognormal distributions of gas-evaporated nanoparticles.^{21,22} Most of these models are based on coagulation theory developed by Smoluchowsky.²³ The Smoluchowsky model deals with a closed system where an initially large number of small particles meet and coagulate. As time passes, the mean particle size increases and the system gradually runs out of small particles. Kiss et al.²⁴ proposed a new approach to the origin of lognormal size distribution of nanoparticles based on residence time, where particle growth occurs during transport through a growth zone due to diffusion and draft. It needs to be pointed out that the lognormal distribution is often postulated in many analytical and numerical models, and the system is forced to stay in the lognormal state. On the other hand, the Weibull distribution, a mixed Weibull and lognormal distribution, and a segmented distribution have been found to better describe the particle size distribution in many systems.²⁵

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The PSD of the PNIPAAm nanoparticles changes dynamically with changes in temperature because of their thermoresponsive nature.²⁶ Understanding of the dynamic change of the PNIPAAm particle sizes provides fundamental information for controlling their end performance. However, none of the published work in this field has dealt with such a process. The objective of this study was to model the diameter distributions of the poly(*N*-isopropylacrylamide-*co*-methacrylic acid (PNIPAAm-MAA) nanoparticles as a function of temperature with a statistical distribution.

METHODS

The polymerization process of the PNIPAAm-MAA particles was discussed in a former article.²⁶ Target amounts of NIPAAm, MAA, BIS, and SDS were added to 120 g of deionized water in a 250-mL reactor. NIPAAm and MAA served as the monomers, BIS as the crosslinking agent, and SDS as surfactant. To control particle size, different MAA to NIPAAm ratios (by mole), and amounts of SDS were used. The formed particles were purified by membrane dialysis against distilled deionized (DDI) water by use of Spectra/Pros with a molecular weight cutoff of 12,000–14,000.

Particle size and size distribution of the copolymers were determined using a Zetasizer Nano ZS system (Malvern Instrument, Worcestershire, UK). A solution of purified PNIPAAm-MAA particles was diluted ~ 100 times with PBS buffer in 4.5-mL Spec-

tro Cuvets for measurement. Measurements were performed over a temperature range of 20–60°C in 0.1M PBS solution. A HeNe laser beam with wavelength of 632.8 nm was applied with a detection angle of 90°. The sample temperature was maintained by a built-in thermostat sample holder with an accuracy of 0.01°C. Results of particle-size distribution were collected with DTS (nano) software (Version 5.0) provided with the instrument. Each sample was measured three times, and the average was used as the sample mean diameter. Z-average diameter was used as the hydrodynamic size, because it is more reproducible than volume and number weighted mean diameter.

Data

Particle diameter data of the PNIPAAm-MAA nanoparticles at MAA/NIPAAm ratios of 0.05 and 0.10 measured from over a temperature range from 20 to 60°C in 5°C increments were used for this study. Figure 1 shows the frequency of the diameters. The histograms suggested that statistical distributions such as the lognormal and Weibull functions might be appropriate in characterizing the diameter distributions of the PNIPAAm-MAA nanoparticles.

Lognormal and Weibull distributions

Let x be diameter of a PNIPAAm-MAA particle in nm, $f(x)$ be the probability density function (pdf),

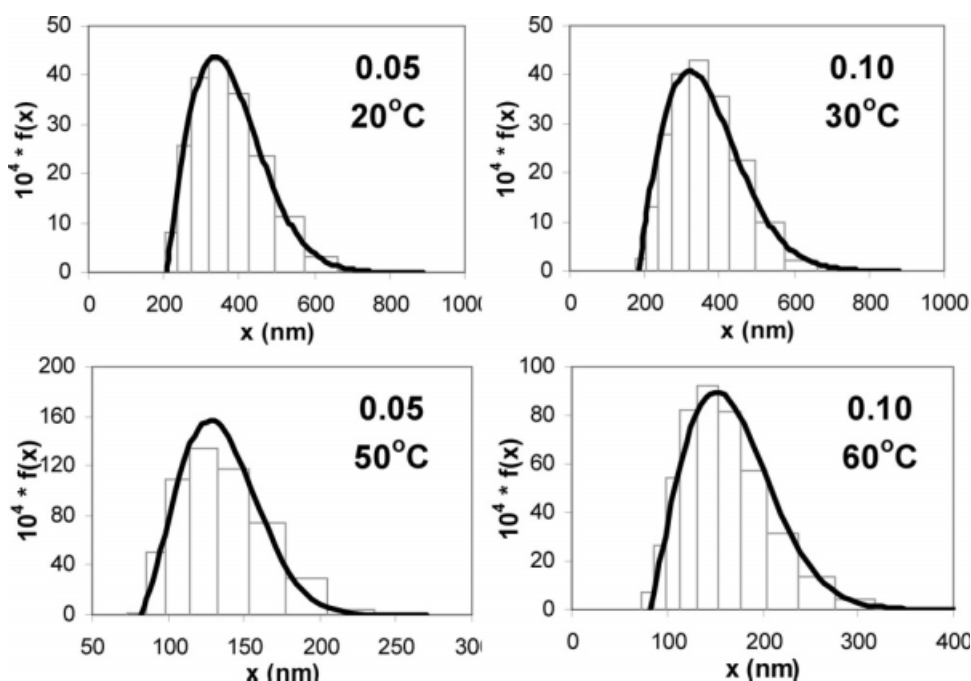


Figure 1 Histograms showing the frequency of diameters of the PNIPAAm-MAA nanoparticles at different temperatures for MAA/NIPAAm ratios of 0.05 and 0.10. The smooth curves represent the Weibull distributions with their parameters predicted from temperature.

and $F(x)$ be the corresponding cumulative distribution function (cdf). On the basis of the shapes of the histograms presented in Figure 1, the lognormal and Weibull distributions were considered in this study to characterize the diameter distribution of PNIPAAm-MAA particles. In both distributions, a location parameter (a) was used to indicate the minimum value that particle diameter can attain.

The lognormal pdf having parameters a , μ , and σ is described as follows

$$f(x) = \left(\frac{1}{(x-a)\sigma\sqrt{2\pi}} \right) \exp \left[-\frac{1}{2} \left(\frac{\ln(x-a) - \mu}{\sigma} \right)^2 \right], x \geq a. \quad (1)$$

Its corresponding cdf is

$$F(x) = \Phi \left(\frac{\ln(x-a) - \mu}{\sigma} \right), \quad (2)$$

where, $\Phi(z)$ is the cdf of the standard normal distribution.

The Weibull distribution has the following pdf and cdf, respectively:

$$f(x) = \left(\frac{c}{b} \right) \left(\frac{x-a}{b} \right)^{c-1} \exp \left[-\left(\frac{x-a}{b} \right)^c \right], x \geq a. \quad (3)$$

and

$$F(x) = 1 - \exp \left[-\left(\frac{x-a}{b} \right)^c \right]. \quad (4)$$

where, a , b , and c are the location, scale, and shape parameters, respectively.

Parameter estimation

The data were not continuous but were classified into groups of unequal (increasing) lengths, i.e., $(x_i - x_{i-1}) < (x_{i+1} - x_i)$, where x_i was the "midpoint" of the i th group. It is clear that x_i was not the true midpoint. The i th group was therefore assumed to span from $\left(\frac{x_{i-1}+x_i}{2}\right)$ to $\left(\frac{x_i+x_{i+1}}{2}\right)$.

The maximum likelihood method was employed to estimate parameters a , μ , and σ of the lognormal distribution and a , b , and c of the Weibull distribution for each sample and each temperature. SAS procedure RELIABILITY²⁷ was used for this purpose.

RESULTS AND DISCUSSION

A lognormal distribution and a Weibull distribution were fitted to each sample and each temperature for MAA/NIPAAm ratios of 0.05 and 0.10. Chi-square tests revealed that the hypothesis that the lognormal distribution fit the observed data was rejected in 17 out of 45 samples (38%) for the 0.05 ratio and 9 out

of 45 samples (20%) for the 0.10 ratio, using a 5% significant level. On the other hand, by use of the same significant level, the hypothesis that the Weibull distribution fit the observed data was rejected in only 1 sample (2%) for the 0.05 ratio and none (0%) for the 0.10 ratio.

These results clearly showed that the Weibull distribution adequately represented the diameter distribution of the PNIPAAm-MAA particles, whereas the lognormal was not deemed appropriate for this purpose.

Changes due to temperature

For both molar ratios of MAA/NIPAAm, values of the location parameter (a) and the scale parameter (b) decreased with increasing temperature (Fig. 2), whereas there was no apparent relationship between the shape parameter (c) and temperature. As temperature increased, the distribution did not really change its shape but became tighter and closer to zero, causing both its mean and variance to decrease (Fig. 3).

Prediction of Weibull parameters from temperature

Cao²⁸ evaluated various methods for predicting parameters of a Weibull function for modeling the distribution of forest tree diameters. Some of these methods required expressing the Weibull parameters as functions of other variables and therefore were

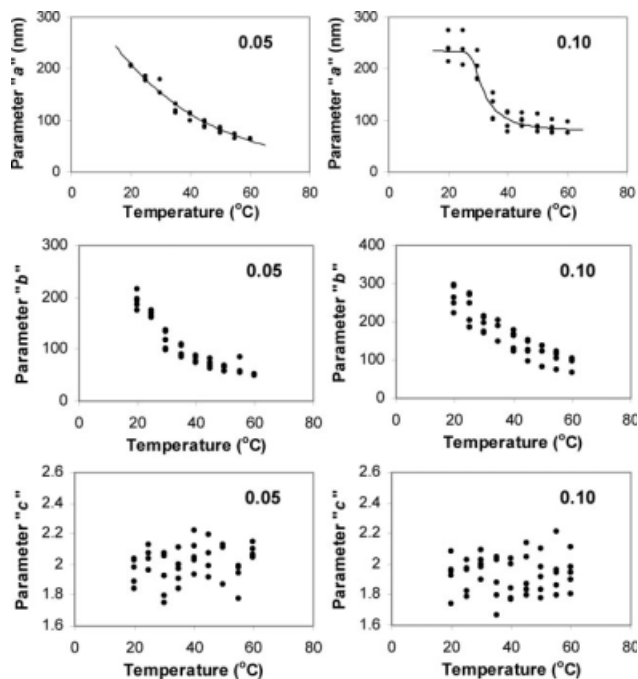


Figure 2 Relationship between Weibull parameters (a , b , and c) and temperature for MAA/NIPAAm ratios of 0.05 and 0.10. The smooth curves represent predictions of parameter "a" from temperature.

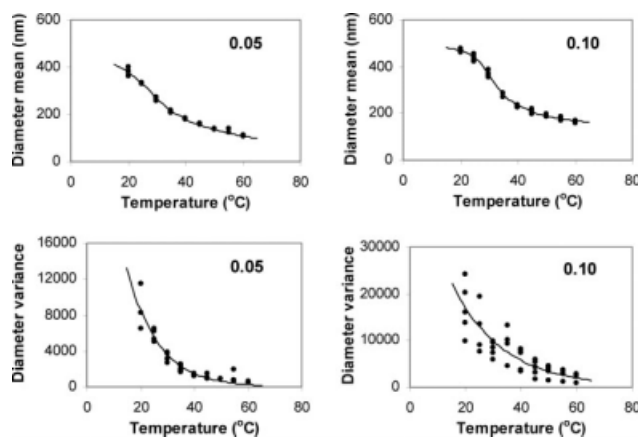


Figure 3 Graph of mean and variance of diameters of PNIPAAm-MAA nanoparticles versus temperature for MAA/NIPAAm ratios of 0.05 and 0.10. The smooth curves represent predictions of the diameter mean and variance from temperature.

not applicable in this study because of the lack of relationship between the shape parameter (c) and temperature (Fig. 2). The method of moments was selected in this study because it seemed most appropriate for these data. This method involved first predicting the Weibull location parameter (a), the diameter mean (\bar{x}), and the diameter variance (s^2) based on temperature (t). In the second step, the Weibull scale and shape parameters (b and c) were recovered from the predicted mean and variance.

The diameter variance was predicted from the following equation:

$$y = b_1 \exp(b_2 t), \quad (5)$$

where, $y = s^2$ and b_i is regression coefficient.

It was difficult to use a single function to describe the relationship between the diameter mean and temperature, as seen from Figure 3. After experimenting with various functions, we obtained reasonable results by using a segmented function, in which two segments were joined together at a join point t_0 as follows:

$$y = \begin{cases} b_1 \exp[-(t/b_2)^{b_3}], & t \leq t_0 \\ b_4 + b_5 t^{b_6}, & t > t_0 \end{cases}, \quad (6)$$

where $y = \bar{x}$.

The two segments were constrained such that the segmented function was continuous and smooth at the join point. As a result, coefficients b_4 and b_5 were expressed as functions of the remaining coefficients:

$$b_4 = b_1 \exp[-(t_0/b_2)^{b_3}] - b_5 t_0^{b_6}, \text{ and} \quad (7)$$

$$b_5 = \frac{-b_1 (b_3/b_2) (t_0/b_2)^{b_3-1} \exp[-(t_0/b_2)^{b_3}]}{b_6 t_0^{b_6-1}}. \quad (8)$$

The regression coefficients for eq. (6) were b_1 , b_2 , b_3 , b_6 , and t_0 . Coefficients b_4 and b_5 were computed from eqs. (7) and (8), respectively.

TABLE I
Regression Coefficients for Predicting Parameters of the Weibull Distribution from Temperature

Dependent variable	Coefficient	0.05 Ratio		0.10 Ratio	
		Estimate	Std. error	Estimate	Std. error
a^a	b_1	388.4195	10.4172	234.1835	7.7376
	b_2	-0.0310	0.0008	32.30957	3.6304
	b_3			18.7560 ^b	23.5928
	b_6			-5.42731	0.7821
	t_0			29.4078	1.6620
	b_4^c			80.5942	-
\bar{x}^d	b_5^c			1.089×10^{10}	-
	b_1	444.9020	19.9542	482.0409	9.4503
	b_2	38.1753	0.4826	37.5941	1.2489
	b_3	2.8018	0.4191	5.7052	1.0647
	b_6	-1.5918	0.1358	-3.0328	0.3027
	t_0	29.9235	0.9492	30.7588	0.9391
s^{2e}	b_4^c	29.6270	-	140.7033	-
	b_5^c	53394.0	-	6.835×10^6	-
	b_1	49425.9	6264.6	49640.0	8582.6
	b_2	-0.0878	0.0053	-0.0539	0.0062

^a The location parameter, a , was predicted from eq. (5) for the MAA/NIPAAm ratio of 0.05 ($R^2 = 0.9751$) and from eq. (6) for the ratio of 0.10 ($R^2 = 0.9143$).

^b This coefficient was not significant ($P = 0.43$). All other coefficients were highly significant ($P < 0.0001$).

^c Coefficients b_4 and b_5 were not estimated from regression but computed from eqs. (7) and (8), respectively.

^d The diameter mean, \bar{x} , was predicted from eq. (6) for the MAA/NIPAAm ratios of 0.05 ($R^2 = 0.9954$) and 0.10 ($R^2 = 0.9938$).

^e The diameter variance, s^2 , was predicted from eq. (5) for the MAA/NIPAAm ratios of 0.05 ($R^2 = 0.9301$) and 0.10 ($R^2 = 0.7275$).

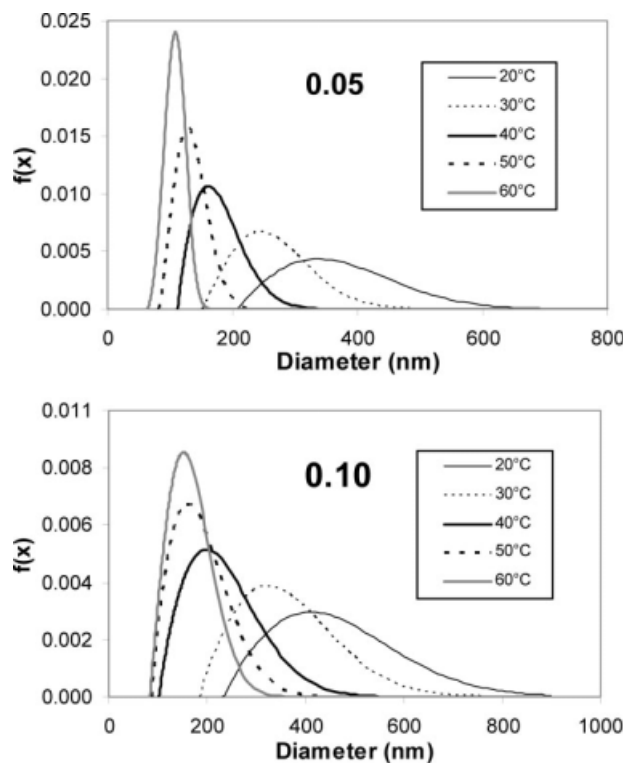


Figure 4 Predicted Weibull distributions at various temperatures for MAA/NIPAAm ratios of 0.05 and 0.10.

The relationship between the Weibull location parameter (a) and temperature was different for MAA/NIPAAm ratios of 0.05 and 0.10. eq. (5) with $y = a$ was used to predict a for the 0.05 ratio, whereas the 0.10 ratio required eq. (6).

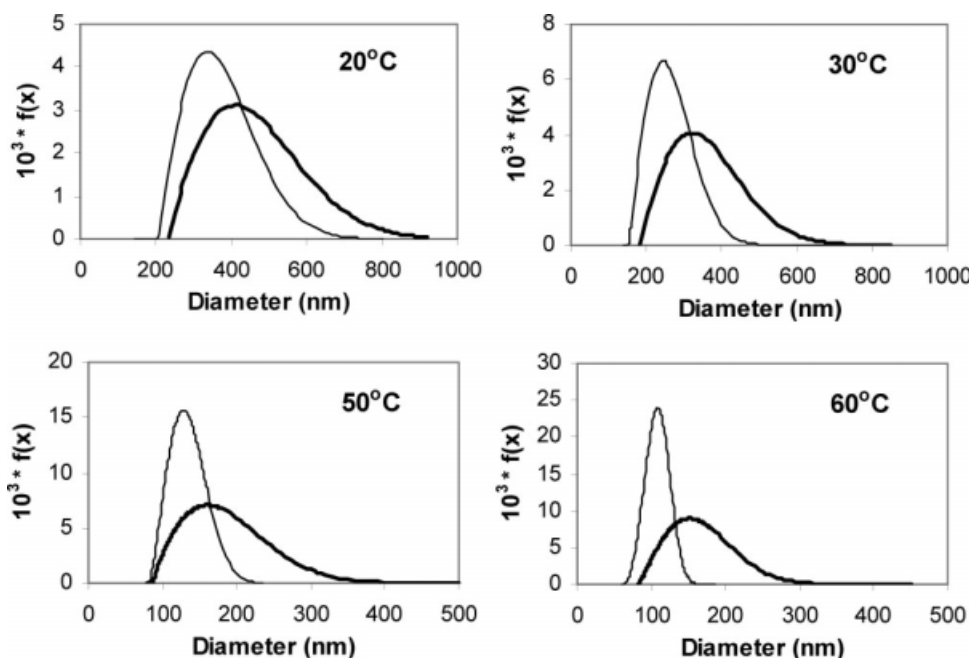


Figure 5 Predicted Weibull distributions for MAA/NIPAAm ratios of 0.05 (thin line) and 0.10 (dark line), by temperature.

Regression coefficients of equations to predict a , \bar{x} , and s^2 from temperature were simultaneously estimated by use of the seemingly unrelated regression option of SAS procedure MODEL.²⁹ These estimates are shown in Table I. All estimates were highly significant ($P < 0.0001$), except for b_3 of the equation to predict a ($P = 0.43$). Predicted values of a , \bar{x} , and s^2 are graphed against temperature in Figures 2 and 3. Weibull parameters b and c can be solved from the following set of equations:

$$(\hat{x} - a)^2 \left[\frac{\Gamma(1 + 2/c)}{\{\Gamma(1 + 2/c)\}^2} - 1 \right] - \hat{s}^2 = 0, \quad (9)$$

$$b = \frac{(\bar{x} - a)}{\Gamma(1 + 1/c)}, \quad (10)$$

where, \hat{x} and \hat{s}^2 = predicted mean and variance of diameters of PNIPAAm-MAA particles, respectively, and

$\Gamma(\cdot)$ = the complete gamma function.

Predicted Weibull distributions

The Chi-square tests revealed that the hypothesis that the predicted distribution fit the observed data was rejected in 36 out of 45 samples (80%) for the 0.05 ratio and 39 out of 45 samples (87%) for the 0.10 ratio, using a 5% significant level. However, the Weibull distributions with parameters predicted by use of the aforementioned method appeared to adequately characterize diameter distributions of

PNIPAAm-MAA nanoparticles for various temperatures (Fig. 1).

Modeling diameter distributions are necessary when distributions for temperatures different from those sampled are desired. Predicted Weibull distributions are also useful for displaying trends in the data. Figure 4 shows predicted Weibull distributions at various temperatures for MAA/NIPAAm ratios of 0.05 and 0.10. As temperature increases, the distribution moves nearer to the origin, at the same time becoming more compact and peaked. A similar trend is observed when the MAA/NIPAAm ratio decreases from 0.10 to 0.05 for each of the temperatures sampled (Fig. 5).

CONCLUSIONS

The Weibull distribution was found in this study to describe successfully the diameter distribution of PNIPAAm-MAA nanoparticles, whereas the lognormal was deemed not adequate for that purpose. The method of moments was used to predict parameters of the Weibull distribution from temperature. The distributions predicted from various temperatures for both MAA/NIPAAm ratios of 0.05 and 0.10 showed trends similar to those displayed in the observed data.

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