Polydopamine Nanoparticle Size Optimization for Smart Drug Delivery Applications

Serkan Yaman[1,2], Nikhil Pandey[1,2], Andres Urias[1], Kytai T. Nguyen[1,2]
1. Department of Bioengineering, University of Texas at Arlington, Arlington, TX 76019.
2. Joint Biomedical Engineering Program, University of Texas Southwestern Medical Center at Dallas, TX 75390, USA.

Statement of Purpose: Recently, polydopamine (PDA) nanoparticles (NPs) have been shown their excellent effectiveness in photoacoustic imaging-guided photo-thermal therapy (PTT) to treat various cancers and demonstrated as a good candidate for temperature-responsive drug delivery platform development [1]. These nanoparticles can be formulated from dopamine via different methods (i.e., oxidation, enzymatic conversion, and so on) [2]. In general, dopamine is slowly oxidized to create PDA NPs, and its polymerization involves many complex steps and external factors [3]. The effects of factors/parameters that determine PDA NP size and yield remains uncertain in the literature, although this effect is important to maintain a good standard PDA NP synthesis protocol. In the meantime, the particle size influences the bio-distribution and various *in vitro* and *in vivo* properties of nanoparticles. Therefore, in this nanomaterial research, we investigated the formulation factors that significantly affect PDA NP size using a factorial design analysis. The factorial simulation tools would enable strong experimental set ups with reduced work force, used materials, and associated time. Firstly, the preliminary experiment series were run to determine levels and factors of the PDA NP reactions. Based on these results, designed experiments and factorial analysis were further performed using a 2-level, 4-factor experimental design to identify the size-factor relation equation for optimizing of synthesized PDA NPs.

Methods: PDA NPs were synthesized using oxidation reactions as previously described [4]. Pre-determined conditions (oxidant, H_2O, monomer concentration, pH, stir rate, and reaction time) were used for dopamine monomers to oxidize and form PDA NPs. In the reaction series, initial dopamine concentration, pH, ammonium hydroxide/water ratio, alcohol/water ratio, stir rate and reaction time were chosen as the investigated formulation factors to be varied in the factorial analysis. Using Design Expert 8.0 software, all preliminary experimental runs were conducted to find the four most influence factors, and the output data was used to run a factorial experiment with a 2-level, 4-factor design **(Table 1)**. The size of resultant NPs was measured via a dynamic light scattering instrument, and morphology of these NPs was confirmed via electron microscopy. All collected data was used to identify the most important factor that affects the size of PDA NPs and to generate a size-factor relation equation and relationship plots.

Results: Among the six examined NP formulation factors, dopamine concentration, pH level, alcohol:water ratio, and ammonia:water ratio have been found to have significant effects on the PDA NP size distribution. Analysis of 2-level, 4-factor factorial design showed that pH levels and dopamine concentrations significantly affect the particle size (**Table 1 & Figure 2**). To confirm the size-factor relation equation generated from factorial analysis, PDA NP synthesis experiments were conducted, and the experimental results were comparable to those predicted from the size-factor relation equation **(Table 2)**.

Factor	Relative Significance of Factor	Low Level	High Level	Response Variable
Dopamine (mg/mL)	2	0.5	2	Nanoparticle Size
pH	1	7.0	9.0	
Alcohol:Water (%)	4	10.0	50.0	
Ammonia:Water(%)	3	0.25	2.00	

Table 1: Data output from Design Expert 8.0 for PDA NP synthesis factorial analysis.

Predicted NP size	DLS Size (nm)	PDA Size;Factor relation
100 nm	149.8 ± 72.5	1/Sqrt(Particle Size) = (0.050)-6.282E-004 *(A)+3.971E-003*(B)+0.019*(C) +8.900E-003*(D)+7.090E-003*(A)*(C) -2.310E-003*(A)*(D)
200 nm	222.7 ± 30.8	
500 nm	500.84 ± 173.2	

Table 2: PDA NP size-factor relation & prediction (**A**: dopamine concentration (mg/ml); **B**: ammonia:water ratio; **C**: pH; and **D**: alcohol:water ratio).

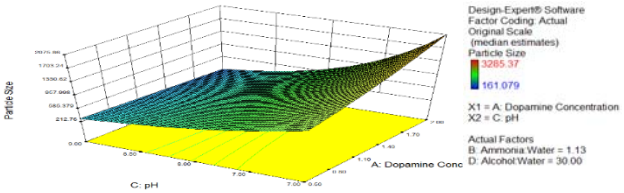

Figure 2: The size-factor relationship plot generated from factorial analysis showing the effects of varying pH levels and dopamine concentrations on the size of PDA NPs.

Conclusions: A series of PDA NP synthesis experiments were conducted with the Design Expert 8.0 factorial analysis software. The results showed that the size distribution of PDA NPs was mainly based on the initial DA concentration and pH of the synthesis reactions. In addition, PDA NPs with a size of interest could be formed using the size-factor relation equation generated from the factorial simulation analysis. As a result, these data can provide researchers to optimize PDA NP synthesis reactions to have more standardized PDA NP formulations for the development of PDA NP-based imaging and drug delivery platforms.

References:

[1]- Han L, Zhang Y, Lu X, Wang K, Wang Z, Zhang H. *ACS App. Mat. & Inter. 2016*; *8* (42):29088–29100.
[2]- Lee H, Dellatore SM, Miller WM, Messersmith PB. *Science 2007*; 318(5849):426-30.
[3]- Sureshkumar M, Lee PN, Lee CK. *J. of Mat. Chem. 2011*; 21(33):12316-20.
[4]- Jiang X, Wang Y, Li M. *Sci. Reports. 2014*; 4(6070).