Supplementary Information

Controlled Drug Release from Polyelectrolyte-Drug Conjugate Nanoparticles

Ruginn Catarata[a], Nilab Azim[a,c], Santanu Bhattacharya [d*], Lei Zhai[a,b,c*]

Determination of Zeta Potential

The zeta potential of the nanpoparticles was determined using the Smoluchowski approximation on the Malvern Zetasizer instrument. The reviewer is correct in suggesting to use a different approximation method to use since the Smoluchowski formula is typical implemented to approximate the zeta potential of micron (0.2μm <) sized particles.

Ohshima's correction to Henery's approximation, equation 28[1], becomes applicable to smaller nanoparticles at relatively higher ionic strengths, $\kappa a < 10$. However, Henry's equation is still applicable but only for low zeta potentials with magnitude less than 50 mV[2,3].

We began with calculating the κa of each pH parameter (Table 2) first by assuming $\kappa\,(nm^{-1}) \approx 3.3[I(M)]^{1/2}$ and resulted in the values provided in the table below. The zeta potential in terms of $\frac{e|\zeta|}{kT}$ was determined as well for each parameter and is provided in the table below. Since the values of κa for pH 6 and 7.4 lied in the region $1 < \kappa a < 10$ and the $\frac{e|\zeta|}{kT} > 4$, equation 28 could not be applied because it no longer becomes a good approximation[1]. Therefore, we considered using Henry's equation since the values of the measured zeta potential fell below 50 mV[2,3] and f(κa) was ~1[2].

Henry's equation describes the relationship between zeta potential (ζ) and the electrophoretic mobility (μ):

$$\mu = \frac{2\varepsilon_r \varepsilon_0 \zeta}{3\eta} \cdot f_H(\kappa a)$$

Where $f_H(\kappa a)$ is the Henry function where κ is inverse Debye screening length (m^{-1}) and a is particle radius (nm), ε_0 is the permittivity of vacuum ($8.854 \cdot 10^{-12} C^2 J^{-1} m^{-1}$), ε_r is a unitless dielectric constant of the solution and η is viscosity ($kg\, s^{-1} m^{-1}$). The Smoluchowski and Huckel approximations assume that $f_H(\kappa a)$ is 1.5 and 1, respectively[4]. Ohshima previously proposed a simplified expression for $f_H(\kappa a)$, which when substituted in the Henry's equation is[5]:

$$f_H(\kappa a) = \left(1 + \frac{1}{2\left[1 + \frac{2.5}{\kappa a\left(1 + 2e^{-\kappa a}\right)}\right]^3}\right)$$

By using the approximate for the Debye screening length [$\kappa\,(nm^{-1}) \approx 3.3[I(M)]^{1/2}$], we get values of slightly above 1 for the $f_H(\kappa a)$ for each parameter. The Ohshima approximation to Henry's function $f_H(\kappa a)$ was then used to calculate the new zeta potential using Henry's equation. The new zeta potential values are essentially the measured values multiplied by 3/2 since the $f_H(\kappa a)$ is ~1. Therefore, we did not think it was necessary to provide newly calculated zeta potentials since the values would remain relative to each other but just multiplied by a constant.

pH	Radius (nm)	$\kappa\,(\mathbf{nm}^{-1})$	$f_H(\kappa a)$	$\frac{e\lvert\zeta\rvert}{kT}$	Henry Approximation Zeta Potential (mV)
4	18.8	9.0E-05	1.0	0.7	-26.1
5	26.4	8.8E-03	1.0	0.9	-34.2
6	30.0	3.1E-01	1.2	1.0	-48.9
7.4	28.9	8.7E-02	1.1	0.8	-31.9

Modeling GEM diffusing from PAA-GEM Nanoparticles

Mathematical equations and models can be used to translate the diffusion curve obtained in vitro to a theoretical analysis of the mass transfer process[6]. We have provided the fitting of four different models: zero order, first order, Higuchi and Korsmeyer-Peppas[7]. The correlation coefficient of each curve was used to determine the best model and the Higuchi model resulted in the best linear fit for both the free GEM and PAA-GEM.

The Higuchi model describes the release to be governed by Fick's law of diffusion by which the drug moves down a concentration gradient out from a porous matrix into solution. Physically it can be described as an inward moving boundary with an inner region having undissolved drug and the outer region of the nanoparticle having dissolved drug, which eventually is released from the polymer matrix to the surrounding solvent[8]. The moving boundary is facilitated by the solvent diffusion into the polymer nanoparticle.

The free GEM release profile best fitted the Higuchi model but also had a linear fit for the Korsmeyer-Peppas model. The Koremeyer-Peppas model was used to determine if there more than one type of release phenomena involved, which can be concluded from the release exponent obtained from the fit equation[9]. The determined release exponent (n) was found to be 0.635 for free GEM, therefore lying in the anomalous transport regime of the release mechanism model. This anomalous transport of GEM can best be concluded arising from the interaction with the dialysis membrane as there are no other components in the system. Thus, in the analysis of the release of GEM from the actual NP system, this release phenomenon can be neglected and therefore, only the Higuchi model is considered. The physically trapped GEM from the NP follows Fickian diffusion and the calculated rate constant describe a slow controlled release system in comparison to free GEM.

References

1. H. Ohshima, “Approximate analytic expression for the electrophoretic mobility of a spherical colloidal particle,” *J. Colloid Interface Sci.*, vol. 239, no. 2, pp. 587–590, Jul. 2001.

2. T. L. Doane, C. H. Chuang, R. J. Hill, and C. Burda, “Nanoparticle ζ -potentials,” *Acc. Chem. Res.*, vol. 45, no. 3, pp. 317–326, Mar. 2012.

3. G. V. Lowry *et al.*, “Guidance to improve the scientific value of zeta-potential measurements in nanoEHS,” *Environ. Sci. Nano*, vol. 3, no. 5, pp. 953–965, Oct. 2016.

4. S. Skoglund, J. Hedberg, E. Yunda, A. Godymchuk, E. Blomberg, and I. Odnevall Wallinder, “Difficulties and flaws in performing accurate determinations of zeta potentials of metal nanoparticles in complex solutions - Four case studies,” *PLoS One*, vol. 12, no. 7, p. e0181735, Jul. 2017.

5. H. Ohshima, “A simple expression for henry’s function for the retardation effect in electrophoresis of spherical colloidal particles,” *J. Colloid Interface Sci.*, vol. 168, no. 1, pp. 269–271, Nov. 1994.

6. C. Mircioiu *et al.*, “Mathematical modeling of release kinetics from supramolecular drug delivery systems,” *Pharmaceutics*, vol. 11, no. 3, p. 140, Mar. 2019.

7. “Mathematical models of drug release,” *Strategy to Modify Drug Release from Pharm. Syst.*, pp. 63–86, Jan. 2015.

8. D. R. Paul, “Elaborations on the Higuchi model for drug delivery,” *Int. J. Pharm.*, vol. 418, no. 1, pp. 13–17, Oct. 2011.

9. P. Costa and J. M. Sousa Lobo, “Modeling and comparison of dissolution profiles,” *Eur. J. Pharm. Sci.*, vol. 13, no. 2, pp. 123–133, May 2001.