Effect of particle surface charge on drug uptake

Maosheng Zheng* and Jie Yu

DOI 10.1515/ejnm-2015-0015
Received February 26, 2015; accepted June 9, 2015; previously published online July 2, 2015

Abstract: In this paper, it aims to build the relationship of statically electric interaction between the surface charge of a particle drug and cellular uptake. The statically electric theory is applied to study the change of wetting between the drug particle and the cell, a factor that enhanced uptake of cells induced by particle’s surface charge is introduced, then it is formulated according to Kelvin theory for dissolving of solid particle in liquid. It is found that the change of contact angle between the surface charged particle drug and the cell can be detected if the Zeta potential reaches to 6 mV in water like solution, an increase of about 11.1% for the uptake could be obtained for a polymer particle with molar mass $M \sim 10$ kg/mol, mass density $\rho \sim 0.9 \times 10^3$ kg/m$^3$, radius $r \sim 15$ nm at temperature 300 K and Zeta potential 10 mV condition as compared with the same particle in water-like solution but without surface charge. The effect of particle surface charge on drug uptake could be interpreted by statically electric theory.

Keywords: cell; drug particle; enhanced uptake; surface charge; wetting.

Introduction

Due to their special physical, chemical, and biological properties, nanoparticles, with diameters ranging from 1 to 100 nm, have been used in various fields (1–4). Different nano-materials, such as carbon nanotubes, silica nanoparticles, fullerene, magnetic nanoparticles, etc. attract much more attention in the engineering and health fields (5–9). In particular, it has been realized that nanoparticles have potentials to enhance delivering drug or genetic materials to targeted cells or organs, it results in the therapeutic delivery procedures being more precise, more effective, and less harmful to healthy tissues and organs (10).

Polymer nanoparticles, such as polyethylenimine (PEI) (11), chitosan (12), and polyglycolic acid (PLGA) (13–15) have been frequently used for drug and gene delivery in the recent researches. Metallic and ceramic nanoparticles, such as Au nanoparticles (16–18), iron oxide (17, 19, 20) and silica nanoparticles (10, 21), have also been studied for drug and gene delivery. The widely used in biomedical fields such as dental, bone tissue engineering (22), orthopedic implants (23, 24) and antibacterial agents (25), hydroxyapatite (HAP), are those bone like ones due to their chemical and structural similarity with bone minerals and good biocompatibility (22). Recently, more attention has been paid to study the possibility of using HAP nanoparticles as carrier for drug and gene delivery because of their great affinity to DNA (2, 10, 26–28). It is necessary to understand the interaction between HAP nanoparticles and the cell, so as to design proper nanoparticles for gene delivery (29).

It is well known that size, shape, and surface charge are the primary parameters of colloidal particles for cellular uptake besides biomolecular approaches. Gao et al proposed a diffusive model to describe the receptor-mediated endocytosis process (30), it gives a good agreement with many cellular uptake experimental results. Other studies indicate that surface charge affects the cellular uptake and biocompatibility of nanoparticles dramatically (31–34).

In this study, the statically electric relationship between the surface charge of the particle drug and cell uptake is built, the change of wetting between drug particle and cell is studied based on statically electric theory. A factor that enhanced uptake of cells induced by surface charge effect is introduced and formulated according to Kelvin theory for dissolving of solid particle in liquid.

Action of particle surface charge with surrounding medium

The interaction between the surface charge of a particle and the surrounding medium is a statically electric one undoubtedly. Consider the particle as a charged...
spherical ball for the simplicity, its surrounding medium will be polarized according to the common statically electric theory in general, and there exists an opposite electric layer near the charged spherical ball due to the polarization action, thus the so-called “double charge layer” forms in between. And furthermore, it builds a spherically electric capacitor visually.

For plane infinite capacitor, its capacity can be written as (35, 36),
\[ C = \varepsilon_0 \varepsilon S_{\text{sol-lyq}} / d, \]
in which, \( \varepsilon_0 \) and \( \varepsilon \) represent the dielectric constant of the vacuum and relative dielectric constant of the medium, respectively; \( S_{\text{sol-lyq}} \) is the interface area of solid and liquid; \( d \) is the thickness of the “double charge layer”.

If the electric potential applied to the “double charge layer” capacitor is \( u \), the increase of free energy per area due to the charge distribution in the liquid can be written as,
\[ \Delta \gamma = \frac{1}{2} Cu^2 / S_{\text{sol-lyq}} = \frac{\varepsilon_0 \varepsilon u^2}{2d}. \]

As to a electric charged liquid droplet, if it is placed on the solid plane, the contact angle will be changed according to the following manner by adding the electro-wetting term \( \Delta \gamma \) into Young’s equation (35, 36),
\[ \cos \theta(u) - \cos \theta_0 = \frac{\Delta \gamma}{\gamma_{\text{lyq-vap}}} = \frac{\varepsilon_0 \varepsilon u^2}{2d \gamma_{\text{lyq-vap}}}, \]
in which, \( \gamma_{\text{lyq-vap}} \) is the free energy of liquid/vapor; \( \theta_0 \) is the contact angle of the liquid in absence of applied voltage and \( \theta(u) \) is the contact angle of the liquid under condition of voltage \( u \) applied. Eq. [3] indicates that the contact angle decreases with \( u^2 \) and independent on particle size.

Similarly, the wetting degree between electric charged drug particle and cell could be improved by Eq. [3] as well provided voltage \( u \) is applied.

Eq. [3] shows that the change of contact angle increases with electric potential (i.e. surface charge) monotonously.

As an example, lets consider water as the medium in Eq. [3]. Since the relative dielectric constant of water \( \varepsilon_{\text{r, water}} \) is about 80, and the dielectric constant of the vacuum \( \varepsilon_0 \) is 8.85×10^{-12} \text{Coulomb}^2/\text{N-m}^2, the free energy of water/vapor \( \gamma_{\text{lyq-gas}} \) is about 72.8 mN/m, if the thickness of the “double charge layer” \( d \) is taken as \( \text{Å} \) in order of magnitude, Eq. [3] shows that a visible change of contact angle \( \theta \) can be detectable, for example, \( \theta_0 - \theta(u) = 1^\circ \) if the electric potential \( u \) applied to the “double charge layer” capacitor is at least 6 mV.

Ref. (31) presented the changes of contact angle with respect to preparation parameters for negatively charged chitosan hydrochloride grafted nano-particles (CMCNP), covalently labeled with rhodamine B(RhB), the size of these particles is about 150 nm. The particle size and Zeta potential were determined by using Zetasizer Nano ZS90, and the contact angle was measured by using JC 2000 A Goniometer (31). The results are cited and shown in Table 1.

The data in Table 1 shows that the contact angle decreases with Zeta potential (i.e. surface charge) obviously, it indicates the validity of Eq. [3].

The decrease of contact angle implies the preferable wetting between the particle and the medium, which might promote the uptake of cells in principle.

The Kelvin theory for dissolving of solid particle in liquid reads (37),
\[ \frac{a}{a_0} = \exp[2\Delta \gamma \cdot M / (\rho r PT)], \]
in which, \( a \) is the instant activity and \( a_0 \) is the original activity of solid particle dissolving in liquid at equilibrium states; \( M, \rho \) and \( r \) are the molar mass, volume density and radius of the particle, respectively; \( P \) and \( T \) are gas constant and absolute temperature, respectively, \( \Delta \gamma \) is the change of surface free energy.

The term \( a/a_0 \) in Eq. [4] is in fact a ratio that reflects the enhancement of the activity of solid particle dissolving in liquid at equilibrium state.

According to Kelvin theory for dissolving of solid particle in liquid, i.e. Eq. [4], the uptake of cells induced by surface charge effect could be increased by a factor,\n\[ f = \exp[2\Delta \gamma \cdot M / (\rho r PT)] = \exp[\varepsilon_0 \varepsilon u^2 \cdot M / (d \rho r PT)], \]

Under condition of polymer particle as carrier, \( M \sim 10 \text{ kg/mol}, \rho \sim 0.9 \times 10^3 \text{ kg/m}^3, \ r=15 \mu m, \ T=300 \text{ K}, \ u=10 \text{ mV}, \ d=1.5 \text{ Å}, \) the factor reaches to \( f \sim 1.11 \), i.e. about 11.1% increase of the uptake will be obtained in this condition as compared with the same particle in water-like solution without surface charge. This has been verified by many experiments (6, 14, 31–34).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Size, nm</th>
<th>Zeta potential, mV</th>
<th>Contact angle, °</th>
</tr>
</thead>
<tbody>
<tr>
<td>RhB-CMCNP (–15, 150)</td>
<td>149.2±4.1</td>
<td>–13.2±0.5</td>
<td>63.5±1.4</td>
</tr>
<tr>
<td>RhB-CMCNP (–25, 150)</td>
<td>157.3±4.7</td>
<td>–23.2±1.7</td>
<td>43.1±1.0</td>
</tr>
<tr>
<td>RhB-CMCNP (–40, 150)</td>
<td>156.0±5.1</td>
<td>–38.4±0.7</td>
<td>38.8±1.0</td>
</tr>
</tbody>
</table>
Zheng and Yu: Effect of particle surface charge on drug uptake

Figure 1 shows the effects of particle radius and electric potential on enhanced uptake factor $f$, the values for $M_r$, $\rho$, and $T$ are taken as 10 kg/mol, $0.9 \times 10^3$ kg/m$^3$, $d=1.5A$ and temperature 300 K, respectively. It can be seen from Figure 1 that particle size (radius $r$) affects the surface charge enhanced uptake factor $f$ significantly though there is no influence of particle size on the changes of surface free energy $\Delta \gamma$ and contact angle. The smaller particle size the greater enhanced action of surface charge uptake factor.

He et al. studied the surface charge effect on cellular (murine macrophage) uptake for 4 types of polymer particles with the size of about 150 nm (31). They took the percentage of fluorescence associated with cells versus the amount of fluorescence present in the feed solution as the expression for the uptake (31). Here their experimental results are cited and shown in Figure 2.

Roser et al investigated the effect of surface charges on in vitro phagocytosis and biodistribution in rats (32).

The Laser Doppler Anemometry with a Malvern Zetasizer IIc was employed to determine the electrophoretic mobility, and the Smoluchowski equation was used to calculate the zeta potential from the electrophoretic mobility (32). The mouse macrophages were characterized using a 1-Naphthylester Diagnostik Kit (32). The correlation between zeta potential and phagocytic index is cited and shown in Figure 3, which was surface modified albumin nanoparticles using mouse macrophages for incubation time 60 min and without serum under condition of phosphate buffer, 5 mM and pH 7.2 (32).

The experimental results in Figures 2 and 3 indicate that the cellular uptake increases obviously with the value of Zeta potential for the 4 type of polymer particles with the size of about 150 nm, and for the surface modified albumin nanoparticles using mouse macrophages, their trends agree with the theoretical prediction of Eq. [5] fundamentally.

**Concluding remarks**

From above discussion, it could be concluded,

1. The correlations between the surface charged drug particle and cell, and the enhanced uptake with surface charge of particle proposed on basis of the fundamental statically electric and Kelvin theory for dissolving of solid particle in liquid in the present study are appropriate;
2. The correlations realize the nature of the interaction between the surface charged particle and cell quantitatively. Available experimental data verifies their validity;
3. The basic picture of surface charge improving cell uptake is as follows: electric interaction in statically
electric double layer→wetting improving between charged drug particle and cell→solid particle dissolving in liquid improvement→cellular uptake enhancement.

Acknowledgments: The support of Shaanxi provincial social development and tackling key problem program 2014-k14-03-02 is acknowledged.

Conflict of interest statement: Authors state no conflict of interest. All authors have read the journal’s Publication ethics and publication malpractice statement available at the journal’s website and hereby confirm that they comply with all parts applicable to the present scientific work.

References


Bionotes

Maosheng Zheng
Institute for Energy Transmission Technology and Application, School of Chemical Engineering, Northwest University, Xi’an, 710069, China, mszheng2@yahoo.com

Maosheng Zheng obtained his PhD degree in materials science & engineering in 1992 at Northwestern Polytechnic University, China. He worked in materials science & engineering for teaching and research in Xi’an Jiaotong University in 1992 till 2006 as a full time professor. Since 2006, he worked in the School of Chemical Engineering at Northwest University for materials science and nano-technology teaching and research as full time professor. His research work focuses on nano-technology, energy resource technology and materials.

Jie Yu
School of Life Science and Technology, Northwest University, Xi’an, 710069, China

Jie Yu obtained her Bachelors degree in polymer materials in 1987 at Northwestern Polytechnic University, China. She worked in the polymer materials and biological engineering fields for teaching and research in Xi’an Jiaotong University in 1993 till 2007. Since 2007, she has engaged in the School of Life Science and Technology at Northwest University for biological medicine teaching and research as senior engineer. Her research work focuses on organic nano-particles, synthesis, surfaces, and their interactions with biological cells.