Journal of Nanotoxicology and Nanomedicine
Volume 2 • Issue 1 • January-June 2017

Drug-Nanoparticle Composites:
A Predictive Model for Mass Loading

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ABSTRACT

Polymeric nanoparticles represent attractive targets for the controlled delivery of therapeutic drugs. Drug-nanoparticle conjugates are convenient targets to enhance solubility and membrane permeability of drugs, prolong circulation time and minimize non-specific uptake. The behavior of drugs-loaded nanoparticles is governed by various factors. Understanding of these effects is very important for design of drug-nanoparticle systems, that could be suitable for treating the particular diseases. The aim of the current study is a complementary molecular docking followed by quantitative structure-activity relationships modeling for drugs payload on polymeric nanoparticles. Twenty-one approved drugs were considered. Docking of drugs was performed towards a simplified polymeric surface. Binding energies agreed well with the observed mass loading. Quantitative structure-activity relationships model supported this data. Effects of electronegativity and hydrophobicity were discussed. Developed model may contribute to the development of other useful nano-sized polymeric drug carriers to deliver a spectrum of therapeutic and imaging agents for medical purposes.

KEYWORDS

Classifie, Descriptors, Drug Delivery, Drug-Polymer Interactions, Molecular Docking, PLGA

1. INTRODUCTION

Drug development is an expensive and time-consuming process. In order to save time and money, in most cases it is more effective to improve efficacy and safety of known drugs, rather than develop new drugs. For this purpose, different methods such as individualized drug therapy, dose titration, and therapeutic drug monitoring were developed (Tiwari, et al., 2012). One of the possible ways of drug delivery is the usage of nanoparticles. Poly(ε-caprolactone), poly(lactic acid), poly(glycolic acid), and their copolymers are the most popular polymers to be used as drug carriers (Jeong, Bae, Lee & Kim, 1997; Brewer, Coleman, & Lowman, 2011). They are safe, highly biodegradable and approved by the US Food and Drug Administration (FDA) (Tiwari et al., 2012; Chiellini & Solaro, 1996). In addition, polymeric nanoparticles are suitable species for the surface modification. Hence, polymeric nanoparticles suitable candidates for drug delivery. Different drugs that can be explored in combination with polymeric nanoparticles include: small molecules, proteins, nucleic acids, diagnostic agents (Morachis, Mahmoud & Almutairi, 2012). Targeted drug delivery using polymeric nanoparticles has a vast potential in diagnosis and treatment (Torchilin, 2007; Singh & Lillard, 2009). Application of such species as drug carriers can notably reduce side effects and increase residence time in the body (Brewer, Coleman, & Lowman, 2011; Scarpa et al., 2016; Mørch, et al., 2015).

DOI: 10.4018/JNN.2017010101

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Polymeric nanoparticles could also be used to deliver multiple drugs simultaneously (Scarpa et al., 2016; Mørch et al., 2015). They can stabilize and protect loaded drugs from degradation (Panyam & Labhasetwar, 2003).

Physical and chemical properties of both polymeric nanoparticles and drugs have influence on drug delivery. Systematical evaluation of the influence of different physicochemical parameters of drugs and nanomaterials was performed in different papers (Morachis, Mahmoud & Almutairi, 2012; Wang & Dormidontova, 2010; Bae, Fukushima, Harada & Kataoka, 2003). For instance, binding affinity and specificity are two important aspects of nanoparticle targeting that characterize the performance of nanoparticle delivery systems (Wang & Dormidontova, 2010). Wang and Dormidontova found that nanoparticle affinity is affected by variations in the binding energy, number of ligands, tether length, density, and nanoparticle's size (Wang & Dormidontova, 2010).

Effectiveness of a drug delivery device is system-dependent on drug loading and drug release. High drug loading capacity is the necessity for a successful delivery (Bae, Fukushima, Harada & Kataoka, 2003). In general, release/loading rates depend on drug solubility, sorption-desorption processes, drug diffusion and erosion/diffusion processes in nanoparticle.

Properties of nanoparticles loaded with drug can be predicted using simulation methods. *In silico* predictions of properties of nanomaterials represent the cutting edge of non-testing methods. For instance, *Costache et al*. modeled drug-polymer interactions in polyethylene glycol-tyrosine copolymer nanospheres (Costache, Sheihet, Zaveri, Knight & Kohn, 2009). However, all atoms simulations usually require big amounts of computer time. Simple and quick methods, such as molecular docking or Quantitative Structure-Property Relationship (QSAR) analysis could be applied to identify candidate materials (Winkler et al., 2014; Sizochenko & Leszczynski, 2016; Rasulev et al., 2017). Such modeling could be used to fill the informational gap between modern theories of mechanisms of nanoparticle's action and property predictions.

2. MATERIALS AND METHODS

Original experimental data of mass loading of 21 approved drugs on poly(dl-lactide-co-glycolic acid) were extracted from literature (Das, Roy, Islam & Saha, 2013). The structures of drugs were further optimized with the Gaussian 09 software package using a protocol which included Density Functional Theory (B3LYP functional, 6-31G(d,p) basis set). A list of the studied drugs is presented in Table 1. Relative chirality of drugs was reflected using Continuous Chirality Measure (CCM) (Pinsky, Zait, Bonjack & Avnir, 2013). The CCM evaluates the degree of chirality of a molecule. The measure is based on the distance between the chiral molecule and the nearest structure that is achiral (Pinsky, Zait, Bonjack & Avnir, 2013). By definition, for given configuration of points $\{P_i\}:=1$, the chirality content is determined by finding the nearest configuration of points $\{k_i\}:=1$ which has an improper element of symmetry and by calculating the distance between the two sets.

Additionally, relative lipophilicity and electronegativity counts were calculated using simplex descriptors (SIRMS-lip and SIRMS-EO) (Sizochenko, Kuz'min, Ognichenko & Leszczynski, 2016). In the framework of SiRMS, molecules were represented as a system of simplexes (fragments of fixed composition, chirality and topology). This approach is utilized to generate so-called simplex fragments (fragments of size 4 atoms). Hydrophobicity of studied compounds (logP) was determined by the sum of non-overlapping molecular fragments (Table 1).

For the purposes of quantitative modeling, modification of M5P classifier was applied. Previously, our team successfully applied M5P algorithm for QSAR modeling of nanoparticles (Sizochenko et al., 2017). M5P methodology combines a conventional decision tree technique with the regression functions at the nodes (Quinlan, 1992). Collected data was randomly split between training and test sets. Training set covers ~ 80% of the initial dataset; related test set covers the remaining ~ 20%. Next, the statistical goodness-of-fit of the M5P model and its predictive ability were assessed using

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