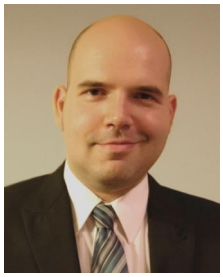
COLLEGE OF ENGINEERING
THE UNIVERSITY OF TOLEDO

UT Engineering New Research Grant Award



Project	Mechanistic Analysis of Polyelectrolyte-Based Colloidal Drug Carriers
Principal Investigator	Dr. Yakov Lapitsky Assistant Professor of Chemical Engineering
Co-Principal Investigator(s)	--
Sponsor(s)	National Science Foundation
Project Duration	December 2011 – November 2014
Sponsor Award Amount	$297,821

ABSTRACT

Intellectual Merits: A fundamental study is proposed to relate the properties of multivalent counterion-crosslinked polyelectrolyte micro- and nanoparticles to their molecular interactions and formation kinetics. Currently, both their preparation and application in drug delivery largely rely on trial and error, and the literature on this subject remains limited to empirical data. While the complexation of oppositely charged polyelectrolytes has been studied for many years, detailed understanding of the particle formation process has been confounded by extremely strong binding, fast kinetics and long timescales of chain rearrangements. The formation mechanism of multivalent counterion-crosslinked polyelectrolyte particles on the other hand, (whose investigation is more tractable due to their weaker intermolecular interactions) remains virtually unexplored. Similar gaps exist in the understanding of their drug release properties, which have been (and continue to be) grossly mischaracterized by experimental methods that are unsuitable for colloidal polyelectrolyte particles. This lack of design guidelines severely limits their performance and, in cases where the drug is expensive, leads to high research and development costs. To address this, the proposed research aims to gain a quantitative and mechanistic understanding of the parameters that govern their (1) structure, (2) stability and (3) drug encapsulation/release properties, by exploring how their colloidal properties evolve with changes in their molecular interactions. This will be achieved by probing the process of particle formation and drug encapsulation/release with an array of molecular and colloidal characterization techniques (e.g., isothermal titration calorimetry, light scattering and stopped-flow spectrofluorimetry), and analyzing the results using existing models for the formation of monodisperse colloids, adsorption and diffusion. Leveraging on the PI's prior work on polyelectrolyte self-assembly and drug delivery, this project will yield three transformative outcomes: (1) it will provide mechanistic and quantitative guidelines for the design and application of polyelectrolyte-based colloidal drug carriers (2) it will bridge existing methods (and mechanistic models) for the preparation of monodisperse colloids from low molecular weight constituents to polyelectrolyte-based colloids and (3) it will yield important mechanistic insight into the process of micro- and nanoparticle formation from pairs of oppositely-charged polyelectrolytes, which cannot be experimentally probed in great detail directly.

Broader Impacts: The proposed work will enable development of safer, more effective and less expensive pharmaceutical products for oral, nasal and ophthalmic drug delivery. Specifically, it will establish essential guidelines for ensuring that emerging (polyelectrolyte-based) drug carriers will deliver drugs to their intended targets, and not lead to overdosing. Furthermore, the fundamental insights gained from this research could advance the design of medical and environmental diagnostics, personal

care products and foods. This will be facilitated by the strong environmental engineering expertise at the University of Toledo, which fosters opportunities for future collaborations. Moreover, the proposed work will train undergraduate, graduate and high school students in the use of materials characterization techniques, and the fundamentals of polymer, colloid and pharmaceutical science. This training will poise them for successful careers in a wide range of industries or academia. Findings from this work will be published in peer-reviewed journals and presented at professional meetings. Importantly, this work will also be integrated with the university's outreach activities. The PI will introduce high school students to stimulus-responsive polyelectrolytes in the *Engineer for a Day* program that the university offers to Toledo Public Schools, and will continue his involvement in the *Engineering for Teachers of Migrant Students* (ETMS; CIVE 4950/5940) distance learning course. ETMS provides graduate training for teachers in rural communities who teach children of migrant farm workers, and aims to develop a set of experiments that demonstrate the importance of mathematics, science and engineering to everyday life. The PI has recently become involved with ETMS, and has already developed several demonstrations that use stimulus-responsive polymers found in household products (e.g., alginate, poly(acrylic acid), and methylcellulose) to reinforce concepts that are learned in high school chemistry. These activities will help increase and diversify the enrollment of science and engineering students. ⁼

NGN: August 22, 2011