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Formulation of peptide and protein therapeutics into nanoparticles by ion pairing for prolonged activity and improved delivery

Robert K Prud'homme, Kurt D Ristroph and **Paradorn Rummaneethorn**
Princeton University, USA

Biologics, the fastest-growing sector of the pharmaceutical marketplace, are an attractive class of therapeutics because of their impressive potency, high selectivity, and reduced off-target effects. But while the effectiveness of these drugs outclasses many of their small-molecule predecessors, administering biologics remains a challenge. Physiological barriers such as chemical digestion (when taken orally), rapid blood clearance (when injected), or thick pulmonary mucus (when inhaled) chemically or physically prevent biologics from reaching their targets and working as designed. To reduce the frequency of dosing, strategies of protecting these proteins and peptides within delivery vehicles have arisen, but the majority of these processes suffer from high losses and poor scalability. We here present a scalable and continuous method of encapsulating water-soluble charged biologics into polymeric nanoparticles. This is done by simultaneously reversibly ionically modifying the biologics of interest with hydrophobic counterions and controllably precipitating the newly-formed hydrophobic complex into nanoparticles via the polymer-directed Flash NanoPrecipitation technique. This combined technique, termed hydrophobic ion pairing Flash NanoPrecipitation (HIP-FNP), is applicable to a wide variety of peptides and proteins, both anionic and cationic. Importantly, the process is continuous, scalable, and achieves encapsulation efficiencies greater than 95%. We herein demonstrate encapsulation of two model proteins: the cationic enzyme lysozyme (MW 14,300 D) and the anionic protein ovalbumin (MW 42,700 D). By altering the identity or amount of hydrophobic counterion used, we can tune protein release rates, an important consideration for prolonged delivery. Importantly, we also show that the proteins' activity has been retained throughout the processing steps. We believe this technique offers a route forward for improving the delivery of many biologic therapeutics and may improve patient comfort and compliance by simplifying dosing regimens.

Recent Publications

1. Pinkerton N M et al. (2014) gelation chemistries for the encapsulation of nanoparticles in composite gel microparticles for lung imaging and drug delivery. Biomacromolecules. 15(1):252-261.
2. D'Addio S M et al. (2072) Determining drug release rates of hydrophobic compounds from nanocarriers. Phil. Trans. R. Soc. A. 374(2072): pii:20150128.
3. D'Addio S M et al. (2013) Optimization of cell receptor-specific targeting through multivalent surface decoration of polymeric nanocarriers. Journal of Controlled Release. 168(1):41-49.
4. D'Addio S M et al. (2013) Aerosol delivery of nanoparticles in uniform mannitol carriers formulated by ultrasonic spray freeze drying. Pharmaceutical Research. 30(11):2891-2901.
5. D'addio S M and R K Prud'homme (2011) Controlling drug nanoparticle formation by rapid precipitation. Advanced Drug Delivery Reviews. 63(6):417-426.

Biography

Robert Prudhomme is a Professor in the Department of Chemical and Biological Engineering at Princeton University, USA. He is the Founding Director of the Program in Engineering Biology. His research program focusses on polymer self-assembly applied to drug delivery. The development of Flash Nanoprecipitation (FNP) in his laboratory enabled the encapsulation of poorly soluble drug compounds and oligonucleotides for therapy directed towards cancer, TB, and injections. FNP is a scalable and continuous process that is enables integrated processing and spray drying for low cost oral and aerosol formulations. Under sponsorship by the Bill and Melinda Gates Foundation, the process is being adopted to formulate new compounds coming from TBA, MMV, and DNDi.

Prudhomm@princeton.edu