Organometallic nanogels for the delivery of nucleotide analogues

Hervé Hillaireau
Unversité Paris-Sud, France

Nanomedicine hav brought tremendous hope of targeted and personalized medicine. In particular, they have improved the bioavailability of poorly soluble drugs, reduced side effects of several drugs, and enabled drug targeting to diseased tissues, especially in the field of cancer treatment. However, a widespread use of nanomedicine still faces several important impediments, especially in the case of hydrophilic drugs for several reasons. (i) Despite variable drug encapsulation efficiencies into nanocarriers, the drug loading achieved is generally low, which limits the drug dose and/or requires the administration of high amounts of excipients (eg. lipids or polymers forming the nanocarrier). (ii) The drug release is often poorly controlled and prone to the 'burst release' effect, and the stability of nanocarriers in physiological media may be unsatisfying, therefore limiting the targeting potential of nanomedicine. (iii) Each drug often requires a specific nanocarrier system, which is often challenging to scale-up, which dramatically limits the applicability into the industry and the clinics [1].

To address these limitations, we have designed a drug delivery platform tailored to hydrophilic drugs, especially nucleotides/nucleotide analogues. This platform relies on the preparation of chitosan-iron coordination complexes, which form nanogels in presence of hydrophilic drugs. Such nanogels act as nanocarriers of therapeutic nucleotides such as adenosine triphosphate (ATP), as well as nucleotide analogues such as azidothymidine triphosphate (AzT-TP).

Our group has first demonstrated the ability of triphosphate group-containing drugs to induce ionotropic gelation of chitosan. This was demonstrated using the nucleotide ATP and the nucleotide analogue AzT-TP. The resulting nanogels can be seen as nucleotide/nucleotide analogue nanocarriers, showing both efficient encapsulation and drug loading, up to 44% w/w [2]. To further investigate the potential of chitosan-metal complexes to improve the nanogel stability in physiological media, coordination complexes of chitosan and Fe(III) have been synthesized and used to form nanogels in presence of ATP, which clearly demonstrated a high resistance to physiological ionic strengths, increasing with the Fe(III) content. These results highlight the potential of metal association to chitosan to form nanogels with tunable stability and drug release profile [3].

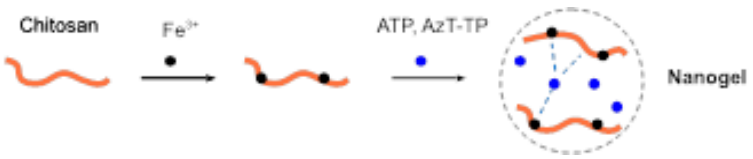

Figure: Formulation of nanogels by ionitropic gelation of chitosan and chitosan-iron complexes, in presence of a nucleotide (ATP) or nucleotide analogue (AzT-TP).

Recent Publications

1. Hillaireau, H. and Couvreur, P. (2009). Nanoencapsulation of antiviral nucleotide analogs. J Drug Del Sci Tech 19, 385–390.
2. Giacalone, G., Bochot, A., Fattal, E., Hillaireau, H. (2013). Drug-Induced Nanocarrier Assembly as a Strategy for the Cellular Delivery of Nucleotides and Nucleotide Analogues. Biomacromolecules 14, 737–742.
3. Giacalone, G., Hillaireau, H., Capiau, P., Chacun, H., Reynaud, F., Fattal, E. (2014). Stabilization and cellular delivery of chitosan-polyphosphate nanoparticles by incorporation of iron. J Control Release 194C, 211–219.

Biography

Hervé Hillaireau is Associate Professor of Pharmaceutical Technology at the School of Pharmacy of Université Paris-Sud since 2009. His research at Institut Galien Paris-Sud relates to the design and the toxicological evaluation of biodegradable nanoparticles as drug nanocarriers, with a focus on: (i) nanocarrier design for nucleoside/nucleotide analogues and nucleic acids delivery in anticancer and antiviral therapies; (ii) nanocarrier surface functionalization for molecular targeting; (iii) toxicological evaluation of biodegradable nanoparticles. He has been supervising or co-supervising 10 PhD theses. He is the author of 4 book chapters and 38 peer-reviewed international research articles, and has recently co-edited a special issue of Advanced Drug Delivery Reviews on Aptamers in therapeutics and drug delivery.

Notes: