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Research with Neutrons Opens New Paths to Predict Behaviour of Local Anesthetics

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Pharmaceuticals. 'This is indeed a very encouraging approach to overcome one of the great challenges faced by pharmaceutical technology, namely being able to predict the release profiles of complexed drugs."

COPENHAGEN—Determining the characteristics or effect of drugs in pure form is considered a routine calculation. What is less known is the behaviour of drugs formulated into delivery systems, which can potentially alter their chemical potency or toxicity.

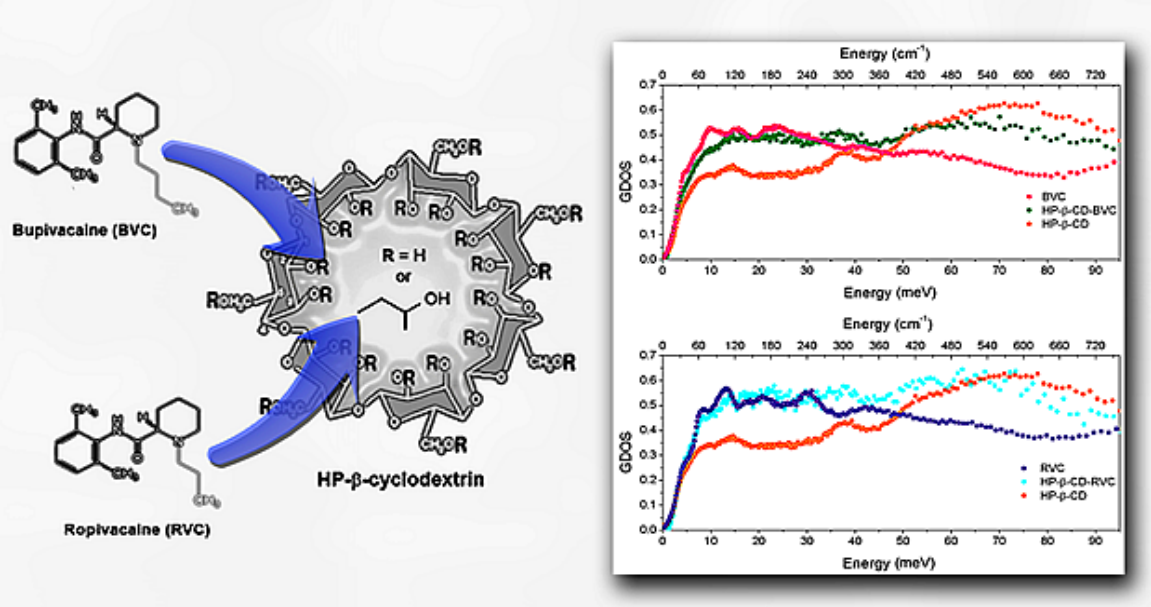
With the help of two neutron instruments at the Institute Laue-Langevin (ILL) in Grenoble, France, researchers recently took a deeper look into the dynamics and mobility of drugs when combined with soluble compounds. It is an important step to further understanding the mechanisms of drug efficacy, an underlying challenge for developing safe and reliable pharmaceuticals.

Three of the study's authors, from left, Murillo Martins, Rosanna Ignazzi and Heloisa Bordallo at the Niels Bohr Institute in Copenhagen. PHOTO: Ola Jakup Joensen/Niels Bohr Institute

Neutrons Opening New Fields of Health Science Research

'Although at its infancy as a tool for understanding advanced drug design, neutron scattering combined with computational calculations has advantages that are unique and inherent to the technique," explains Heloisa Bordallo, one of the authors of the recently published study and an advisor to the Scientific Activities Division at the European Spallation Source (ESS). Bordallo is associate professor of X-ray and neutron science at the Niels Bohr Institute (NBI) at the University of Copenhagen (UCPH). 'Neutrons penetrate matter easily, are sensitive to hydrogen and can access different molecular motions."

Designed to produce up to two orders of magnitude more neutron brightness than current facilities, ESS will enable neutron scattering experiments in health science that are currently out of reach.



The scheme on the left represents bupivacaine (BVC, C18H28N2O) and ropivacaine (RVC, C17H26N2O) molecules being inserted into the HP-β-cyclodextrin (HP-β-CD) sugar cage. On the right, the experimentally determined density of states (GDOS) at room temperature of BVC and RVC before and after complexation with HP-β-CD (HP-β-CD-BVC and HP-β-CD-RVC, respectively) depicts the distinct effects of complexation over both anesthetics. IMAGES courtesy of the International Journal of Pharmaceutics

Murillo Martins is the lead author of the study and is currently a post-doc in the X-ray and neutron science group at NBI: 'We have shown that this [neutron scattering combined with computational calculations] is indeed a very encouraging approach to overcome one of the great challenges faced by pharmaceutical technology, namely being able to predict the release profiles of complexed drugs."

Step Toward Better Drug-Delivery Systems

The team carried out the research while it was exploring methods to develop novel drug-delivery systems that extend the analgesia effect as well as diminish the toxic effect of the

drugs for patients. Two common local anesthetics, bupivacaine (BVC) and ropivacaine (RVC), were individually tested with cyclodextrin (HP-β-CD). The latter is a soluble complexing agent whose chemical structure is known to be favourable to host several molecules.

To observe molecular changes in the treated anesthetics, measurements were carried out using ILL's cold neutron, time-focussing, time-of-flight spectrometer IN6, and IN13, the facility's thermal neutron backscattering spectrometer. These were followed by thermal analysis and density functional theory (DFT) calculations of the samples. Results showed the complexation with HP-β-CD produced a stronger effect on the mobility of BVC, an anesthetic often used in surgical procedures.

The study was published last month in the *International Journal of Pharmaceutics* by a large group of researchers from, among others, NBI/UCPH, ILL, ESS, the University of Campinas and Federal University of ABC in Brazil, and Sweden's Chalmers University of Technology.

Ref.: Murillo L. Martins, Juergen Eckert, Henrik Jacobsen, Éverton C. dos Santos, Rosanna Ignazzi, Daniele Ribeiro de Araujo, Marie-Claire Bellissent-Funel, Francesca Natali, Michael Marek Koza, Aleksander Matic, Eneida de Paula, Heloisa N. Bordallo. Probing the dynamics of complexed local anesthetics via neutron scattering spectroscopy and DFT calculations. International Journal of Pharmaceutics, Volume 524, Issues 1–2, 30 May 2017, Pages 397–406.

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