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RESEARCH NEWS STORY

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Chiba University

Unlocking Precise Composition Analysis of Nanomedicines

Researchers precisely quantify ions, nanoparticles, and aggregates of the same element, addressing the key regulatory gap in nanomedicine evaluation

Current regulations for nanomedicines overlook the effects of the different forms of the same element, such as ions, nanoparticles, and aggregates. In a recent study, Japanese researchers developed a new analytical method combining an asymmetric flow field-flow fractionation system and mass spectrometry to separately quantify these forms. This technique allows for better quality control and safety evaluation of metal-based nanomedicines, promoting their development and clinical use, with applications also extending to food, cosmetics, and the environment.

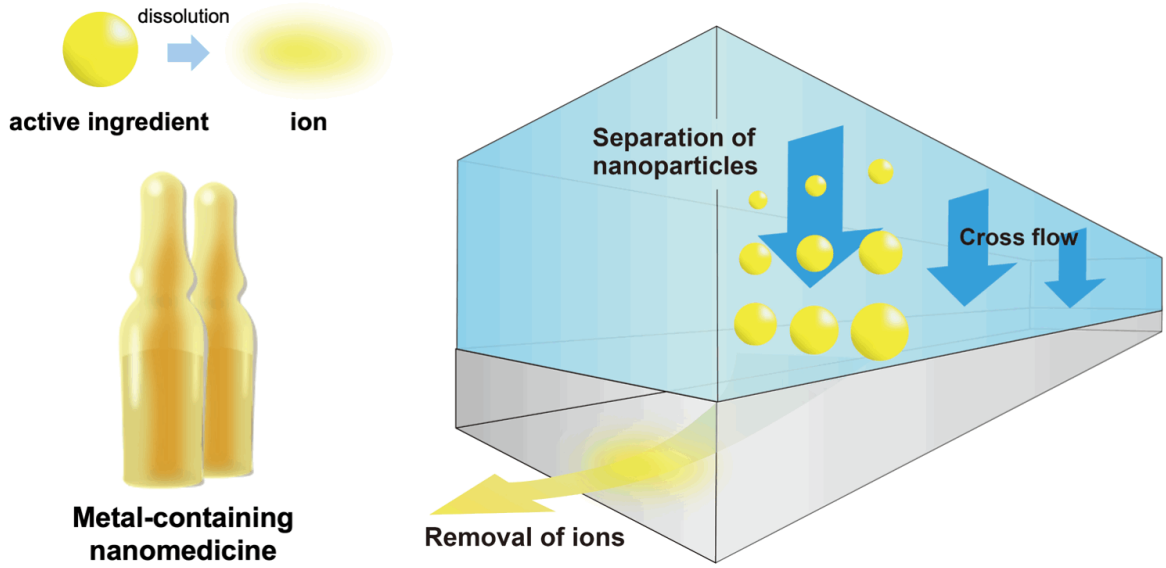

Image title: Overview of the proposed nanomedicine analytical method
Image caption: Conceptual image of the separation of nanoparticles (active ingredients) and ions (elemental impurities) in nanomedicines using an asymmetric flow field-flow fractionation system.
Image credit: Assistant Professor Yu-ki Tanaka from Chiba University
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Nanomedicines, especially those based on nanoparticles, are revolutionizing healthcare in terms of both diagnostics and therapeutics. These particles, often containing metals like iron or gold, can serve as contrast agents in medical imaging, act as nutritional supplements, and even function as carriers for drug delivery. Thanks to their unique properties plus careful engineering, nanomedicines can reach and accumulate in places within the body that conventional medicines cannot, making them promising for cancer detection and treatment. However, the same characteristics that make nanomedicines valuable also present challenges in ensuring their safety and quality.

Current pharmaceutical guidelines, including those from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), have a significant blind spot: they evaluate only the total amount of elements present in a medication without distinguishing between their different forms, such as ions or differently sized particles. This distinction is crucial because these different forms can have different effects on the body, including varying toxicity profiles.

Against this backdrop, a research team led by Assistant Professor Yu-ki Tanaka from the Graduate School of Pharmaceutical Sciences, Chiba University, Japan, has developed a new analytical method to address the existing regulatory gap. Their study, which was made available online in the journal *Talanta* on April 8, 2025, introduces a technique to separately quantify ions, nanoparticles, and aggregated particles in nanomedicines. Co-authored by Yasumitsu Ogra and Sana Hasegawa, also from Chiba University, the study showcases how this method can improve quality control for these advanced pharmaceutical products. "*By incorporating a novel evaluation method that addresses a previously overlooked issue in current evaluation guidelines, we can ensure the safe use of metal-based nanomedicines such as Resovist® and Ferinject®*" explains Dr. Tanaka.

The researchers combined two existing technologies—asymmetric flow field-flow fractionation (AF4) and inductively coupled plasma mass spectrometry (ICP-MS). They used the AF4 method in a novel way, taking advantage of its initial 'focus step.' During this step, particles are held inside the AF4 channel by two opposing flows. Using a special permeable membrane, cross-flows filter out the tiniest dissolved particles (ions), enabling quantification based on the differences in ICP-MS signals between samples with and without ion removal—namely, with and without the focus step. Once the ions are separated, the system then uses AF4's standard separation process to sort the retained nanoparticles by size. Finally, the ICP-MS device attached to the output can determine the approximate number of nanoparticles of each size. This combination enabled the team to distinguish between free metal ions, small hydroxide colloids, and nanoparticles of various sizes, all containing the same metal element.

They tested their approach on Resovist®, a nanomedicine used as a contrast agent in liver magnetic resonance imaging scans. The analysis revealed that only 0.022% of the iron in Resovist® was present in ionic form. At approximately 6.3 micrograms per milliliter, this negligible amount falls well below levels of concern. Additionally, the team confirmed that the active nanoparticles were smaller than 30 nanometers in diameter, with some aggregates around 50 nanometers. Importantly, no large aggregates were detected, which could reduce the effectiveness of the contrast agent. These results confirm both the safety and stability of Resovist® as a nanomedicine.

The proposed technique is particularly relevant for emerging cancer treatments that use gold nanoparticles as drug delivery systems or metallic particles for photothermal therapy. These advanced treatments rely on the 'enhanced permeability and retention (EPR) effect,' by which nanoparticles leak from blood vessels around tumors and accumulate in cancerous tissue. "*Since many novel nanomedicines consist of metal-based nanoparticles as their active ingredients, providing reliable methods for evaluating their safety and quality control will promote their development and clinical use*," notes Dr. Tanaka.

Additionally, this novel analytical approach extends beyond pharmaceuticals. It can also assess the safety of metal nanoparticles in food additives, cosmetics, and environmental samples—helping to ensure public health across multiple sectors. The researchers showcased its versatility by successfully analyzing both negatively charged ions (silicon) and positively charged ions (iron), indicating its potential for a wide range of nanomaterials.

Overall, by offering a more comprehensive assessment of the composition, quality, and stability of nanoparticles, this research paves the way for safer and more effective nanomedicines and nanoparticle-based technologies.

About Assistant Professor Yu-ki Tanaka
Yu-ki Tanaka is an Assistant Professor at the Graduate School of Pharmaceutical Sciences at Chiba University, Japan. He received his Doctor of Science degree from Kyoto University in 2017. His research interests include heavy metals, toxicity, single-cell/particle analysis, and isotopic composition analysis. He has over 30 publications to his name, with 1,900 reads and more than 300 citations. He is a member of notable academic societies, including the Pharmaceutical Society of Japan, the Japanese Society of Toxicology, and the Japan Society for Plasma Spectrochemistry.

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Reference:
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