Impurities in sugar excipients could cause drugs to fail

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Credit: Daniel Weinbuch

Sugar excipients, needed to stabilize medicines, can be unsafe for patients due to an impurity discovered recently by Daniel Weinbuch. "The biopharmaceutical industry should now consider new excipient quality criteria for safer drug development," he says. PhD defence on 13 December.

Modern medicines are folded like origami

Biopharmaceuticals, the fastest growing class of therapeutics, are very successful in treating chronic and life-threatening diseases, such as multiple sclerosis, diabetes and cancers. The active substances are often very large proteins such as antibodies, which are about a thousand times larger than small molecules such as ibuprofen. These large molecules are often very fragile, because they need to be folded properly, almost like origami, to fulfill their function.

Damaged proteins can be harmful for the patient

If such proteins are damaged during production, storage, shipment, or administration, they can unfold and aggregate. They form into particles that can even become large enough to be seen with the naked eye. The immune system in the body of the patient might attack these particles, especially those in the nanometer and micrometer size. This reaction, which is called unwanted immunogenicity, can cause life-threatening immunological side effects.

New techniques identify harmful particles

Particles of nanometer and micrometer size are omnipresent and do not necessarily have to originate from the therapeutic protein itself. "It was very important to establish new techniques in order to understand where these particles come from and how dangerous they might be for the patient," says Weinbuch, who did his PhD research at the Leiden Academic Centre for Drug Research (LACDR) in collaboration with Coriolis Pharma.

Weinbuch: "When we started our research project, there were very few analytical techniques available to measure and differentiate nanometer and micrometer particles." He, therefore, evaluated new and emerging techniques during his PhD, such as resonant mass measurement and flow

imaging microscopy.

Stabilizing sugar can make drugs unsafe

Sugar excipients are commonly used for many therapeutic proteins and other drugs as a stabilizing ingredient. "We found that sugar excipients themselves contain nanometer-sized particles, which can damage proteins and make drugs unsafe," says Weinbuch. "Potentially, these nanoparticle impurities in sugar could themselves even trigger the immune system – causing unwanted immunogenicity. We are investigating that right now."

Safe drug development

People were not aware of this issue before, according to Weinbuch. He advises new regulatory requirements for safer drug development. "The biopharmaceutical industry needs to be aware of potentially harmful impurities in their excipients, which are added to the drug products. Also the sugar industry has the challenge of producing sugars excipients without these impurities."

Second chance for failed drugs

Weinbuch's research is an important step towards the development of safer and more efficient biopharmaceutical drugs. "If a drug fails, it might not be due to the drug substance itself but due to an improper formulation. Using safe formulation excipients potentially gives failed drugs a second chance."

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