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TITLE: In situ determination of alum filling evenness and sedimentation in pharmaceutical products using water NMR

Key Investigator
Bruce Yu
Christopher Fox
Marc Taraban

Field
Pharmaceutical

Technology
NMR
Quality Control
Vaccine
Drug Manufacturing

Advantages
Contact-free, non-destructive
Fast and Reliable
In Situ testing
Continuous monitoring

Status
Available for licensing

Patent Status
U.S. Patent 11/585,770
U.S. Patent 11/543,371
U.S. Patent Appl. 18/170,114
U.S. Patent Appl 18/149,233

UMB Docket Reference
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External Reference
American Pharmaceutical Review

Summary
The invention describes a fast and non-destructive technique to determine the evenness of alum particle filling levels and/or sedimentation in pharmaceutical products, using water proton NMR. The technique allows manufactures to monitor consistency in alum filling and resuspension in vials, emulsion droplet size, emulsion stability, and antigen-alum complex stability.

Market
Aluminum adjuvants, particularly aluminum salts such as aluminum hydroxide and aluminum phosphate, are widely used in vaccines to enhance their immunogenicity. These adjuvants help to stimulate the immune system and improve the body's response to the vaccine by prolonging the presence of the antigen in the body and inducing a greater level of antibody production. They have also been shown to increase the duration and strength of immune responses to antigens and reduce the amount of antigen required in a vaccine dose, resulting in lower vaccine costs.

The need for quality control (QC) testing of alum-containing pharmaceutical products arises due to their propensity to experience sedimentation and phase separation during manufacturing, leading to products with varying levels of alum adjuvant. This can, among other issues, result in a lack of uniformity and reduced efficacy of the vaccine.

Currently, destructive testing technologies are required for product quality control of these products. Existing quality control techniques involve removing the drug substance from its container, perturbative steps such as dilution, pH adjustment, and other sample preparation techniques, and analysis, which require highly trained personnel. The analysis can be time-consuming and do not allow for real-time monitoring and detection of drug formulation changes, making it diffiult to identify issues in stability and process controls.

Therefore, there is a need for in-situ methods that allow continuous monitoring of alum containing pharmaceuticals to accurately and non-destructively to ensure the safety and efficacy of vaccines and other products containing alum adjuvants. This non-destructive QC method developed by UMB inventors has numerous advantages over the current destructive methods:

1. Contact-free in situ testing: This method does not require the removal of the drug from its container which reduces the risk of contamination and minimizes the need for sample preparation.
2. Fast and reliable: The technique is fast and reliable, providing accurate results in real-time.
3. Reduced need for highly trained personnel: The method can be automated and made continuous therefore requcing the need for highly trained personnel for analysis - reducing the cost and time involved in QC testing.
4. Improved uniformity and stability: Provides a way to optimize the manufacturing process and ensure uniformity and stability of pharmaceutical products in a non-destructive way, allowing every vial to be tested – eliminating stastical sampling.
5. Reduced manufacturing costs: By identifying and troubleshooting issues with uneven filling and sedimentation on a continuous basis, this method can help companies reduce quality and manufacturing costs.
6. Research tool: This method can also be used to study the behavior of alum particles in pharmaceutical products and their impact on drug efficacy and safety.

Contact: Mark Wozniak
Mark.Wozniak@umaryland.edu
410-706-7293

University of Maryland, Baltimore
620 W. Lexington St., 4th Floor
Baltimore, MD 21201

Although there are no studies indicating the cost of poor quality in alum containing vaccines,

it is estimated that the cost of poor quality in the US pharmaceutical industry can average 15% of revenue (ASQ (2017)). Globally, it is estimated that the cost of poor quality costs the pharmaceutical industry around $14 billion per year, with issues such as manufacturing defects and non-compliance with regulatory requirements contributing to the majority of the costs.

The global market for vaccines alone is expected to reach over $100 billion by 2026, driven by the increasing incidence of infectious diseases and the need for vaccination programs. The market for injectable drugs (other than vaccines) is also growing, driven by the rise in chronic diseases such as diabetes, cancer, and autoimmune disorders. The demand for alum-containing pharmaceuticals is expected to continue to grow as new vaccines and injectable drugs are developed to address these diseases.

Technology

Researchers at the University of Maryland, Baltimore have developed a non-destructive, in situ method that employs water proton NMR to determine the evenness of alum filling levels and sedimentation in pharmaceutical products. The technique is fast, reliable and uses the transverse relaxation rate of solvent NMR signals to provide insight into the extent of alum particle sedimentation and filling levels.

Products containing alum, such as vaccines with alum adjuvants, are highly prone to sedimentation and phase separation during the manufacturing process. This can result in vaccines with inadequate or excessive amounts of alum adjuvant, which may lead to less-than-optimal immune responses in immunized individuals. The use of NMR relaxation rates, specifically the transverse relaxation rate constant R2 of solvent molecules, can provide valuable information on the evenness of alum particle filling levels and the extent of sedimentation in products such as filled and sealed vaccine vials, ensuring consistency in alum filling and resuspension.

However, the contact-free in situ method described in the patent application can detect solute association through the solvent NMR signal, thereby providing an attractive alternative for quality control.

The non-destructive and in situ characteristics of this approach render it particularly well-suited for a variety of applications, including but not limited to:

- Ensuring uniformity and stability of pharmaceutical products through quality control during manufacturing
- Reducing the incidence of uneven alum filling and sedimentation by optimizing manufacturing processes
- Verifying the shelf-life stability of pharmaceutical products to prevent degradation over time
- Determining which formulations of pharmaceutical products exhibit the most uniform filling and least sedimentation by comparing different options
- Evaluating the effects of various processing conditions on alum filling and sedimentation in pharmaceutical products
- Identifying and resolving issues with pharmaceutical products that exhibit uneven filling or sedimentation
- Developing new pharmaceutical product formulations that exhibit improved uniformity and stability
- Conducting research into the behavior of alum particles in pharmaceutical products and their impact on drug efficacy and safety.

Technology Status

Technology is ready for licensing and commercialization.

Contact: Mark Wozniak
Mark.Wozniak@umaryland.edu
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