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Process Analytical technology by ultrasounds for industrial product control

Abstract

Process Analytical Technology (PAT) is a regulatory and scientific framework introduced by the Food and Drug Administration (FDA) to promote innovation and efficiency in pharmaceutical manufacturing by enabling in-line, real-time process monitoring and quality control, consistent with quality by design (QbD) principles, rather than solely through conventional laboratory testing (quality by testing approach). In this work, a new PAT tool was developed for implementation in an injectables manufacturing plant. Considering the sterility and cleanliness constraints associated with injectable products, a non-invasive ultrasound technique, using a pulse-echo configuration, was selected as the most suitable approach. Additional advantages include rapid analysis, robustness and straightforward implementation. Herein we present a method for quality control of saline physiological solution for infusion (NaCl 0.9%) developed with the new PAT.

Keywords: Injectables, Process Analytical Technology (PAT), Quality by Design (QbD), Ultrasound

Introduction

In modern pharmaceutical production, PAT is a key enabler of continuous manufacturing, supporting automated feedback and feed-forward control loops that ensure product consistency 1. PAT is closely aligned with to QbD principles, which emphasizes proactive quality assurance based on process knowledge and identification of Critical Quality Attributes (CQAs) and Critical Process Parameters. By establishing relationships between CQAs, CPPs and product quality, manufacturers can operate within a design space approved by regulatory authorities, ensuring consistent quality while allowing flexibility in process optimization 2.
Regulatory agencies, including FDA and EMA encourage PAT adoption, especially when associated with Real-Time Release Testing (RTRT) [3]. Aligned with these principles, our team developed an acoustic PAT tool and applied it to determining NaCl concentration in physiological saline solution for infusion.

Setup

The experimental setup (Figure 1) includes an ultrasonic probe operating in pulse-echo mode, a pulser-receiver to send an electrical pulse to the probe and receive the echoes after propagation in the solution, a temperature probe, a signal-processing board, and dedicated software. This configuration enables non-invasive, real-time measurement of acoustic velocity in the solution.

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Results

To evaluate the CQA NaCl concentration, calibration was performed using solutions ranging 0.45-1.35% (w/v) NaCl, at temperatures from 15 to 40 °C (1°C increments). Sound speed was measured under each condition. The data was fitted under a full quadratic 3D polynomial model. The resulting response surface (Figure 2) shows excellent predictive performance, with an RMSE of 0.032 and an adjusted R^2 of 0.99.

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Conclusion

The ultrasound-based PAT tool proved robust and reliable for determining NaCl concentration in physiological saline solution for infusion. The strong predictive performance confirms acoustic velocity as a suitable surrogate for this CQA. The non-invasive nature, compatibility with sterile and closed systems, and rapid data acquisition make this PAT highly advantageous for the pharmaceutical industry, particularly for injectables. Moreover, the method aligns with regulatory priorities for PAT adoption and supports future integration into automated control strategies and RTRT.
Overall, our ultrasound PAT represents a practical, scalable technology capable of enhancing process understanding, improving quality control, and supporting the transition toward next-generation pharmaceutical manufacturing.

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