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Identification of falsified and substandard drug products through stable isotope analysis

ELSE HOLMFRED

Stanford University

In 2024, 3.4 trillion defined daily doses of prescription and over-the-counter medicines were distributed globally. The World Health Organization reported in 2017 that 10.5% of all drugs in low- and middle-income countries are substandard or falsified, representing an estimated US$30.5 billion in spending. This highlights the urgent need to address the growing public health and socioeconomic problem of falsified medical products infiltrating global markets. Developing accurate experimental methods to evaluate drug production and ensure product quality is, therefore, critical.

This project investigated the use of stable light isotope ratio mass spectrometry (IRMS) with ^{2}H, ^{13}C, and ^{18}O analyses to: 1) identify unique isotopic signatures of solid drug products and commonly used excipients, 2) assess isotopic signal stability across pharmaceutical batches, and 3) reveal falsified and substandard pharmaceuticals through IRMS. Twenty-seven ibuprofen drug products were collected from six countries, representing diverse formulations with 20–82% active pharmaceutical ingredient and 6–18 excipients. Based on ibuprofen formulation strategies, 27 common excipients were selected for IRMS analysis to establish the analytical procedure.

Sample preparation involved only ball milling the tablets prior to analysis. Approximately 150 µg of each sample (n=3) was encapsulated and analyzed using TC/EA IRMS calibrated against certified reference materials. Analyses conducted over consecutive weeks showed high data reproducibility. As expected and consistent with previous studies in biogeochemistry and food science, ^{13}C exhibited the lowest isotopic variation, followed by ^{18}O and ^{2}H. Isotopic standard deviations for drug products (^{2}H ≤5.29‰, ^{13}C ≤0.37‰, ^{18}O ≤1.75‰) were higher than for mono-ingredient excipients but remained generally low.

Distinct isotopic signatures were determined for both drug products and excipients, enabling differentiation among pharmaceutical manufacturers and between formulations with varying API levels. Isotopic signal stability across batches was verified by analyzing (n=3) nine products from a single manufacturer with different batch numbers and packaging. The within-batch isotopic variation (^{2}H -44.78±3.51‰, ^{13}C -22.20±0.20‰, ^{18}O 33.59±1.75‰) was lower than the variation among different products. Substandard and falsified drug products demonstrated distinct stable isotope signatures compared to genuine products, supporting efforts to develop new methodologies that ensure safe pharmaceuticals and human health.