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Stable Isotope Method to Measure Drug Release from Nanomedicines

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Abstract

Existing methods to measure nanomedicine drug release in biological matrices are inadequate. A novel drug release method utilizing a stable isotope tracer has been developed. Stable isotope-labeled drug is spiked into plasma containing nanomedicine. The labeled drug equilibrates with plasma components identical to the normoisotopic drug released from the nanomedicine formulation. Therefore, the ultrafilterable fraction of the isotope-labeled drug represents a reliable measure of free normoisotopic drug fraction in plasma, and can be used to calculate nanomedicine encapsulated and unencapsulated drug fractions. To demonstrate the utility of this method, we performed a plasma drug release study with both a fast releasing commercial docetaxel formulation, Taxotere®, and a delayed releasing nanomicellar formulation of a docetaxel prodrug, Procet 8. The instability of the unencapsulated prodrug in plasma allowed us to compare our calculated prodrug release and docetaxel conversion with the actual docetaxel concentration measured directly without fractionation. Drug release estimates for the fast releasing Taxotere formulation demonstrated accuracy deviation and precision (%CV) of <15%. For the controlled release Procet 8 formulation, we calculated a slow release and conversion of the prodrug in rat plasma that was highly correlated with the direct docetaxel measurement (R^2=0.98). We believe this method will have tremendous utility in development and regulatory evaluation of nanomedicines, and aid in determination of generic bioequivalence.

Keywords: Drug release method; Stable isotope dilution; Nanomedicine; Nanotechnology; Fractionation in biological matrix

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