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Cover Story

Novel approach to measure drug release from nanomedicines

Over the last few decades, a large number of attempts have been made to bring nanomedicine drug delivery platforms from the laboratory to the clinic, but with little success. Most of the nanomedicine have been focused on targeted drug delivery to tumors. It has been very difficult to determine the drug amount that is actually delivered to the target. Usually, the drug pharmacokinetics is measured to establish the drug efficacy. It is still a challenge to characterize the drug pharmacokinetic profiles of nanomedicine, which is fundamental to their therapeutic efficacy. Despite the initial expectation that nanomedicine would provide better treatment, e.g., through targeted drug delivery, it has not proven to be any superior to the existing delivery systems. This is very disappointing, but a few generic nanomedicine have been surfaced on the market. A liposomal doxorubicin follow-on product was approved by the FDA in 2013, and many more are sure to follow.

Generic products are required to demonstrate bioequivalence, i.e., pharmacokinetic similarity. Upon systemic administration of a nanomedicine, the active drug molecule exists in several states, a nanomedicine-encapsulated fraction, and a nanomedicine unencapsulated fraction (i.e., a released fraction) composed of protein-bound and free-unbound forms. In order to establish the bioequivalence of generic nanomedicines, regulatory agencies require quantification of both the encapsulated and unencapsulated drug populations [1]. Currently, however, reliable methods to fractionate and quantify these drug populations do not exist [2], and nanomedicine pharmacokinetic studies typically only measure total drug, encompassing both the nanoparticle encapsulated and unencapsulated drug.

The current methods for measuring nanomedicine drug release are not robust or universally applicable. Many of these methods rely on protein binding approaches or extraction techniques optimized for small molecule drugs, examples being solid phase/liquid-liquid extraction, ultrafiltration, ultracentrifugation, and equilibrium dialysis [2]. While a method may work well for a specific nanomedicine, these are not broadly applicable and each has their own set of limitations. Drawbacks of existing methods include long equilibrium times, sample dilution, and process induced drug release resulting from interaction with destabilizing chemistries. Furthermore, these existing methods do not possess the ability to accurately and precisely measure all drug populations simultaneously, including the free-unbound drug which is the biologically active fraction and often represents less than 5% of unencapsulated drug.

The stable isotope method developed by the Stern group in this issue offers a relatively simple approach to addressing this rather complex issue [3]. This method does not suffer from many of the limitations of current methods, such as the long equilibrium times or process artifacts, and can measure all drug populations simultaneously. Utilizing a stable isotope of the active drug, e.g., ^{2}H or ^{13}C, this technique can accurately differentiate and quantify nanomedicine encapsulated and unencapsulated drug fractions, including free-unbound drug. Stable isotopically labeled tracer is spiked into plasma, equilibrating with protein identically to the non-labeled drug released from the nanomedicine. Ultrafiltration of the plasma sample results in rapid separation of the free-unbound drug from the encapsulated and protein-bound forms. Highly sensitive and selective mass spectrometry analysis of the fractionated sample then allows for the accurate and precise measurement of the encapsulated and unencapsulated drug fractions. The ability to measure the free-unbound forms of highly protein bound drugs and nanomedicines with very low drug release is a potential limitation. This issue, however, is resolving with advancements in accurate mass detection and ion focusing that result in ever lower mass spectrometry detection limits.

The stable isotope method described by the Stern team has significant potential to inform and influence the development and regulatory approval of nanomedicine products. This method is expected to aid in development of accurate pharmacokinetic models, platform optimization and assessment of interpersonal variability. As the nanomedicine field is expanding and maturing, more nanomedicine products are expected. Our hope is that the Stern method can be used to develop more effective new formulations, in addition to generic nanomedicine products. With all the time and effort poured into the nanomedicine field over the last few decades, it remains hopeful that nanotechnology-based research will provide breakthrough formulations that can treat various diseases more effectively.

References

[1] FDA, Draft guidance on doxorubicin hydrochloride, http://www.fda.gov/downloads/Drugs/…/Guidances/UCM199635.pdf2014.
[2] V.V. Ambardekar, S.T. Stern, NBCD Pharmacokinetics and Drug Release Methods, in: D.J.A. Crommelin, J.S.B. de Vlieger (Eds.), Non-Biological Complex Drugs, The Science and the Regulatory LandscapeSpringer International Publishing 2015, pp. 261–287.
[3] S. Skoczen, S.E. McNeil, S.T. Stern, Stable isotope method to measure drug release from nanomedicines, J Control Release 220 (2015) 169–174.

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