Rational Design of Nanomedicine In Vitro Release Tests via computational approaches

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Background: Drug release from nanomedicines is a complicated process that depends directly or indirectly on numerous factors, including critical quality attributes (CQAs), critical material attributes (CMAs) and critical process parameters (CPPs). During the product development of nanomedicines, *In vitro* (IVR) release tests are commonly employed to understand drug product performance. However, due to the complexity of nanomedicine products and the diversity of drug release methods employed, there is a gap in the fundamental understanding of key drivers of drug release from nanomedicine formulations. Hence, this gap causes a bottleneck in the development and regulatory approval of nanomedicine products. To reduce the experimental burden associated with nanomedicine *IVR* test method development, this project aims to employ computational methods to predict drug release from nanomedicine formulations, which will be used to uncover key parameters influencing drug release behaviour, to guide the development of new IVR tests.

Methods: A structured query language (SQL) database was created for data extracted from 21 research papers, resulting in 222 *IVR* profiles with differing formulations, components, drugs and *IVR* method conditions. Non-linear least squares optimisation was used to fit six common kinetic models to each profile, where the goodness of fit was assessed via mean absolute error (MAE) and Akaike's information criterion (AIC). The best model's parameters defined the *IVR* profile operating space. Then, k-means clustering was used to identify and characterise parameter clusters which represent distinct classes of *IVR* profiles with similar temporal profiles.

Results: Across the 222 *IVR* profiles, the Weibull model had the lowest MAE and AIC, indicating sufficient versatility to describe the range of shapes of *IVR* profiles extracted. KMC performed on fitted Weibull parameters was used to identify 5 classes of *IVR* profiles, each with similar temporal profiles.

Conclusions: An automated kinetic model fitting process was developed to identify the Weibull model as the best fit over 222 *IVR* profiles extracted from literature. A novel statistical framework was developed, to characterise and cluster *IVR* profiles with similar temporal profiles, which will enable further analysis to identify key factors (CQAs, CPPs and methodological conditions) contributing to each type of drug release behaviour.