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Editorial

PK MODELLING FOR NANOMEDICINE APPLICATIONS

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Abstract

The purpose of this editorial to convey the importance of physiologically-based pharmacokinetic (PBPK) modelling in the development of nanomedicines. PBPK modelling integrates in vitro drug specific data into a mathematical description of the anatomical, physiological and molecular processes mediating absorption, distribution, metabolism and elimination (ADME) to simulate pharmacokinetics. The mechanistic understanding of the molecular, anatomical and physiological events of nanoparticle distribution has a beneficial impact on development of novel nonomedicine assessment strategies.

Key Words: Nanoparticle, Nanomedicine, ADME, PBPK, Nanotoxicity.

Main Text

The delivery of therapeutic agents is characterised by numerous challenges including poor absorption, low penetration into target tissues, non-specific dissemination throughout the body and high clearance. The low bioavailability of poorly soluble drugs remains a serious concern for drug development programmes in the pharmaceutical industry. It is estimated that more than 60% of new drug candidates are poorly soluble in water, inhibiting development programmes and ultimately the success of new treatments (Moss and Siccardi 2014). Moreover, the lack of drug penetration in tissues, where exposure is most needed can have a detrimental influence on therapy efficacy and toxicity. The merging of nanotechnology and medicine has resulted in new approaches to design specialized pharmaceuticals, called as nanomedicine. The European Science Foundation defines nanomedicine as 'the science and technology of diagnosing, treating and preventing diseases and traumatic injury, of relieving pain and of preserving and improving human health using molecular tools and molecular knowledge of the human body'. The National Cancer Institute and FDA follow a more restrictive definition: "the understanding and control of matter at dimensions between approximately 1 and 100 nm, where unique phenomena enables novel applications," mirroring the definition of

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nanotechnology put forth by the National Nanotechnology Initiative. For most pharmaceutical applications, nanoparticles are defined as having a size up to 1000 nm. The application of nanotechnology to drug delivery is gaining momentum and is expected to dramatically proliferate over the coming years. Several nanomedicine strategies have emerged as advanced approaches to enhance drug delivery and improve the pharmacodynamics across several diseases. To date, 247 nanomedicine products have been approved or are in various stages of clinical study and the global nanomedicine market has been recently predicted to reach $528 billion by 2019 (Siccardi and Owen 2016). In the last 10 years, it is estimated that more than one thousand companies have been engaged in development of nanotechnology applications in medicine.

The wide variety of nanoformulation designs means that a large overwhelming, ranges of delivery strategies are available for radical improvement of drug pharmacokinetics. However, efficacy and toxicity of drugs can also be negatively influenced by nanoformulation distribution: insufficient absorption and diffusion into tissues may compromise drug activity, while excessive nanoformulation accumulation could lead to tissue-specific toxicity (related to the drug, the nanoformulation or potentially both). Consequently, understanding the interactions between nanoformulations and the human body is of central relevance for the engineering of future treatment strategies, and a thorough investigation of the processes regulating nanoformulation disposition is essential to optimize effective and safe nanoformulations for drug delivery. Several processes mediate the distribution of nanoformulations in the human body and the ADME properties of nanoformulations can differ substantially from traditional formulations. In most cases, nanoformulation ADME is not fully characterized and can vary based on the class of the nanoformulations. Physiologically-based pharmacokinetic (PBPK) modelling is now widely recognised as a useful pharmacological tool to simulate the pharmacokinetics and distribution of drugs. PBPK modelling can be applied to medicine optimisation either during preclinical/ clinical development or post-licensing. Indeed, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) regulatory guidelines were recently updated to include PBPK modelling for the purpose of dose finding, assessing drug-drug interactions, and investigating the utility of dose adjustment in special populations (e.g. during pregnancy). PBPK modelling integrates *in vitro* drug specific data into a mathematical description of the anatomical, physiological and molecular processes mediating absorption, distribution, metabolism and elimination (ADME) to simulate pharmacokinetics.

PBPK models are commonly based on two approaches: blood-flow limited and membrane-limited. The former approach assumes that blood and tissues are in equilibrium instantaneously and the compartments are well stirred, whether the latter assumes that the diffusion of nanoparticles in tissues is regulated by the permeability of capillary or tissue cell membrane. The best option for nanoformulations is unclear and is likely to differ depending on the choice of technology.

It is clear that PBPK modelling can assist in answering questions that cannot otherwise be examined in pre-clinical development without a heavy burden on pre-clinical species. PBPK modelling has the potential to dramatically reduce the number of animals needed during preclinical development (Thomas 2009). Thus, validated nano-specific PBPK modelling approaches represent a pivotal advancement for refining, replacing and reducing the use of preclinical species during development programmes. However, modelling approaches for nanomedicine applications are currently in their infancy compared to small molecule drugs. The processes regulating pharmacokinetics and distribution of nanoparticles are known to differ from conventional small molecule drugs, and there is a current paucity of knowledge across different nanomedicine platform technologies, which are needed for the development of robust predictive tools to maximise the efficacy and safety of novel technologies. The mechanistic understanding of the molecular, anatomical and physiological events that define nanoparticle distribution is required, and will serve to have a beneficial impact on development of novel nanoparticle assessment strategies.

PBPK Applications

The application of PBPK modelling is very promising and a few researchers have successfully adapted their models for nanomedicines. Lin et al. 2008 developed a PBPK model to predict the PK of quantum dots in mice using whole-body PBPK. A distribution coefficient was used to simulate the diffusion of nanoparticle in tissues based on *in vitro* data and could predict animal PK with good accuracy.

PBPK modelling of five PLGA nanoparticle formulations prepared with different versions of monomethoxypoly(ethyleneglycol) (mPEG) (PLGA, PLGA-mPEG256, PLGAmPEG153, PLGA-mPEG51, PLGA-mPEG34) has been generated, investigating the relationship between nanoparticle properties (size, zeta potential and the number of PEG molecules per unit surface area) and distribution parameters. The multivariate regression in the study generated significant linear relationships between nanoparticle properties and distribution parameters. Subsequently, this semi-mechanistic model was

successfully utilized to predict the distribution of a sixth nanoparticle (PLGA-mPEG 495) in mice (Li et al., 2012). This study emphasizes the potential that PBPK modelling has to predict *in vivo* properties of nanoformulations prior to experimental testing.

Innovative PBPK models have been developed for long-acting injectable nanoformulations for anti-HIV therapy, predicting the optimal dose and drug release rates across a panel of commonly prescribed drugs [Rajoli et al. 2015] and for the predicting distribution of superparamagnetic iron oxide nanoparticles (SPIONs) in animals and humans, providing a quantitative estimate of nanoparticle diffusion and accumulation in tissues and organs [Silva et al 2015]. However, more work is required to realise the potential of the PBPK modelling for nanomedicines.

Conclusion

PBPK modelling can provide quantitative evaluation of the influence of nanoformulation properties on their absorption, diffusion and clearance. The integration of these property–distribution relationships in PBPK models may have extensive benefits in nanomedicine research, giving opportunities for innovative development of nanotechnologies. The Fig. 1 represents the PBPK based optimization process to generate novel nanoformulations with desirable PK.

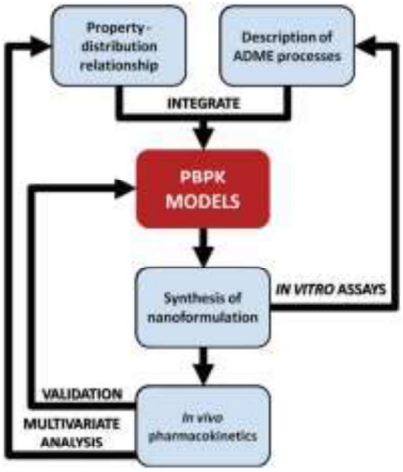

Fig.1: PBPK modelling based optimization process

Future research efforts should focus upon a critical understanding of the interactions between nanomaterials and relevant organs, with consideration of how these processes

may differ according to physical properties of the nanomaterial including composition, size, surface charge and morphology.

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