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REVIEW

Optimizing nanomedicine pharmacokinetics using physiologically based pharmacokinetics modelling

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The delivery of therapeutic agents is characterized by numerous challenges including poor absorption, low penetration in target tissues and non-specific dissemination in organs, leading to toxicity or poor drug exposure. Several nanomedicine strategies have emerged as an advanced approach to enhance drug delivery and improve the treatment of several diseases. Numerous processes mediate the pharmacokinetics of nanoformulations, with the absorption, distribution, metabolism and elimination (ADME) being poorly understood and often differing substantially from traditional formulations. Understanding how nanoformulation composition and physicochemical properties influence drug distribution in the human body is of central importance when developing future treatment strategies. A helpful pharmacological tool to simulate the distribution of nanoformulations is represented by physiologically based pharmacokinetics (PBPK) modelling, which integrates system data describing a population of interest with drug/nanoparticle *in vitro* data through a mathematical description of ADME. The application of PBPK models for nanomedicine is in its infancy and characterized by several challenges. The integration of property–distribution relationships in PBPK models may benefit nanomedicine research, giving opportunities for innovative development of nanotechnologies. PBPK modelling has the potential to improve our understanding of the mechanisms underpinning nanoformulation disposition and allow for more rapid and accurate determination of their kinetics. This review provides an overview of the current knowledge of nanomedicine distribution and the use of PBPK modelling in the characterization of nanoformulations with optimal pharmacokinetics.

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Abbreviations
ABC, accelerated blood clearance; ADME, absorption, distribution, metabolism and elimination; BBB, blood–brain barrier; mPEG, monomethoxypoly (ethyleneglycol); NE, nanoemulsion; PBPK, physiologically based pharmacokinetics; PEG, polyethylene glycol; PK, pharmacokinetics; PLGA, poly(d,l-lactic-*co*-glycolide); SDN, solid drug nanoparticle; SLN, solid lipid nanoparticles

Introduction

Acceptable pharmacokinetics (PK) of drugs can be impeded by several factors, including poor absorption, low penetration into target tissues and high clearance. Insolubility of drugs, with the resulting low bioavailability, 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 (Sareen *et al.*, 2012; Sikarra *et al.*, 2012). Moreover, the lack of drug penetration in tissues where exposure is most needed can have a detrimental influence on therapy efficacy and toxicity.

Numerous nanomedicine strategies are currently being assessed to improve drug delivery. Nanomedicines include nanoparticles (defined as solid submicron particles consisting of polymers or inorganic material) and liquid-based drug nanocarriers such as nanoemulsions (NEs). Nanoformulations can be produced to contain a drug (or drugs), antibody,

detection probe as well as several other substances, which may be associated with the particle in various ways (Kreuter, 1994). Many nanoformulations can be effectively absorbed and subsequently concentrated in tissues through passive targeting, exploiting both the physicochemical characteristics of the nanocarriers and the specific properties of the tissues of interest. Different strategies can also be applied for active targeting of tissues, pathogens and cancer cells.

The wide variety of nanoformulation designs means that a large, almost overwhelming, range of delivery strategies are available for research and application. Polymers can be used as containers for drug molecules, either by forming solid polymer matrix nanoparticles to encapsulate drugs, or through the construction of vehicles such as block copolymer liposomes/vesicles, micelles and NEs (Wischke and Schwendeman, 2008). Direct non-covalent or covalent conjugation of drugs to polymers have been successfully used to enhance circulatory times and deliver drugs through triggered/controlled release (Joralemon *et al.*, 2010). A wide variety of inorganic oxides have been used to create nanoparticles, such as gold (Thakor *et al.*, 2011), silver (Ong *et al.*, 2013; Zhang *et al.*, 2013), silica (Wu *et al.*, 2013) and iron (Ittrich *et al.*, 2013). However, the influence that these formulations can have on drug PK is only partly understood.

A helpful pharmacological tool to inform the design of nanoformulations and thus optimize their PK is represented by physiologically based pharmacokinetics (PBPK) modelling. This modelling technique has been successfully used for traditional formulations in drug development programmes as well as simulations of relevant clinical scenarios (Siccardi *et al.*, 2012; 2013; Karlsson *et al.*, 2013). PBPK modelling is a bottom-up technique which aims to simulate drug distribution by combining system data describing a population of interest (e.g. demographics, physiology, anatomy and genetics) with *in vitro* drug data (e.g. Caco-2 permeability, protein binding, intrinsic clearance, lipophilicity) through a mathematical description of absorption, distribution, metabolism and elimination (ADME). This modelling technique gives a complete overview of all the physiological and anatomical processes involved in drug distribution, offering the opportunity to identify important determinants of PK. For traditional formulations, absorption can be simulated considering the dynamic interplay between dissolution, passive permeability and the affinity/activity of metabolic enzymes and transporters. Drug distribution is simulated by evaluating tissue volumes and the diffusion of drugs into tissues, which is influenced by physicochemical properties (Poulin and Theil, 2002). Moreover, tissues and organs are connected by virtual blood and lymphatic flows. To simulate clearance, *in vitro* metabolism data can be used and integrated into the model using scaling factors. Interpatient variability is observed in all of the above processes, and virtual human and animal populations can be simulated capturing interindividual variability by considering anatomical and physiological characteristics, and their covariance. The development of PBPK models for nanomedicine is characterized by several challenges, mainly because of the current partial understanding of the molecular processes regulating nanoparticle distribution.

In this review, we describe what is known of the main processes regulating ADME for nanoformulations. We also discuss strategies to optimize the design of nanoformulations, focusing on the use of mechanistically based ADME modelling for nanomedicine.

Importance of nanoformulation PK

Nanoformulation delivery systems have the potential to radically improve drug PK. 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 (Figure 1). In most cases, nanoformulation ADME is not fully characterized and can vary based on the class of the nanoformulations. The preferred routes of administration for nanoformulations are oral, transdermal, ocular, nasal, pulmonary and i.v., which we discuss in this section.

Oral administration

Certain nanoformulations can enhance the absorption of drugs by releasing drug into the lumen in a controlled manner, thus reducing solubility issues. The intestinal wall is designed to absorb nutrients and to act as a barrier to pathogens and macromolecules. Small amphipathic and lipophilic molecules can be absorbed by partitioning into the lipid bilayers and crossing the intestinal epithelial cells by passive diffusion, while nanoformulation absorption may be more complicated because of the intrinsic nature of the intestinal wall. The first physical obstacle to nanoparticle oral absorption is the mucus barrier which covers the luminal surface of the intestine and colon (Corazziari, 2009; Johansson *et al.*, 2011). The mucus barrier contains distinct layers and is composed mainly of heavily glycosylated proteins called mucins, which have the potential to block the absorption of certain nanoformulations. Modifications can be made to produce nanoformulations with increased mucus-penetrating properties (Ensign *et al.*, 2012).

Once the mucus coating has been traversed, the transport of nanoformulations across intestinal epithelial cells can be regulated by several steps, including cell surface binding, endocytosis, intracellular trafficking and exocytosis, resulting in transcytosis (transport across the interior of a cell) with the potential involvement of multiple subcellular structures. Moreover, nanoformulations may also travel between cells through opened tight junctions, defined as paracytosis (Tuma and Hubbard, 2003). Non-phagocytic pathways, which involve clathrin-mediated and caveolae-mediated endocytosis and macropinocytosis, are the most common mechanisms of nanoformulation absorption by the oral route, although

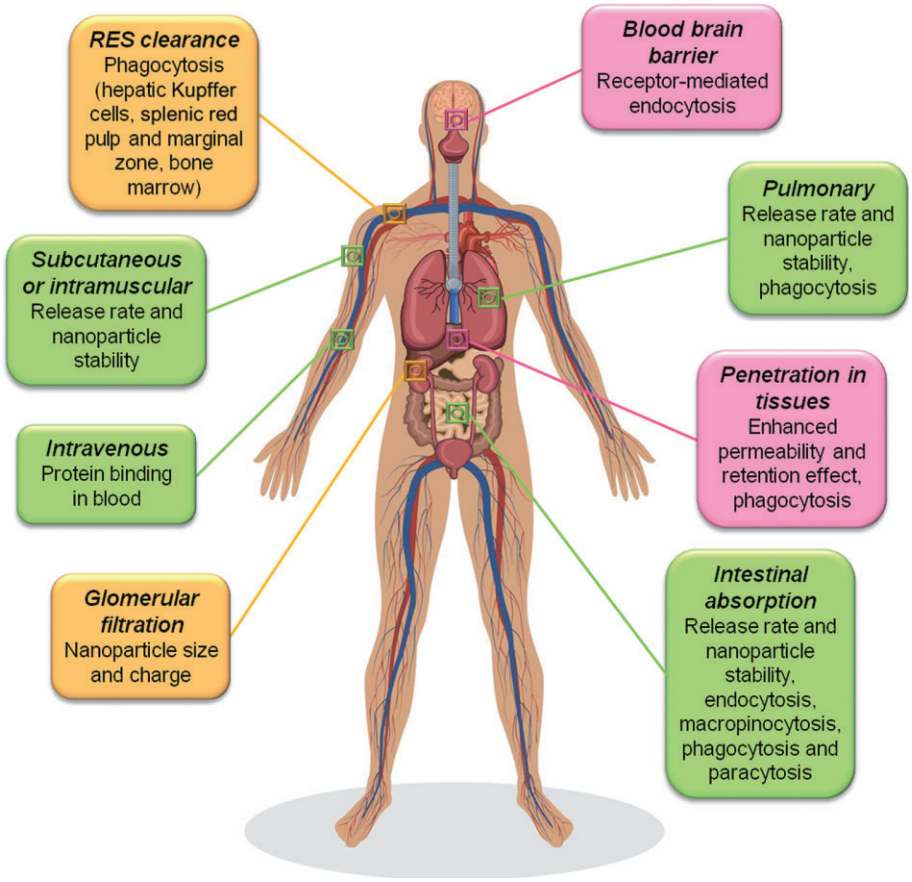

Figure 1

A selection of issues relating to the administration (green boxes), distribution (pink boxes) and elimination (orange boxes) of nanomedicines. RES, reticuloendothelial system.

heterogeneity in the efficiency of these processes has been described for different types of nanoformulations. Consequently, it is difficult to identify a predominant process determining transcytosis of nanoformulations (Hillaireau and Couvreur, 2009; Smith *et al.*, 2012; He *et al.*, 2013).

Alternative administration routes

The inability of certain nanoformulations to undergo efficient oral absorption necessitates alternative administration routes. Also, the use of non-oral administrations can provide additional benefits, such as direct targeting to the desired site of action (Patel *et al.*, 2012) and an extended period of drug action (van 't Klooster *et al.*, 2010).

The skin provides a desirable route of nanomedicine administration, as it avoids the risks associated with i.v. therapy and the inconveniences associated with varying gastric pH, emptying time and first-pass hepatic metabolism. However, administration of drugs is not easy because of the impermeable nature of the skin (Menon *et al.*, 2012; Rehman and Zulfakar, 2013). Transdermal administration has been optimized for nanoformulations, such as solid lipid nanoparticles (SLNs) and NEs, which are characterized by good biocompatibility, lower cytotoxicity and desirable drug release modulation (Cappel and Kreuter, 1991; Gide *et al.*, 2013; Khurana *et al.*, 2013).

Topical ocular drug delivery provides a useful administration route for nanomedicines treating ocular pathologies, but utilization is disadvantaged by the multiple defensive barriers of the eye (de Salamanca *et al.*, 2006). Corneal and conjunctival epithelial cells are connected by intercellular tight junction complexes that limit the entrance of exogenous substances. In addition, the tear film can trap drugs and nanoformulations, removing them via the lacrimal drainage system. Consequently, an efficient ocular drug delivery system has to interact with the ocular mucosa, protect the drug from chemical or enzymatic degradation and allow drug delivery to the ocular tissue. Different nanotechnologies have been utilized to overcome these barriers, helping the drug reach and target conjunctival epithelial cells (Alonso and Sánchez, 2004). Successful administration of nanoformulated intraocular pressure-lowering drugs (Hathout *et al.*, 2007; Chen *et al.*, 2010) and antiapoptotic drugs (Nkansah *et al.*, 2008) has been achieved *in vivo*. In addition, intravitreal administration of nanomedicines has been used to overcome absorption issues (Jiang *et al.*, 2007).

Nasal administration of certain nanoformulations has been assessed, hypothesizing that nanoformulations may penetrate the nasal mucosal membrane. Nanoformulations can cross the membrane using a transmucosal route by endocytosis or via a carrier- or receptor-mediated transport process

(Illum, 2007). Proof-of-concept has been achieved *in vivo*, for example by nasal administration of chitosan nanoparticles of tizanidine to increase brain penetration and drug efficacy in mice (Patel *et al.*, 2012).

The lungs are a promising route of administration for drug delivery because of the large surface area, ease of access and the thinness of the air-blood barrier. The lumen of the bronchial airways is lined with a thin layer of serous fluid, upon which floats a layer of mucus helping to entrap aerosolized particles. The action of the cilia, present on the ciliated columnar epithelium, propels the mucus layer towards the proximal airways, where it can be eliminated. The mucus barrier, metabolic enzymes in the tracheobronchial region and macrophages in the alveoli are the main barriers for penetration of drugs. Particle size is a major factor determining the diffusion of nanoformulation in the bronchial tree, with particles in the nano-sized region more likely to reach the alveolar region and particles with diameters between 1 and 5 μm expected to deposit in the bronchioles (Musante *et al.*, 2002; Patton and Byron, 2007). A limit to absorption has been shown for larger particles, presumably because of an inability to cross the air-blood barrier (Ryan *et al.*, 2013). Particles can gradually release the drug which can consequently penetrate into the blood stream or, alternatively, particles can be phagocytosed by alveolar macrophages (Bailey and Berkland, 2009).

Certain nanoformulations have a minimal penetration through biological membranes in sites of absorption and, for these, i.v. administration can be the preferred route to obtain an efficient distribution in the body (Wacker, 2013). Although long-term drug exposure has been demonstrated in certain cases (van 't Klooster *et al.*, 2010), the use of i.v. injection for multiple short-acting treatments is limited because of inconvenience and safety issues.

Distribution in tissues and organs

Once a drug-containing nanoformulation has entered the systemic circulation, the subsequent distribution into tissues can begin. The distribution of nanoformulations can vary widely depending on the delivery system used, the characteristics of the nanoformulation and potentially the variability between individuals (organ size, body fat index, etc). Another important factor to understand is the rate of drug loss from the nanoformulations, as the distribution characteristics of both the free drug and nanoformulated drug will most likely differ greatly. The main function of certain types of nanoparticles, for example solid drug nanoparticles (SDNs), is the improvement of drug absorption, which does not require them to arrive intact in the systemic circulation. Consequently, the distribution and the clearance of these drugs would not be altered. Other nanotechnologies, however, are capable of surviving the absorption process, therefore altering the distribution and clearance of the contained drug.

On reaching the systemic circulation, nanoformulations come into contact with numerous proteins which can give rise to the formation of dynamic nanoformulation-protein coronas (Tenzer *et al.*, 2013). The protein corona influences nanoformulation size and physicochemical characteristics, consequently affecting processes such as nanoformulation degradation, cellular uptake (Paula *et al.*, 2013), accumulation and clearance (Peng *et al.*, 2013). Nanoformulation-protein coronas can also influence the body, potentially causing pathologies such as inflammation (Saptarshi *et al.*, 2013) and haemolysis (Tenzer *et al.*, 2013). Proteins can adhere to nanoformulations through forces such as Van der Waals interactions, hydrogen bonding and solvation, thus generating protein coronas with environment-specific stability and characteristics. In human blood, a protein corona normally consists of serum albumin, immunoglobulins, fibrinogen and apolipoproteins (Hellstrand *et al.*, 2009; Ge *et al.*, 2011; Jansch *et al.*, 2012). For some nanoformulations, more abundant proteins such as albumin and fibrinogen may initially non-specifically bind to nanoformulations and subsequently can be replaced by other proteins having higher binding affinity (Saptarshi *et al.*, 2013). Therefore, the distribution of these nanoformulations is less simple to determine theoretically and further research is needed in this area.

Nanoformulations of a certain size and composition are able to diffuse in tissues through well-characterized processes, such as the enhanced permeability and retention effect, while some nanoformulations might accumulate in specific cell populations, allowing the targeting of specific organs. The enhanced permeability and retention effect is the mechanism by which high molecular weight drugs, prodrugs and nanoparticles tend to accumulate in sites of inflammation or cancer, which are tissues with increased vascular permeability (Matsumura and Maeda, 1986). Tumour blood vessels have large pores, ranging from 100 nm to several hundred nanometers in diameter, as compared with normal vessel junctions of 5–10 nm (Hobbs *et al.*, 1998). Consequently, nanoformulations can be designed to preferentially penetrate tumour tissue. As an additional factor, the lymphatic system in tumours might be impaired, increasing the retention of macromolecules and nanoformulations (Maeda *et al.*, 2000). In some cases, this targeting method is not very effective, and the size-dependency, slow time frame and variability from tumour to tumour limit the effectiveness of the treatment (Maeda *et al.*, 2000; Iyer *et al.*, 2006). Tumours may be 'desmoplastic' (rich in stromal cells and extracellular matrix) or 'cellular' (largely composed of cancer cells) (Chauhan and Jain, 2013), which will effect nanomedicine distribution in tumours. There is evidence that tumour penetration of nanomedicines can be minimal beyond the blood vessels (Jain and Stylianopoulos, 2010). Consideration of these factors would be crucial when creating PBPK models investigating drug tumour penetration.

Complex biological barriers can protect organs from exogenous compounds and the blood–brain barrier (BBB) represents an obstacle for many therapeutic agents (Varatharajan and Thomas, 2009). Many different types of cells including endothelial cells, microglia, pericytes and astrocytes are present in the BBB which exhibits extremely restrictive tight junctions, along with highly active efflux mechanisms, limiting the permeation of most drugs (Begley, 2004). Transport through the BBB is restricted to small lipophilic molecules and nutrients that are carried by specific transporters. One of the most important mechanisms regulating diffusion of nanoformulations into the brain is endocytosis by brain capillary endothelial cells. Recent studies have correlated particle properties with nanoformulation entry pathways and processing in the human BBB endothelial barrier, indicating that uncoated nanoparticles have limited penetration through the

BBB and that surface modification can influence the efficiency and mechanisms of endocytosis (Lee *et al.*, 2000; Georgieva *et al.*, 2011). In many cases, low penetration of nanoformulations into tissues can be a major barrier for the treatment of diseases and the use of ligands to enhance this process of uptake into tissue represents a promising solution (Ruoslahti, 2012). Tumour-penetrating peptides have been utilized which can activate bulk tissue-specific transport pathways, targeting receptors present in the tumour vasculature such as annexin1 (Oh *et al.*, 2004; Hatakeyama *et al.*, 2011), plectin-1, (Kelly *et al.*, 2008) and neuropilin-1 (Teesalu *et al.*, 2009).

The migration of monocytes in numerous tissues and in sites of inflammation, infection and tissue degeneration provides a unique mechanism to improve drug delivery (Murphy *et al.*, 1975; Lameijer *et al.*, 2013). Indeed, monocytes and macrophages have a central role in the pathogenesis of several diseases, such as HIV (Crowe *et al.*, 2003), tuberculosis (Philips and Ernst, 2012), leishmaniasis (Farah *et al.*, 1975), cancer (Biswas and Mantovani, 2010), diabetes (Cnop *et al.*, 2005), inflammatory bowel disease (Heinsbroek and Gordon, 2009), rheumatoid arthritis (Szekanecz and Koch, 2007) and chronic obstructive pulmonary disease (Barnes, 2004), making these cells desirable drug targets in themselves. Nanoformulations can be engineered, controlling size and surface charge, to allow for their active uptake by monocytes and macrophages through phagocytosis. Monocytes and macrophages are characterized by a broad variety of receptors, which can be actively targeted using nanoformulations combined with specific ligands (Kelly *et al.*, 2011).

Elimination and clearance

A wide range of processes can regulate the clearance of nanoformulations, from chemical and enzymatic degradation to renal and biliary elimination. Nanoformulations may undergo degradation in penetrated tissues or circulating blood, gradually releasing their content. Degradation kinetics is an important variable that controls drug release and complicates the design of optimal drug delivery systems with predictable drug release properties (Mohammad and Reineke, 2013).

The immune system is responsible for removing foreign objects from the body, including not only pathogens but also any material it may be in contact with, including nanoformulations. The accelerated blood clearance (ABC) phenomenon is sometimes observed, where a delayed immune response can cause rapid clearance of certain nanoformulations (Abu Lila *et al.*, 2013). It is of fundamental importance to achieve a thorough understanding of the way nanoformulations interact with immune cells and all related consequences. Macrophages in the liver are a major pool of the total number of macrophages in the body. Around 8.6×10^5 Kupffer cells are present in 1 g of human liver tissue (Friedman *et al.*, 1992) and this cell population possesses numerous receptors for selective phagocytosis of opsonized particles (receptors for complement proteins and for the fragment crystallizable part of IgG). Small inorganic nanoparticles are effectively phagocytosed by Kupffer cells which can have a central role in the generation of active oxygen species, TNF-α and NO, resulting in liver injury (Sadauskas *et al.*, 2007; Chen *et al.*, 2013). Cells with phagocytic activity are also present in the spleen which is another major site for nanoformulation elimination (Vyas and Malaiya, 1989). Nanoformulations containing polyethylene glycol (PEG) are characterized by prolonged presence in the systemic circulation by inhibiting receptor interactions and thus preventing phagocytosis by the mononuclear phagocytic system (Bazile *et al.*, 1995). Renal clearance is one of the most important mechanisms mediating nanoformulation excretion. The glomerular endothelium is characterized by fenestrations of 50–100 nm, with capillaries having a basement membrane (300 nm thickness) as well as podocytes with phagocytic function. The renal clearance of larger nanoformulations is restricted and examples are given in subsequent sections.

Types of nanoformulations

The distribution of nanoformulations is influenced by many factors, including its physicochemical properties and composition, route of administration and characteristics of the individual to which the nanoformulations are administered. The most promising types of nanoformulations used for drug delivery include inorganic nanoparticles, SDNs, SLNs, NEs, liposomes, polymeric nanoparticles and dendrimers (Figure 2). Drugs can be contained inside a nanoformulation, or, as is sometimes the case with inorganic nanoparticles and dendrimers, attached to the surface. Hybrid nanoformulations, which contain elements of more than one nanoformulation class, are also possible, thus complicating classification.

A common goal of nanomedicine research is to increase the bioavailability of drugs and to manipulate movement of drug to target sites in the body. Table 1 gives examples of improvements in drug PK in selected nanoformulation studies. In this section, we will review some interesting applications used for the different nanodelivery systems and the physiological and molecular processes regulating their absorption, distribution, metabolism and elimination.

Inorganic nanoparticles

A wide variety of inorganic oxides have been used to create nanoparticles, such as gold (Thakor *et al.*, 2011), silver (Ong *et al.*, 2013; Zhang *et al.*, 2013), silica (Wu *et al.*, 2013) and iron (Ittrich *et al.*, 2013). The potential uses of inorganic nanoparticles vary greatly and can include molecular diagnostics (Radwan and Azzazy, 2009), photoacoustic imaging (Lu *et al.*, 2011), targeted drug delivery (Assifaoui *et al.*, 2013; Chamundeeswari *et al.*, 2013), photothermal therapy (Huang *et al.*, 2006) and non-viral gene-delivery vectors (Sitharaman *et al.*, 2008). A particularly fascinating use of iron oxide nanoparticles has been to actively target specific tissues using an external magnetic influence (Dilnawaz *et al.*, 2010). The biodistribution, elimination and potential toxicity of inorganic nanoparticles vary wildly depending on materials used, and have been reviewed previously (Waalkes, 2000; Choi *et al.*, 2007; Pelley *et al.*, 2009; Almeida *et al.*, 2011; Bachler *et al.*, 2013). As a paradigm example, we have focused here on silver nanoparticles.

Following i.v. injection, silver nanoparticles are rapidly removed from the blood and widely distributed to organs, in particular the liver, lungs and spleen (Lankveld *et al.*, 2010).

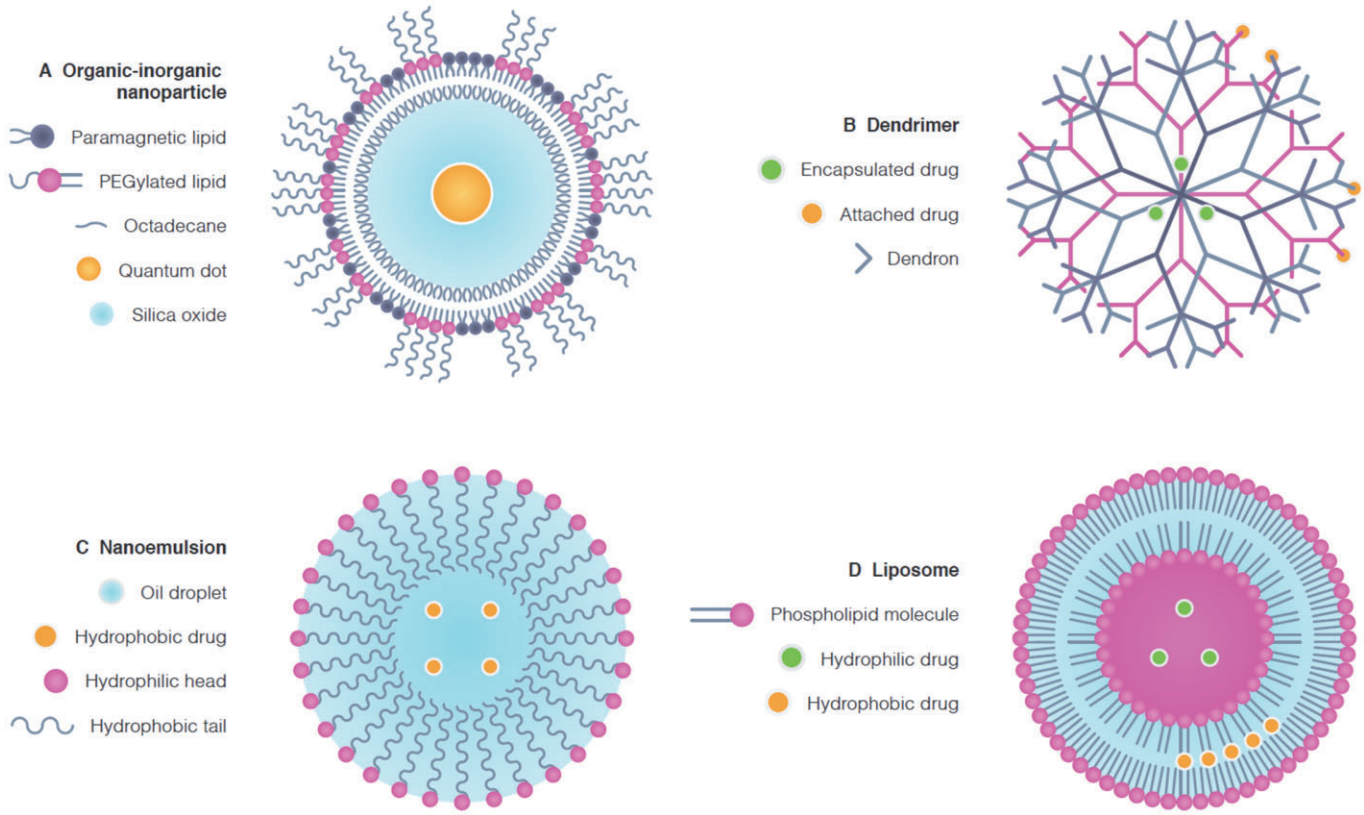

Figure 2

Examples of nanodelivery systems.

Table 1

Examples of improved drug exposure and tissue distribution achieved in nanoformulation studies *in vivo*

Drug	Formulations	Dose	Outcome	Reference
Tamoxifen	SLN	p.o.	↑156% plasma exposure	Hashem *et al.*, 2013
Olanzapine	SLN	p.o.	↑330% plasma exposure	Sood *et al.*, 2013
Isoniazid	SLN	p.o.	↑478% plasma exposure	Bhandari and Kaur, 2013
Lopinavir	SLN	p.o.	↑95% plasma exposure	Negi *et al.*, 2013
Vincristine	Liposome	i.v.	↑66% plasma exposure, no increased patient toxicity	Yan *et al.*, 2012
Doxorubicin	Liposome	p.o.	Reduced patient toxicity	O'Brien *et al.*, 2004
Efavirenz	SDN	p.o.	↑301% plasma exposure	McDonald *et al.*, 2013
Rosuvastatin	Nanoemulsion	p.o.	↑145% plasma exposure	Balakumar *et al.*, 2013
Chlorambucil	Nanoemulsion	p.o.	↑91% plasma exposure and >2-fold increase in tumour growth suppression	Ganta *et al.*, 2010
Primaquine	Nanoemulsion	p.o.	↑28% plasma exposure and ↑40% liver exposure	Singh and Vingkar, 2008
Zidovudine	Dendrimer	i.v.	↑1320% lymph exposure 3 h post-dose	Gajbhiye *et al.*, 2013
Celecoxib	Nanopolymer	p.o.	↑191% plasma exposure 3 h post-dose	Morgen *et al.*, 2012

SDN, solid drug nanoparticle; SLN, solid lipid nanoparticle.

The size of the silver nanoparticles can influence distribution, with particles larger than 20 nm being more readily accumulated in tissue. The silver ion in the body is changed to silver sulphide via mercaptan interaction, and is also metabolized to silver glutathione for biliary secretion (Ballatori and Clarkson, 1985). The major elimination route of intact 33 nm silver nanoparticles was found to be the kidneys via tubular secretion (Malfatti *et al.*, 2012). A PBPK model has been created which predicts the exposure of silver nanoparticles in both rats and humans (Bachler *et al.*, 2013).

SDNs

SDNs are lipid-free nanoparticles which are used to improve the oral bioavailability and exposure of poorly water-soluble drugs (Chan, 2011; Tanaka *et al.*, 2012). Constituents include drug and stabilizer, and SDNs are produced using a 'top-down' (high pressure homogenization and wet milling) or bottom-up (solvent evaporation and precipitation) approach (Zhang *et al.*, 2011). Our group has developed efavirenz SDNs which exhibit around fourfold higher PK exposure after oral administration to rodents, compared with free drug (McDonald *et al.*, 2013; Siccardi *et al.*, 2013). In a separate study, a single s.c. injection of rilpivirine SDN resulted in a constant release of around 25 ng mL^{-1} for 20 days, providing evidence that s.c. injections of antiretroviral SDNs could be used for long-acting therapy (Baert *et al.*, 2009). It is not fully known whether SDNs remain intact following oral absorption, and therefore the relevance of SDN distribution and elimination *in vivo* is poorly understood.

SLNs

SLNs consist of a lipid (or lipids) which is solid at room temperature, an emulsifier and water. Lipids utilized include, but are not limited to, triglycerides, partial glycerides, fatty acids, steroids and waxes (Mehnert and Mader, 2001). Different combinations of lipid and emulsifier can be used to create unique SLN properties, such as drug release rate and pH sensitivity, although the effects this have on the SLNs *in vivo* is poorly understood. Due to their lipid core, SLNs are most suited for delivery of highly lipophilic drugs, although enhanced delivery of hydrophilic drugs, such as the antitubercular drug isoniazid, has been achieved *in vivo* (Bhandari and Kaur, 2013). The use of SLNs to deliver siRNA and siRNA-drug combinations have also been demonstrated (Lobovkina *et al.*, 2011; Yu *et al.*, 2012).

SLNs have successfully been used to improve the absorption of drugs. Olanzapine-loaded cationic SLNs showed a 4.3-fold increase in olanzapine exposure (Sood *et al.*, 2013) and 2.6-fold increase in tamoxifen exposure (Hashem *et al.*, 2013) compared with free drug.

The *in vivo* fate of SLNs are determined by several factors, including the inherent stability and physicochemical properties of the SLNs, the biological and enzymatic surroundings of the administration site and the distribution process from the administration site. Using pulmonary (Videira *et al.*, 2012), s.c. (Harivardhan Reddy *et al.*, 2005) and oral (Cavalli *et al.*, 2000; Zara *et al.*, 2002; Paliwal *et al.*, 2009) dosing strategies, SLNs have been shown to target the lymphatic system *in vivo*.

An advantage of using SLNs is that formulations are believed to be safe and easily cleared from the body. Organic solvent is not required for SLN production, and the lipids which are used are usually biodegradable, thus reducing the risk of SLN-accumulation-associated toxicities. This degradation provides further benefits, as the size and choice of lipid influences the elimination rate of SLNs, with longer lipids generally outlasting smaller lipids and waxes lasting longer than triglycerides, allowing for controlled release of drug. Due to the solid status of SLNs, elimination is generally slower than with liquid-lipid-based nanoformulations.

Interestingly, PEGylated solid lipid particles have an increased clearance rate following repeat i.v. or s.c. administration (Zhao *et al.*, 2012a,b). This phenomenon is caused by immune response to the PEG and subsequent removal of SLNs from the circulation, an example of the ABC process, although the exact immunological events have not yet been characterised (Abu Lila *et al.*, 2013).

NEs

Liquid droplets of less than a 1000 nm dispersed in an immiscible liquid are classified as NEs. NEs represent excellent carriers for transport of hydrophobic and hydrophilic substances and can find application in i.v. (Ichikawa *et al.*, 2007), oral (Sun *et al.*, 2012), transdermal (Khurana *et al.*, 2013), nasal (Bahadur and Pathak, 2012) and ocular (Badawi *et al.*, 2008) drug delivery. The rate of lipolysis and the organ-specific elimination of NEs are influenced by the choice of constituents and route of administration, which allows for a more controlled release of drug. Oral administration is the route of choice for chronic therapy and NEs can effectively enhance oral bioavailability of small molecules, peptides and proteins. The mechanisms through which NEs mediate higher oral absorption are improved drug solubilization, protection from enzymic and chemical hydrolysis and increased permeability because of surfactant-induced membrane fluidity. The hydrophobic core of the NEs is an ideal environment for drugs with poor solubility in water and the surfactants present in the formulation favour the solubilized state in the GI tract. Biopharmaceutics Classification System class II compounds (high permeability, low solubility) are ideal candidates for NEs and their PK can be greatly enhanced through this nanotechnology. Paradigmatic examples of this are represented by drugs such as ramipril, ezetimibe (Bali *et al.*, 2010) and anethol trithione (Han *et al.*, 2009) where the bioavailability has been increased 2.3-, three- to four- and two- to threefold, respectively, compared with traditional formulations. In a study using Balb/c mice, orally dosed saquinavir in flax-seed oil NEs provided more than twofold increased exposure in brain, compared with free drug (Vyas *et al.*, 2008).

Polymeric nanoparticles

Polymeric nanoparticles are solid particles typically around 200–800 nm in size which can be created using both synthetic and natural polymers. The natural polymers used are generally biodegradable and can include as examples gelatine, cellulose, chitosan and gluten (Zhang *et al.*, 2007). Synthetic polymers such as polyactides, poly(d,l-lactic-*co*-glycolide) (PLGA) and PEG allow for a high level of degradation control. PEG can be adsorbed or covalently attached to the surface of nanoformulations and has been shown to reduce the interaction between nanoformulations and

proteins because of its hydrophilicity and repulsion effect (Moghimi, 2002), reducing opsonization, complement activation, phagocytosis and clearance mechanisms (Bazile *et al.*, 1995). It appears evident that the chain length, shape and density of PEG on the particle surface are important parameters affecting nanoformulation PEG stealth activity (Gref *et al.*, 2000). In the study by Gref *et al.* (2000), the ideal molecular weight, density and content of PEG were optimized to minimize the amount of plasma protein absorbed, thus reducing uptake by polymorphonuclear leukocyte and human monocytic cells (THP-1).

Different polymers are often used in combination, forming copolymers with potentially beneficial properties, such as pectin-PLGA (Liu *et al.*, 2004) and alginate–chitosan-PLGA (Zheng *et al.*, 2004). Polymers can also be blended with or attached to other nanoformulation types, such as polymer-liposome complexes used for targeted codelivery of drug and gene to cancer cells (Wang *et al.*, 2010). These properties make polymer nanoparticles an extremely versatile tool for improving drug delivery.

Polymeric nanoparticles can be used to increase the bioavailability of drugs and other substances, compared with traditional formulations (Morgen *et al.*, 2012), and the size of polymeric nanoparticle has been shown to influence oral absorption. The absorption potential of chitosan nanoparticles of sizes 300 to 1000 nm were assessed, with 300 nm showing greater permeation in both Caco-2 cells and rat oral dose studies (He *et al.*, 2012). Polymer-coated nanoparticles are capable of actively targeting tissues such as hepatocytes, lymph nodes and tumours (Muthiah *et al.*, 2013), therefore allowing for targeted therapy and avoidance of organ-specific toxicity. Clearance of polymeric nanoparticles is dependent on several factors, such as choice of polymer and copolymers, polymer size, polymer charge and the existence of active tissue targeting. Trends in clearance have been observed, with positively charged nanoparticles larger than 100 nm being eliminated predominantly via the liver (Alexis *et al.*, 2008).

Polymeric nanoparticles are capable, both purposefully and inadvertently, of affecting the host immunological response. This can lead to issues, as a long-term polymer-specific immune response has been observed in subsequent studies (Ishida *et al.*, 2007; Wang *et al.*, 2007). Time-dependent immune system stimulation by nanoformulations may influence PK, as phagocytosis-driven increases in nanoformulation clearance would potentially occur.

Dendrimers

Dendrimers are tree-like, nanostructured polymers that have received significant attention as drug delivery systems, because of their well-defined size, tailored structure and potentially favourable biodistribution (Biricova and Laznickova, 2009). Dendrimer-based drug delivery systems can be manufactured to provide theoretically almost any size, but are commonly 10–20 nm in diameter and show promise as agents for imaging (Kobayashi and Brechbiel, 2004), gene therapy (Dufes *et al.*, 2005), drug delivery (Svenson, 2009) and biological adhesive (Joshi and Grinstaff, 2008).

Due to the near-infinite variety of possible dendrimer structures, an understanding of how these structures will relate to ADME/PK is a problematic task. Properties specific to each dendrimer, such as size, shape, charge, hydrophobicity and hydrodynamic weight, may all potentially alter disposition *in vivo*, as could attachments to the dendrimer structure such as PEG, drugs, RNA or antibodies (Kaminskas *et al.*, 2011). Further research is needed to understand these relationships to ensure optimum disposition and to avoid toxicity issues.

Liposomes

Liposomes are spherical vesicles consisting of a phospholipid bilayer. A variety of lipids can be utilized, allowing for a degree of control in degradation level. In addition to oral dosing, liposomes can be administered in many ways, including intravenously (McCaskill *et al.*, 2013), transdermally (Pierre and Dos Santos Miranda Costa, 2011), intravitreally (Honda *et al.*, 2013) and through the lung (Chattopadhyay, 2013).

Encasing drug in liposomes can dramatically increase drug exposure. In a PK study using Kunming mice, danorubicin liposomes had a 13-fold higher $AUC_{0\text{-}48h}$ compared with free drug (Ying *et al.*, 2011). Drug in liposomes often show greater PK variability than free drug, which is exacerbated when the clearance rate of the liposomes is low (Schell *et al.*, 2013). This could potentially prevent the use of liposomes to deliver drugs with a small therapeutic window.

Liposomes have the potential to radically alter tissue distribution of encapsulated drugs, which allows for targeting of tissues, such as the lymphatic system and brain (Cai *et al.*, 2011; Lai *et al.*, 2013), but this can also lead to increased toxicity. As an example, in a tumour-expressing CD1 mouse study, liposome encapsulation increased zoledronic acid 20- to 100-fold in liver, seven- to 10-fold in tumour tissue and twofold in bone, which resulted in more than 50-fold increase in drug-associated toxicity in animals but no additional inhibition of tumour growth (Shmeeda *et al.*, 2013). Liposomes can be combined with synthetic polymers to form lipid-polymer hybrid nanoparticles, extending their ability to target specific sites in the body (Hadinoto *et al.*, 2013).

The clearance rate of liposome-encased drugs is determined by both drug release and destruction of liposomes (uptake of liposomes by phagocyte immune cells, aggregation, pH-sensitive breakdown, etc.) (Ishida *et al.*, 2002). In a PK study using Kunming mice, docetaxel clearance was reduced from 19.9 to 7.5 L h^{-1} kg when liposome-encased, resulting in a 81% increase in $t_{1/2}$ (Zhang *et al.*, 2012). As noted with solid lipid particles, liposomes attached to PEG also show ABC responses following repeat doses (Suzuki *et al.*, 2012).

PBPK and nanotechnology: challenges and limitations

It is clear that nanoformulations can have radically different ADME properties compared with traditional formulations. Furthermore, there are a large number of nanotechnologies currently available, each with hugely varying PK properties, and in some cases with limited understanding of factors influencing distribution. The development of PBPK models should consider specific nanoformulation characteristics and consequently novel algorithms and modelling strategies will be required.

As previously described, nanoformulations can effectively ameliorate insolubility of orally administered drugs through controlled release or increase bioavailability by alternative mechanisms of diffusion through luminal barriers. However, these alternative mechanisms would need to be considered for the design of accurate PBPK absorption models. For obtaining release rates, *in vitro* assays could be used to analyse nanoformulation breakdown dynamics in gastrointestinal fluids using dialysis (Lazzari *et al*., 2012; Wallace *et al*., 2012). The absorption of nanoformulations through skin or other barriers can be clarified through different experimental approaches (Saraceno *et al*., 2013). The findings generated through these experimental investigations can be subsequently integrated in PBPK models through specific algorithms, mathematically describing the physiological and anatomical characteristics of the absorption processes.

The propensity of a drug for penetrating and leaving tissues is an important parameter in complete PBPK models. The tissue distribution of standard free drug can be determined by direct measurement of drug in tissues *in vivo*, usually in animals. However, this method is expensive and time consuming, as sensitive detection methods are often required. Furthermore, results may not be suitable for use in human PBPK models, as drug tissue distribution in animals may not correctly predict what occurs in humans. *In vivo* drug distribution studies of nanoparticles would potentially be prohibitively expensive, labour-intensive and wasteful, considering the extremely large selection of technologies to assess. Blood-to-tissue ratios of free drugs can be predicted using physicochemical properties, such as lipophilicity, pKa and plasma protein binding (Poulin and Theil, 2002). This approach, however, is unlikely to successfully predict the penetration in tissues for most nanoformulations because of the range of factors not usually considered for standard free drug.

The mechanistic structure of models for nanomedicines may need to differ from standard formulations. 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. Moreover, the penetration of nanoformulations in specific subtissue and subcellular compartments may be required, for example for modelling pH-sensitive breakdown in acidic environments such as lysosomes.

The size and shape of nanoformulations will potentially influence their access to particular sites in the body (Gentile *et al*., 2008) and can also dictate the level of hepatic filtration, tissue extravasation and kidney excretion. These factors can be integrated into PBPK models by the inclusion of defined rules limiting movement between compartments. This would require information of the size and shape of the nanoformulation, as well as physiological parameters such as endothelium pore sizes in different tissues. The active targeting of nanoformulations to particular sites in the body further complicates PBPK modelling. Intracellular compartments may be targeted, such as the use of nanodiamonds conjugated to antibodies to target the mitochondria (Mkandawire *et al*., 2009) and PLGA nanoparticles conjugated to nuclear localization signal peptides to target the nucleus (Misra and Sahoo, 2010). Active targeting could be integrated into PBPK models by including preferential transportation kinetics based on affinity of the nanoformulation for the molecular target, subpopulation of cells or tissue.

Characteristics of the nanoformulation surface which can influence uptake into cells, such as charge and functional groups, should be considered for PBPK modelling. The effect of surface roughness and charge on the cellular uptake of polymeric/silica nanoparticles in HeLa cells has been recently investigated, and rough nanoparticles are internalized by the cells more slowly and by an unidentified uptake route compared with smooth nanoparticles (Schrade *et al*., 2012). Moreover, nanoparticles with negative charges are internalized with higher efficiency compared with positively charged ones, independent of the surface roughness (Schrade *et al*., 2012). The interaction between gold nanoparticles (with different hydrophobicity, charge density and ligand length) and lipid bilayers has been clarified, investigating physicochemical properties favouring penetration through the bilayer. Hydrophobic and anionic nanoparticles did not have any significant interactions with the bilayer and different charge densities may induce pore formation or nanoparticle wrapping, resembling the first stages of endocytosis. Consequently, through the tuning of charge density, it can be possible to favour the internalization of nanoparticles into cells through different mechanisms such as passive translocation (low charge density) or endocytosis (higher charge densities) (McCaskill *et al*., 2013).

Due to the slow movement of lymph fluid and the propensity of traditionally administered drug formulations to be absorbed into the blood circulation, the lymphatic system is not routinely included in PBPK models. However, the lymphatic system can be an important factor in PK determination in particular cases. For example, a study using PBPK modelling to predict antibody disposition included a functioning lymphatic system, consisting of a single compartment connected to the existing tissues, which was used to improve the accuracy of the model (Abuqayyas and Balthasar, 2012). Considering that the lymphatic system has been shown to be integral to the disposition (Aji Alex *et al*., 2011) of certain nanoformulations, a full inclusion of this system into future PBPK models is desirable.

Excipients included in nanoformulations have the potential to alter the activity of drug metabolism enzymes *in vitro* (Martin *et al*., 2013). However, the effects of many nanoparticle excipients on the activity and expression levels of metabolism enzymes and drug transporting proteins *in vivo* are not fully characterized. This information would be particularly relevant in cases where the PK of a nanoformulation, an encapsulated drug or concomitant drugs is influenced by the affected enzymes. Previous PBPK models have included inhibition and induction mechanisms for metabolism enzymes (Fenneteau *et al*., 2010; Ke *et al*., 2012; Yamashita *et al*., 2013) and drug transporters (Gertz *et al*., 2013) and this element can also be included in PBPK models for nanomedicines.

The metabolism of free drug is usually achieved by enzymic reactions, often involving the cytochrome P450 (phase I) and UDP-glucuronosyltransferase (phase II)

enzymes in the liver, although numerous other pathways exist. Drug elimination in standard PBPK models is usually achieved via the simulation of liver, kidneys and gut clearance. With nanomedicines, however, a more complicated scenario can occur where multiple alternative organs and tissues are also capable of elimination. The elimination of nanomedicines can mean both the removal of intact nanoformulation from the body and also the degradation of nanoformulations (and subsequent release of drug) in plasma, tissues and organs. Potential elimination sites may include the reticuloendothelial system (Owens and Peppas, 2006), tissues with specific pH (Kim *et al*., 2008) and compartments within cells (Misra and Sahoo, 2010) (Mkandawire *et al*., 2009), as well as other sites. New elimination mechanisms may become important in traditional organs of clearance, for example the destruction of nanoparticles by Kupffer cells in the liver (Sadauskas *et al*., 2007).

Many of the nanomedicine-specific PBPK models to date have included data obtained from animals as a surrogate for clinical data, although it is not fully understood how nanomedicine PK data from animals will relate to humans. Physiological parameters that may limit nanoformulation transport, such as membrane pore sizes, can differ between species. It is therefore important that the most relevant animal species is used to obtain required data for human models. PBPK models can also be applied to simulate drug and nanoformulation PK in animal species so that PBPK modelling may be included in preclinical screening of nanoformulations, reducing the number of animals used for experimentation. Several PBPK models for animals have been developed for traditional formulations, giving reliable prediction of drug distribution in different species such as rodents, dogs and monkeys (Willmann *et al*., 2010; Wong *et al*., 2010; Geenen *et al*., 2013; Yang *et al*., 2013). The application of this tool in toxicological and pharmacokinetic studies has been thoroughly discussed in recent reviews (Thomas, 2009; Bessems *et al*., 2013) and the extension of this technique for the reduction of animal use in the discovery and development of nanoparticles is desirable.

Taken together, these factors could potentially be crucial for designing accurate PBPK models. As the factors governing nanomedicine PK become increasingly understood, these multiple factors can be combined and the effects on PK assessed using PBPK modelling.

PBPK and nanotechnology: current examples

As previously emphasized, several limitations of PBPK model designs may reduce the precision and accuracy of nanoparticle PK prediction. A comprehensive description of the nanoparticle ADME is essential to improve the quality of the simulations and consequently a detailed understanding of the molecular and physiological processes regulating nanoparticle disposition should be prioritized. Although a limited number of applications have so far been developed, the potential of this technique is extremely promising. We have evaluated some of the publications to date, observing how the authors have adapted their models for nanomedicines.

The first study describing a PBPK model for nanoformulations was published in 2008, predicting the PK of quantum dots in mice using whole-body PBPK. The authors included a distribution coefficient to simulate the diffusion of nanoparticle in tissues based on *in vitro* data, and could predict animal PK with good accuracy (Lin *et al*., 2008). Subsequently, another PBPK model for quantum dot PK was developed, considering the experimental data from Lin *et al*. (2008) and other reports (Lee *et al*., 2009). The authors extrapolated tissue-to-plasma coefficient values from experimental rat data and developed a blood-flow-limited model to simulate the PK of quantum dots. The model did not accurately predict the tissue distribution of quantum dots, particularly in the first hour post-dose, potentially because of an insufficient number of compartments included in the simulation (blood, skin, muscle, kidney, liver and 'other tissues'), with the lymphatic system also being absent. Additionally, quantum dot metabolism and elimination was not included.

A PBPK model for the simulation of inhaled carbon nanoparticles has been developed, integrating imaging data collected in humans using radioactive 99m-technetium-labelled nanoparticles (Pery *et al*., 2009). The model included small nanoparticles and free 99m-technetium (both able to translocate between compartments) and also large nanoparticles (unable to translocate between compartments). Elimination was assumed only for free 99m-technetium via the kidney and 24 tissue compartments were included in the model, although the lymphatic circulatory system was absent. This publication successfully included several factors which are likely to be relevant to nanomedicine PK, such as particle size-related limitations to tissue distribution and also degradation of nanoparticles post-dose.

Silver nanoparticles PK has been modelled using a PBPK approach, simulating the correlation between particle sizes, tissue penetration and the consequent effect on toxicity and health risks. Unfortunately, experimental data could not be matched completely in the model, possibly because of the effects of other nanoparticle characteristics, such as surface charge and coating, which were not included in the PBPK model (Lankveld *et al*., 2010).

PBPK modelling of five PLGA nanoparticle formulations prepared with different versions of monomethoxypoly (ethyleneglycol) (mPEG) (PLGA, PLGA-mPEG256, PLGA-mPEG153, 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.

Temporal exposure and elimination of five gold-dendrimer composite nanodevices in mice bearing melanoma was evaluated using a PBPK model (Mager *et al*., 2012). The authors concluded that, as specific binding ligands were lacking, size and charge of composite nanodevices governed most of their *in vivo* interactions. A PBPK model for ionic

silver and nanoencaspulated silver was developed on the basis of toxicokinetic data from i.v. studies. The authors validated the model structure for both silver forms by reproducing exposure conditions (dermal, oral and inhalation) of *in vivo* experiments and comparing simulated with real pharmacokinetic data for plasma and tissues. Interestingly, in all of the cases examined, the model could successfully predict the distribution of both ionic silver and 15–150 nm silver nanoparticles not coated with PEG. The PBPK model was also used to asses relevant scenarios of exposure to silver nanoparticles, such as dietary intake, use of three separate consumer products and occupational exposure (Bachler *et al.*, 2013).

As with models developed for traditional formulations, PBPK models for nanomedicines can be integrated with the mathematical simulation of therapeutic activity and/or host toxicity. The pharmacodynamics of nanoparticles is strictly dependent upon the penetration of nanoparticles in tissues and the interaction with the therapeutic targets. These phenomena can be influenced by several factors, defining complex interplay which can be successfully represented through mathematics. Pharmacodynamic models have been published for several different disease areas and their relative therapies, such as cancer (Bravo and Axelrod, 2013), malaria (Patel *et al.*, 2013), diabetes (Wilkins *et al.*, 2013) and human immunodeficiency virus (Jacqmin *et al.*, 2008; Duwal *et al.*, 2012). Drug resistance and response to anticancer therapy have been simulated using a semi-mechanistic pharmacodynamic model for the delivery of anticancer agents to hepatocellular carcinoma using nanoparticles (Pascal *et al.*, 2013). The authors were able to predict increased efficacy of nanoparticles through a mathematical modelling framework based on first principles of drug and cell mass conservation, describing the cellular uptake of drugs and death rates of tumour cells.

Conclusion

The effects of chemical components and nanoformulation properties on the bodily distribution of nanoformulations are clearly both significant and theoretically predictable, but large and essential knowledge gaps exist and necessitate future research. Moreover, universal property–distribution relationships for all utilized materials are unlikely, unless the effect of a specific physicochemical property is extremely predominant. Besides describing nanoformulation distribution and pharmacokinetic parameters, 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. This approach will not only improve our understanding of the mechanisms underpinning nanoformulation disposition and allow for more rapid and accurate determination of their kinetics, but will also help clarify interactions between different nanoformulation properties, identifying antagonistic or synergistic effects. Consequently, the design and development of nanoformulations can be informed by this modelling approach to generate novel nanoformulations with desirable PK (Figure 3).

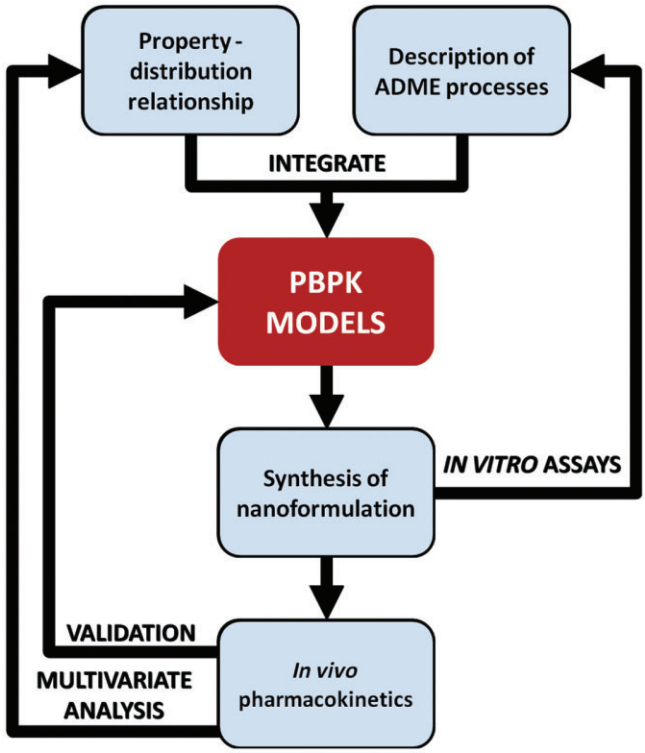

Figure 3

Flow chart representing an optimization process based on PBPK modelling and interactions between the different stages. *In vitro* assays can include but are not limited to chemical stability, enzymic degradation, cellular permeation, transcellular permeability and phagocytic uptake.

The development and application of PBPK models for nanomedicine is strictly dependent on the analysis of a broad range of information from different scientific disciplines. Knowledge from material chemistry, polymer synthesis, molecular and clinical pharmacology and mathematical modelling should be integrated in order to obtain a more comprehensive understanding of nanoformulation PK and, ultimately, to improve nanoformulation design. Consequently, an interdisciplinary approach is necessary and collaborative research between chemists, pharmacologists and modellers should be prioritized for the generation of nanoformulations with optimal PK.

Conflict of interest

M. S. has received financial support from Simcyp Ltd and Janssen Ltd.

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