The emerging role of physiologically based pharmacokinetic modelling in solid drug nanoparticle translation☆

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Abstract

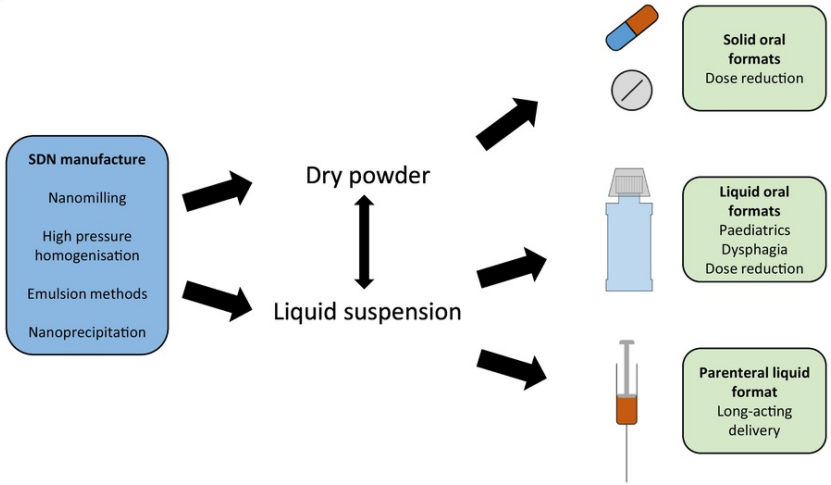
The use of solid drug nanoparticles (SDN) has become an established approach to improve drug delivery, supporting enhancement of oral absorption and long-acting administration strategies. A broad range of SDNs have been successfully utilised for multiple products and several development programmes are currently underway across different therapeutic areas. With some approaches, a large range of material space is available with diversity in physical characteristics, excipient choice and pharmacological behaviour. The selection of SDN lead candidates is a complex process including a broad range of *in vitro* and *in vivo* data, and a better understanding of how physical characteristics relate to performance is required. Physiologically-based pharmacokinetic (PBPK) modelling is based upon a comprehensive integration of experimental data into a mathematical description of drug distribution, allowing simulation of SDN pharmacokinetics that can be qualified *in vivo* prior to human prediction. This review aims to provide a description of how PBPK can find application into the development of SDN. Integration of predictive PBPK modelling into SDN development allows a better understanding of the SDN dose-response relationship, supporting a framework for rational optimisation while reducing the risk of failure in developing safe and effective nanomedicines.

Keywords: sSolid drug nanoparticle; pPharmacokinetics; Physiologicallybased pPharmacokinetic (PBPK) modelling; dDesign

1.1 Introduction

Research and development of nanotechnologies and manufactured nanomaterials is undergoing sustained and rapid expansion with the numerous bespoke biomedical applications. The processes that underpin nanomedicine pharmacokinetics and pharmacodynamics are not as fully characterised as for conventional small molecule medicines, and this complicates the development, optimisation and regulatory evaluation of novel nanomaterials. Nanomedicine strategies have emerged as advanced approaches to enhance drug delivery and improve the treatment of several diseases, through either augmented drug absorption, distribution, or residency within the systemic circulation. Protection of the active pharmaceutical ingredient (API) from degradation can increase the length of time for which drugs are present in the blood circulation and tissues, and coupling with active targeting ligands for cells or tissues is showing potential to improve the therapeutic index for many APIs.

Solid drug nanoparticles (SDNs) are predominantly composed of the API itself, whereby the drug particle surface is stabilised using surfactant and/or polymer excipients [1]. SDNs can be administered orally as solid formats, or resuspended to generate a nanoparticle dispersion for liquid oral or parenteral administration (Figure 1). APIs with low aqueous-solubility represent ideal candidates for SDN approaches, for which many processes are available for their manufacture [2]. Importantly, SDN formation does not involve the use of polymer, lipid or inorganic nanocarriers, which distinguishes this approach from many other nanotechnologies being investigated for drug delivery applications. Because complex carrier systems are not employed, and stabilisers tend to be drawn from those used in many established medicines (*i.e.* GRAS or CDER listed excipients [3]), SDNs suffer less regulatory uncertainty and achieve higher drug-excipient loading than other approaches.



~~Figure 1~~Fig. 1 Overview of solid drug nanoparticle manufacture and application. Different manufacturing processes produce either a liquid suspension that can be used directly for liquid applications, or a dry powder that can be filled directly into capsules o further processed into tablets. Suspensions can be further processed to produce solid formats, and dry powders can be redispersed to form liquid medicines. Parenteral formats require either production using sterile manufacture, or post-sterilisation (*e.g.* irradiation).

alt-text: Fig. 1

Nanotechnologies have the potential to generate exciting advances across numerous fields but understanding short-, medium-, and long-term safety is essential to development of nanomedicine applications. As for any medicine, a robust understanding of the exposure-response relationship is needed along with a thorough understanding of the likely plasma and tissue exposure in patients. Consequently, understanding the interactions between nanomaterials and the human body is essential for efficient development of safe and effective applications in medicine. The investigation of nanomedicine distribution is based on a variety of experimental methods and emerging computer-based approaches have been highlighted as effective tools to streamline the development of innovative formulations. Computational models to simulate the interaction with biological systems represent valuable pharmacological tools to facilitate development and regulation, as has already been achieved with small molecules. Indeed, *in silico* modelling has already gained significant traction for predicting pre-clinical efficacy, toxicity and distribution of small molecules, as well as dose-prediction for first-in-human trials [4, 5]. The approach is also being widely employed in the post-marketing environment for assessing novel treatment strategies, and predicting the magnitude of drug-drug-interactions or the likely impact of pharmacogenetic variation [6, 7]. Physiologically-based pharmacokinetic (PBPK) modelling has emerged as a powerful computational tool to simulate the distribution of small molecules and is now being employed for nanoparticle-based therapeutics.

The purpose of this review is to summarise the existing data for application of PBPK modelling to drug delivery as it relates to SDN development and implementation. Current gaps in knowledge and areas for further study are also highlighted.

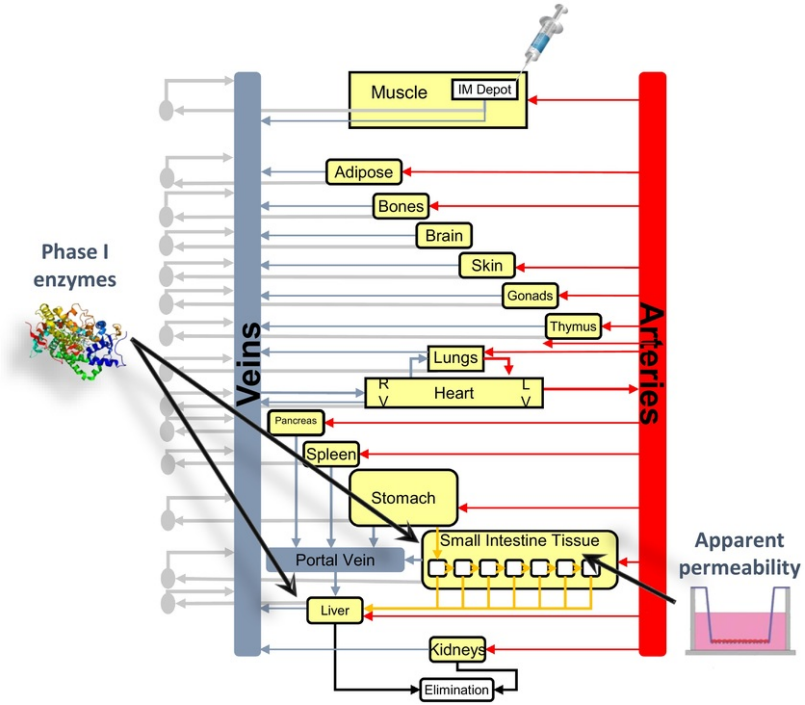
~~2.~~2 Recent advances in solid drug nanoparticle (SDN) applications

The majority of currently clinically used nanomedicines involve the use of SDNs [8]. SDNs can be produced using a variety of approaches including emulsion-based methods, nanoprecipitation [9], or high-pressure homogenisation [10], but the most commercially successful approach to date has involved nanomilling [3]. SDNs have been used predominantly for either improved oral drug delivery, or as long-acting injectables (LAI) *via* intramuscular delivery. One of the most successful areas of application has been the improvement of oral bioavailability of poorly water-soluble APIs and this nanotechnology has been successfully utilised for multiple products such as Emend® (aprepitant), Triglide® (fenofibrate), Rapamune® (sirolimus), TriCor® (fenofibrate) to name but a few. SDNs have been highly successful for LAI strategies, through which therapeutic or preventive plasma concentrations of drugs are sustained for a period of weeks to months, allowing infrequent and regular administration [8]. LAI formulations provide long-term exposure, which may be of particular benefit in chronic disease or for indications where adherence to therapy is essential for desirable clinical outcomes. Indeed, the desirability of lower frequency administration has been consistently observed in patient attitude surveys [11, 12]. Multiple SDN development programmes are currently underway across several therapeutic areas. For example, the authors are involved in several development programmes to bring forward oral and LAI SDN products for treatment and prevention of infectious diseases [13].

~~3.~~3 Modelling and simulation approaches applied to SDN development and implementation

~~3.1.~~3.1 Physiologically-based pharmacokinetic (PBPK) modelling

PBPK modelling is based on a detailed understanding of the processes underpinning drug distribution and the impact that SDN formation can have upon this at the site of administration [14, 15]. Importantly, irrespective of the route of administration of SDNs, the nanoparticles are thought to dissolve prior to or immediately on absorption to release small molecule APIs into the systemic compartment. Therefore, the critical considerations for PBPK modelling of SDNs relate to the manner in which they are absorbed either in the gastrointestinal tract or from the intramuscular depot site, and once absorbed PBPK models are identical to those for small molecule delivery (Fig~~ure~~. 2). Consequently, a specific representation of mechanisms underpinning SDN and drug absorption through different routes of administration is necessary.



~~Figure 2~~**Fig. 2** Graphical representation of a physiologically based pharmacokinetic model. Experimental data are integrated in to a mechanistic description of drug distribution to support a simulation of pharmacokinetics in virtual individuals. Relevant routes of administration (*e.g* oral and long acting IM) can be represented considering formulation specific characteristics. Grey lines represent the lymphatic circulation.

alt-text: Fig. 2

PBPK modelling requires that anatomically meaningful compartments are defined which integrate specific properties of a given organ or tissue (*i.e.* blood flow, mass, permeation limits) with drug characteristics, to create a mathematical representation of the human body [16]. PBPK modelling then combines mathematical equations to describe the anatomical, physiological and molecular processes regulating pharmacokinetics with relative *in vitro* data to simulate and predict distribution of the drug. Experimental *in vitro* data such drug dissolution, apparent permeability through the intestinal barrier, or interaction with the intestinal mucus can be integrated in a mechanistic description of oral absorption to evaluate bioavailability [17]. Similarly, *in vitro* systems can be used to capture drug release rates from the formulation for applications in LAI [18, 19]. Therefore, the impact of SDN formation on these mechanisms and robust *in vitro* systems to capture the differences are prerequisite to accurate modelling.

Once absorbed, drug distribution in tissues and organs is simulated considering regional blood and lymphatic flows, transporter activity and drug physicochemical properties influencing tissue to plasma ratio. Processes mediating drug degradation and elimination in tissues such as the liver and kidney can be investigated *in vitro* through standardised approaches to provide an estimate of apparent clearance, which following integration with data on enzyme expression in patient and organ size, can support a quantitative prediction of total clearance [20]. All the above pharmacokinetic processes are characterised by intra- and inter-patient variability which can be accurately represented through a mathematical description of environmental and patient-specific factors affecting drug distribution [21]. Firstly, variability in anthropometric, anatomical, physiological and molecular characteristics of the patient population have been extensively described and this set of equations constitute an essential element in the design of PBPK models [21]. Additionally, environmental factors such as food and concomitant drugs can influence relevant

drug distribution processes and dedicated experimental and computational approaches can allow robust prediction of their effect on intra- and inter-patient variability. Overall, it is therefore possible to simulate a virtual but realistic population of patients and to allow the simulation of pre-clinical and clinical studies [21]. Importantly, because small molecules predominate systemically after administration of SDNs, base models can be accurately qualified post-absorption with available clinical or preclinical data even before SDNs are developed. Therefore, for SDNs everything other than drug absorption can be qualified prior to simulation, which dramatically reduces uncertainty compared to applications in nanocarrier medicines where the carrier is introduced systemically to specifically modulate the distribution and clearance. Nanomaterials that reach the systemic circulation as intact particles are characterised by fundamentally different biodistribution, which is mediated by a broad variety of processes such as penetration through the vascular fenestration or uptake by phagocytic cells. Modelling approaches for nanoformulations were recently summarised in a review with specific focus on challenges in model development, validation and regulatory priorities [22].

PBPK models have relevant limitations and a full understanding of these implications is critical to meaningful application of this computational approach. The reliability of PBPK models is strictly related to a detailed description of processes regulating drug distribution, and consequently a partial description of relevant DMPK mechanisms will result in limited accuracy for predictions. Absorption can also be mediated by phagocytic cells and subsequently nanomaterials can reach the lymphatic circulation resulting in different pharmacokinetic patterns. The *in vitro* approaches used to capture this are therefore pivotal, influencing the quality of pharmacokinetic predictions. Thus, a full qualification of the experimental methodology is essential to support a successful integration of *in vitro* data into PBPK models. Moreover, a suboptimal description of patient characteristics can lead to a poor prediction of pharmacokinetic differences in the population of interest, limiting opportunities for application (*e.g.* dose stratification).

Modelling of drug pharmacokinetics is increasingly used by both academic groups and pharmaceutical industries and numerous computational platforms have been described. Various commercial platforms are available (*i.e.* Simcyp, GastroPLus, *etc.*) which provide comprehensive packages for simulations with user-friendly interfaces. PBPK models can also be developed by users with more flexible computational platforms (*i.e.* MATLAB, R, *etc.*) which require a more detailed understanding of model assumptions and structure, but provide greater opportunities for exploring novel mechanisms.

~~3.2.~~3.2 Complimentary computational approaches

Other computational techniques can be integrated with PBPK modelling in order to fill gaps needed for simulation. For example, quantitative structure–activity relationship (QSAR) studies are theoretical models that relate the structure of molecules to their pharmacological properties (distribution patterns, toxicity, *etc.*). QSARs are quantitative relationships based on data analysis approaches such as multivariate linear regression and random forest, aiming to identify molecular descriptors predicting biological activity [23]. The molecular descriptors can be the structural, geometrical and physicochemical properties of the whole molecule or isolated functional groups, and QSAR models can be developed and validated through multiple training sets of well characterised molecules. The validated model can then be applied to novel, uncharacterised molecules providing a quantitative estimate of the variable of interest. The application of QSAR to pharmacokinetics provides the opportunity to estimate key paramenters for the prediction of distribution (Volume of distribution, systemic clearance, protein binding, *etc.*) and the integration of QSAR models into a PBPK framework supporting the simulation of pharmacokinetic profiles for candidate drugs and therefore allowing the selection of candidates with optimal pharmacokinetic potential. It is important to recognise that such approaches themselves have limitations that may increase uncertainty in model prediction. However, this can provide a useful starting point for model development in the absence of empirical experimental data, and since SDNs release dissolved drug systemically the field can draw upon a wealth of QSAR data that has been generated over several decades.

~~4.~~4 Applications of PBPK modelling

~~4.1.~~4.1 The application of PBPK modelling to oral SDN development

Although pharmacokinetic modelling has only been recently applied in the nanomedicine field, several paradigms exist as examples for integration of PBPK in the rational design and development of SDNs. Importantly, this has been rapidly possible due to a comprehensive qualification and validation of existing modelling approaches for small molecules. For example, the authors recently demonstrated how a predictive computational approach was able to deliver a very precise simulation of genetically-influenced differences in pharmacokinetic exposure for the antiretroviral efavirenz [24]. Moreover, an *a priori* PBPK prediction of the pharmacokinetic consequences of efavirenz dose reduction was validated across relevant pharmacokinetic parameters on completion of the pharmacokinetic sub-study imbedded within a phase III clinical trial [24].

The authors have also applied PBPK to prediction of pharmacokinetics after oral delivery of SDNs manufactured with poorly soluble drugs with low permeability. SDNs are likely to adhere to the intestinal mucus creating a high concentration *in situ* and therefore favouring absorption by saturating active transporters and/or accessing particle-specific mechanisms. As described through the use of FRET dyes within dual-component SDNs for the characterisation of cellular permeability through intestinal cell monolayers, movement of intact dual-component particles was reported, suggesting a paracellular mechanism for enhanced absorption [1]. Overall SDNs can therefore improve absorption of APIs through multiple mechanisms and experimentally this effect has been clearly described through traditional high throughput methodology. In multiple reports, increased apparent permeability through Caco-2 cell monolayers (a well standardised approach to investigate oral absorption of drugs) has been described for SDNs compared to solutions of APIs [1, 24]. Interestingly, not all SDNs have been shown to result in higher absorption rate *in vitro*, with several SDN formulations exhibiting lower apparent permeability compared to controls. This highlights the importance of SDN physical properties and excipient choice in mediating pharmacological benefits, and SDNs with higher z-

average diameters were demonstrated to have better permeability and simulated pharmacokinetics [24].

Integrating the experimental analysis of intestinal permeability into a PBPK model is essential to fully understand SDN potential and help the translation of valuable candidates. Physiological and molecular processes can be successfully represented in PBPK modelling, supporting a computer-based simulation of the absorption of SDNs and therefore a quantitative prediction of the pharmacokinetic benefits resulting from the administration of SDNs. If models are successfully qualified, SDN pharmacological potential can be evaluated through the integration of experimental data into a mathematical representation of intestinal absorption, drug distribution and elimination in virtual patients or pre-clinical species. This strategy has recently been applied to rationalise the selection of optimal SDN candidates and simulated pharmacokinetics resulting from SDN administration has been confirmed through clinical studies. PBPK modelling of experimental *in vitro* data predicted an increase in bioavailability for an optimised efavirenz SDN to nearly 100% and a theoretical dose reduction of 50% to achieve similar exposure to the traditional clinically used formulation [25]. Importantly, this prediction was subsequently confirmed in a preliminary first-in-human healthy volunteer clinical trial [13].

~~4.2.~~4.2 The application of PBPK modelling to parenteral SDN development

Computational pharmacokinetic modelling can also provide a rational framework for the selection of candidate APIs for LAI SDN development. Moreover, the approach can aid identification of minimal dose requirements and optimal formulation characteristics to support sustained exposure over the dosing interval. Multiple therapeutic areas are being explored for LAI development, and these are characterised by a broad spectrum of pharmacological options and in many cases there is a need for combination therapies. Consequently, rationalising administration strategies requires consideration of multiple complex formulation, pharmacokinetic and pharmacodynamic priorities. Computational modelling provides the opportunity to simulate relevant scenarios and therefore support identification of strategies with a higher chance of success. For example, HIV treatment is based on the combination of multiple agents and current treatment and prevention strategies are almost exclusively based upon oral administration. Notwithstanding, LAI SDN formulations have recently been developed with rigorous pre-clinical and clinical testing [26], and rilpivirine LA and cabotegravir LA have shown great promise for treatment and pre-exposure prophylaxis [27]. It is widely expected that the coming years will see a proliferation of LAI SDN medicines for HIV, but the selection of drug candidate for future development is extremely complex. Recently, the authors reported use of a PBPK model to simulate theoretical pharmacokinetics resulting from LAI administration of experimental and established antiretroviral drugs to identify suitable API candidates and prerequisite formulation behaviours [14].

Similarly, for other disease areas, LAI strategies could greatly simplify drug administration especially when Directly Observed Therapy (DOT) is necessary such as is the case for tuberculosis [28]. Recently, modelling simulations have been used to explore if SDNs can support LAI strategies for the prevention and treatment of tuberculosis infection, helping a more rational selection of established and experimental APIs for future research [29]. Minimal dose and dosing frequency where also simulated to evaluate if LAI administration could be implemented within the constraints of existing treatment protocols.

An additional complication is the limited clinical implementation of this long acting strategies for vulnerable patients, when multiple logistical and ethical barrier can complicate clinical investigations. Physiological changes and altered expression of drug metabolism enzymes in elderly and pregnant women can influence drug pharmacokinetics, efficacy and toxicity [30, 31]. Vulnerable patients have higher incidence of co-morbidities and therefore complex polypharmacy. In ~~paediatric~~pediatric patients, growth consist of a continuum of biologic events and the development of relevant metabolism enzymes is not linear, complicating the investigation of PK especially in very young patients [32, 33]. Additionally, comorbidities can impact molecular and physiological factors influencing drug distribution. The mathematical description of these effects has been successfully implemented in PBPK models and therefore further supports the application of computational approaches. Overall, for vulnerable patients the design of clinical investigations of novel formulations is extremely complex and consequently this is comprehensively investigated in a very limited number of cases [34]. Characteristics of specific sub-populations of patients can be represented mathematically and successfully integrated in PBPK models, allowing the prediction of pharmacokinetics in vulnerable populations and therefore the simulation of innovative administration strategies [35]. The application of long acting administrations for special population represents an extremely valuable strategy due to particularly poor adherence patterns for patients such as neonates and children [36]. Existing daily oral formulations for children are often liquid based on different solvents, with poor palatability and dosing can be complex [36]. PBPK models can be applied to identify suitable dosing strategy for SDN long acting administration in children. For HIV treatment a recent publication explored multiple options for dosing in pediatric children based on WHO weight bands, with the overall aim of achieving similar exposure to adults treated with validated regimes [35]. The identified dosing strategies are a rational platform for future clinical investigations and therefore can simplify the dose finding process.

It is important to recognise that the ambition of the LAI projects described above were to inform future SDN development by assessing what is feasible in an API-specific manner, and what would be required from an SDN formulation to achieve it. As such, this work was not conducted with data available with SDN formulations, and is therefore pre-emptive in nature. This is partially due to the current paucity of knowledge relating to the *in vitro* and *in vivo* behaviour of SDN LAI formulations [8]. Recently, the authors reported an LAI SDN formulation of atovaquone, which was able to protect mice from exposure to *plasmodium berghei* sporozoites for 28 days following a single intramuscular administration [37]. Importantly, several formulations were developed as part of this programme, providing critical formulation, pharmacokinetic and pharmacodynamic data that can be employed for future PBPK model refinement.

~~4.3.~~4.3 A role for PBPK in reducing the number of animals used in SDN development

A strategised integration of PBPK modelling in SDN and more broadly in nanomedicine development has the potential to effectively reduce the use of preclinical animal-based models. It is estimated that worldwide more than one thousand companies are currently developing nanotechnology applications in medicine and consequently had, are or will use preclinical animal models to investigate nanoparticle pharmacokinetics and distribution. More widespread application of predictive PBPK modelling in this type of investigation has the potential to support a more informed selection of which species to study as well as an effective quantification of animals needed to achieve sufficient accuracy. Therefore, PBPK modelling has the potential to greatly reduce the overall number of animals used in nanomedicine development. Computational approaches provide a quantitative prediction of nanoparticle distribution in tissues that would require validation in a few groups of animals, supporting the Replacement, Reduction and Refinement (3Rs) of preclinical species in research and development. There are barriers to achieving widespread uptake of PBPK modelling in the nanomedicine community, which are driven by model complexity and current gaps in mechanistic knowledge. However, fuelled by the needs highlighted by regulatory authorities, significant adoption is expected in the coming years.

5.5 Summary and conclusions

Modelling approaches for nanoparticle applications are currently in their infancy compared to small molecules, and the processes regulating distribution of nanoparticles are known to be substantially different. PBPK models can assist in answering questions that cannot otherwise be examined in pre-clinical development and clinical studies as well as streamline the regulatory process. They provide the opportunity for rational design of nanomedicines, identifying strategies to maximise the efficacy and safety of novel technologies. A mechanistic understanding of the molecular and physiological events that define nanoparticle distribution can have a beneficial impact on development of novel nanoparticle assessment strategies and on the characterisation of toxicological risk. There is a clear need for increased application of such computational approaches to nanomedicine development and regulatory process, which is underpinned by a more thorough understanding of the factors influencing nanoparticle behaviour. This is further strengthened by how the broad variety of materials used for synthesis and their potential combinations define an inexhaustive list of delivery strategies available across sectors.

Computational pharmacokinetic modelling has potential to provide an extremely valuable tool for the design of nanomaterials. More specifically, PBPK modelling has been proven to help the optimisation of SDN for multiple administration strategies and different disease areas. SDNs are a nanotechnology with several applications in the enhancement of oral bioavailability and sustained release of APIs, but their optimisation is a complex process based on a broad range of *in vitro* and *in vivo* data. Frequently, SDN synthesis generates a high number of potential candidates and the direct testing of all nanoparticles *in vivo* would have multiple ethical and logistical barriers. A detailed understanding of the processes underpinning SDN pharmacology combined with well characterised *in vitro* data and predictive computational models, will allow a rational selection of valuable formulations so that those without value can be killed early in development. Integrated approaches *in silico*, *in vitro* and pre-clinical *in vivo* methodologies will enhance essential knowledge of SDN pharmacology while defining an optimal framework for the identification of nanoformulations with higher pharmacological potential.

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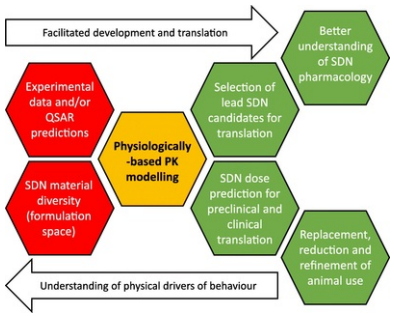

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