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The Current Landscape of Novel Formulations and the Role of Mathematical Modeling in Their Development

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Abstract

Drug delivery is an integral part of the drug development process, influencing safety and efficacy of active pharmaceutical ingredients. The application of nanotechnology has enabled the discovery of novel formulations for numerous therapeutic purposes across multiple disease areas. However, evaluation of novel formulations in clinical scenarios is slow and hampered due to various ethical and logistical barriers. Computational models have the ability to integrate existing domain knowledge and mathematical correlations, to rationalize the feasibility of using novel formulations for safely enhancing drug delivery, identifying suitable candidates, and reducing the burden on preclinical and clinical studies. In this review, types of novel formulations and their application through several routes of administration and the use of modeling approaches that can find application in different stages of the novel formulation development process are discussed.

Keywords

PBPK, Nanomedicine, Long-acting, Pharmacokinetics and drug metabolism, Pharmacometrics, Drug development

The development and clinical application of pharmaceutical agents can be complicated by numerous factors, including (but not limited to) issues related to the route of administration, distribution to site of action, metabolism of compounds, and subsequent elimination. Novel formulations can be used for enhancing drug distribution, increasing absorption and penetration in relevant tissues/cells, and limiting metabolism and elimination.

The application of nanotechnology for medical purposes is termed *nanomedicine* and is defined as the use of nanomaterials for diagnosis, monitoring, control, prevention, and treatment of disease.[1] While this review focuses predominantly on novel formulations for drug delivery, it is important to note that nanoformulations can find application in a broad range of fields including energy, electronics, food, and agriculture as well as other areas of health and medicine, including medical imaging, diagnostics, and translational research.[2] The extent to which nanomaterials can find application in such a wide range of fields is largely related to the vast diversity among technological platforms that can be exemplified by their use in nanomedicine.

The development of nanoformulations for drug delivery relies on the comprehensive understanding of the overall delivery strategy in connection with the physical composition of formulations, their specific route of administration, the interaction with the active pharmaceutical ingredient (API), and their distribution. To date, formulations exist that are gaseous, liquid (solutions, emulsion, and suspensions), semisolid (creams, ointments, gels, and pastes), and solid (powders, granules, tablets, and capsules). These are approved for use in a number of conditions including cancer, schizophrenia, diabetes, human immunodeficiency virus (HIV) and other infections (Table 1). They might be administered by subcutaneous (SC), intramuscular (IM), intravenous, intradermal, or intraperitoneal injection or infusion, or else, transdermally, orally, or across mucous membranes such as those in the lung, nasal passage, vagina, or rectum. The dosing strategy and pharmacokinetic (PK) properties of the technological platforms can be modeled using different computational approaches based on mechanisms of nanoformulations/drugs distribution.

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Table 1. FDA-Approved Drug Products of Injection Delivery Based on Advance Drug Delivery System

Technology	Drug Name	API	Composition	Company	Indication	Approval Date	Reference
Liposome	*Doxil*[a]	*Doxorubicine hydrochloride*	*HSPC and PEG*	*Janssen*	*Ovarian cancer, sarcoma, myeloma*	*1995*	148
	Ambisome	Amphotericin B	HSPC and DSPG	Astellas	Fungal infection	1997	149
	Depocyt	Cytarabine	DOPC and DPPG	Pacira	Lymphomatous	1999	150
	Exparel	Bupivacaine	DOPC and DOPE	Pacira	Local anesthetic	2011	151
	Marqibo kit	Vincrinstine sulfate	Eggs sphingomyelin	Talon	Acute lymphoblastic leukemia	2012	152
	Onivyde	Irinotecan hydrochlorine	DSPC and MPEG-2000-DSPE	Ipsen	Adenocarcinoma of the pancreas	2015	153
Microsphere	Lupron depot	Leuprolide acetate	PLGA	Abbvie	Advanced prostatic cancer	1995	154
	Sandostatin lar	Octreotide acetate	PLGA	Novartis	Acromegaly	1998	155
	Trelstar	Triptorelin pamoate	PLGA	Allergen	Advanced prostate cancer	2000	156
	Definity	Perflutren	DPPA, DPPC, and MPEG-5000-DPPE	Lantheus	Ultrasound contrast agent	2001	157
	Risperdal consta	Risperidone	PLG	Janssen	Schizophrenia, bipolar I disorder	2003	158
	Vivitrol	Naltrexone	PLG	Alkernes	Alcohol dependence	2006	159
	Bydureon	Exenatide synthetic	PLGA	Astrazeneca AB	Type 2 diabetes	2012	160
	Signifor lar	Pasireotide pamoate	PLGA	Novartis	Acromegaly	2014	161
	Lumason	Sulfur hexafluoride lipid-type microspheres	DSPC	Bracco	Ultrasound contrast agent	2014	162
	Bydureon bcise	Exenatide	PLGA	Astrazeneca AB	Type 2 diabetes	2017	163
	Triptodur kit	Triptorelin pamoate	PLGA	Arbor	Central precocious puberty	2017	164

(*Continued*)

Table 1. Continued

Technology	Drug Name	API	Composition	Company	Indication	Approval Date	Reference
Suspension and nanoparticle	Bicillin L-A	Benzathine penicillin	Dispersion	King Pharma	Rheumatic fever	1952	165
	Depo-Provera	MPA	Dispersion (microcrystalline suspension)	Pharmacia & Upjohn	Contraception	1959	166
	Atridox	Doxycycline hyclate	PLA	Tolmar	Chronic adult periodontitis	1998	167
	Eligard	Leuprolide acetate	PLGA	Tolmar	Advanced prostate cancer	2002	168
	Abraxane[b]	*Paclitaxel*	*Protein nanoparticle*	*Abraxis*	*Metastatic breast cancer, non–small cell lung cancer*	*2005*	169
	Somatuline depot	Lanreotide acetate	Nanotude	Ipsen	Acromegaly	2007	170
	Zyprexa relprevv	Olanzapine pamoate	Microcrystal	Eli Lilly	Schizophrenia	2009	171
	Invega sustenna	Paliperidone palmitate	Nanocrystal	Janssen	Schizophrenia	2009	172
	Feraheme	Ferumoxytol	Carbohydrate-coated iron-oxide nanoparticle	Amag	Iron deficiency anemia	2009	173
	Abilify maintena	Aripiprazole	Nanocrystal	Otsuka	Schizophrenia	2013	174
	Ryanodex	Dantrolene sodium	Nanocrystal	Eagle	Malignant hyperthermia	2014	175
	Invega trinza (3-month)	Paliperidone palmitate	Nanocrystal	Janssen	Schizophrenia	2015	176
	Aristada	Aripiprazole lauroxil	Nanocrystal	Alkermes	Schizophrenia	2015	177
	Sustol	Granisetron	Ortho ester	Heron	Nausea and vomiting	2016	178
	Sublocade	Buprenorphine	PLGA	Indivior	Moderate to severe opioid use disorder	2017	179
	Perseris	Risperidone	In situ forming gel	Indivior	Schizophrenia	2018	180
	NA	Leuprolide mesylate	NA	Foresse	Prostate carcinoma	Submission	181
	Cabenuva	Rilpivirine Cabotegravir	Dispersion Dispersion	Janssen ViiV	HIV HIV	Clinical trials	182
Emulsion	Intralipid	Soybean oil	Fat emulsion	Fresenius	Parenteral nutrition	1975	183
	Haldol	Haloperidol decanoate	Oil depot	King Pharma	Schizophrenia	2000	184
	Cleviprex	Clevidipine	Lipid emulsion	Chiesi	Reduction of blood pressure	2008	185
	Smoflipid	Fish oil	Lipid emulsion	Frenenius	Parenteral nutrition	2016	186
	Cinvanti	Aprepitant	Lipid emulsion	Heron	Acute and delayed nausea and vomiting	2017	187

API, active pharmaceutical ingredient; DOPC, dioleoylphosphatidylcholine; DOPE, dioleyoylphosphatidylethanolamine; DPPG, dipalmitoylphosphatidylglycerol; DSPC, distearoylphosphatidylcholine; DSPE, distearoylphosphatidylethanolamine; DSPG, distearoylphosphatidylglycerol; HSPC, hydrogenatedsoyphosphatidylcholine; MPA, mycophenolic acid; MPEG, methoxypolyethyleneglycol; NA, not applicable; PEG, polyethylene glycol; PLA, polylactide; PLG(A), poly(lactic-co-glycolic [acid]).

[a]First US Food and Drug Administrationapproved nanodrug.

[b]First US Food and Drug Administrationapproved nanotechnology-based target drug delivery.

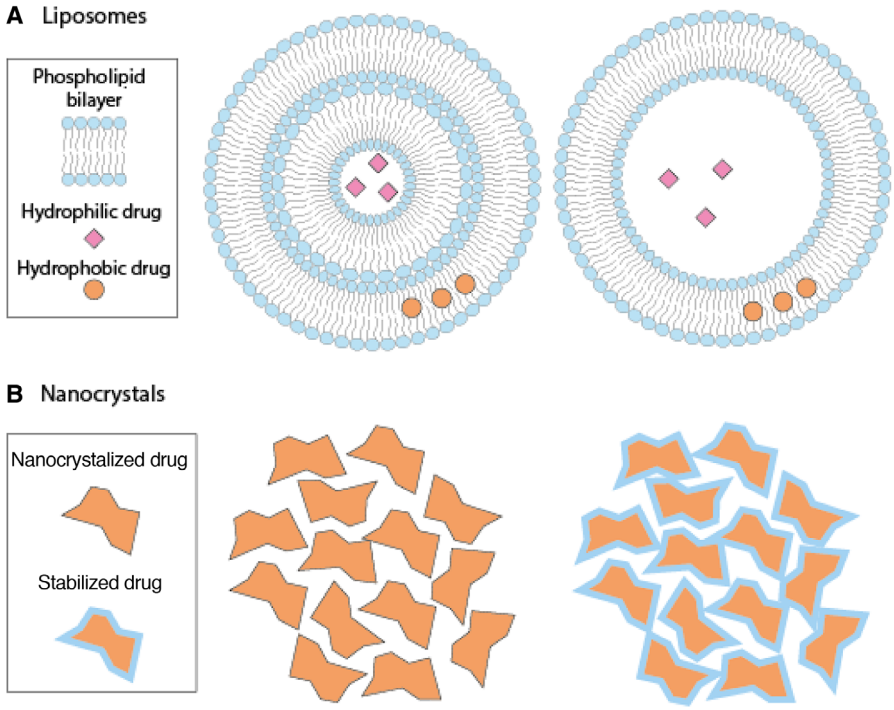


Figure 1. Liposome and nanocrystal nanoformulation drug delivery systems.

Goals to improve drug absorption and distribution, while taking into account metabolism and elimination of therapeutic agents invoke a manipulation of both the composition, structure, and compound encapsulation, while also modifying the delivery mechanisms for those drugs. These modifications might enhance biodistribution of drugs in a number of ways, for example, by preventing degradation, targeting materials to the site of action or enhancing absorption (eg, for hydrophobic compounds).[3]

Extensive preclinical tests are essential to characterize the suitability of novel pharmacological agents. For decades this has been largely reliant on the use of a variety of models including in vitro models and animal in vivo models. Both model systems are characterized by relevant limitations related to physiological differences, methodological complexity, and ethical barriers. Mathematical models can support the integration of findings generated through in vitro and in vivo models, resulting in a more rational application of existing approaches and the reduction of animal use.

In this review, we describe some of the past and recent advances in novel formulations and how mathematical modeling can support formulation development and optimization.

Novel Formulations

The landscape of nanoformulations has evolved over the years, and here we outline some past and present formulation strategies currently under development.

Nanoformulations

In the early 1960s, iron nanoparticles (NPs) were proposed as a treatment for anemia.[4,5] Since then, the field of nanomedicine has grown rapidly with the manufacture of a wide variety of nanomaterials including inorganic, polymeric, solid drug nanoparticles (SDNs), solid lipid NPs, nanoemulsions, dendrimers, nanocrystals, and liposomes (Figure 1).[6-12]

Definitionally, nanomaterials broadly comprise natural, incidental, or manufactured particles within the size range of 1 to 100 nm for at least 50% of the particles.[13] This means nanomaterials can be incredibly varied in their structure and composition and still defined nanomaterials. Materials can act as carriers for APIs, be the active ingredient in and of themselves or be attached to different types of molecules. They can be modified in a variety of ways to enhance PK increasing bioavailability, altering distribution, metabolism, and elimination.[3,14,15]

A series of recent reviews identified 28 nanomaterials currently approved for clinical use by the Food and Drug Administration or the European Medicines Agency with many more currently under clinical trial.[16,17] The majority of these approved nanomedicines are indicated for use in cancer treatment, some for iron replacement, for imaging and diagnostics, and as vaccines.[18-20] Table 1 summarizes products approved for use by the Food and Drug Administration for a wide range of medical purposes including cancer, schizophrenia, infectious diseases including HIV and

diabetes, and for contraception. The first clinically approved nanomedicines, and perhaps the best characterized to date, were liposomes. Liposome-based nanomaterials are made up of natural and/or synthetic lipids and surfactants built up into single or concentric phospholipid bilayers that are physiologically similar to biological membranes.[8] This similarity allows enhanced bioavailability and the ability of the materials to cross biological barriers with relative ease. Due to the biocompatibility of liposomes, these nanomaterials offer many clinical benefits as drug delivery vehicles.[8,21,22] They can be used to encapsulate drugs, protecting the body until the material reaches the target tissue.[23,24] The protective capacity of the liposome also affords the defense of the API from metabolism and degradation.[25] This also confers a challenge of therapeutic liposome use—the drug encapsulated within the liposome does not become bioavailable until the drug is released.[22,26,27] Careful consideration of the properties of both the liposome structure and the drug characteristics is required to ensure slow release of the drug within the appropriate time frame. For example, highly hydrophobic drugs, such as paclitaxel, are not well retained within liposomes and are not considered good candidates for delivery using liposomal NPs.[22,28] Liposomes can also be modified by altering the constituents of the outer layer or the pH of the lumen of the liposome in order to better retain drugs with certain characteristics.[21] Liposomes are particularly valuable in cancer therapeutics due to the comparatively larger size of nanomaterials compared to small molecule drugs. In normal healthy tissue, blood vessels typically create a barrier too tight for larger liposomes to pass; however, tumor sites have characteristic "leaky" blood vessels comprising the enhanced permeation and retention effect. This allows the passive targeting of liposomes to these tissues.[8,29]

Another relevant technological platform with great potential to enhance drug delivery is represented by nanocrystals. Nanocrystals are pure, solid, crystalline particles with a mean diameter <1 μm. These materials differ significantly from liposomes in the sense that they are a carrier-free NP. Instead of acting as a delivery system, encapsulating an active compound, the material itself is the active compound. They provide an excellent opportunity in the administration of hydrophobic drugs, which cannot be encapsulated well in liposomes and often have poor solubility and bioavailability when administered without nanoformulation.[30] Nanocrystalization increases the surface area-to-volume ratio, improves dissolution rates, and enhances solubility of hydrophobic drugs. A number of nanocrystal drug products have been approved for medical use with oral dosing, for a range of indications including for the treatment of pain, inflammation, hypercholesterolemia, and immunosuppression.[7] Nanocrystals or SDNs are also widely used for long-acting (LA) and sustained-release strategies as described in the section below.

The great complexity of the variety of structure of nanomaterials provides significant challenges—at present, many nanoformulations have poor bioavailability when administered orally, which might be ameliorated by novel formulation techniques such as those described below. Similarly, distribution can be hampered when nanoformulations are exposed to the blood as the complexity of these materials makes them particularly susceptible to adduct formation. Proteins circulating in the blood can bind to the nanomaterial, forming a protein corona, and altering the PK of those materials.[31-33] Nanomaterials are also frequently subject to immunological responses both increasing the risk of side effects in the body, and increasing degradation and elimination of the material.[31,34,35]

Biopharmaceuticals

Since the 1970s' discovery of recombinant DNA technology and subsequent invention of recombinant human insulin, biopharmaceuticals have become increasingly important agents in medicine.[36-38] With the exception of vaccinations, biopharmaceuticals predominantly comprise therapeutic proteins including cytokines such as interferons, interleukins and hormones, enzymes, coagulation factors, and monoclonal antibodies.[38]

In particular, monoclonal antibodies (mAbs) provide an opportunity for rapid development of novel formulations for the use in a range of diseases including cancer. mAbs themselves were first developed in the 1970s with the fusion of myeloma cells and mouse spleen cells; however, the scope of application of these proteins provide such opportunity to revolutionize treatment that the potential of novel formulation using these principles are myriad. This can include the application of new types of mAbs to medical problems that are without adequate treatment options, such as chronic pain. Chronic pain presents a unique problem in that the pain experienced by patients no longer serves its usual function supporting injury management; in fact, often chronic pain is not associated with any remaining injury or bodily damage.[39] In many cases, the pain experienced is related to neuronal plasticity that has upregulated the response to pain signals in that patient's body. Thus, new studies are investigating the value of mAbs that target nerve growth factor itself.[40]

Other novel opportunities in the formulation of mAbs include the development of novel administration routes: until very recently, all mAbs have been delivered intravenously over the course of 2 to 3 hours, but recent advances mean orally administered mAbs are under clinical trial.[41-43] A lack of bioavailability of these proteins is the limiting factor for alternative de-

livery systems. Similarly, protein pharmaceuticals lack adequate stability, presenting another avenue for the development of novel formulations.[43] LA routes of administration might offer some opportunities in the delivery of biopharmaceuticals (see the Long-Acting Formulations section).

Drug Delivery Systems

Modified Drug Release. Modifying the kinetics by which drugs are released into the body offers a variety of benefits to patients that can make treatment more sustainable and enhance patient compliance. In contrast to immediate-release formulations, which might require a high frequency of dosing in order to maintain the minimum effective concentration of a drug, modified release—such as delayed or controlled release—can change the plasma concentration profile of a drug over time.[44,45]

Delayed Release/Sustained Release. Drug delivery systems have long been modified to delay or extend the release of the API. Delayed-release delivery systems typically prevent release of a drug until a specific criterion has been met. For example, oral pills might be coated in a polymer that prevents release of the drug in the stomach.[46] This is of particular value for drugs that might irritate the mucosa of the stomach or prevent the breakdown of drugs that are unstable in the acidic environment of the stomach. Once the tablet has passed through the stomach and into the alkaline small intestine, the drug may then be released.

Alternatively, drug delivery systems have been developed that extend the release profile of the drug. These sustained- or extended-release formulations rely on a variety of systems to slow their release, such as distribution of the drug within a matrix of rate-limiting and inert ingredients that the drug then diffuses through inside the body.[47,48] Some of these systems also rely on the complete or partial degradation of the matrix so that the drug is released in its totality. Another drug delivery system that allows an extended release profile is reservoir systems in which an insoluble barrier surrounds a water-soluble drug. On ingestion the reservoir barrier becomes porous allowing gradual release of the drug.[49] Osmotic-release drug delivery systems rely on an insoluble membrane encapsulating a water-soluble drug that is released under osmotic pressure via an exit port in the membrane as water is osmotically drawn inside the system (Figure 2).[49]

Targeted Release.

Cell-Based Delivery Systems. A variety of cell types have been considered as drug carriers using a range of mechanisms both for introducing the drug to the

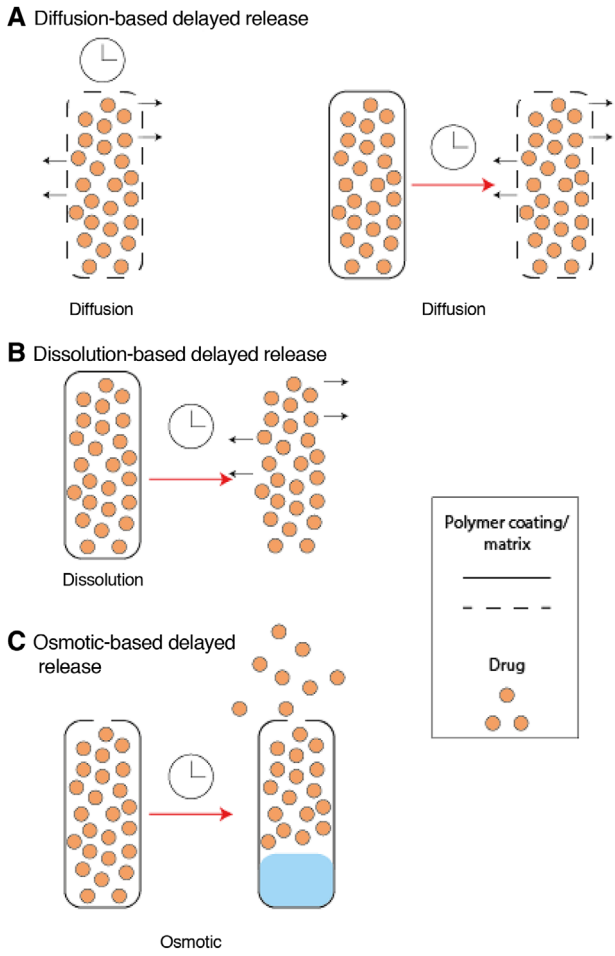


Figure 2. Examples of delayed-release drug delivery systems.

cells and to release the drug to the target tissue as required (Figure 3).[50] There are many advantages to cell-based drug delivery, including a reduced immune response to the drug, reduced side effects, enhanced biocompatibility, and the ability to use different cell types to target the drug to specific tissue types. Introduction of drugs to different cell types, including red blood cells, platelets, macrophages, and stem cells, can be achieved using a variety of techniques, either making use of native trafficking systems of the cells themselves, or using various techniques to permeabilize the cells artificially.[51] Macrophages have been identified as a valuable cell target for such use as a drug carrier. Macrophages are specialized cells that undertake phagocytosis—a process by which the cells can engulf external particles by reorganizing the membrane around those particles. This process requires targeting signals recognized by proteins on the cell membrane. It is therefore possible to target drugs to macrophages by attaching these targeting signals to the drug (or, as is often the case, the nanocarrier of the drug) to trigger phagocytosis.[52,53] Once inside the cell, there are

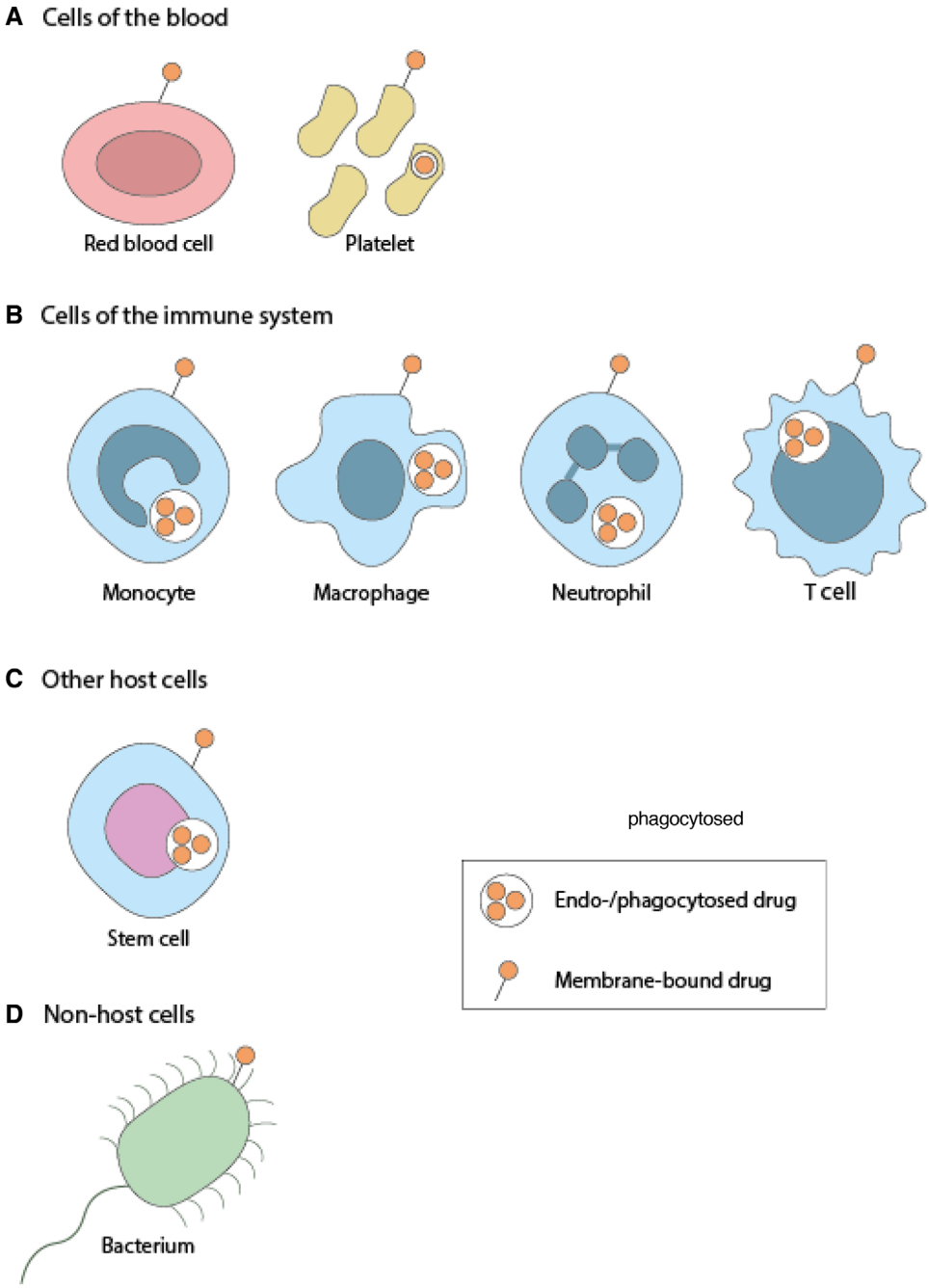


Figure 3. Examples of cell-based drug delivery systems and possible drug-loading techniques.

many additional things to consider before the drug can be delivered to the target tissue. First, maintenance of the carrier is important: Once macrophages undertake phagocytosis, they break down the engulfed material by fusion of the nascent phagosome with the degradative lysosome. To prevent degradation of the drug, one option is to chemically inhibit the lysosomal breakdown within the cells. Alternatively, protection of the drug with certain types of nanoparticle might hold some value. The final, and perhaps greatest, challenge when using cells as carriers for drug delivery, is encouraging those cells to release their cargo in a safe and efficient way. While some ultrasound disruption has been tested, it results in widespread cell death of the carrier cells.[54] Alternative options are still under investigation, making this a prime opportunity for novel solutions to make cell-based delivery systems truly viable in the clinic.

Long-Acting Formulations. Chronic diseases necessitate continuous therapy for long time periods; however,

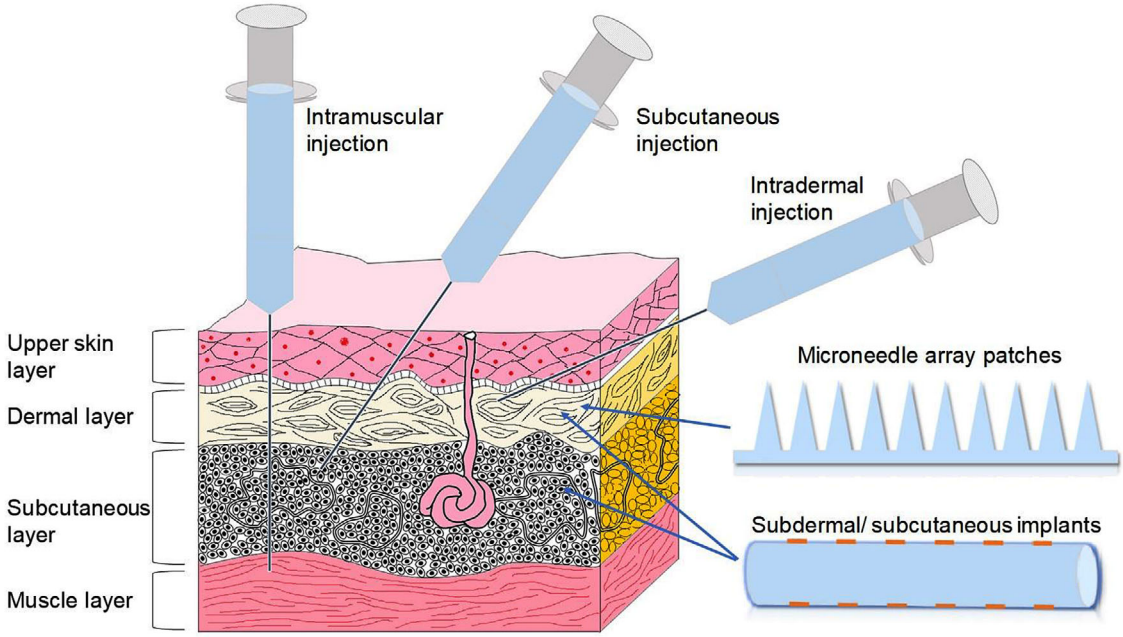


Figure 4. Various delivery devices and routes of administration for long-acting formulations.

daily oral dosing is associated with pill fatigue, side effects, and suboptimal adherence[55-57] with low adherence rates of 60% to 75% for oral antiretroviral therapy[58,59] and between 50% and 85% for tuberculosis (TB) treatment.[60] LA formulations represent an alternative form of dosing regimen that can support the controlled release of drugs, supporting effective concentrations over a long period of time, thus providing uninterrupted treatment. The duration of action for LA agents can vary across disease area and formulation strategies; however, drug candidates that provide continuous therapy at least for a 7-day period have been categorized as LA formulations.[61]

Novel LA parenteral formulations through the IM, SC, or intradermal (Figure 4) route of administration have several advantages over conventional oral formulations. The absorption of oral formulations through the gastrointestinal tract is limited by biological barriers such as low and variable pH in the stomach and small intestine that can lead to the degradation of the active ingredient, low drug solubility, drug lipophilicity, and suboptimal release of drugs from the formulations. Taken together, these define the fraction absorbed through the small intestine and intestinal and hepatic first-pass metabolism.[62] The administration of nanoformulations through the parenteral route can result in the generation of a depot, which releases the drug in a slow and controlled manner over a long period of time. The development of LA formulations is primarily influenced by PK and pharmacodynamic (PD) characteristics of the drug candidates, considering that the overall objective is to maintain effective concentrations for extended time periods at the site of action while not exceeding toxic concentrations. Drugs administered for LA purpose should also have specific physicochemical properties defining the compatibility with the administration strategies (eg, low solubility for injectable nanocrystals and SDN and moderate solubility for implants); high potency—requires low concentrations in plasma to achieve therapeutic effect; and long elimination half-life.[61]

LA strategy has long been used in the fields of contraception and psychosis.[57,63] It has also stirred interest in the field of chronic infectious diseases mainly for treatment of malaria, HIV, and TB.[64-67] Different routes of administration such as IM, SC, intradermal, and implants, can be used for delivery of LA formulations, but most importantly they should provide safe and efficacious treatment and be suitable for a broad range of patient populations and desired PK profile (injection site, dose, frequency, etc.).[68] Contraceptives such as medroxyprogesterone acetate and norethisterone enanthate are administered as IM or SC formulations, whereas levonorgestrel and etonorgestrel are administered as implants.[63,69] Aripiprazole, haloperidol, paliperidone palmitate, risperidone, and olanzapine are LA injectable antipsychotics that have significant advantages over oral formulations for the treatment of schizophrenia.[70,71] Currently, 2 antiretrovirals—cabotegravir and rilpivirine LA IM nanoformulations—are in phase III clinical trials for 4-weekly and 8-weekly administration.[72] LA SDN

formulation of atovaquone, an antimalarial, was designed and evaluated in C5BL/6 mice.[64] Bedaquiline is a second-line anti-TB drug used in the treatment of multidrug-resistant TB, which has a long elimination half-life, and a recently developed LA IM formulation of bedaquiline for treatment of latent TB showed sustained activity for at least 12 weeks in BALB/c mice.[67] An alternative technological platform that can provide sustained release of drugs is microneedle patches, supporting the intradermal administration of small molecules and peptides.[73,74]

The LA approach has been increasingly used for the delivery of protein therapeutics. As described above, proteins have some advantages over small molecules such as high selectivity, targeted binding, and high potency. However, due to their physiochemical characteristics—high susceptibility to degradation in the stomach pH, large molecular size, and hydrophilicity—oral administration is not effective due to their poor absorption, and they are generally administered parentally. Recent advances in protein design, characterization, and formulation design have enabled their use for LA therapy.[75,76] Various formulation designs including polymer-based microparticles or NPs, PEGylation, liposomes, hyperglycosylation, polymer or photoactivated implants, and gels are used to improve the safety and efficacy of the proteins and prolong the duration of these administered proteins.[75,77] Various protein therapeutics that are currently in the market are based on poly(lactic-co-glycolic [acid]) polymers that control the release of the drug such as leuprolide acetate, buserelin acetate, triptorelin pamoate used for treatment of prostate cancer, octreotide acetate, lanreotide for acromegaly, and growth hormone.[78] Another delivery strategy that has led to products available in the market is PEGylation, a technique where covalently attached polyethylene glycol (PEG) to a therapeutic protein increases its molecular size thereby improving terminal half-life. Peginesatide, an erythropoietin for the treatment of anemia and peginterferon alfa-2b for treatment of hepatitis C and melanoma, among others, are 2 PEGylated proteins approved by the Food and Drug Administration.[79]

Gene therapy, which is the treatment of existing genetic abnormalities by inserting genomic material intracellularly is achieved using various vectors to provide prolonged therapy. Some delivery carriers for gene therapy include lipids, polymers, and viral vectors, namely, those derived from adenovirus, retrovirus, pox, herpes simplex, and adeno-associated vectors.[80] Viral vectors, after modification to control their replication, act as genetic carriers that have high specificity and are more efficient than conventional lipids and polymers. Choice of viral vectors usually depends on numerous factors such as the target site of delivery, duration of transgene expression, inflammatory response, and genotoxicity.[81] Among the viral vectors, lentiviruses are capable of providing long-term expression and high specificity for both dividing and nondividing cells with low immune response.[82] Lentiviral vectors with clotting factor IX in mesenchymal stem cells isolated from umbilical cord blood provide sustained expression over a 6-week time period in vitro and may have application for patients with hemophilia B with the deficiency of factor IX.[83] In a separate study, 2 patients with adrenoleukodystrophy treated with hematopoietic stem cell gene therapy expressing adrenoleukodystrophy protein using a lentiviral vector had long-lasting adrenoleukodystrophy protein expression over 12 to 16 months with neurological benefits.[84]

Although LA formulations have several advantages over traditional formulations, they can be characterized by a few limitations. For parenteral LA formulations, individuals can experience pain at the site of administration, and drug diffusion into the surrounding tissues from the depot may cause lesions and irritation.[57] Several surveys indicate the preference of LA injectables over oral medication; however, individuals with needle phobia may not prefer the parenteral route.[61,85,86] Darville et al have observed the formation of granuloma, macrophage infiltration, and inflammation at the depot site post-IM injection of LA paliperidone palmitate, describing a multifactorial scenario at that site of injection.[87] Following administration of an injectable LA formulation, the removal of the nanoformulation and the discontinuation of treatment would require surgical expertise, if any complexities arise. To address this problem, recently, there is a high demand to modify existing injectable contraceptives to implants, namely, long-acting reversible contraceptives to ease the removal process in case of complications.[88] In the case of proteins, their size can be a limiting factor leading to slow release and subtherapeutic levels. Stability of the protein is another issue during long-term treatment, and a slight change in pH can affect the stability, leading to protein degradation.[75] Viral vectors have the advantages described above; however, they can be difficult to create, limiting the production, and can instigate unwanted immunological responses and genotoxic effects.[89]

Modeling

We previously described the current landscape of the field of pharmaceutical formulation. Advances in this field have been supported largely by the use of in vivo and in vitro model systems. However, these systems can be characterized by several limitations, reducing the relevance and translational value of experimental findings. Animal models used to study PK do not

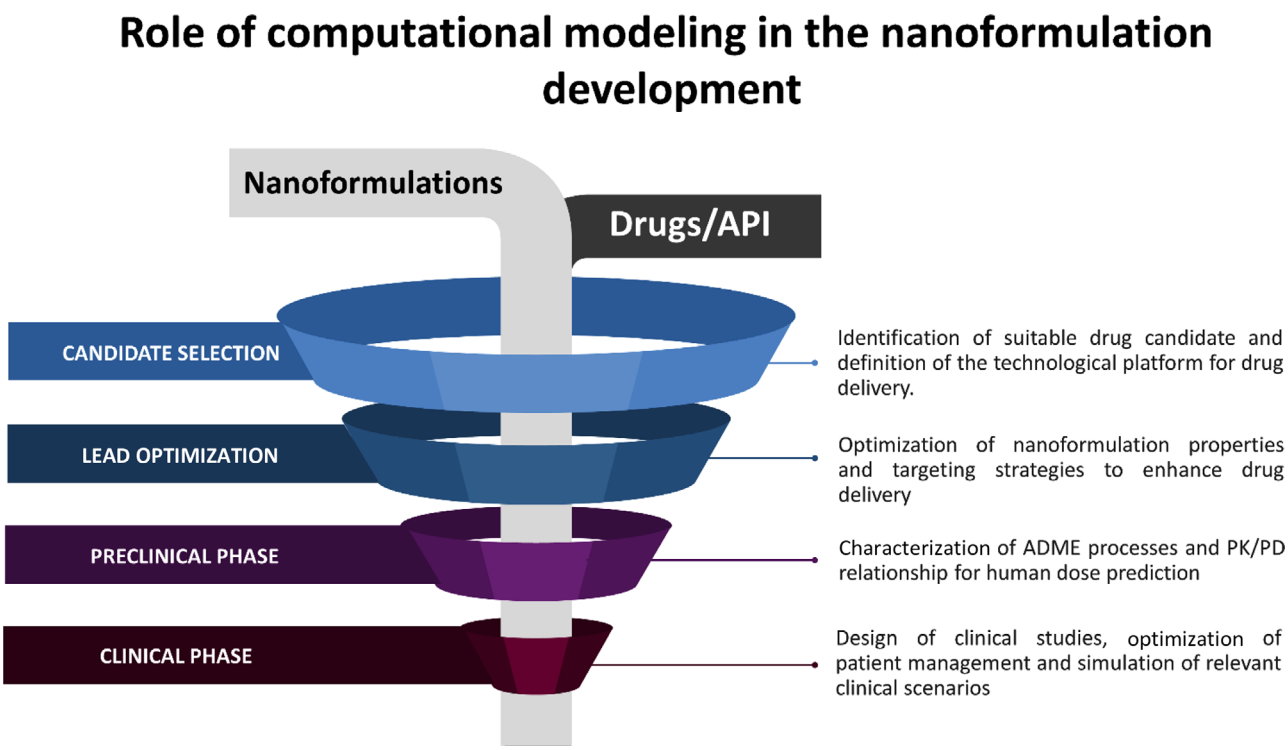


Figure 5. Integration of computational modeling for the design, development, and optimization of novel formulations. ADME, absorption, distribution, metabolism, and elimination; API, active pharmaceutical ingredient; PK/PD, pharmacokinetic/pharmacodynamic.

always serve as the best models for the quantitative description of processes in humans. Rats and mice, for example, have more rapid metabolism and elimination than humans, and different animal species might have variable absorption rate through different administration routes compared to humans. Similarly, in vitro assays have protocols that do not fully represent physiological conditions and have only limited complexity compared to in vivo environments. Mathematical modeling supports the integration of different types of data into a mechanistic description of PK and PD, facilitating a better understanding of a more complex system with adjustments for differences between humans and animals.

The ultimate goal of mathematical modeling in supporting the design of novel formulations is the rational identification of dosing strategy, route of administration, and formulation characteristics resulting in optimal PK and PD. Computational tools are essential for increasing throughput, reducing the burden of animal testing, increasing understanding of the mechanisms underpinning distribution, efficacy, and safety and generating novel hypotheses to support a more informed development of formulations (Figure 5).

For validation and use, all mathematical models rely on the generation of real-world data relating to the formulation of interest, which can include in vitro, in vivo, and clinical data in addition to physicochemical data relating to the formulations of APIs.

Quantitative Structure–Activity Relationships/ Quantitative Structure–Property Relationships

A quantitative structure–property relationship (QSPR) is based on the correlation of the physicochemical characteristics of a chemical substance and its properties. It involves the identification of molecular or structural descriptors and the association with informative data or properties using statistical or nonstatistical techniques. Quantitative structure–activity relationship (QSAR) methods have been applied in the development of relationships between molecule characteristics and different biological properties.[90] Classical QSAR studies include the assessment of ligands with their binding sites, inhibition constants, rate constants, and other biological end points. The methods evolved from Hansch and free Wilson's 1- or 2-dimensional linear-free energy relationships, Crammer's 3-dimensional QSAR to Hopfinger's 4th, and Vedani's 5th and 6th dimensions.[91]

Certain limitations to QSPR have been identified. Although hundreds of different parameters are used in QSAR studies, they are still not appropriate for the description of some important interactions, such as the membrane partition of drugs. QSAR techniques are also limited in their use for understanding the drug action in the whole body.[90] Moreover, experimental assays cannot be replaced by QSAR models because of various limitations of real-world situations and in vivo parameters.[91]

Quantitative Nanostructure–Activity Relationship

The description and prediction of biological effects of NPs are challenging. First, the high structural complexity and diversity of NPs and the development of quantitative parameters for the characterization of structural and chemical NP properties represent relevant limitations. Second, systematic physicochemical, geometric, structural, and biological studies of NPs are limited, hindering the development and validation of statistically significant computational models as these procedures require relatively large amounts of data.[92] These complexities contribute to the difficulties of using in vitro and in vivo models in isolation. Mathematical modeling is therefore a valuable tool in order to assess these greater complexities as a wide range of nanomaterial properties can be incorporated into the models.

Recent examples in predicting properties and activities using quantitative nanostructure–activity relationship (QNAR) methods include how the physicochemical properties can be predicted for nanomaterials.[93] Major roadblocks for the application of QNAR methods to modeling biological properties of NPs are (1) insufficient experimental data on the composition of the biocorona on nanoparticle surfaces (2) the lack of in vitro data predictive of in vivo effects of nanomaterials, and the paucity of "nanoparticle-specific" descriptors.[94] Some examples of QNAR are currently available in the literature and include applications related to human nanotoxicity[95,96] and ecotoxicity.[97,98] Additionally, some authors have tried to determine biological end points more valuable for absorption, distribution, metabolism, and elimination (ADME) studies as described below.

A library of 109 magnetic nanoparticles (MNPs) in which a superparamagnetic nanoparticle (cross-linked iron oxide NPs with amine groups) was decorated with different synthetic small molecules.[99] The MNPs were screened against different cell lines (PaCa2 human pancreatic cancer cells, U937 macrophages cell lines, resting and activated primary human macrophages, and human umbilical vein endothelial cells) to measure their uptake. Each MNP was represented by a unique set of descriptors determined by the conjugated small molecules. Nearest Neighbor and QNAR models were developed relying on chemical descriptors and MNP cellular uptake.[92] The QNAR models were capable of blindly predicting the PaCa2 cell uptake of the entire set of 109 MNPs with a correlation coefficient equal to 0.72 and a mean absolute error of 0.18. Lipophilicity was found to be the most discriminating factor; it is quantified by several descriptors, such as logP. In the other cell lines, cellular uptake revealed no significant variations correlating with NP structural properties.

In another study, multiple NPs (23 cross-linked iron oxide derivates, 19 pseudocage nanoparticle based based, 4 monocrystalline iron oxide nanoparticle based, 3 quantum dot based, and 2 iron based) were tested in vitro against four cell lines (monocytes, hepatocytes, endothelial, and smooth muscle) in 4 different assays: adenosine triphosphate content, reducing equivalents, caspase-mediated apoptosis, and mitochondrial membrane potential, at 4 different concentrations, resulting in a 51 × 64 biological data matrix.[100] The authors also reported 4 experimentally measured descriptors for 44 out of 51 tested NPs. The analysis implemented an external 5-fold validation procedure and the entire data set was split 5 times into a modeling set including 80% of the nanoparticle data set, and the external validation set, comprising the remaining 20% of the NP data set. For each NP, the entire 64-dimensional vector (4 cell lines × 4 assays × 4 doses) was combined into 1 single averaged biological response and defined 2 binary classes using an arbitrary threshold equal to –0.4. Results showed that support vector machine modeling has good prediction abilities, with external accuracy as high as 73%. Other QNAR models were built to predict cellular uptake using similar data and a variety of different computational approaches.[92,98,101,102]

An additional study focused on the interaction between gold NPs with A549 or HEK293 cells for 24 hours in order to support the development a QNAR model capable to predict cellular uptake. Multiple descriptors were used to inform the QNAR model capable of predicting with high predictabilities (R^2 from 0.995 to 0.967). Seven gold NPs were designed with predicted bioactivities and experimental data confirmed the modeling predictions. In addition to predicting cellular uptake, relevant factors influencing gold NP cellular uptake can be obtained by analyzing modeling results. Unsurprisingly, the hydrophobic potential (indicated by logP values) is the most important descriptor. Nanohydrophobicity has additionally being predicted through a QNAR approach.[103] Currently, commercial software tools can only predict physicochemical properties for new small molecule drugs but none are available for new nanomedicines. The nanohydrophobicity model was developed based on surface chemistry simulation of a set of gold NPs with various surface ligands. The predicted nanohydrophobicity showed high correlations with experimental results.[103]

QSARs can allow the determination of useful descriptors that can be used to help the evaluation of investigational new drugs. Unfortunately, in many cases, it gives nonspecific information on general processes that are already known, hardly quantifiable, and with no significant impact in the screening decision. Future improvements can be expected to divide the general

processes into specific and sensitive descriptors that can have a real impact in the discovery phase.

Quantitative Structure–PK Relationships

The accurate prediction of many ADME parameters can be complicated by multiple factors. The underlying physiological processes are complex and, in several cases, only poorly characterized. Other key aspects for development of a global, predictable, and transferable QSPkR model include: access to larger databases of standardized materials, detailed mechanistic understanding, and standardized workflow. QSPkR models for small molecules have been deployed for the prediction of volume of distribution at steady state, plasma protein binding, and drug clearance of acidic and basic drugs.[104] Nanoformulation PK studies could be used to develop nano-QSPkR models, but their development might be hindered by similar limitation as encountered with standard formulations such as the insufficiency of high-quality experimental data for ADME parameters, the incomplete knowledge on the underlying mechanisms, and the lack of standardized procedures and acceptance criteria for QSPkR modeling.

Physiologically Based Pharmacokinetics

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical description of mechanisms regulating ADME, which can support the simulation of drug and nanoformulation distribution by combining system data describing a population of interest with in vitro drug-specific data. This modeling technique represents an overview of the physiological and anatomic processes involved in the distribution, supporting the prediction of exposure variability in patients.

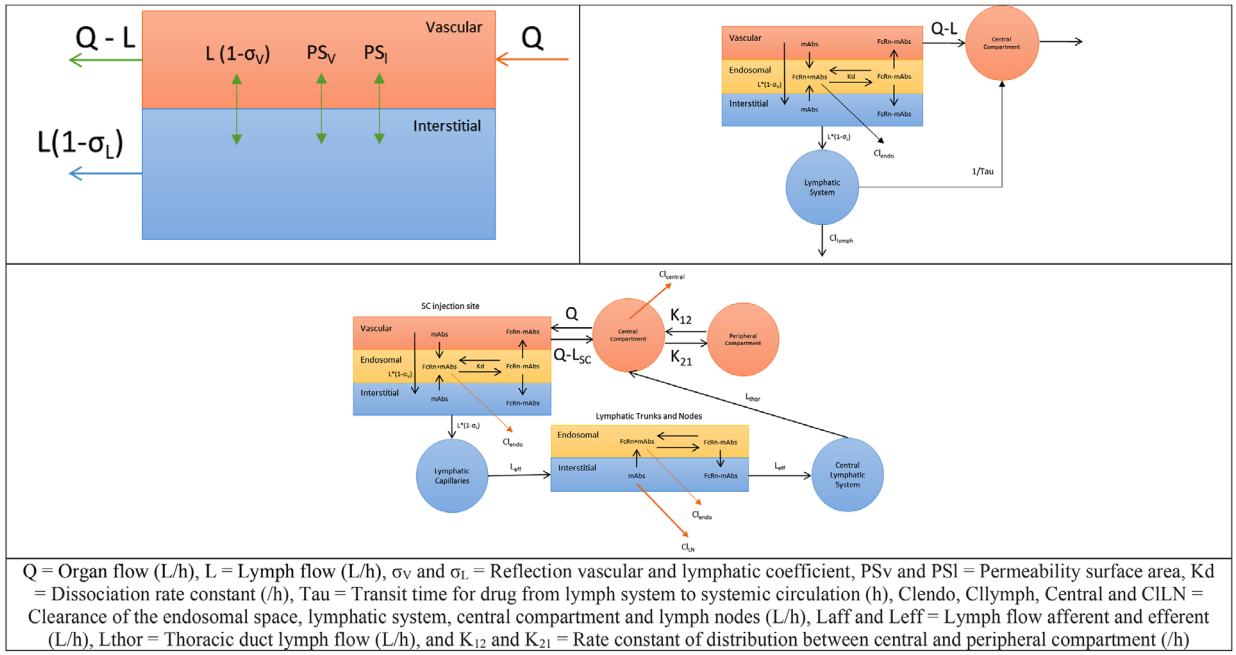
PBPK modeling has been used across multiple disease areas and for multiple applications and therapeutic options.[105-107] For brevity, here we focus on its application in nanomedicine and therapeutic proteins.

The development of PBPK models for nanomedicine is characterized by several challenges, mainly related to the limited understanding of the molecular, cellular, physiological, and anatomic processes regulating nanoparticle distribution. PBPK modeling can support a better understanding of the mechanisms underpinning nanoformulation disposition and allow for more rapid and accurate determination of their distribution. Furthermore, there are a large number of technological platforms, which are characterized by different PK properties. The development of PBPK models should consider specific nanoformulation characteristics, and consequently novel algorithms and modeling strategies will be required.[11]

In the past 2 decades, more than 20 PBPK models of NPs used in pharmaceutical products have been published for assessing quality, safety, and efficacy.[108,109] One of the first models for nanomedicine was published in 1999 and tried to provide a mechanistic description of distribution for liposomally encapsulated doxorubicin.[110] The first PBPK model described was a 4-compartment (blood, tissue, reticuloendothelial system, and tumor) blood flow–limited PK model. The tumor compartment was divided into 3 parts: capillary and interstitial, which form the extracellular space, and the tumor cell. The drug release was simulated in the blood compartment or in the extracellular space compartment following a first-order rate constant. The same rate constant was applied on the interstitial and reticuloendothelial system unidirectional transports and on the free drug moves. Progressively, other models have been created such as a 4-compartment (plasma, tissue, tissue, and tumor) hybrid PBPK model for liposomal formulation in mice introducing a permeability parameter based on blood vessel diameter and plasma volume fraction[111] or a liposomal blood flow–limited PBPK model in human using tissue-to-plasma ratio partition coefficients.[112] PBPK models become more and more complex, with liposomal and nonliposomal compartments with a saturable unidirectional clearance uptake parameter and bidirectional permeability–surface area coefficient to study amphotericin B in rat and mouse,[113] and the concept of "deep tissue" with association and dissociation rate constant was also proposed in a more recent rat PBPK model for docetaxel.[114]

Liposomal formulations are not the only nanoformulations investigated using PBPK modeling. Polymeric formulations (polyacrylamide NPs and polyacrylamide-PEG NPs) were first modeled in 2011[115] using slowly perfused organ compartment or saturable rapidly perfused organ compartment models as did multiple other studies.[116-118] A mechanistic model considering dose dependency, the size of the PEG-coated gold NPs, and the endocytosis of NPs using Hill function has also been developed.[119]

While quantum dot and metallic formulation PBPK models have been established,[120-124] the final example of NP formulation models using PBPK modeling we will consider in this review is those for nanocrystal formulation. A human blood flow-limited whole-body PBPK model for an IM injectable formulation of rilpivirine and cabotegravir using a first-order drug release rate was generated.[125] The model was able to predict observed clinical data with good accuracy. A flow-limited PBPK model in rat for an intravenous injection of anticancer agents was recently developed.[106] The authors have modeled a specific liver and spleen NP uptake and drug release. The in vitro drug release was also investigated with a dialysis technique, but it did not fully represent the real behavior of drug nanocrystals. Nevertheless, this approach could be useful for the char-



Q = Organ flow (L/h), L = Lymph flow (L/h), σ_V and σ_L = Reflection vascular and lymphatic coefficient, PSv and PSl = Permeability surface area, Kd = Dissociation rate constant (/h), Tau = Transit time for drug from lymph system to systemic circulation (h), Clendo, Cllymph, Central and ClLN = Clearance of the endosomal space, lymphatic system, central compartment and lymph nodes (L/h), Laff and Leff = Lymph flow afferent and efferent (L/h), Lthor = Thoracic duct lymph flow (L/h), and K_{12} and K_{21} = Rate constant of distribution between central and peripheral compartment (/h)

Figure 6. Schematic representation of different models representing absorption of parenteral formulations.[126-128]

acterization and comparative analyses of drug release from different formulations.

SC injection is important for therapeutic proteins (TPs): mAbs, peptides (insulin, growth hormone, and interferon) and proteins (erythropoietin). The exact mechanism underlying SC absorption is not completely understood, and the accuracy of prediction in humans remains limited.[113] Current PBPK models make several assumptions: for example, generic models describe the interstitial space, also called the extracellular matrix, as a gel-like consistency, and negative charge space based on its components (collagen, elastin, and glycoaminoglycans) (Figure 6). Furthermore, drug transport from the interstitial space is assumed to depend on active and passive (diffusion) transport to reach the blood system and on convection to reach the lymphatic system. Size and polarity of the TPs limit the direct diffusion through the endothelial wall.[126] Recently, the drug diffusion through blood capillaries was described as zero-order kinetics and the lymphatic absorption as first-order kinetics with a lag time.[113] In a recent study, the PK of 12 TPs with molecular weight between 8 and 150 kDa was simulated using a 2-pore framework following SC dosing.[126] The 2-pore model considers the hydrodynamic radius of the drug as the cutoff for drug diffusion: If radius is bigger than the pore radius, diffusion transport is absent in the model. Another minimal PBPK model comprising a mechanistic neonatal Fc receptor model into the endosomal space to understand the sequential transit of mAbs and to estimate lymphatic clearance was recently generated,[127] and a quantitative model, including clearance through the lymphatic transport and the neonatal Fc receptor capacity, to describe the absorption process for mAbs following SC or IM administration was also developed.[128]

All the above model examples represent mechanistic description of drug distribution following administration through advanced material for drug delivery and NPs (Figure 6). The validation of such mechanistic PBPK models can have numerous positives insights: (1) to prove and explain the presence of underlying mechanisms, (2) to allow the prediction in various scenarios, and (3) represent the initial framework for more complex models. The application of PBPK models requires several considerations: (1) an over- or misparameterization model can lead to the validation of nonphysiologic model and to mistrust conclusions, (2) the implementation of nonverifiable processes or nonquantifiable parameters can lead to nonusable models, and (3) the assumptions considered in the model should be based on biological plausibility.

Furthermore, PBPK modeling can find application in multiple phases in the development and optimization of novel formulations. The integration of mechanistic and PBPK models can support a more rational identification of drug candidates to be coupled with advanced materials for drug delivery. Specifically, drug characteristics can have a major influence on distribution and compatibility with different technological platforms. Predictive mechanistic models can help in identifying the most suitable drug candidates for specific dosing strategies, through the simulation of a combination of different routes of administration, doses, and

formulation characteristics.[105,129] Additionally, PBPK modeling can include a detailed description of formulation geometric and special characteristics and their influence on the diffusion and distribution of nanomaterials and small molecules in localized tissues such as the SC and IM spaces.[130] The mechanistic modeling represents an opportunity to virtually test different design strategies of formulations and consequently to rationally identify optimal characteristics for further development. This approach requires a sufficient description of molecular, physiological, and anatomic processes underpinning nanoformulation absorption and distribution, which can extensively vary based on the technological platform as well as the route of administration. For example, for IM injectable LA formulations, only a relatively limited understanding of local tissue mechanisms influencing the drug release from the site of administration is currently available, and initial studies have indicated multifactorial scenarios in which chemical degradation, neoangiogenesis, and inflammation interact in the definition of drug absorption.[87] Moreover, PBPK models can support the simulation of drug distribution in animals defining opportunities to refine, replace, and reduce the use of preclinical species in the investigation of novel formulation. The coupling of animal and human PBPK models is an exciting prospect to inform the bridging of PK and therefore streamline the development of novel formulations.

An essential component of the mechanistic modeling is represented by the complementary experimental in vitro assays for the quantitative description of mechanisms regulating nanoformulation distribution. To date, only a limited number of methods are available for the experimental investigation of key processes and a comprehensive standardization of these approaches is lacking, limiting the applicability of In-vitro to In-vivo extrapolation (IVIVE) extrapolation analysis. Examples of quantitative assays include nanoformulation stability and release rate in various biological media, permeability through biological membranes, and uptake by key populations of cells such as macrophages.

Another relevant area of application is related to the simulation of PK in specific populations of patients. The investigation of novel formulations and dosing strategies in vulnerable populations can be challenging due to numerous ethical and logistical barriers. In fact, a limited number of therapeutic options are available for populations such as neonates and pregnant women, and specific dose adjustment could be required for the elderly, obese patients, and patients with comorbidities.[107] The integration of the physiological and anatomic description of patient populations into PBPK models for the simulation of LA formulations or NPs allows the prediction of exposure variability in specific subpopulations of patients and the identification of optimal dosing strategies for stratified patient groups.[107] PBPK models have been successfully applied to simulate PK in multiple populations, including the elderly, neonates,[107] obese patients, patients with comorbidities, and pregnant women.

This approach can be further expanded to other areas such as the simulation of complex clinical scenarios in which multiple environmental and patient-specific factors can have an influence on the biodistribution of nanomaterials or LA formulations. Drug-drug interactions are a common and clinically relevant example of multifactorial processes complicating the management of therapies in patients.[131] This can be exacerbated in LA formulations, which can be characterized by sustained exposure over a long period of time. PBPK models have been effectively deployed to predict drug-drug interaction magnitude and clinical relevance for traditional oral formulations and more recently also for LA and nanoformulations.[132]

Systems Pharmacology

Quantitative systems pharmacology (QSP) is an emerging drug and disease modeling system that integrates the prediction of PK with PD at the physiological, cellular, and molecular levels. QSP modeling is used during drug discovery and development phases to investigate the mechanism of action of drugs in specific organs/tissues. QSP models can support the simulation of receptor-substrate interactions, cause-and-effect profiles, and drug potency.[133] Similar to PBPK models, QSP models can assess drug disposition in blood, various organs and tissues, and in tissue interstitium when integrated with PBPK models, and they represent a computational framework where PK simulations can be further integrated with a mechanistic description of intracellular disposition and interaction with targets. QSP models can go a step further to assess disposition intracellularly and also analyze binding and efflux of drug/NP in the cell, thereby providing a complete PK and PD profile.[134] The contrasting difference between PBPK models and complex QSP models is the area of focus. PBPK models emphasize the disposition of the drug in the body; however, QSP models focus on the additional aspect of what the drug does to the body.[135] Disposition of a modified messenger RNA (hUGT1A1-modRNA) that helps restore hepatic expression of UGT1A1, delivered using lipid NPs, was described using a QSP model. The simulated QSP model indicated the elimination and uptake of lipid NP across liver hepatocytes and release and transcription of hUGT1A1-modRNA, leading to the increase in clearance of bilirubin.[136] Another QSP model for the treatment of pneumocystis pneumonia (PCP; an opportunistic infection in hosts with immune defects including HIV) was developed, since the existing

treatment of PCP with trimethoprim-sulfamethoxazole results in serious side effects and treatment failures. Although there are alternative drugs such as atovaquone, clindamycin-primaquine, echinocandins, and pentamidine isethionate, they result in PCP relapse. The QSP model was constructed to identify novel therapies with optimal PK/PD characteristics.[137] QSP models can potentially allow a detailed understanding of the biological interactions; however, they demand extensive input data to provide predictions, and often these models can lead to overfitting when the quality of the input data is low.[138] A strategic integration of QSP modeling in the development of novel formulations for drug delivery can provide a computational framework to simulate the potential downstream effect of nanomaterials on drug distribution and consequently on efficacy and toxicity.

Molecular Dynamics/Quantum Mechanics

With recent advancement in computational power and graphic processing, sophisticated modeling approaches that heavily rely on computer specifications are on the rise.[139] Molecular dynamics (MD) is one such upcoming modeling technique that can represent the interaction between novel molecular structures and biological macromolecules.[140] To design and develop a nanomedicine, numerous prerequisites would be necessary, including stability of the NPs, control over the drug release rate, and targeting ability.[141] As an example, a prediction model generated using MD for the evaluation of globular protein adsorption onto the NPs showed good agreement with experimental data.[142,143] PBPK or QSP models can be combined with MD models to create integrated approaches that describe not only the disposition and activity of the compound of interest but also the interaction and activity of different excipients present in the administered formulation with various biological matrices across the body. This type of model integration across multiple computational techniques can provide a thorough picture of the formulation PD.

In addition to this novel modeling technique, quantum mechanics (QM) is another field of study that can evaluate reactions between various atoms and molecules including biological fragments. QM can be useful to study the interaction between numerous cellular components and nanomaterials to predict the resulting effects in terms of pharmacological activity or toxicity.[140] MD models along with QM models can offer better understanding of the interactions between biological structures and nanoformulations, supporting the design of active targeting strategies, and the selection of NP components. Although at present the existing computing power and the complexity surrounding the simulations of QM is a major drawback, the development of quantum computers can drastically reduce the computational time and improve the use of QM.[144]

Machine Learning/Artificial Intelligence

Artificial intelligence (AI) is a branch of computer science with multiple applications in various fields of study that acquire novel information, define decision making, and design novel methods.[145] AI is being rapidly introduced in health care as it has numerous advantages in the field of drug development. Machine learning (ML) is a subfield of AI, which typically consists of 3 categories: supervised, unsupervised, and reinforcement learning. Supervised learning is mainly used for ADME toxicity prediction, drug efficacy, and classification of disease diagnosis through classification and regression methods. Discovery of disease and relative target subtypes can be done using unsupervised learning where interpretation is solely based on input data.[146] Reinforcement learning is used in the decision making of drug design and experimental design in an environment specific to a drug class or therapeutic area.[145]

ML can be used as part of QSAR to build models that can predict NP characteristics such as cellular uptake, cytotoxicity, drug loading and release profile, NP adherence to the target site, size of the NP, and its polydispersity as shown in various studies.[147] Examples of AI applications in the nanomedicine field include the evaluation of a 4-drug combination regimen to minimize toxicity in control cell lines and maximize apoptosis in breast cancer cell lines. Drug-dose ratios of the 4-drug regimen nanodiamond-doxorubicin, nanodiamond-bleomycin, nanodiamond-mitoxantrone, and unmodified paclitaxel were successfully optimized in various cell line types.[62] To conclude, although AI is not currently being used actively during drug approvals, with the day-to-day increase in the number of available data and improvement in predictive power of ML algorithms, opportunities for using AI to assist in the field of drug discovery and development will quickly arise.

Conclusion

The types of novel formulations and their use in safe and efficacious treatment discussed in this review represent a central pillar for the definition of new paradigms for drug delivery. Computational modeling is an attractive platform that integrates nanomaterial-specific data and anatomic and physiological descriptors to provide PK and PD predictions that could be useful in the identification of potential drug candidates and formulations. The development of technological platforms and nanoformulations is characterized by multiple challenges across different stages, including (1)

the selection of suitable drug payload and nanoformulation strategies, (2) the identification of the optimal geometric and physicochemical properties, (3) the evaluation of the compatibility with overall formulations and routes of administration, (4) the integration of various experimental and preclinical data to better characterize nanoformulation distribution, (5) the prediction of PK/PD in humans, and (6) the management of potential clinical scenarios or dosing in specific populations of patients. A strategic application of modeling approaches can support the design of novel formulations through a multidisciplinary integration of different data sets to rationally streamline the development process.

Conflicts of Interest

M.S. has received research grant funding from Janssen and ViiV. All other authors having nothing to declare.

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