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Review article

Revisiting the *in-vitro* and *in-vivo* considerations for in-silico modelling of complex injectable drug products

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ABSTRACT

Complex injectable drug products (CIDPs) have often been developed to modulate the pharmacokinetics along with efficacy for therapeutic agents used for remediation of chronic disorders. The effective development of CIDPs has exhibited complex kinetics associated with multiphasic drug release from the prepared formulations. Consequently, predictability of pharmacokinetic modelling for such CIDPs has been difficult and there is need for advanced complex computational models for the establishment of accurate prediction models for *in-vitro-in-vivo* correlation (IVIVC). The computational modelling aims at supplementing the existing knowledge with mathematical equations to develop formulation strategies for generation of predictable and discriminatory IVIVC. Such an approach would help in reduction of the burden of effect of hidden factors on preclinical to clinical translations. Computational tools like physiologically based pharmacokinetics (PBPK) modelling have combined physicochemical and physiological properties along with IVIVC characteristics of clinically used formulations. Such techniques have helped in prediction and understanding of variability in pharmacodynamic parameters of potential generic products to clinically used formulations like Doxil®, Ambisome®, Abraxane® in healthy and diseased population using mathematical equations. The current review highlights the important formulation characteristics, *in-vitro*, preclinical *in-vivo* aspects which need to be considered while developing a stimulatory predictive PBPK model in establishment of an IVIVC and *in-vitro-in-vivo* relationship (IVIVR).

1. Introduction

Current therapeutic regimens against the major diseases require the administration of multiple agents being dosed multiple times at definite intervals [1]. Such chronic treatments have often presented variable results in terms of safety and efficacy of the intended formulation leading to poor quality-of-life among patients with subsequently reduced adherence to prescribed therapies [2]. Consequently, therapeutic drugs have often been either administered using multiple dosing of the formulations at short intervals or using complex injectable drug products (CIDPs) [3]. CIDPs are long-acting formulations of hydrophobic and amphipathic therapeutic agents which have tendency to form *in-vivo* depots presenting differentiated and modulated delivery of the agents. The CIDPs include micron or nanosized lipid and polymer-based carriers with suitable opportunities to deliver the therapeutic doses of the drug over the desired period of time [4]. Since, all these complex injectable formulations have presented differentiated and modulated drug release profiles as compared to their simple injectable formulations, the entire group of liposomes, nanoparticles, polymeric depots, suspensions and prodrugs have been included in the group of CIDPs [5]. Traditionally, these formulations have been designed to enhance patient compliance, mitigate the issues associated with drug delivery at the intended sites, modulate drug half-life, and improve therapeutic outcomes. Over the last few years, development of effective CIDPs has been a major focus of the researchers to deliver the cargo in naïve state [6]. CIDPs have presented complex combination of release kinetics and have been frequently associated with multiphasic drug release from the prepared formulations. Importantly, the development of generic versions to approved clinical therapeutics would necessitate the development of appropriate discriminatory testing release parameters which would

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ensure the safety and efficacy of the patients [7]. Consequently, simple pharmacokinetic modelling for such CIDPs has been difficult and there is need for advanced complex computational models for the establishment of accurate prediction models for *in-vitro-in-vivo* correlation (IVIVC) [8].

CIDPs have been traditionally tailored to present chronic therapeutic action over long periods (days or months) post their administration *via* intravenous, intramuscular, soft tissue infiltration or subcutaneous routes [9]. Design and development of such formulations present the healthcare professionals with improved therapeutic success. Regulatory agencies have approved several CIDPs of therapeutic agents like bupivacaine, doxorubicin hydrochloride, paliperidone palmitate, aripiprazole, naltrexone, buprenorphine among others (Table 1) [10,11]. Replicating CIDPs with the same raw materials, the same composition, same structure and same manufacturing process at large scale has been challenging. Most of the innovator companies have dotted line CDAs in place which prevent the supply and usage of the API and excipients in generic products same as that of the innovator products [12]. Often innovator companies have faced issues with the reproducibility of the manufacturing and such instances have resulted in product recalls [5]. A classic example of the same was that of manufacturing of liposomal Doxorubicin by Ben Avenue laboratories [13]. CIDPs have often presented distinct pharmacokinetic (PK) flip-flop properties with the rate constant of drug absorption being slower than that of elimination. Consequently, the terminal phase of the drug profile from these products have reflected the rate of absorption instead of the rate of elimination contrary to the products exhibiting linear pharmacokinetics [14]. Developing generic products for such innovator formulations has been challenging due to the presence of variable pharmacokinetic properties

Table 1
List of controlled release parenteral formulations (CIDPs) approved by USFDA for the treatment of various diseases.

Drug	Product name	Company	Type of drug delivery	Indication	Date of approval	First Generic available
			Liposomes			
Amphotericin B	AMBISOME™	ASTELLAS	Injectable, liposomal; lyophilized injection	Fungal infections	08/11/1997	12/14/2021
Doxorubicin HCl	DOXIL™	BAXTER HLTHCARE CORP	Injectable, liposomal; injection	Ovarian Carcinoma, Kahler disease, AIDS-Related Kaposi's Sarcoma	11/17/1995	02/04/2013
Daunorubicin and Cytarabine	VYXEOS™	CELATOR PHARMS	Injectable, liposomal; lyophilized injection	Newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	08/03/2017	No
Bupivacaine	EXPAREL™	PACIRA PHARMS INC	Injectable, liposomal; infiltration	Postsurgical local analgesia, regional interscalene brachial plexus nerve block	10/28/2011	No
Irinotecan	ONIVYDE™	IPSEN INC	Injectable, liposomal; injection	Metastatic pancreatic adenocarcinoma	10/22/2015	No
Amikacin sulfate	ARIKAYCE KIT™	INSMED INC	Suspension, liposomal; inhalation product	Refractory *Mycobacterium avium* complex (MAC) lung disease	09/28/2018	No
			Polymeric nanosuspension			
Paclitaxel	ABRAXANE™	ABRAXIS BIOSCIENCE, LLC	Injectable, lyophilized nanosuspension injection	Metastatic breast carcinoma, locally advanced or metastatic non-small cell lung cancer (NSCLC), metastatic adenocarcinoma of the pancreas	01/07/2005	04/12/2022
Sirolimus	FYARRO™	AADI BIOSCIENCE	Injectable, lyophilized nanosuspension injection	Locally advanced non-operable or metastatic malignant perivascular epithelioid cell tumor	11/22/2021	No
			Microspheres			
Risperidone	RISPERDAL CONSTA™	JANSSEN	Microsphere IM injection	Schizophrenia and bipolar disorder	10/29/2003	No
Leuprolide acetate	LEUPRON DEPOT™	ABBVIE ENDOCRINE INC	Microsphere IM injection	Advanced prostatic cancer	01/26/1989	No
Naltrexone	VIVITROL™	ALKERMES	Microsphere IM injection	Alcohol dependence	04/13/2006	No
Octreotide acetate	SANDOSTATIN LAR™	NOVARTIS	Microsphere IM injection	Acromegaly	11/25/1998	No
Triptorelin pamoate	TRELSTAR™	VERITY	Microsphere IM injection	Advanced prostatic cancer	06/15/2000	No
Minocycline hydrochloride	ARESTIN™	ORAPHARMA	Microsphere for administration in periodontal pockets	Adult periodontitis	02/16/2001	No
			Intramuscular Depot suspensions			
Paliperidone palmitate	INVEGA SUSTENNA™	JANSSEN PHARMS	1-month injectable IM depot suspension injection	Schizophrenia	07/31/2009	No
Paliperidone palmitate	INVEGA TRINZA™	JANSSEN PHARMS	3-month injectable IM depot suspension injection	Schizophrenia	05/18/2015	No
Paliperidone palmitate	INVEGA HAFYERA™	JANSSEN PHARMS	6-month injectable IM depot suspension injection	Schizophrenia	05/18/2015	No
Aripiprazole monohydrate	ABILIFY MAINTENA KIT™	OTSUKA PHARM CO LTD	Injectable IM depot suspension injection	Schizophrenia and bipolar disorder	02/28/2013	No
Aripiprazole lauroxil	ARISTADA INITIO KIT™	ALKERMES INC	Injectable IM depot suspension injection	Schizophrenia	06/29/2018	No
Cabotegravir	APRETUDE™	VIIV HLTHCARE	Injectable IM depot suspension injection	HIV-1	12/20/2021	No
Cabotegravir; Rilpivirine	CABENUVA KIT™	VIIV HLTHCARE	Injectable IM depot suspension injection	HIV-1	01/21/2021	No
			Subcutaneous Gels			
Granisetron	SUSTOL™	HERON THERAPS INC	Injection, extended release; subcutaneous	Chemotherapy induced nausea and vomiting	08/09/2016	No
Lanreotide acetate	SOMATULINE DEPOT™	IPSEN PHARMA	Subcutaneous injection	Acromegaly	08/30/2007	No

and difficulty in interchangeability with clinical discomfort over proposed therapeutic equivalenced switches [15]. Therefore, development of such formulations requires identification of critical parameters which can affect the pharmacokinetic profiles while presenting similar or lesser toxicological effects in clinical set up [16]. One-way of identification of these parameters includes computational modelling which may effectively combine existing knowledge and establish mathematical equations for generation of dependable relationship between *in-vitro* characteristics as well as *in-vivo* profiles. Such an approach would help in reduction of the burden of effect of hidden factors on preclinical to clinical translations [17]. Importantly, identification of biorelevant critical quality attributes (CQAs) of active substance as well as its formulation and built-in predictive IVIVC mathematical modelling would help in development of formulations with tailored pharmacokinetics. Computational tools like physiologically based pharmacokinetics (PBPK) as well as physiologically based biopharmaceutical model (PBBM) modelling have combined physicochemical and physiological properties along with IVIVC characteristics of clinically used formulations [18]. Such computational techniques have helped in prediction and understanding of variability in absorption, distribution, metabolism, and elimination (ADME) parameters of generic to clinically used formulations like Doxil®, Ambiosome®, Abraxane® in healthy and diseased population using mathematical Eqs. [19]. The current review highlights the important formulation characteristics, *in-vitro* and preclinical *in-vivo* (systems pharmacology) aspects which need to be considered when developing a PBPK/PBBM model for establishment of an IVIVC and *in-vitro-in-vivo* relationship (IVIVR) (Fig. 1) [20]. The development of good IVIVR ensures that the drug product exhibits comparative biological as well as biopharmaceutical performance consistently throughout its life cycle [21].

1.1. Types of CIDPs

CIDPs are long-acting medications that can administer active substances through extended period. These have been formulations of hydrophobic and amphipathic therapeutic agents developed in form of

Fig. 1. Establishment of effect co-relations (output) between *in-vitro* profile data, *in-vivo* parameters and in-silico development tools for effective prediction of therapeutic outcomes.

depot or surface tailored micro/nano sized lipid or polymer-based carriers with suitable differentiated and modulated opportunities to deliver therapeutic doses of agents. Traditionally, the approaches adopted for design of therapeutic equivalent CIDPs include optimization of release profiles from formulations as well as optimised *in-vivo* clearance. However, prior to identification of various important parameters for modelling, an overview and understanding of the various types of CIDPs are important.

1.1.1. Polymeric CIDPs

Polymer based entrapment or encapsulation of therapeutic agents present in micro-sized matrices have been referred to as microencapsulation. These micro-encapsulations include the drug uniformly dispersed in continuous polymeric matrix (matrix microspheres) or present as reservoir or core inside shell-like wall (core-shell microspheres). Such systems have been made from single or multiple polymers of either natural, semisynthetic or synthetic nature [4]. The most widely used polymers for the generation of such CIDPs are poly-lactic acid (PLA) and poly (lactic-*co*-glycolic acid) (PLGA) with drug release being modulated based on the intrinsic composition (ratio) and the relative molar mass of the polymers being used. The major mechanisms of *in-vitro/in-vivo* drug release from such polymer based CIDPs include polymer erosion and degradation, stimuli responsive, injection microenvironment modulated, drug diffusion, water-mediated, desorption, polymer healing and dissolution from inside the matrix to the external medium [22]. Importantly, the development of appropriate discriminatory models representing the burst release of the agent from surface followed by subsequent controlled release from the core-shell microspheres has presented challenges to the effective IVIVC correlations [10]. Approved polymer based CIDPs include Risperdal Consta™, leupron depot™ and Sandostatin LAR™ among others [22] (Table 1).

1.1.2. Liposomes

Liposomes are lipid-based carrier vesicles which may be morphologically unilamellar, multilamellar or multivesicular and have been among the most widely approved CIDPs. Depending on the hydrophobicity of the therapeutic agent and its physicochemical properties, these may be entrapped either in the inner aqueous layer (Hydrophilic) or the lipid bilayer (Lipophilic) [6]. Drug loading in these carriers may be accomplished through either active loading (loading against transmembrane gradient), passive loading (direct entrapment), passive equilibration (drug loading in preformed liposomes) or electrostatic charged interaction with lipids [23]. These formulations may be modulated to improve the carrier's residence time (grafting using polyethylene glycol (PEG)) or targeted passively (based on surface charge) or actively (with ligands against surface overexpressed targets) [24]. Multivesicular liposomes are micron sized lipid carriers with multiple honeycomb shaped structures present within outer lipid membrane (eg. Depofoam™ technology). Post the intrathecal or infiltration at the site, these formulations present sustained release of the drug over 4–15 days with possibility of the modulation of drug release by varying the composition of the lipids [25]. The modified release of drug depends on lipid properties and composition, interactions between the lipid and the encapsulated drugs, aqueous phase composition, surface modifications and osmolarity [26]. Further, properties such as hydrodynamic diameter, zeta potential and morphology would modulate the *in-vitro* release (IVR) profiles while presenting challenges to the development of pharmaceutically equivalent and bio-equivalent formulations [9]. Importantly, the development of appropriate discriminatory models for free drug content and release profiles representing the various phases of release of the agent from lipid carrier has presented challenges to the effective IVIVC correlations of formulations like Ambiosome™, Doxil™, Exparel™, Onivyde™ and Vyxeos™ among others [10].

1.1.3. Oil based depots

Microemulsion formulations and oil-based injectable depots present suitable carriers for hydrophobic drugs. These approaches often include solubilization of the steroidal drugs using co-solvents, surfactants and oils. Further, chemical modification approaches such as conjugation of drugs with fatty acids like decanoate, enanthate, caproate among others, which form controlled release prodrug depots post subcutaneous or intramuscular injections are also used [27]. The development of such conjugated formulations presents improved partitioning and localization of the agents leading to prolonged action of drugs such as Hydroxyprogrogesterone caproate (Maken™), Nandrolone decanoate (Deca-Durabolin™) and Testosterone enanthate (Xyosted™) following parenteral administration [28]. The important parameters for development of generic formulations include appropriate solubilization of the drugs in oily vehicle, prodrug hydrolytic potential, viscosity of vehicle, extent of depot formation, haemolytic potential, and drug release from oil to surrounding tissues into blood [29]. These factors would invariably be important parameters in development of appropriate models of *in-vivo* drug release [10].

1.1.4. Depot suspensions

Hydrophobic agents have been formulated in suspensions using suspending agents. Formulating such agents into micron sized or nanosized suspensions would induce change in their physicochemical properties like particle size and solubility among others. Nanosizing based NanoCrystal technology™ (Janssen Pharmaceuticals) has been used for the preparation of long acting atypical antipsychotic Invega Sustenna® (paliperidone palmitate ester) [30]. Nanoparticulate compositions of hydrophobic palmitate ester prodrug of the palperidone have resulted in development of 3 month and 6 month-controlled release formulations. The intrinsic solubility of the active agent, hydrolysis rates of the ester produg, the particle size and kinetics of dissolution have been identified as important *in-vitro* parameters affecting the IVR of such suspensions [31].

1.1.5. Long-acting hydrogels

Hydrogels (polymeric and supra-molecular) are three-dimensional expandable polymeric systems suitable for drug delivery of hydrophobic agents through stents and tissue engineering [32]. While supramolecular hydrogels have been formed as entangled networks by self-assembling into nano sized fibers and helices, polymeric hydrogels may be formed through chemical cross-linking or matrix formation around the therapeutic agent [33]. The generation of such structural reticulated channels have presented good loading opportunities for controlled drug delivery systems for hydrophobic agents. Important considerations while designing of IVIVC models for these agents would include multiphasic IVR (burst release, lag phase and exponential release) [32]. The drug release profile will be affected by different mechanisms including release from the polymeric structures (diffusion-controlled, swelling-controlled, chemically-controlled), drug release from the hydrogel entrapped particles, diffusion across matrices and release from hydrogel [34,35]. Polymer as well as hydrogel characteristics, hydrogel geometry, drug release from the matrix, internal and external particle size, zeta potential, swelling ratio, hydrogel mesh characteristics, hydrophobicity of drug *etc.* may be the rate controlling factors for modelling of IVIVC of these formulations [4,10,36]. Fibrinogen and thrombin based artificial supramolecular extracellular matrix was formulated to reduce the spread of neoplastic metabolites. These systems presented suitable opportunities for loading of the drugs to prevent the reoccurrence of the tumors [37].

1.1.6. Long-acting implants

Drug loaded polymeric systems may be moulded or cast into various shapes (implants) for delivery of therapeutic agents over extended period. Development of such formulations may improve the patient compliance while having reduced dosing variabilities, toxicities,

improved therapeutic efficacy and improved patient adherence by reducing dosing [38]. Suitable examples of such systems include intrauterine devices, subcutaneous implants and injectable PLGA depots (SinoFuan™, Zoladex™, Propel™, Implanon™, Nexplanon™, Vantas™) among others [38]. The development of discriminatory and simulative IVR method would be difficult due to extended period of release. Importantly, for such formulations, development of the in-silico models needs to include the time variables based on the mechanism-based kinetics of drug release from the polymeric network in addition to existing parameters of polymer characteristics, size, porosity, morphology and surface potential [39–41]. Additionally, the role of *in-situ* physiological conditions, translocation of the drug from the depot to surrounding tissues and subsequently to plasma as well as absence of adequate plasma concentrations need to be built in the IVIVC models. Development of time-based accelerated drug release methods correlating the drug release profiles need to be developed which then can be scaled to real time profiles [42].

1.2. Generic CIDPs and need of in-silico modelling

Current research in drug delivery focuses on development of generic formulations against innovator CIDPs to ameliorate the availability of active therapeutics with similar safety as well as efficacy profiles as that of the reference formulations but at an affordable cost. Assessment of interchangeability between the two formulations would require the development of discriminatory dissolution methods and availability of biorelevant *in-vitro-in-vivo* correlations (IVIVCs) to provide modelling tools that will help with formulation development and bioequivalence study designs for generic CIDPs [4]. The development would require linking the critical quality attributes (CQA) to *in-vivo* performance for bioequivalence (BE) assessment and use of population pharmacokinetic-pharmacodynamic (PK-PD) modelling with statistical evaluation for reduction in residual variability as well as AAFE (absolute average-fold error). Establishment of such in-silico modelling shall help in the identification of appropriate PK metrics, allowing bioequivalence estimation for parallel design studies having manageable sample number and assessment of chances of failure of the comparative bioequivalence studies.

Additionally, modelling the consequences of localised chronic inflammation in tissue on drug release (diffusion mediated) and/or drug stability on exposure caused by prolonged therapy with CIDPs need to be built in to reduce the inter-patient variabilities [43]. CIDPs release drugs in different parts of the body and have highly complex structures with multiple potential mechanisms of drug release. Change in one formulation variable can change the release mechanism. Hence, it is important to understand what the IVIVC modelling for the CIDPs intend to achieve especially for the determination of the generic equivalents [44]. The regulatory agencies including the USFDA have often focussed on the necessity of Q1Q2Q3 sameness of the complex products prior to them being nominated as generic equivalents to the existing clinically used innovator products [45]. To facilitate the development of complex generic products, regulatory bodies have often ascertained the need of having pharma-equivalence and bioequivalence studies being bridged by IVIVC modelling to reduce the chances of clinical failures along with explanations to patient variabilities in the PK/PD profiles. Such strategies include the need of characterization using orthogonal techniques (Pharmaequivalence) along with IVIVC modelling for the assessment of the differences between the proposed generic product and innovator product [46]. Importantly, the building of PBPK models requires inclusion of the innovator data requisites establishing Q1Q2Q3 similarity with innovator product and then integrating the *in-vitro* data with the in -vivo data from the SBOA (Summary basis of approval) or using literature available in the public domain exploring the PBPK/PBBM modelling for the formulation [47]. Additionally, it should be noted that attempts to establishing IVIVC/IVIVR have often been intended to gain mechanistic understanding of the product with aim to reduce the risk of bioequivalence failures and the approach may not suffice the regulatory requirements for obtaining biowaiver (like that observed in oral formulations) [48]. These studies would help to identify right biorelevant *in-vitro* tools for the test product and establish the QTPP. This QTPP is essential for ensuring the safety and efficacy of the patient when treated with the generic equivalent as compared to that of the innovator product [49]. Consequently, IVIVC modelling has been considered as a key inclusion in the product development studies. While the approach of IVIVC based predictions are still in its infancy, considerable progress has been made by various biopharmaceutical research groups for the predictability of the IVIVC for liposomes, nanoparticles and microspheres [50].

1.3. Critical aspects of modelling

The development of suitable in-silico computations has been aimed to provide alternative bioequivalence pathways for predictability of *in-vivo* functioning in clinical set up based on *in-vitro* profiling of CIDPs. These are aimed at assessment and mitigation of the chances of failure in clinical setup. Importantly, modelling can be used to improve the understanding of the product while building in *in-vitro-in-vivo* relationship during product development [51]. Such models may help in creation of virtual bioequivalence and optimization of dosing regimens allowing the possible establishment of bio-waivers while extrapolating the results across populations and reducing study times. Although, existing literature indicate towards the presence of correlation between the drug profiles of *in-vitro* dissolution along with *in-vivo* pharmacokinetics, nature of the relationship has not been mapped into predictive models. The development of such comprehensive models having high predictability of *in-vivo* drug release based on dissolution has been complicated by the presence of array of various physicochemical, biopharmaceutical and biological factors [52]. Since, the approved CIDPs have presented various compositional differences, the development of an appropriate discriminatory method would require the incorporation of appropriate factors which may affect the *in-vivo* product performance. Similar to model development for other dosage forms, the modelling of the CIDPs would involve a step wise identification of discriminatory and biorelevant *in-vitro* parameters. Important parameters which may impact the *in-vitro* dissolution of CIDPs include particle size and its distribution, morphology, surface area, surface potential, membrane properties among others. Building a model incorporating these factors affecting the performance of the formulation would further require appropriate tailoring to meet the requirements of each CIDPs [53]. After incorporation of the parameters, parameter sensitivity analysis (PSA) needs to be tested for the optimization of levels of selected parameters. The PSA would lead to the development of design space which may facilitate the quality-based development of the products. However, a proper understanding of the importance of each of the *in-vitro* parameters need to be developed to assess the potential challenges associated with them.

1.3.1. Particle size and its distribution (PSD)

Incorporation of the particle diameter as an important component of the PBPK modelling may help in improving the effective IVIVC predictions of the formulations. The hydrodynamic diameter and its distribution present an important parameter to be considered as particle size affects the pharmacokinetic profiles, bio-distribution, drug release and clearance of various particulate carriers. The size of these nanosized and micron sized formulations have been determined using photon correlation spectroscopy (PCS). The development of the generic equivalents to the innovator nanosized CIDPs would require attainment of the population bioequivalence (PBE) as detailed by the product specific guidance. The similarity index of PSD profiles (F_2 values close to 90) may ensure that the area under the curves (AUC) between two formulations in comparative BE studies are equivalent [54]. The polydispersity of the particles would present an integral parameter in the model development. In case of monodispersed formulation, D_{50}/ *Z*-

average and SPAN/ polydispersity index (PDI) have been considered as primary bioequivalence parameters while D_{10} and D_{90} have been considered as secondary determinants of formulations like Abraxane™, Doxil™, Onyvide™, Vyxeos™ among others [55]. However, the determination of homogeneity in particle distribution, need to be ascertained quantitatively using orthogonal techniques like nanoparticle tracking analysis (NTA), field flow fractionation (FFF), Tunable Resistive Pulse Sensing (TRPS) for individual particle size and asymmetrical flow field-flow fractionation (AF4) for formulations such as Ambisome™ [56]. Variability in population equivalence of size and polydispersity index may present differences in *in-vivo* pharmacokinetic parameters. This variation may be assessed from the variation in the *in-vitro* dissolution profiles and detection of such changes may help in the reduction of difference in the efficacy of the generic formulation. Formulations presenting heterogenous particle distribution present further complications in establishing the similarity of pharmacokinetics, population bioequivalence and *in-vivo* drug release. PBE of such multimodal distributions may be assessed using simulated probability metrics such as Euclidean distance, Kolmogorov-Smirnov distance, and earth mover's distance (EMD) [57]. The particle size of depot forming micron sized CIDPs (eg. Exparel™, Lupron depot™) intended for extended-release profiles presents further complications [58,59]. The morphology of Exparel™ has honeycomb lipidic structures with the release of the drug, Bupivacaine being a function of internal particle size and overall particle size [58]. Drug release profiles from certain matrix and core-shell microspheres have been governed by particle size of the formulation and the polymeric composite structures presenting controlled release. Additionally, the drug release profiles from depots has been influenced by propensity and degree of agglomeration at the site of administration which would be affected by the input particle size in suspension. Importantly, development of IVIVC models built using biorelevant metrics of particle size with appropriate validation may improve the predictability of outcomes of BE studies. Modelling of the drug release profiles have been evaluated for aripiprazole and medroxyprogesterone CPRFs using PBPK modelling [54,60]. Thus, particle size plays crucial role in PBPK modelling and development of effective IVIVC for predictions of the formulations [61].

1.3.2. Surface charge

The electric potential at the surface (Zeta potential) of the formulations has presented an important parameter in the biological fate of CIDPs [24]. While, the safety profile and the tissue distribution of the CIDPs are often determined by the surface potential, many of the nanoparticulate formulations are surface regulated to reach the intended site of action [62]. The surface engineered nanocarriers Vyxeos™, has presented preferential active bone marrow uptake in malignant myeloblasts while having limited distribution in the other tissues [31,63]. Additionally, the difference in surface potential of the paclitaxel formulations (Abraxane™ and Taxol™) have been shown to present potential therapeutic effect in reduction of the stem cell generation during treatment of triple negative breast cancer [64]. The surface potential of formulations have often been affected by their qualitative and quantitative composition. The presence of pegylation, phosphatidylglycerol, charged polymers, cationic lipids among others has an impact on both systemic circulation time and interactions with the target tissue [65]. Pegylation of the nanocarriers have shown to prevent opsonization, increase the plasma circulation time and increase the potential of accumulation at the physiological extremities [66]. The nature and the extent of the surface charge has been reported to influence the loading and efficacy for singular or co-delivery approaches of gene delivery of siRNA and mRNA [67,68]. Various reports have suggested that reduction of the zeta potential to neutral surface potential has led to physiological aggregation of the nanocarriers [69]. Traditionally, colloidal dispersions having charge between 0 ± 30 mV have been considered to be unstable and require stabilization of the formulation using freeze-drying techniques [70]. However, nanoliposomal formulations like Doxorubicin hydrochloride (Doxil™) having surface potential of -12 ± 2 mV has presented stability in the suspension form [55]. Incorporation of surface charge into PBPK modelling may allow more accurate predictions of *in-vivo* performances of the CIDPs [71].

1.3.3. Morphology and membrane properties

The morphology of the CIDPs have played a key role affecting release profiles. While liposomal doxorubicin (Doxil™) has been reported to have extended-release profile owing to formation of the doxorubicin sulphate nanocrystals and surface pegylation, liposomal bupivacaine (Exparel™) has extended release due to its micron sized honeycomb structure and presence of tricaprylin [13,58]. Further, the presence of an additional bilayer in Vyxeos™ due to lipid migration at the time of cytarabine loading has presented with simultaneous release of the drug with daunorubicin in 5:1 M ratio [72]. Additionally, the presence of components like membrane/ matrix forming lipids, polymers, surfactants *etc.* in the CIDPs have influenced the *in-vitro* release. The assessment of the membrane properties like lipids phase transition temperature (Tm) and enthalpy (ΔH) present important parameters indicative of the membrane uniformity and rigidity [23]. The microcalorimetric evaluation of these properties provides suitable insights into the regulation of the drug release mediated through the membrane properties and may be helpful in development of generic to clinically used formulations [55,73]. For example, the presence and population of asymmetrical tubular structures in generic (Lambin™) and innovator formulations of liposomal Amphotericin B (Ambisome™) have shown to affect the safety, efficacy, toxicity and bioequivalence of the product [74–76]. Thus, incorporation of quantitative parameters associated with morphology and membrane properties while building the PBPK models may improve the predictability of the IVIVC and aid in the development of generic CIDPs [61].

1.3.4. In-vitro drug release

The development of appropriate discriminatory *in-vitro* dissolution testing methods for CIDPs have presented considerable challenges [77]. Importantly, the development of such methods for comparative evaluation of the drug products are dependent on the hydrophilicity of the drug and the nature of the formulation [55,58,78]. While the USFDA has detailed out the simulative conditions for the *in-vitro* release profiles of some CIDPs (eg. Doxil™, Exparel™ among others), the development of the appropriate drug release profiles has been kept as onus for the sponsor companies [79,80]. Several methods have been employed for the real time evaluation of drug release from the formulations including dialysis and reverse dialysis [81]. Essentially, the separation of the released drug from the CIDPs has been crucial to development of such methods [82]. The separation of the free drug using centrifugation technique has been associated with potential for drug leakage owing to increased shear force and has resulted in irregular/unsuitable drug release profiles [83,84]. Solid phase extraction (SPE) and combination of molecular weight cut off filters with centrifugation techniques allows for faster separation and quantification of the drug entrapped in the CIDPs. Such approaches have been useful in cases of simulation of the release profiles of lipophilic drugs [85,86]. Importantly, the development of the *in-vitro* dissolution profiling has been a stepwise procedure which has been influenced by a number of factors. The first step in the development of an *in-vitro* release test for CIDPs would be to choose a suitable release medium based on the physicochemical properties of the drug, suitable hydrodynamics and an adequate dialysis membrane with an appropriate molecular weight cut-off (MWCO) [87]. The second step would be the assessment of the *in-vitro* hydrodynamics which may be presented by rotational flow provided by magnetic stirrer or continuous flow provided by the USP type II or type IV apparatus flow through cell apparatus [88,89]. Further, as a third step, the accelerated dissolution conditions need to be developed to evaluate the possibility of batch-to-batch differences of the drug products alogn with establishment of the correlation with the *in-vivo* performance especially in case of the

extended-release products. Additionally, as a guide for further correlation of *in-vitro* release testing for CIDPs, pharmacokinetic (PK) models has been used to estimate the *in-vivo* release profiles. Such profiling can be modelled to obtain release constants for use in the PBPK modelling of CIDPs. *In situ* forming implants (ISFIs) have shown degradation profiles *via* bulk erosion and have been primarily formulated with many biodegradable polymers which are crystalline or semicrystalline in nature, such as polylactide (PLA), poly(lactide-*co*-glycolide) (PLGA), or polycaprolactone (PCL) [90]. The rate at which drug may be released from such polymeric matrices have been determined by polymeric properties like degree of crystallinity, average molecular mass, molecular structure, and degradation constants [91]. Traditionally, drug release from these formulations have often been non-linear with initial burst release followed by sustained release often presenting a biphasic or triphasic release [58].

Post the design of the appropriate dissolution technique for the CIDPs, the demonstration of statistical equivalence between the generic version and its innovator product is performed. Although, Euclidean distance transformation, f2 (similarity factor) has been used for equivalence testing, use of such statistical tools lacks control over incidence of type-I errors [92]. Consequently, alternative multivariate statistic, Mahalanobis distance has been used for the quantitative estimation of the dissimilarity between the two dissolution profiles [93]. However, this method also suffers from the bias of approximation of estimation of point distance as well as lack of product independent determination of equivalence [94]. Further, the T2EQ derivative of Mahalanobis distance which has incorporated the margin of internal equivalence, has been used as dissolution dissimilarity statistic while presenting improved estimation of the profiles [92]. The *in-vitro* drug release profiles and statistic have often been used as input formulation parameter in pharmacokinetic or PBPK models for CIDPs as it represents a direct indicator of its *in-vivo* performance [95].

2. Pharmacokinetic analysis and PBPK modelling

2.1. Pharmacokinetic analysis

Thorough analysis of pharmacokinetic data is necessarily required for operational modelling. Pharmacokinetic analysis of data obtained from bioequivalence or clinical studies include noncompartmental analyses (NCA) and compartmental analysis (CA). NCA represent the model independent analysis and have been widely used for the PK modelling as they present simple and faster modes in analysis and are independent of any assumptions [95]. The most unique advantage of NCA has been that the analysis is independent of patient-to-patient variability and from regulatory standpoint, this model has been considered feasible for pharmacokinetic data analysis [96]. NCA determines pharmacokinetic parameters including Vss (volume of distribution), CL (clearance), Cmax (maximal serum concentration), definite integral AUC (AUC), and $t_{1/2}$ (terminal half-life) from the integrated plasma cumulative concentration–time curve obtained during the studies. Such analysis has provided important fundamental data needed to understand fate of drug (*viz.* the rates as well as degree of absorption and elimination), which primarily has necessitated in preclinical and toxicological studies prior to clinical evaluation. Importantly, NCA analyses has been useful in characterising drug's ADME profiles and may be supplemented with further complex models in case of requirement of additional detailed information or lack of predictive PK information of the drug such as variability, characteristics across multiple studies, and dosage adjustments across populations [97].

Compartmental analysis has been useful when determination of therapeutic doses and their intended dosing regimens need to be proposed future clinical studies. In these models, the human system has been represented as finite interconnected, well mixed and kinetically homogeneous pockets arranged in series or parallel to each other. The rate of drug transfer between these compartments and the rate of elimination from these compartments are often assumed to follow first-order kinetics [98]. These models have used empirical physiological approaches and has been more complex as compared to NCA analysis. This type of modelling necessitates understanding of system-specific processes (volume of targeted segment) and ADME properties (permeability, clearance) to define initial values of developmental model. Owing to these, there has been increased chances of potential variability in the predictability of the results due to differences in the assumptions made at the time of analysis [99].

Additionally, the curve fitting of observed pharmacokinetic data has been used in both compartmental and population-based models [100]. Typically, the number of compartments and their proposed parameters (*e.g.*, one- or two-compartment PK models) provide an overall estimate of pharmacokinetics while bearing little resemblance to the species-specific physiological properties. Due to this, detailed efforts need to be made for individualized ADME profiling of therapeutic agents. On the other hand, physiologically based pharmacokinetic modelling (PBPK) have relied on more mechanistic interpretation of the PK analysis results [101]. Consequently, the population based PBPK modelling been developed for co-relating *in-vitro* performance to *in-vivo* relevance.

2.1.1. PBPK modelling

Population-based PK analysis has helped to understand type of response (typical or average) and variability in drug concentrations response in a given population along with the using mathematical Eqs. [102]. Development of such models has helped to address the differences of clearance between male and female subjects or pharmacokinetic differences between fasted *vs* fed conditions [103]. Further, population-based models have explained variability aspects in PK data as well as identified variable parameters that may affect adjustments in therapeutic dose or changes in regimen based on difference in targeted populations, thereby assisting in decision making. These modelling approaches employ concentration-time data accumulated from multiple subjects along with pooled values from multiple studies. The true value of such an approach is analysing and forecasting the results when sufficient data are not available in phase 2 or 3 clinical trials [104]. Various applications of this modelling include exposure response relationship, allometric scaling, clinical trial simulations, IVIVC, and model-based equivalence.

PBPK models have used individual tissues in the body as building blocks or compartments [105]. Typically, the main tissues of body namely kidney, liver, brain, gut, heart, lung, spleen, muscle, and adipose tissues, are included (Fig. 2) [51].

The remaining organs have frequently been unified into a single separate compartment when they are not the target organ while certain cellular structures have been ignored when they present non-significant terms in mass-balance equations. Often, tissues with similar kinetics have been clubbed together to simplify the model (*e.g.*, minimal PBPK model) [107]. An important consideration for designing of PBPK models is that all compartments have been liked through circulatory haematological and lymphatic system connections. Depending on the type of CIDPs, drug clearance has been defined in drug-metabolizing tissue compartments, such as the liver and kidney [51]. Further, each individual tissue unit in the model has been described based on limitations mediated through perfusion or permeability. Perfusion-limited models have operated based on premise that the drug associated with tissue can quickly attain distribution equilibrium with that present in the blood. This approach suggests blood perfusion of active therapeutics to be the rate limiting step for its penetrability into tissue cell membranes. Tissue cell membranes have been considered diffusional barriers to drug in permeability-limited models as tissue cell membranes divide the compartments into intracellular and extracellular space [108]. Further, active surface transporters of therapeutics have been built in these models by including the cellular components associated with bidirectional transporting mechanisms. The model parameters associated with uptake and/or efflux transporters, like affinity and capacity, have been

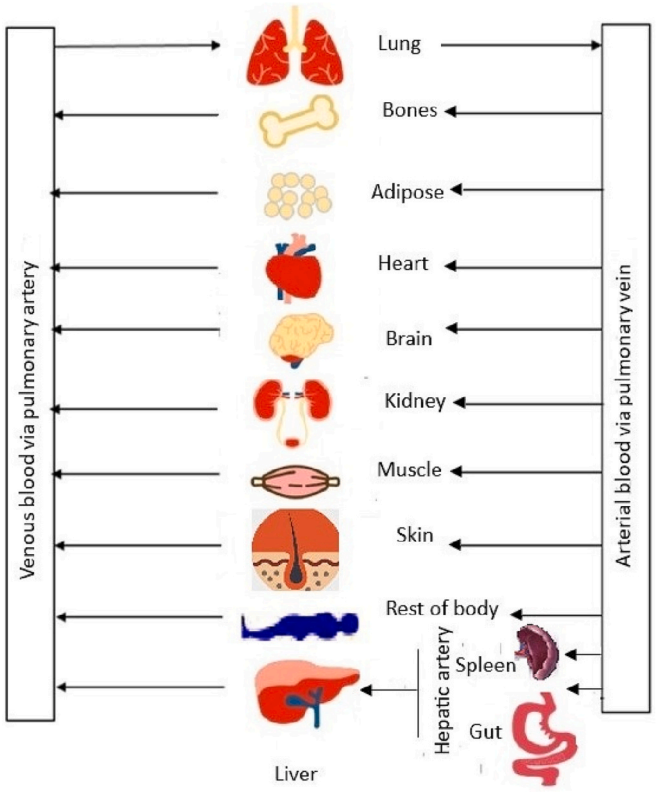

Fig. 2. Flowchart of generic physiologically based pharmacokinetics model (Adapted with permission [106]).

usually derived from experimental cell-based assays and are often adjusted using *in vitro-in vivo* extrapolation (IVIVE) approaches [109].

These models have incorporated drug-specific parameters (clearance and tissue partition coefficient k_p) and biological factors (tissue volume, blood distribution, presence of metabolizing enzymes as well as transporters). These factors together define the fate of the drug post administration and ADME inside the human tissue network. The drug product-specific parameters have often been scaled from a variety of representative *in-vitro* systems. *In-vitro* measurements can be used to scale liver clearance using recombinant enzymes, liver microsomes, or hepatocytes [96]. Based on the individual physicochemical characteristics (lipophilicity, surface charge among others), tissue distribution as well protein binding potential, in-silico determination of important parameters like drug partition coefficients may be done. Use of such extrapolation approaches allows prediction of the plasma and tissue concentration–time profiles without *in-vivo* studies while being helpful in the early-stage screening of drug discovery (Fig. 3) [110]. PBPK modelling can be used to identify sources of PK variability by separating drug-specific parameters from physiological parameters [111]. The mechanistic nature of PBPK models may be used to extrapolate the PKs to different disease states (*e.g.*, liver and kidney dysfunction), special populations (*e.g.*, geriatric/paediatric population, non-pregnant/ pregnant women) and different species [112–117]. Hence, PBPK models have been useful for investigative drug development at all stages from screening of lead candidates to their potential clinical evaluations.

These models have been traditionally implemented as an expression of differential equations outlining the advent of mass balance considering assumptions while simplifying the PKPD of therapeutic agent. Initial parametric values may be obtained from *in-vitro* measurements, relevant data available from published literature in peer-reviewed journals, or statically significant preliminary simulated estimates (Fig. 4). While, physiological parameters may be fixed as predefined values in the model, the therapeutic agent specific parameters can be optimised by fitting the available experimentally derived data into the model. Importantly, the mass transfer assumptions and optimised parameter values must be validated using datasets that were not used for optimization process [109]. Additionally, building PBPK models has often been an incremental ongoing process with the model being

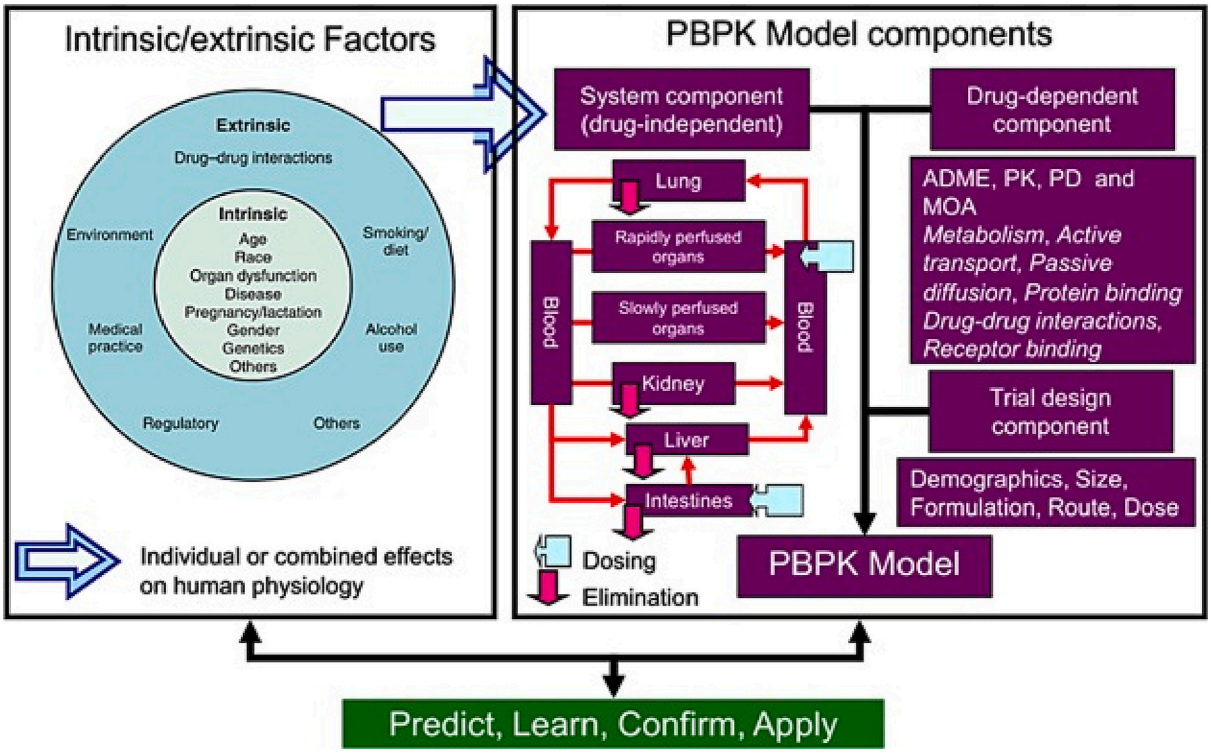

Fig. 3. Assessment of effect of extrinsic and intrinsic factors on pharmacokinetic and pharmacodynamic profiles post administration of therapeutic agent using simulation and modelling pproaches ofd PBPK (Reproduced with permission from [110]).

Fig. 4. Flowchart of implementation of PBPK models.

frequently updated whenever new data becomes available. The validated PBPK model can then be used to predict drug PK and tissue distributions in various scenarios, such as IVIVC development, dosage form design, different dosing regimens, special populations, or cross-species [117]. The development of predictive PBPK models based on combination of available *in-vitro, in-vivo* data along with in-silico tools further needs to be supplemented with localised physiological conditions which the CIDPs may encounter post administration.

2.1.2. Physiological considerations for model building

The modelling approaches necessitate the inclusion of appropriate physiological properties which may impact the efficacy of the formulation post administration of CIDPs. The role of physiological considerations may be explained using the example of intramuscular injection where injection depth serves as an important parameter, influencing region of localization, release and absorption rate for drug. Importantly, muscle tissue has more vascularity as compared to subcutaneous tissue. The administration of shallow injection may lead to localization in subcutaneous fat layer, which may adversely affect absorption and distribution of drug [118]. Further, parameters like product lattice, dissolution rate, histological structures, vascularity at site, phase transfer, partitioning and diffusion to the vascular system have been found to be important in deciding the fate of formulation post intramuscular injection. Generally, the mean absorption times of drugs from aqueous or oily suspensions have been reported to be longer as compared to formulations in form of solutions, which may be attributed to hydrophilicity, differential solubility and presence of alternate polymorphic forms in the suspensions [119]. Further, the release kinetics has an important role in the overall release, absorption and fate of such formulations. While dissolution has been reported to follow majorly zero order, phase transfer and diffusion processes has showed first order release. The presence of mixed order kinetics has often altered the biological dissemination of the agents from the theoretically anticipated routes and subsequently need to be interwoven in PBPK models [12].

Further, the drug release from intramuscular depots has been governed by physiological factors such as the rate of ingress of surrounding tissue fluids into the depot; the dissolution of the drug from the lattice; the diffusion of release drug from the oil to the water phase and subsequently to interstitial fluid; proximity to vascular and lymphatic drainage [29]. Dissolution rate has been an important rate-controlling component in the drug release of the injected suspensions, being governed by the elements of Noyes-Whitney law (surface area, diffusion coefficient, concentration gradient and particle size) [120].

The availability and ingress rate of interstitial fluids into the depot lattice have been influenced by physiological factors. Low degree of vascularisation in the subcutaneous fat layer significantly reduces the release rate of drugs injected into the fat layer [121]. The presence and size of the unstirred tissue layer in response to reduced vascularization affects the dissolution rate. The level of vascularization, presence of biological barriers between the vascular system and drug depot have been found to affect the drug release owing to different kinetics associated with these processes [122]. Injection site reactions and the inherent role of infiltrating macrophages are important parameters that may affect pharmacokinetics of drug administered from intramuscular site [123]. Additionally, other factors that may influence their pharmacokinetics include effective depot volume, volume of muscle tissue, percent unbound drug in muscle compartment, level of lymphatic drainage, immune cell layer thickness, diffusion layer thickness, average surface area in immune cell layer and percent unbound in immune cell layer [124,125]. Consequently, it is important to map and integrate the physiological conditions associated with the injection site as well as diseased tissue to improve the prediction capabilites of PBPK models. While identification of essential contributing factors is important, their assimilation into suitable models necessitates the building in of relevant data bases. Potentially effective model building can be achieved by using such databases [109].

2.2. Building the database and modelling

2.2.1. Compilation of available data

The first step in model construction would be screening and collection of all relevant information such as physicochemical properties of drugs, formulation parameters and biological factors. The physicochemical properties would include molecular structure, intrinsic solubility, dissociation constant, partition coefficient, permeability, particle size, density, solubility at different pH values, blood to plasma partition ratio and percent binding potential with plasma protein. The formulation parameters would include information such as dose, dose volume, dosing frequency, dosage form, dissolution studies in biorelevant media, polymer/lipid degradation rates, viscosity *etc.* The biological factors would include *in-vitro* clearance, enzyme and transporter information responsible for metabolism; specific information of the species or population to be studied and available *in-vivo* data such as time dependent plasma concentration profiles of the agent (for various species, administration routes, dosage forms, or dosing frequencies) and similar profiles of agent in relevant tissues. Importantly, the default physiological parameters should be kept constant and changed only when special cases such as variation in demographic factors needs to be included [61]. Based on experimental data availability and while considering all the factors, one should progress to building the appropriate models.

2.2.2. Building base model

The behaviour of drug distribution post administration may be described by selecting an appropriate distribution model. For a specified compound under consideration, the choice of the distribution model shall remain constant and consisted for describing the distribution pattern irrespective of the change in the animal species or intended administration protocol under consideration. Different distribution

models may be compared, and clearance parameters may be estimated by comparing simulations to *in-vivo* PK measurements after intravenous administration [51]. The clearance parameters should also take into consideration experimental *in-vivo* data while be calculated using regression equations. If multiple elimination pathways are anticipated to exist, mass balance of input and elimination data need to be ascertained. Further, partition coefficients between various components of the body along with the other compound-specific parameters need to be optimised for inclusion to attain the best fit for the existing experimental data [103]. Importantly, the number of parameters which need to be optimised are often small considering the majority of them being addressed or present in the model database itself. The compound-specific parameters in distribution models have been typically kept constant across different species or administration protocols [20]. Further, in case of the selected drug distribution models and parametric adjustments being insufficient to describe the intravenous data, it would be important to include other processes such as active transport or enzymes which may be involved in the distribution process. Additionally, experimental data for new processes (*e.g.*, K_m and K_d, values, abundance of enzyme, binding partner) and that for different doses (demonstrating dose-nonlinearity) must be included for identification of Michaelis-Menten parameters for transporters or clearances [61]. If intravenous data is not available or feasible to study, alternate route solution data (eg. Oral) can be used for model development. After establishment of intravenous/solution model, the model should be extended to study oral administration. At this stage, none of the distribution/metabolism or excretion parameters should be altered and only the parameters which may modify the characteristics of oral absorption (eg. biorelevant solubility, intestinal permeability, enterohepatic cycling, fed study related parameters, formulation related parameters etc) can be modified if required. Once, the appropriate base model is developed, it is important to extend the predictability of it to CIDPs by incorporating various factors associated with the formulations.

2.2.3. PBPK model for CIDPs

After establishing the base model, the model can be extended to long acting CIDPs. Apart from intravenous administration, localised drug release and absorption mechanistic considerations should be included in the PBPK model. Importantly, one should consider the incorporation of dynamics of different administration scenarios like cumulative immediate/staggered/delayed release and diffusion rates (from injection site) post administration. The influence of such components and the need for their inclusion in developed PBPK models have been detailed in subsequent sections [43].

The complexities presented to development of appropriate predictive models for a wide range of CIDPs have been highlighted by polymeric core-shell microspheres. Building a model for these drug delivery has presented challenges due to the unavailability of standardised *in-vitro* dissolution/release experiments, the extended-release time along with variability of *in-vivo* dosing tissue environments among patient populations [126]. *In-vivo* factors that may affect the rate and mechanism of PLGA degradation and the diffusion of released API away from the microparticles include inflammatory tissue response; the presence of enzymes, which may affect polymer degradation; the presence of lipids, which may affect API diffusion; the presence of other endogenous compounds that may affect the pH environment; fluid volume and convection [127].

Further, each CIDP and its target disease presents variable conditions which need to be considered while preparing predictive methods indicating required CQAs. As such there can be no single prototype model which may be applicable to all CIDPs and they need to be customized according to the needs of the formulation [128]. These include not only *in-vitro* dissolution/release experiments, but also mechanistic models for simulating *in-vitro* dissolution experiments and PBPK models for translating *in-vitro* data into *in-vivo* behaviour. One strategy may be to evaluate the effect of formulation parameters on *in-vitro* drug release using mechanistic modelling of dissolution experiments for CIDPs. Following that, a PBPK model may be used to translate the findings from *in-vitro* dissolution modelling to predict the *in-vivo* behaviour of these formulations as well as to evaluate physiological responses and potential of inter-subject variability [129]. The various steps involved in process of development of level A IVIVC have been presented in Fig. 5 [79]. Since, the *in-vitro* dissolution profiles have presented an important parameter in the building of the PBPK model, the details of modelling the same has been described here under.

2.2.4. Modelling of in-vitro drug release profiles

The *in-vitro* drug release profiles have been considered integral and critical to the development of a model for CIDPs. It has been used as a primary tool for monitoring drug product consistency and stability, while providing a simple and reliable predictor of *in-vivo* functioning of drug formulation. Modelling of *in-vitro* drug release data is essential for developing the model as it provides mechanistic insights into release kinetics. The modelling can be done using a variety of programmes, including DDsolver as an add-in tool in Microsoft Excel [130]. Importantly, the best model has been selected based on number of statistical parameters when evaluated for normal distribution test. Parameters such as correlation coefficient (observed/ predicted), coefficient of determination (actual/ adjusted), mean square error, standard deviation of the residuals, sum of squares, weighted sum of squares, akaike information criterion (AIC) and model selection criterion (MSC). Among these predictors, modulated coefficient of determination, AIC and MSC have often been used as suitable discriminatory predictors of the appropriate models. Further, when comparing models having different number of parameters, AIC/MSC should be used instead of the corresponding actual parameter as the they tend to decrease when models have been over-fitted. Similarly, between two models, the one with a lower AIC value may be considered to present better predictability. However, the levels of AIC which may present statistically significant differences between models are difficult to be determined owing to unknown distribution of the AIC values [131]. Importantly, MSC is the normalized modified reciprocal of AIC allowing it to be scale independent better predictor between the available models. The model having largest MSC (values$>$2) has often been considered to present the available model which can be fitted to the available *in-vitro* data. Although, DDsolver can calculate all the aforementioned criteria for assessment of the normal distribution being exhibited by dissolution models data, the selection of mechanistic model should not only be accepted based on goodness of fit but also the model's mechanistic plausibility. Consequently, it is important to establish useful correlations between mechanism-based models and empirical mathematical models [132]. Additionally, choice of the statistical predictors is central to the establishment and predictability of IVIVC models while evaluating the bioequivalence between formulations (Fig. 6) [133].

2.2.5. Deconvolution methods of IVIVC

The establishment of correlation between mechanism-based models and empirical models have been achieved using the deconvolution methods. These methods have been associated with conversion of the plasma concentration into *in-vivo* release profile to build a two-step model of IVIVC. There are several deconvolution methods reported in the literature, including Wagner-nelson (WN), Loo-Riegelman (LR), numerical deconvolution, point area method, and curve fitting method [133]. WN assessment may be applied only to single compartment modelling of IVIVC of drugs and depends on mass balance theory (Table 2). The model does not require intravenous data for calculation of elimination constant (K_{el}) as it assumes equal constants across all routes of administration. But in case of flip-flop kinetics intravenous data is preferred [134]. LR analysis with this method can be applied to therapeutic agents which follow two-compartment PK and has been governed by the mass balance theory (Table 2). The point-area method allows the approximation of the absorbed fractions at extravascular and

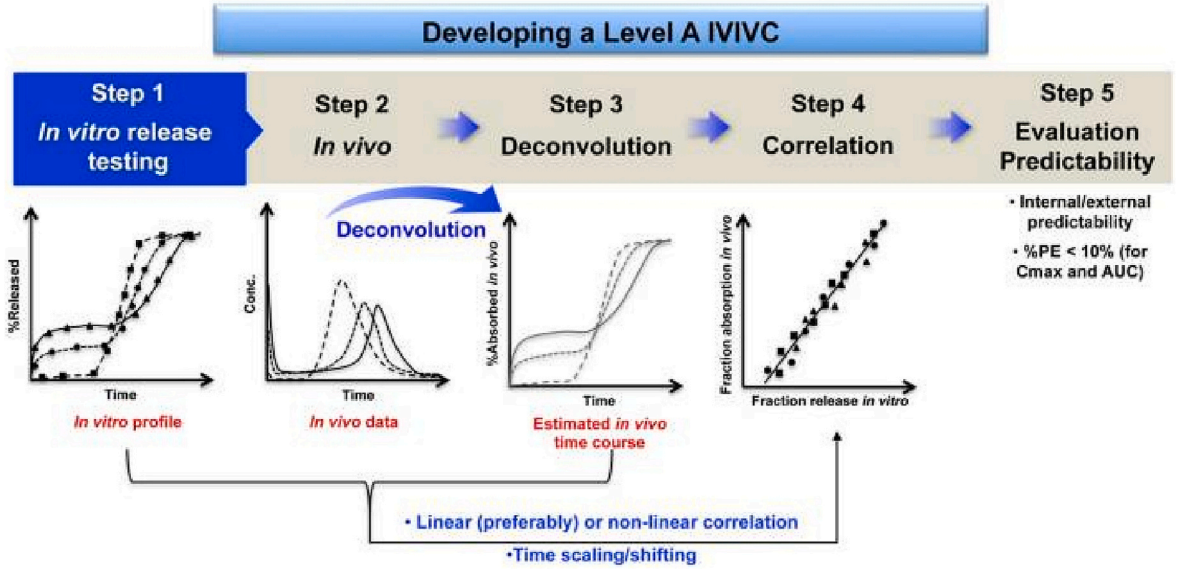

Fig. 5. Stepwise approach for development of IVIVC for CIDPs formulations (Reproduced with permission from [79]).

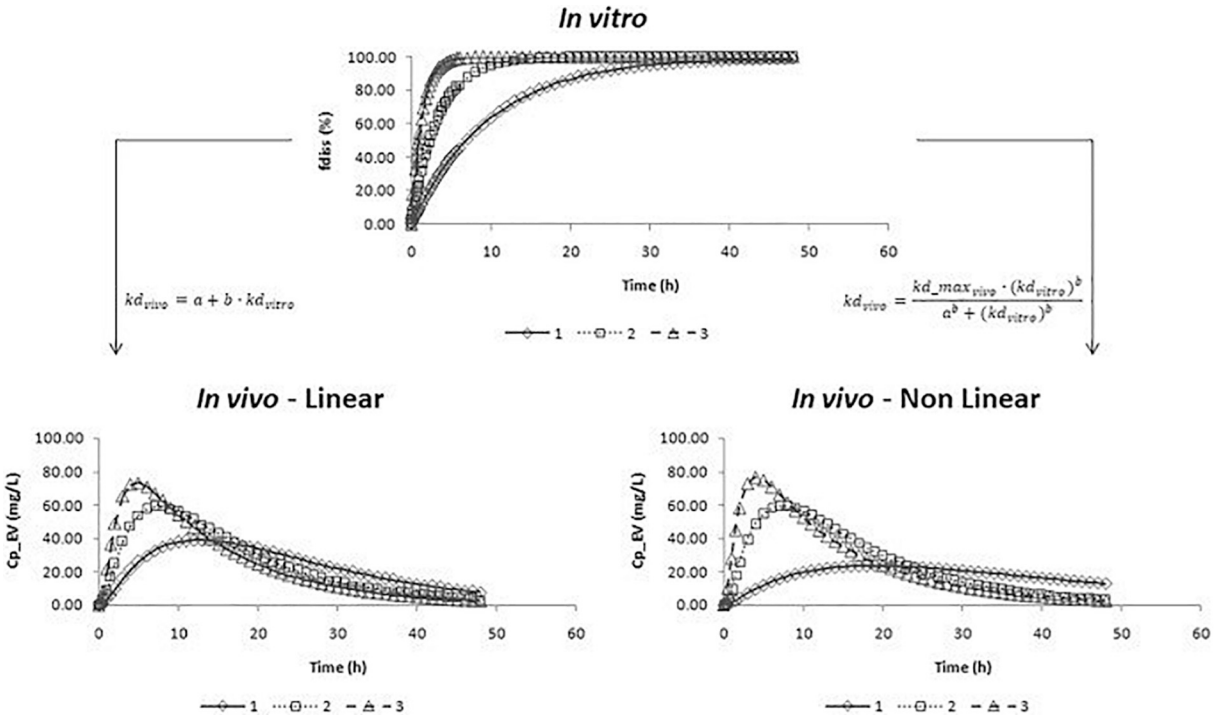

Fig. 6. Simulation for assessment of bioequivalence of three formulations [1–3] using the statistical predictors in IVIVC (Reproduced with permission from [133].

intravascular sites irrespective of the drug behaviour using model independent approaches to build a PK model. This method may be applied when the profiling is done at constant time intervals with anti-transforms being calculated for the transfer function at a particular time point. This predictor gives the bioavailability of the formulation in terms of time-based absorption when zero order and first order kinetics are being followed [135].

Model dependent curve fitting method characterizes PK profiles of the therapeutic agent using simultaneous adaptation of plasma concentration considering the intravenous administration and extravascular dissemination. Post determination of the absorption constant, the sum of squared estimate of errors (SSE) are calculated as predictor of the bioavailability considering one-compartment models [136].

Peripheral compartment concentrations of the drugs as an approximate solution are calculated based on empirical equations, considering small and linear sampling intervals [133]. Traditionally, for deconvolution-based modelling the fate of the drug has not been governed by any pharmacokinetic model and often have been applied to linear systems. In these methods, biological systems have been characterised by an input source (generally considered as site of absorption) and the resultant variable response, occurring due to multiple factors affecting the disposition (impulses). These methods may be used to estimate an input function, for a given set of system response and unit impulse response of the system [19]. Importantly, the unit impulse response must be obtained through the reference administration of the intended CIDPs [137].

Table 2
Various deconvolution methods for development of PBPK models for IVIVC.

Deconvolution method	Equation	Terms	Theory
Wagner-Nelson method	$Fa = \frac{Ab}{Ab\infty} = \frac{C_p + k_{el}.[AUC]_0^t}{k_{el}.[AUC]_0^\infty}$	Ab = Amount of drug absorbed at time t Ab∞ = Amount of drug absorbed at time infinity. Fraction of drug absorbed is fa = Ab/Ab∞ C_p = Plasma drug concentration at time t k_{el} = Elimination rate constant AUC_0^t = Area under the curve from time 0 to time t AUC_0^∞ = Area under the curve from time 0 to time infinity	• Model dependent method • For One compartment • Based on the mass balance theory. • Does not require IV data, Kel calculated from extravascular data • Assumption IVKel = EVkel • Flip-flop kinetics can occur, in that case Ka need to calculated.
Modified Wagner-Nelson method	$A_b(t_n) = \sum_{i=1}^{n=1} * \int_{t_i}^{t_{i+1}} * \left[\frac{V_{max}.C(t)}{C(t)+K_m} + k_{el}.V_1.C(t)\right]dt + V_{ss}.C(t_n)$	A_b (t_n) = Amount of drug absorbed at each time t_n V_1 = Central compartment volume of distribution V_{ss} = Steady-state volume of distribution V_{max} = Maximum elimination rate K_m = Michaelis constant that reflects the capacity of the enzyme system. C(t) = Average serum drug concentration between time points t_i and t_{i+1}	• Model dependent method • Used in Non-linear kinetics • Applied to study subcutaneous absorption of biotechnological drug
Loo-Riegelman Method	$F_a = \frac{Ab}{Ab\infty} = \frac{C_p + \left[\frac{D_t}{V_p}\right] + k_{el}.[AUC]_0^t}{k_{el}.[AUC]_0^\infty}$ $\frac{D_t}{V_p} = \frac{k_{12}.\Delta C_p \Delta t}{2} + \frac{k_{12}}{k_{21}}.(C_p)_{t_{n-1}}(1 - e^{k_{21}\Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21}\Delta t})$	Ab = Amount of drug absorbed at time t Ab∞ = Amount of drug absorbed at time infinity. Fraction of drug absorbed is F_a = Ab/Ab∞ C_p = Plasma drug concentration at time t k_{el} = Elimination rate constant AUC_0^t = Area under the curve from time 0 to time t AUC_0^∞ = Area under the curve from time 0 to infinity $\frac{D_t}{V_p}$ = Apparent tissue concentration t = time of sampling for sample n; t_{n-1} = time of sampling for the sampling point preceding sample n $(C_p)_{tn-1}$ = concentration of drug at central compartment for sample n - 1	• Model dependent method • For two compartment • Based on mass balance theory • Requires IV data to compute Kel and other kinetic constants.
Deconvolution method	Equation	Terms	Theory
Curve fitting method	$IV \rightarrow C_{IV} = \frac{D_{IV}}{V_d}.e^{-k_{el}.t}$ $EV \rightarrow C_{EV} = F.\frac{D_{EV}k_a}{V_d k_a - k_{el}}.(e^{-k_{el}.t} - e^{-k_a.t})$	C_{IV} = Plasma Concentration from intravenous route C_{EV} = Plasma Concentration from extravascular route F = Fraction bioavailable k_a = Absorption rate constant k_{el} = Elimination rate constant V_d = Volume of distribution	• Model dependent method • Cumulative profiling of plasma concentration after dual administration though intravenous and extravascular routes.
Point area method	$G(t_n) = \left[\frac{C_{P_{EV}}(t_n) - \sum_{i=2}^{n} * AUC_{IV}^{t_{i=1}\rightarrow t_i}.G(t_{n-i+1})}{AUC_{IV}^{0\rightarrow 1}}\right]$	$C_{P_{EV}}(t_n)$ = Extravascular plasma concentration at each time t_n $AUC_{IV}^{0\rightarrow 1}$ = Area under curve for intravenous administration for specified period $AUC_{IV}^{t_{i=1}\rightarrow t_i}$ = Area under curve for intravenous administration for ith time $G(t_n)$ = Transfer function	• Model independent method • Combined data from intravenous (IV) profiles and extravascular (EV) profiles. • Time intervals should always be same
Numerical Deconvolution	$C(t) = \int_0^t f(t).C_\delta.(t-\tau).d_\tau$	C_δ = Unit impulse response function C(t) = Drug concentration at time t f = Dissolution rate	• Model independent method • Can be applied to linear systems • IV or immediate release data is required to compute unit impulse response

Although, use of deconvolution methods has been riddled with these limitations, the USFDA has recommended the usage of this aforementioned two-step modelling for IVIVC. The European Medicines Agency (EMA) regulates the deconvolution methods for exploratory usage while requiring the development of appropriate IVIVC methods using one-step convolution approaches [133]. It has been widely assumed that deconvolution methods tend to be linear and do not show invariance with time profiles.

The various models used in deconvolution of IVIVC are mentioned in Table 1. Post selection of the model, the establishment of the bioequivalence of the generic version to the innovator CIDP requires the shape of the *in-vivo* release profiles to be matched [138].

2.2.6. Time scaling of in-vitro in-vivo release profiles

Post the selection of best suited model, appropriate scaling of the model needs to be done for matching the contour of the *in-vivo* release profile and assessment of bioequivalence. Traditionally, the Levy plot has been used for determining time scaling [139]. The Levy plot involves the plotting of times based *in-vitro* and *in-vivo* drug release profiles indicating cumulative percentage of the agent being absorbed and dissolved. For time scale, T_{sc}, a regression term has often been established and used ($t_{invitro} = T_{sc} \bullet t_{invivo}$). The time scaling approach has been often applied for relation of fraction of $drug_{absorbed}$ *vs* fraction of $drug_{dissolved}$ in level A- IVIVC. Importantly, for a discriminative dissolution method, the time scaling of the profiles used should be consistent across all tested formulations used to evaluate for the IVIVC. The resultant relationship shall present a different contour from the traditional linear plots of % $drug_{absorbed}$ *vs* %$drug_{dissolved}$ at given timepoint. Further, IVIVC after time scaling must have a linear 1:1 theoretical relationship (slope equal to one and intercept to 0). The consequent step in model development would be to built-in predictability, correlating the ability of developed dissolution profiles in predicting the traditional *in-vivo* BE predictors (C_{max}, AUC_{0-t}) based on the established IVIVC. However, experimental analysis has shown that such regression relationships have often been non-linear. Additionally, the development of the regression model has often been subjectively driven by assumptions of incorrect hypothesis in order to account for different lag times, change in relationship after a certain percentage, or other challenges related to data characteristics [140]. Further, instead of incorporating regression variables in traditional Levy plot to establish IVIVC, IRF (Inverse Release Function) approach may be adopted for each formulation. The IRF characterizes the various phases of absorption and dissolution, while providing *in-vitro* dissolution rate as a function of fraction of dose (FD%) which is the indicative of the fraction of dose being released from carrier, absorbed at the various sites and entering systemic circulation post *in-vivo* administration. Additionally, it calculates the time at which FD% equals the fraction of the total absorbed drug ($FD\%_{abs}$) [141].

In the case of CIDPs, key challenges in time scaling have been the multi-phasic *in-vivo* release profile and differentiated mechanisms of drug release associated with IV-IV release. This may be addressed by using nonlinear time scaling, while including various phases of drug release using different dissolution models and assigning appropriate weightage for parameters to develop a model indicative of the different phases [142]. Owing to the various limitations associated with the deconvolution method, various regulatory agencies have indicated the development of convolution-based models for IVIVC.

2.2.7. Convolution based IVIVC model

The convolution-based methods are one-stage modelling approaches, which directly establish the relation between the *in-vivo* release and the *in-vitro* release [143]. The advantage associated with these methods against two stage methods has been that the relationship between the *in- vitro* release and plasma concentrations of the drug are set up in one step, allowing the modelling to be focused with its ability to predict the *in-vivo* behaviour [144].

This strategy has been performed for stepwise-linear approximation for release functions presenting nonlinearity to characterize the differentiated PK profiles associated with CIDPs which have presented varied release characteristics. The specific modelling goal was aimed at key questions about the optimal development of CIDPs by simulating the PK time course, resulting from different therapeutic dosing strategies [145]. Convolution-based modelling was implemented in NONMEM for case studies using PK data of CIDPs developed using different technologies like intramuscular injection of matrix microspheres, nanosuspension as well as subcutaneous injection of biodegradable polymer-based core-shell microspheres. Comparative evaluation of performance of the convolution-based modelling and conventional parametric models for theophylline showed that non-parametric input functions presented descriptors of data which were more accurate. The data showed better representation in terms of global measure of goodness of fit (Akaike information criterion and Bayesian information criterion) or in terms of fitted model performance (the percent prediction error on Cmax and $AUC_{(0-t)}$) [43,146]. After the development of the model using deconvolution or convolution method, it is important to evaluate for its effectiveness.

2.2.8. Assessment of model characteristics

Post development of model, its evaluation constitutes a step for integrating the model's completeness. In general, model evaluation should be done by running various scenarios and pushing the developed model to establish the edge of failure. Importantly, the outcome of the evaluation has been determined by the intended CQAs which were established as a part of goal statement for the model development [99]. Often, models have been evaluated by comparing simulated *versus* experimental concentration–time profiles, C_{max}, AUC, along with absolute bioavailability based on percent prediction error or the correlation coefficient. [147,148]. However, due to uncertainties associated with the evaluation, re-evaluation criteria may be used when comparing theoretical model based simulated results with experimental data. It is important to assess the consistency of model prediction using additional data as a part of external validation [149]. Such data may include (not been limited to) parameters in response to different doses, dosage regimens, administration routes, fasting and fed conditions, variability in species, disease conditions and genotypic various populations [150]. As a basic requirement for the consistency of the model for a given drug, all drug-dependent parameters, calculation methods for distribution, and cellular permeability should be similar or having a constant allometric approach across all species [151]. However, while building the model, sufficient care should be taken to incorporate the effect of disease condition on the biological activities associated with the formulation and include the same in the model to increase its sensitivity [152]. Further, if certain parameters need optimisation for the model sensitivity, a plausible physiological explanation, such as species-specific processes, mechanism of drug metabolism should be discussed and incorporated as suitable constants [153]. Additionally, based on the availability of PK data in specific populations, the model may also be evaluated using adjusted physiological parameters incorporating the allometric changes associated with them [154].

Traditionally, sensitivity analysis has been performed to understand the uncertain scenarios that may come across during development and the performance of the model. [155] Sensitivity analysis has often helped in identification of the most sensitive parameters associated with a specified model output (*e.g.*, plasma concentration or PK parameters) [156]. Testing of edge of failure scenarios and establishment of design space further helps to understand the capability of model while improving the chances of mitigation of future uncertainties [117]. The various steps included for development of the representative IVIVC modelling have been presented in Fig. 7.

Since depot forming CIDPs have presented extended IVRT profiles, there have been approaches to assess the similarity between formulations by creating accelerated conditions of drug release for better mechanistic understanding as compared to real time analysis [157].

2.2.9. Real time vs accelerated time testing for IVIVC

The extended duration of controlled drug release from polymeric depots have been attributed to delayed degradation of the matrix and has often complicated the IVRT profiling of the such CIDPs [158]. The real time IVRT profiling of such formulations for identification of prototype may become very time-consuming and may become bottleneck to the development of CIDPs. Consequently, it would be pertinent to

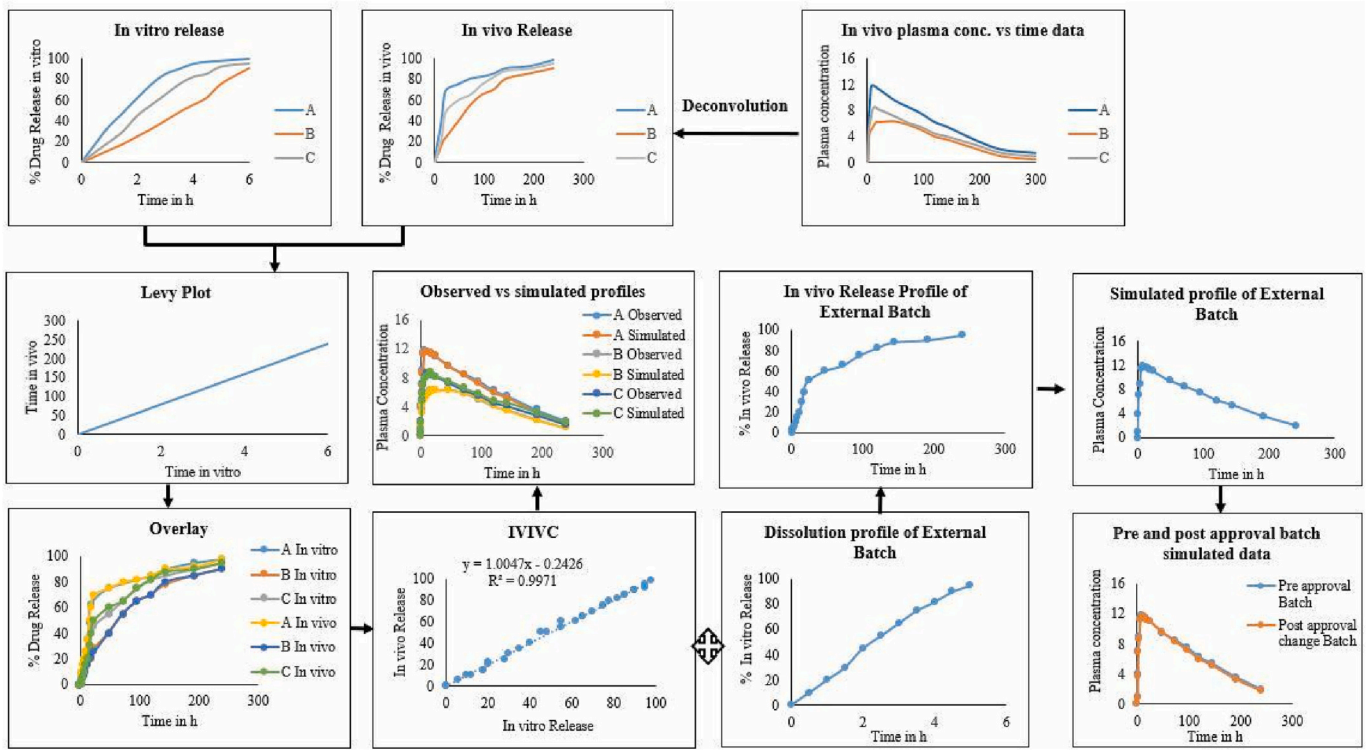

Fig. 7. Flowchart indicating the development of PBPK models for IVIVC of CIDPs. (three formulations A, B and C were taken for representation purpose).

modify the IVRT methods in a way to obtain similar results within reduced timeframe [159]. Various research groups have been involved in building up of improved IVRT profiles of biodegradable depots by varying different parameters of dissolution testing (buffer medium composition, medium temperature, type of apparatus, presence/absence of surfactants or permeation enhancers among others) [160].

Polymer/lipid based CIDPs have often exhibited triphasic drug IVRT profiles consisting of initial burst, intermediate lag and secondary near-complete release ($t_{80\%}$). For efficient predictability and discriminatory behaviour of developed accelerated IVRT, it needs to be correlated with real time profiles considering all the three phases of drug release [161]. Such accelerated dissolution profiling may help in ascertaining the characteristics of the formulation and quality release of the CIDP in a shorter duration provided the mechanism of drug release remains unchanged. This QC tool would invariably reduce the turnaround time from the manufacturing of the drug product to its utilization in the clinics for treatment of various disease conditions [162]. Prior to development of the appropriate IVRT profiles, it is necessary to understand the mechanistic changes which may be encountered by these CIDPs when the subjected to variations in the dissolution parameters. The use of elevated temperatures has been associated with free volume diffusion, variations in the polymeric mobility across the matrix along, accelerated mechanisms of release (erosion/ hydration/diffusion/ degradation) with enhanced rates of drug diffusion (especially when performed at temperatures near their second-order phase transition, T_g) [163]. Generally, such accelerated studies are not designed at temperatures higher than T_g as the product characteristics would be drastically impacted by the plasticization of the polymer matrix leading to altered release [164]. Accelerated release profiling of peptide/protein CIDPs were tested using higher temperatures than the simulative physiological conditions. The accelerated IVRT profiling (done at 55 °C) exhibited good correlation with the real time profile (at 37 °C) with the results being validated by robustness and discriminatory power of the test. [157].

Similar studies by Zolnik et al., showed morphological alterations for formulation having prepared using different molecular weights of PLGA (5,25,28,70 kDa) in USP flowthrough cell apparatus at different temperatures (45/53/60/70 °C). The IVRT results showed that predictability of the mechanism of drug release (erosion/diffusion) and real time release correlation was better for lower molecular weight PLGA than that of higher ones. Additionally, the effect of variation in pH is important for the appropriateness of the accelerated IVRT profile as medium pH drastically alters the kinetics of polymer hydrolysis. While bulk erosion of polymeric construct has been observed for the pH values till 7.4, surface erosion has been predominant at pH values>7.4. The presence of bulk erosion facilitates the drug release from the CIDPs as the degradation products present an acidic microenvironment and facilitates the transport by forming pore channels [165]. Incorporation of surfactants or organic solvents have often accelerated IVRT profiling for depot formulations [166,167].

Although such testing has been majorly developed with the polymer-based depot systems, a recent study has suggested mechanical stress induced on the accelerated IVRT as alternative to real time IVRT profiling for Bupivacaine liposome Injectable suspension (Exparel®) [58,168]. The various tested parameters for accelerated IVRT profiling of CIDPs have been summarised in Table 3.

3. Case studies of *in silico* modelling of CIDPs

While the development of appropriate PBPK models have shown enumerable challenges, requiring the optimization considering various aspects of formulations and disease, these approaches have presented enumerable opportunities for generic drug formulation developers. Having an imperative understanding of the case studies of various types of CIDPs is important to evaluate the advantages offered by the already developed PBPK models for such formulations and identifying their potential role in formulation development. Hence, the following sections describe the examples of reported PBPK modelling of CIDPs. [137,175].

Table 3
Summary of various tested parameters for accelerated IVRT profiling of CIDPs (Adopted from open source review [80]).

Factor	Condition (°C)	IVRT method	Drug	References
Temperature	45	Continuous flow	Risperidone	[169]
	45,53,60,70		Dexamethasone	[165]
	40, 50, 55, 60	Sample and separate	Leuprolide	[170]
	40, 45,50,55		Thymopentin	[171]
	45,50,55		Risperidone	[172]
	50, 55,60	Dialysis membrane	Leuprolide	[173]
	45,53,60,65		5-fluorouracil	[174]
pH	2.4	Continuous flow	Dexamethasone	[165]
	1.3, 7.4, 10.8	Dialysis membrane	5-fluorouracil	[174]
	4.7, 7.0	Sample and separate	Thymopentin	[171]
	5.0,7.0,9.0		Risperidone	[172]
Organic solvent	Acetonitrile, ethanol, acetone 10% (*v*/v)	Sample and separate	Thymopentin	[171]
	Ethanol 10, 20, 30% (v/v)		Risperidone	[172]
Osmolarity	280, 370, 560, 700, 840 mOsm/L	Dialysis membrane	5-fluorouracil	[174]
	300, 500, 700 mOsm/L	Sample and separate	Risperidone	[172]
Mechanical Stress	Rotational speed	Sample and separate	Bupivacaine	[168]

3.1. PBPK model of liposomal amphotericin B

A PBPK modelling framework was evaluated for investigating the animal biodistribution of amphotericin B post administration AmBisome™ and correlating the same with human pharmacokinetics. Concentration profiles of Amphotericin B in plasma as well as tissues post drug delivery after single/ multiple doses of non-liposomal and liposomal formulation in animals were mined from literature in public domain. Human PBPK model was built considering potential individual organs of biodistribution while including allometric parameters considering the body weight of species. The saturation kinetics of the uptake of nanoliposomes in organs of reticuloendothelial system was assessed using non-Michaelis-Menten mechanisms. The developed dual PBPK model exhibited demonstrated good predictability for simulation of drug exposure in human tissues. The modelling framework presented suitable opportunities for IVIVC comparative evaluation of generics against AmBisome™ therapy while presenting pathophysiological parameters affecting PKPD of the formulation [176]. As a part of compartmental framework, similar PBPK approach was utilized based on ADME profiles of Ambisome™ clinical trial data. The circulation half of carrier free and carrier associated drug was calculated from the total amphotericin concentration-time profile and correlated with accumulation potential of nanocarrier post infusion. Results indicated that the drug was majorly released in the plasma while not being available for targeted delivery (absolute average fold error < 2) and presenting suitable strategies for establishment of generic bioequivalence using partial AUC as a predictor [71].

The role of the presence of albumin during drug release of Ambisome™ was probed by Fotaki et.al using the PBPK model based on plasma PK data from healthy volunteers. The model exhibited comparative IVIVC profiles while presenting good predicted correlation in hypo-albuminaemic patients having fungal infection. Further, the model was able to predict the release pattern of the hydrophobic drug from the liposomes along with albumin uptake of the drug and its potential activity in fungal infected patients (Fig. 8) [177].

3.2. PKPD modelling of liposomal doxorubicin

A hybrid model was developed by Harashima et.al to correlate the systemic disposition of liposomes with the targeted exposure of the free API. Compartmental modelling was used to describe the systemic pharmacokinetic parameters for doxorubicin released and that remaining encapsulated in the liposomal carrier. The target tissue tumor was listed as an individual compartment to describe the disposition of encapsulated and released doxorubicin in tumors. The tumor compartment contained capillary, interstitial, and tumor cell sub-compartments and linked to the systemic compartment by blood flow to the tumor *via* the capillary sub-compartments [178]. The plasma release profiles of the liposomes were evaluated using this hybrid model as an attempt at predicting the accumulation potential of released doxorubicin in tumors

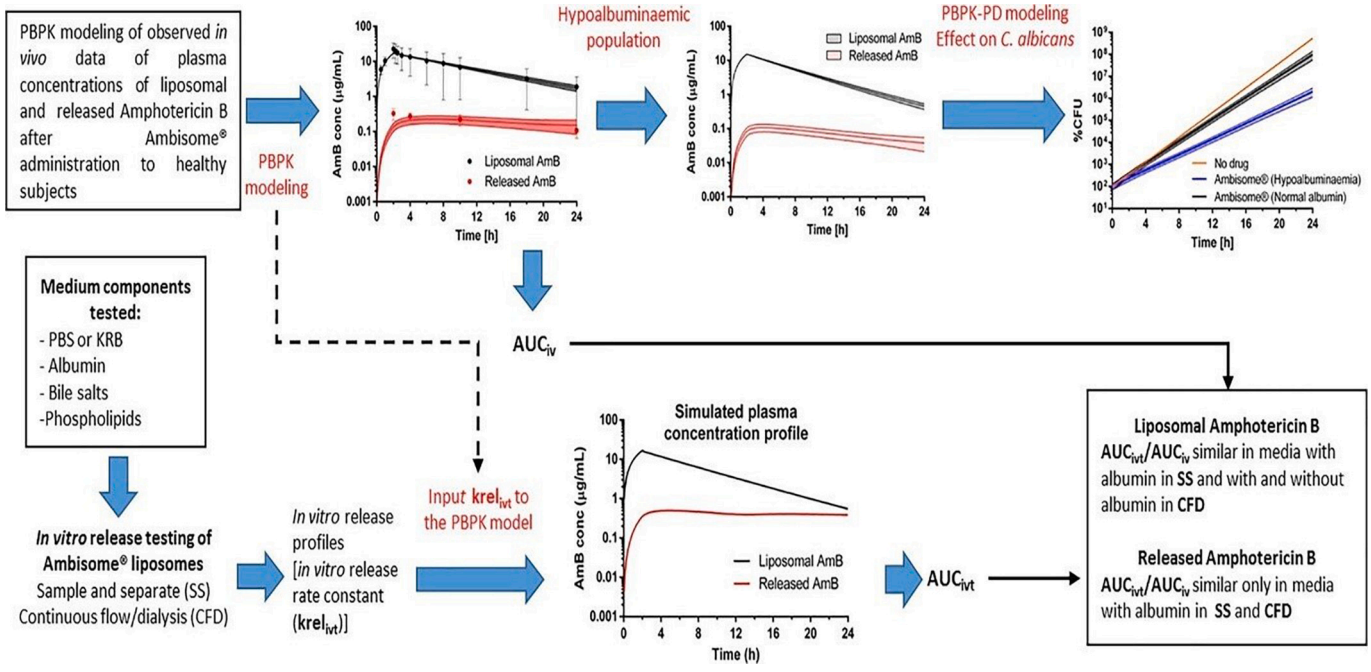

Fig. 8. Development of PBPK model for Liposomal Amphotericin B (Figure reproduced with permission from [177]).

in order to demonstrate the presence/absence of PK–PD relationship. The developed PK–PD framework was then used to assess the influence of the physicochemical and physiological properties of the liposomes on the exposure of the tumor to free doxorubicin and the anti-tumor effect [71].

This modelling approach has been further tested for the estimation of the antitumor efficacy of liposomal doxorubicin by Harashima et al. A partial- PBPK model was developed aimed at the pharmacokinetic parameters along with plasma distribution of free as well as liposomal doxorubicin post administration. The model was assimilated considering blood, tumor, organs of MPS, with other tissues been clubbed together as compartments. The carcinoma compartment was classified further into vasculature, interstitium and cellular sub-components. Presence of different mechanisms of drug translocation and model parametric components have been separately used for describing the mass balance between the encapsulated as well as free forms of the agent in blood. The accumulated free drug in tumor interstitium along with that of cellular space were based on pharmacodynamic model for improving the predictability of anticancer effect. Parametric sensitivity testing for efficacy on model simulation was found to be dependent on drug release constant along with clearance rate of MPS components. The simulation results concluded that a formulation with a doxorubicin release rate constant of 0.06 h^{-1} would achieve maximum efficacy [179].

The IVIVC profiling of clinically used liposomal doxorubicin was revisited using the human clinical data by Modh et.al for the use of the liposomal doxorubicin injection using Stella®Architect (version 1.9.2, Lebanon, USA) (Fig. 9). The physico-chemical characteristics of hydrodynamic diameter distribution, surface potential and dissolution rates were taken as key determinants for correlating with predicted *in-vivo* profiles. The *in-vitro* behaviour of the drug using modified dissolution apparatus (dispersion releaser) under the biorelevant conditions was evaluated. The released drug concentration and that associated with the nanocarrier were calculated based on the V_d (nanocarrier and carrier free drug) using the 3RPT (parametric-reciprocal powered time). The calculations were based on classical two compartmental modelling (systemic and peripheral), with IVIVC presenting a good correlation coefficient (0.94107 for formulation) [180].

An attempt was made by Montanha et.al at integrating the *in-vitro* experimental data into computational methods for simulation of ADME (absorption, distribution, metabolism and elimination) properties of the injected nanoliposomes. The authors developed a mechanistic approach based PBPK model (m-PBPK) for prediction the biodistribution of Doxil™ in animals and humans. The biophysical considerations of in-transit stability in biofluids, passive uptake by cells and macrophages were built in the model using Simbiology v. 9.6.0 (MATLAB R2019a). The AAFE values were found within 2 folds for all the PK parameters, representing similarity between the simulated and observed results. Both the models showed increased accumulation of nano-liposomes in organs of reticuloendothelial system [181].

3.3. PBPK of depot formulations

The IVIVC modelling approaches have been tested by Rajoli et.al to establish the therapeutic dosing regimens strategies for controlled release injectable polymeric depots of antiretroviral cabotegravir as well as rilpivirine in adolescent population (3–18 years). Human PBPK models were established to represent the pathophysiology, molecular and cellular processes as well as age-related differences in tested population using allometric equations. The tested models were validated for controlled release delivery of these two drugs post intramuscular injections in adults. Further, depending on the observed physiological characteristics of the targeted population, the model was modulated and validated based on similar investigated literature. Based on the model, the optimised monthly dose of the drug combination was identified for administration to achieve intended maintenance content post the achievement of maximal therapeutic concentrations (determined during efficacy studies of formulations). Interestingly, the pharmacokinetic parameters generated through simulations from the model were found to be similar to observed clinical values in adults. Additionally, the simulated prediction of the optimal therapeutic concentrations of the two drugs were obtained based on the PK data from weight dependent

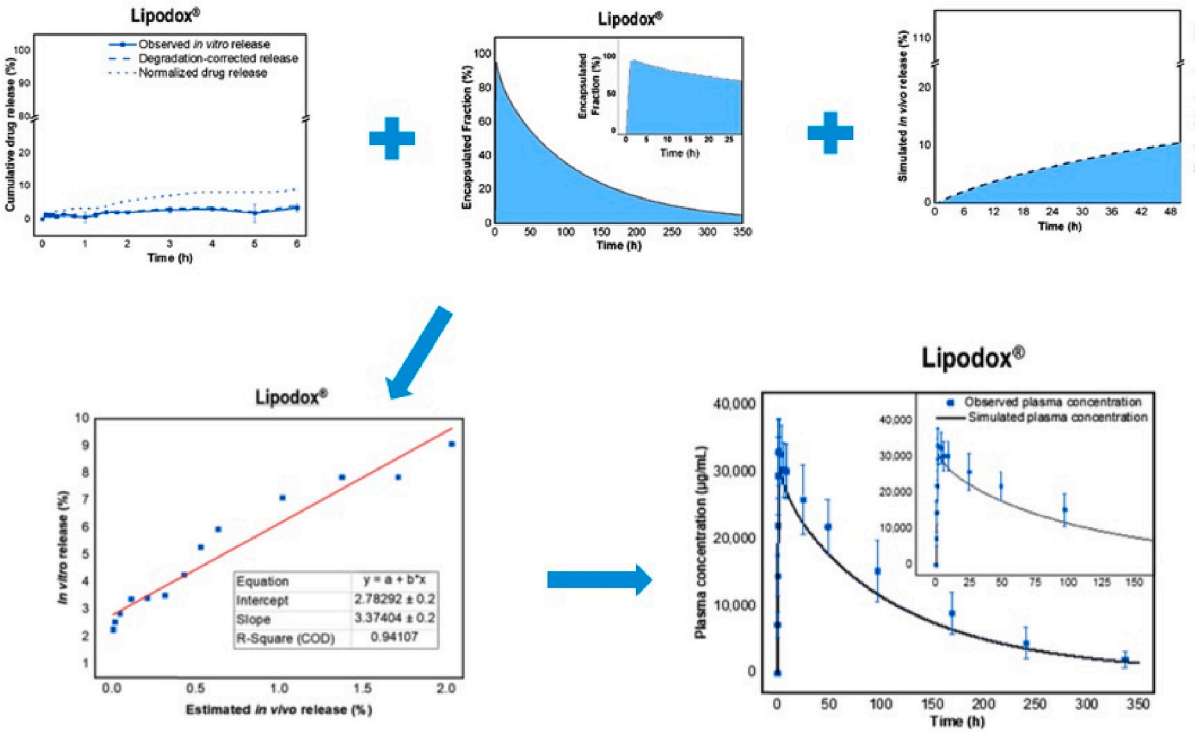

Fig. 9. Application of IVIVC to the human clinical data for generic liposomal doxorubicin injection (Figure reproduced with permission from [180]).

clinical dose of various age groups of targeted population. The intramuscular loading concentrations were found to be ranging from 200 to 600 mg (cabotegravir) and 250–550 mg (rilpivirine) depending on the weight of the patient (15 to 70 kg). The corresponding maintenance dose were found to be 100–250 mg (cabotegravir) as well as 150–500 mg (rilpivirine) over the same range. The reported findings represent a rational platform for the identification of suitable dosing strategies and laid the foundation for prospective clinical investigation of LAI formulations in children and adolescents [182].

3.4. PBPK model of microparticles and microspheres

The IVIVC modelling was used by Gao et.al for estimation of PK parameters along with the mechanistic overview of release from CIDP prodrug microparticles loaded with medroxyprogesterone acetate (depo-subQ provera 104™). The depot presented a Sauter diameter measurement of 5.08 ± 1.63 μm and the dissolution of the drug from depot matrix was observed to be governed by absorption of the agent and subsequent efficacy of the formulation. The developed model was substantiated with available clinical human PK data from three trials. The effect of variation in patient population, *in-vivo* drug release patterns and change in injection site was evaluated using *in-vitro* release profiling using biorelevant simulative of subcutaneous interstitial medium in novel modified USP type II apparatus (Fig. 10). The model presented good correlation between the *in-vivo* clinical parameters (C_{max}, T_{max} and $AUC_{0\text{-}inf}$) and simulative *in-vitro* release profile in 55% FBS (fetal bovine serum) while showing discriminatory behaviour capable of detection of changes in the formulation characteristics [183].

Similar modelling was attempted by Rawat et.al for the evaluation of IVIVC correlation of risperidone core-shell microspheres (Risperdal Consta™). The accelerated and real time dissolution profiles were established using modified USP type-IV instrument and compared with the deconvoluted PK clinical data. The dissolution data exhibited biphasic release pattern over a month with initial burst release accompanied by slow release attaining the therapeutic plateau. Mechanistically, the release was found to be affected by presence of immune-components, interstitial volume, pH at depot site and polymer phase transition temperature. The accelerated release profiles at high temperatures (50–55 °C) exhibited good correlation with the *in-vivo* data while having similar mechanistic release profiles when tested below glass transition temperature (T_g ~ 48 °C). The developed method presented good IVIVC profile and may be useful for the development of generic formulations [184].

3.5. PBPK modelling of depot nano-formulations

The pharmacokinetics for intramuscular injection of sustained release nano-formulations of antiretroviral drugs was simulated using PBPK modelling by Rajoli et al. The study was initiated based on identified compatibility between the combination of oral anti-retroviral drugs, theoretical therapeutic dose and intended dissolution rate when administered as controlled release formulations aimed at dosing on weekly and monthly basis. A population physiology model was used to create virtual patients with organ weights and cardiac output being allometrically scaled using age, body mass index, and weight as factors. For simulation purpose, Caucasian population of healthy volunteers (mean age- 39 years, range 18–60) were created. A complete human body PBPK model was assimilated based on mathematical descriptors for pathophysiological, molecular and cellular functions which could have altered the PK profiles. Validated equations were used to calculate the V_d (volume of distribution) and functions governing ADME of the drugs during model development. Physicochemical properties, permeability, intrinsic clearance and induction of cellular enzymes were introduced into the model based on the available literature. Simbiology™ (in MATLAB, version 2013b) was used to predict PK of ARVs nano-formulations. The developed PBPK models were validated with the simulated data based on oral clinical PK profile of the therapeutic agent. Validation of such model for rilpivirine (RPV) was done using the PK data of long-acting formulation which had been evaluated earlier. Further, simulations were carried out for different anti-retroviral drugs based on variations in dosing and dissolution rates. Absorption and translocation based compartmental modelling were used for simulated validation of these drugs based on their oral PK profiles. Additionally for nano-depots, two new compartments, one each for depot present in muscular tissue and released drug transitioning from muscle to plasma was introduced. Further, it was assumed that release was governed by dose of drug and followed first order kinetics in order to create simulated data for these formulations from the oral clinical data. Dose and release rate combinations of eight ARVs (tenofovir, dolutegravir, rilpivirine, efavirenz, raltegravir and emtricitabine) were optimised to give predicted median plasma concentrations above the protein binding corrected IC_{95} (PBIC95 Results) or IC_{95} values at 7- or 30-days after administration [185].

3.6. PBPK modelling for long-acting intramuscular implants

Design strategies for development of potential CIDPs implants was simulated for anti-tubercular drugs (bedaquiline, rifapentine, isoniazid, delamanid) in adult patients for latent tuberculosis treatment (LTBI) by

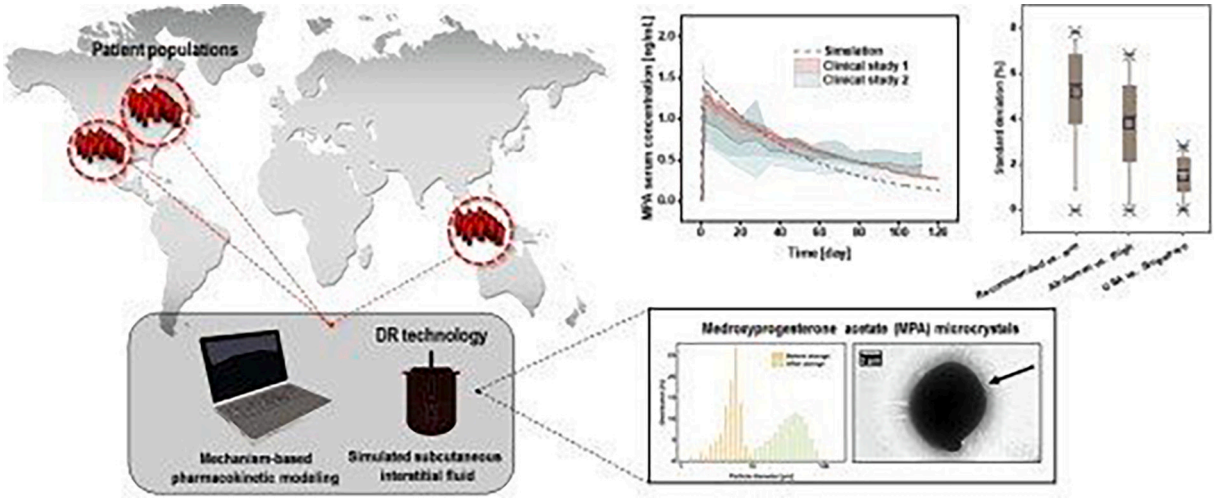

Fig. 10. Application of IVIVC to the human clinical data for medroxyprogesterone acetate microparticles (Figure reproduced with permission from [183]).

Rajoli et al. Long-acting injectable (LAI) formulations or implants were assumed as possible solution to the unmet needs associated with disease treatment. The PBPK models for these drugs were developed, quantified and validated by integrating the composite of existing clinical data, physicochemical properties, the drug distribution mechanism, dissolution and target population-based PK data. For the simulation of the dose ranging and their release for the therapeutic efficacy (IC_{50}), plasma levels were assumed at higher than trough levels based on the dosing intervals for each drug. Consequently, the model determined 1-month intramuscular implants formulations delivering delamanid (1500 mg) and rifapentine (250 mg) while having presenting suitable elimination profiles of 0.001–0.0025 h^{-1} (delamanid) and 0.0015–0.0025 h^{-1} (rifapentine) as ideal therapeutic options. Similarly for the remaining two drugs dosing/week or biweekly *via* intramuscular route was found to be suitable. Such findings helped to identify possible dosing regimen and theoretical release rates when administered with antitubercular implants. The adoption of such strategies may help in easing the problem of sub-optimal adherence while providing suitable drug delivery strategies to mitigate the complexities associated with LTBI treatment [186].

3.7. PBPK modelling for micro needle array patches

Systemic PK profiles of cabotegravir and rilpivirine was simulated using a novel PBPK model post administration post intradermal delivery of micro needle array patches (MAP) by Rajoli et al. Validation of the developed model was ascertained using real time PK data assimilated from controlled release nano-formulations of rilpivirine in rats and in humans post administration through intramuscular and intradermal routes. These model-based simulated data was then designed into MAP nano-formulations intended to keep plasma drug concentrations greater than trough values for the desired therapeutic response. Simulated dosing of cabotegravir MAP indicated that for a particular weight of adult patient (70 Kg), therapeutic efficacy may be achieved using a dosing regimen of q4-weekly (loading- 360 mg; maintenance- 180 mg) having predetermined release rates and 60 cm^2 patch size. Similarly, rilpivirine MAP having similar regimen characteristics have defined release rates, particular dose (loading- 1080 mg; maintenance- 540 mg) was determined. Further, designing of smaller sized patches with capability to deliver the similar doses of drug on weekly basis was explored. Further, use of MAP for reduced duration was considered as a suitable alternative for these drugs than controlled delivery approaches. The dosing regimen having release rate of 7×10^{-3} to 9×10^{-3} h^{-1} for cabotegravir was estimated at 60 mg/week while that for rilpivirine having release of 7×10^{-3} to 9×10^{-3} h^{-1} it was found to be 180–270 mg/week. Such modelling approaches has helped in determining the optimal drug concentrations having desired release rates for both these drugs when delivered using MAP. The approach provided a computational platform to aid in the rationale-based development of intradermal administration strategies to address issues associated with chronic oral ARV administration [187].

3.8. PBPK modelling for subcutaneous implants

The pharmacokinetic profile of subcutaneous implants of Tenofovir Alafenamide (TAF) was predicted using PBPK model by Rajoli et.al to evaluate the minimum required dose to achieve effective therapeutic doses for HIV pre-exposure prophylaxis (PrEP). As pre-requisite, simulated results having values $\leq$ observed mean $\pm$ standard deviation was considered for qualification as well as validation. Historical data was used for generation of simulated results when delivered using implants, while the plasma concentrations of the prodrug as well as nascent drug with varied drug release rates ($n = 500$). The model was further used for the estimation of the simulated intracellular concentrations (peripheral erythrocytes, tissues of cervix and rectum) of tenofovir diphosphate (TFV-DP). The developed model was used for predicting the minimum dose of the prodrug required to attain monthly sustained levels of intracellular levels of active metabolite (48 fmol/10^6 cells). Further, simulations were done for dose ranging studies of the three forms of the drug based on variable release rates (1.0–1.6 mg/day). The PBPK modelling showed attainment of IC_{50} values in PBMCs (peripheral blood mononuclear cells) required a target dose of 1.4 mg/day of released TAF to generate therapeutic levels of TFV-DP. Similarly, the tissue TFV-DP concentrations were predicted to be 1.5–2.0 fmol/10^6 cells (cervix) and 0.9–1.1 fmol/10^6 cells (rectum) when implants had varied release rates (1.3–1.6 mg/day). The resultant simulations presented the required minimum dosing regimen (1.4 mg/day) for TAF subcutaneous implants that may be developed as suitable drug delivery vehicles for affording protection levels against the virus over a prolonged delivery of 0.5–1 years. Consequently, such modelling approaches may help in design of future subcutaneous implants to mitigate adherence issues for effective PrEP applications [188] .

The IVIVC profiling was attempted by Schliecker et.al for Buserelin implants using model dependant and independent methods. Since the drug release was predicted to be mediated through various processes (dissolution, erosion and diffusion), theoretical mixed kinetic models of Higuchi as well as Korsmeyer-Peppas were used for evaluation of the *in-vitro* profiles. The level A and B IVIVC showed sufficient correlation coefficient of 0.986, 0.983 indicating the presence of mixed drug release *in-vivo* kinetic profiles being impacted by diffusion as well as erosion-based mechanisms. The study presented definite IVIVC modelling approach to mitigate the multiphasic drug release profiles affected by multiple mechanistic pathways [189]. The case studies discuss the novel approaches used by scientific community to gain mechanistic understanding of *in vivo* performance of these complex injectable products. These approaches include developing customized PBPK models by addition of differentiated compartments, defining various uptake pathways, extending the models to different populations, design of controlled release formulation strategies, developing biorelevant and bio predictive drug release methods, use of existing data in the domain for development of PBPK models, development of modified drug release testing apparatuses and use of different modelling platforms [190]. The key takeaways from the various PBPK modelling of CIDP has been summarised in Table 4.

3.9. Simulation software for PBPK modelling

The two modelling tools, Simcyp® and GastroPlus®, present specialised modelling within PBPK framework having database of physiological parameters that provide flexibility and capability to support complex models. Modelling and simulation software such as Matlab-Simulink, Berkeley Madonna, and ACSL/acslXtreme have been commonly used for IVIVC modelling [71]. Pery et al., have reported the use of MCSim for PBPK modelling of carbon nanoparticles [191]. These software packages have been used for routine tests like parametric estimation, optimization, linearity, sensitivity, simulation and analysis of the obtained data. Specific PBPK software packages like Berkeley Madonna, acslXtreme, and Matlab-Simulink have been used along with their features of equation databases and visual graphical outputs to improve user-friendliness. For PBPK modelling of small molecules and therapeutic proteins, modelling and simulation tools such as Stella, ADAPT, and SAAM II have been reported [21]. Further, the software MathWorks have added SimBiology, which includes a library of common PK models and allows for customization as well as integration of PBPK models [192]. MCSim has presented open-source software package that includes suites of model generator as well as a simulation engine. The software presented capabilities of performing Monte Carlo simulations and Bayesian analysis of PBPK models through Markov chain of Monte Carlo methods [193].

Table 4
Summary of the key takeaways derived from the various PBPK models for the CIDPs.

Formulation & Route	Modelling approach	Highlights & key learnings	References
Amphotericin B/ Liposomal formulation IV administration	PBPK model for animal to human correlation	Customized PBPK models to predict human pharmacokinetics from animal data	[176]
	PBPK model integrated with biopredictive drug release medias	Development of new biopredictive drug release medias which can be integrated in the PBPK model for better predictability	[177]
	Hybrid compartmental model to correlate the systemic disposition of liposomes with the targeted exposure of the free API	Predicting the accumulation potential of released doxorubicin in tumors in order to demonstrate the presence/absence of PK–PD relationship.	[178]
Doxorubicin/ Liposomal formulation IV administration	Partial PBPK model for the estimation of the antitumor efficacy of liposomal doxorubicin	Separate carcinoma compartment development and used in the model. This approach can further be explored to mimic the *in vivo* conditions.	[179]
	IVIVC using Stella®Architect	New 3RPT (parametric-reciprocal powered time) approach used.	[180]
	m-PBPK model using Simbiology v. 9.6.0 (MATLAB R2019a)	The biophysical considerations of in-transit stability in biofluids, passive uptake by cells and macrophages were built in the model to simulate ADME.	[181]
Cabotegravir and Rilpivirine/ controlled release injectable polymeric depots for intramuscular administration	PBPK model	Served as platform for the identification of suitable dosing strategies and laid the foundation for prospective clinical investigation of LAI formulations in children and adolescents.	[182]
Tenofovir, Dolutegravir, Rilpivirine, Efavirenz, Raltegravir and Emtricitabine	PBPK model using Simbiology (MATLAB R2013b)	Use of available oral PK data, therapeutically derived dose and intended drug release rate were integrated in PBPK model to simulate intramuscular PK after once a week and month administration.	[185]
Bedaquiline, Rifapentine, Isoniazid, Delamanid/IM Implants	PBPK model	Integration of existing clinical data, physicochemical properties, the drug distribution mechanism, dissolution, and target population-based PK data to design strategies for one month IM implant.	[187]
Cabotegravir and Rilpivirine/ Intradermal delivery of micro needle array patches	PBPK model	The approach provided a computational platform to aid in the rationale-based development of intradermal administration strategies to address issues associated with chronic oral ARV administration	[187]
Tenofovir Alafenamide/ subcutaneous implants	PBPK model	Evaluation of minimum required dose to achieve effective therapeutic doses for HIV pre-exposure prophylaxis (PrEP).	[188]
Buserelin implants	IVIVC using model dependent and independent methods	Provided definite IVIVC modelling approach to mitigate the multiphasic drug release profiles affected by multiple mechanistic pathways	[189]

4. Challenges and future opportunities

4.1. Challenges

The complex generic drug product development against the established platform technologies have presented inherent challenges pertaining to the establishment of pharma-equivalence of the generic formulations against that of reference listed product prior to bioequivalence. Such manifestations become important in case of formulations presenting multiphasic drug release. For example, the multivesicular liposomes (MVL) loaded with Bupivacaine (Exparel™) have been characterised to have multiphasic drug release highlighted by initial burst release, lag phase and secondary erosion mediated release over a period of 140 h [194]. However, the development of appropriate IVIVC model of the formulation has been affected by presence of pathophysiological properties at the infiltration site and physicochemical properties of the formulation [195]. This amphipathic drug has been shown to be present in the inner aqueous core as well as the lipid layers in the micron sized honeycomb morphology presented by Exparel™. The formulation has shown mixed release kinetics being affected though mechanisms of dissolution, erosion and internal rearrangement (Fig. 11). Since, the product is administered at the surgical site and release profile of the anaesthetic has been reported to be affected by the pathophysiology of the infiltration site, the internal as well as morphology of the product [12]. However, the development of appropriate IVIVC would require incorporation of the parameters in the model for determination of the discriminatory changes in the aseptically manufactured drug product. The localization of the drug as well as rearrangement of the lipids during solvent stripping step have been reported to be critical to the release profile from the formulation [196]. Factors such as tissue around the infiltration area, vasculature and lymphatic drainage, immunological components and interstitial microenvironment have been found to be affecting the drug release [197]. Subsequently, the absence of appropriate *in-vitro* release methods and simulative animal models has increased the complexity associated with

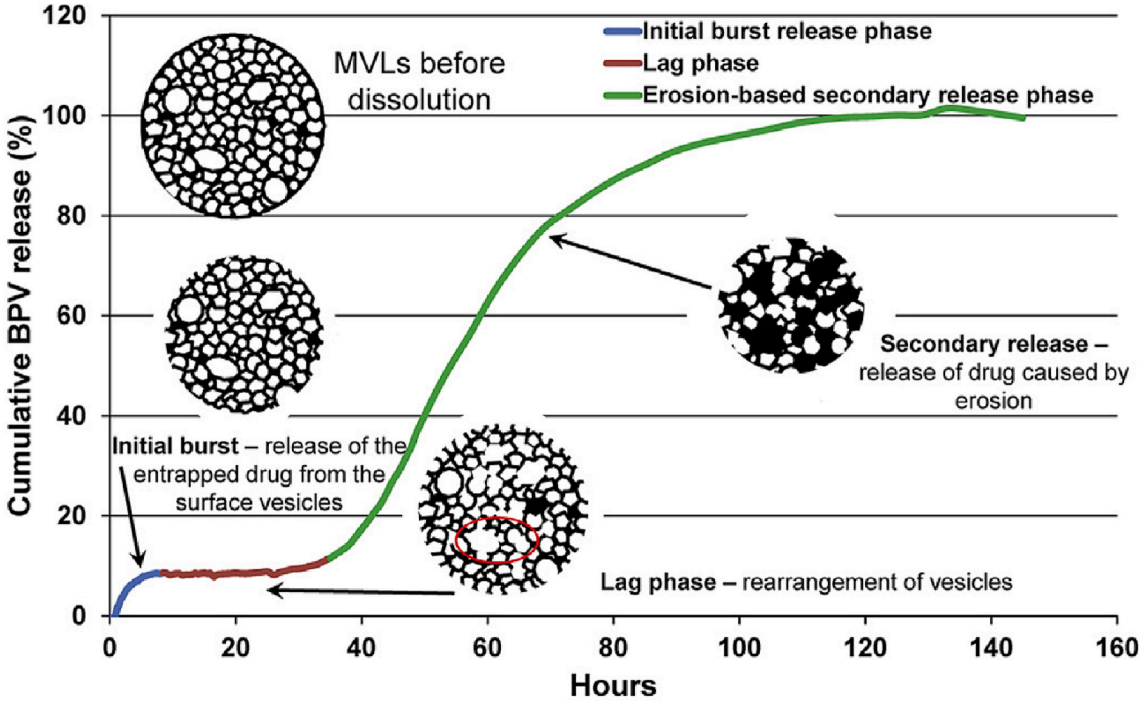

Fig. 11. Scheme indicating mechanism of drug release from Bupivacaine multivesicular liposomes. (Figure reproduced with permission from [58]).

these CIDPs. Manna et al. has presented an innovative reverse osmosis based *in-vitro* release method for the real time determination of drug release using USP type II apparatus [58]. Incorporation of quantitative estimates for aforementioned parameters along with suitable discriminatory *in-vitro* profiles have presented challenges for the development of predictive IVIVC models and to aid the development of generic bioequivalent product [198].

The *in-vivo* release of the drugs are often affected by the nature of the polymeric matrix and interactions associated with them, leading to challenges in development of predictive IVIVC [199]. For example, the release profiles of biodegradable PLGA based octreotide matrix microspheres (Sandostatin LAR™) have been reported to be influence by *co*-polymer molecular mass; molar ratio of lactide to glycolide; branching and end capping types of polymer chain (glucose star or linear); potential interactions between drug and excipients; manufacturing conditions of the matrix microspheres and their physicochemical properties. The dissolution from depot matrix was reported to extend over 56 days under normal physiological conditions with lag phase of approximately 14 days and exponential release beyond this period. Such profiles have been attributed to the strong non-covalent interactions between octreotide and star PLGA copolymer. These structural conformations, bioerosion kinetics along with the degradation profiles of the polymeric matrix require development of appropriate *in-vitro* dissolution profiles to mimic the *in-vivo* conditions of drug release [200]. Similar modified dissolution approaches were tested for the evaluation of the drug release from the subcutaneously administered PLGA core-shell microspheres of risperidone having compositions similar to Risperdal Consta™ [201,202].

Further, the development of IVIVC models for co-presence of multiple drugs in morphologically diverse CIDPs may be challenging. Current chemotherapeutic regimens necessitate the use of multiple drugs for the effective treatment of the targeted disease [31]. The bilamellar and multilamellar nature of the dual drug (daunorubicin and cytarabine) liposome in Vyxeos™ has presented considerable challenges for the effective development of effective IVIVC models [203]. The formulation has been reported reduced systemic distributed along with accumulation in malignant megaloblasts while presenting clinically effective 5:1 synergistic molar ratio during *in-vivo* release [204]. The co-delivery of two drugs, their preferential localization of them within the liposome, number of lamellae reversible uptake of the formulation into the bone marrow, the tumor microenvironment, potential of lymphatic drainage and variable pharmacokinetics has resulted in reduced predictability of IVIVC [63].

Similarly, the pathophysiology of the diseased tissue may affect the predictability of the IVIVC. Onivyde™ has been indicated for the metastatic adrenocarcinoma of pancreas (mPDAC) and has exhibited improved cytotoxicity with reduced systemic side effects of irinotecan [205]. The PK profile has been shown to present first order elimination being described by double compartment model. The disease has shown complex molecular heterogeneity with the tumor microenvironment being characterised by presence of excess fibrotic stroma and extracellular matrix, serving as barrier to chemotherapy [206]. The presence of these structures has resulted in reduced passive uptake of therapeutic agents, increased tumorigenesis, metastasis and presence of drug resistance. Further, the presence of stroma has been associated with increased disease progression associated with ADM (acinar-to-ductal metaplasia) as well increased immunoregulation [207]. Further, the effectiveness of irinotecan formulations has been reported to be dependent on the rate of conversion and intracellular levels of its cytotoxic metabolite SN38 [208]. Consequently, the development of appropriate IVIVC profiles would necessitate the identification of simulative *in-vitro* dissolution techniques, the incorporation of the rate of release of the drug from the complex and carrier, release as well as percolation through the stroma associated with the mPADC and intracellular conversion of drug into active metabolite [209,210].

The predictability of the IVIVC modelling has also been reported to be affected by nature of drug, especially hydrophobic drugs. These drugs have shown altered PK profiles associated with the albumin upon release from the CIDPs. The intrinsic binding potential of drugs with the plasma protein have resulted in differentiated *in-vivo* profiles when compared to *in-vitro* dissolution and necessitate the development of stimulatory release medium as well as responsive models [211]. Amphotericin B complexed with the lipid mediated through covalent linkage with DSPG-Na (1,2-Distearoyl-sn-glycero-3-phospho-rac-(1-glycerol) sodium salt)

in liposomal carrier Ambisome™. After administration of the nanocarrier, the amount of free drug, potential binding with the plasma albumin as well as dissemination of the agent from the nanocarrier to the fungal infected cells have been reported to affect the IVIVC profiles of the CIDP [177]. Similarly, the albumin bound nanoparticulate formulations of paclitaxel and sirolimus have presented drug exchange with carrier albumin and circulating intravascular-extravascular HAS (human serum albumin). Post intravenous infusion, the nanocarrier has been reported to dissociate into discrete complexes which have tendency to bind to glycoprotein 60 (gp60) [212]. These are further associated with transcytosis through scaffolding proteins across the endothelial cell to the tumor interstitium while affecting the role of SPARC (Secreted protein acidic and rich in cysteine) in fibrolasts as well as tumor cells [213]. The development of appropriate IVIVC models would necessitate the inclusion of these physiological components while building simulatory mechanistic parameters which the nanocarrier may be subjected during transit to tumor site for appropriate prediction of real time biological scenarios [214]. Importantly for the drugs having high protein binding capabilities, IVIVC modelling should be biorelevant while having pertinent clinical characteristics for the development of generics to these formulations [215].

Despite presenting various challenges in the development of predictable PBPK models for IVIVC, model based approaches have presented suitable opportunities and have been integral to the development of generic equivalents to the clinically approved CIDPs while being able to predict the *in-vivo* profiles of NDA drug products [216].

4.2. Future opportunities

Imperative to the development of the new drug delivery platform technologies, an important approach would be the integration of the IVIVC parameters for the predictability of the biological activity of the product.

The development of predictable IVIVC for any CIDP involves a multifaceted approach. Initial steps for generation of such models would include developing an understanding of the components of the formulation, the mechanism and important components affecting the drug release, discriminatory factors and the rate limiting components [217]. The complete characterization of the drug product as well as drug substance using orthogonal techniques. The state of the active substance inside the CIDP, the structural composition and architecture need to be well characterised prior to initiation of IVIVC model development. Selection of appropriate biorelevant media which mimics the physiological conditions which the CIDP would encounter in its therapeutic journey forms an important step such IVIVC. Next step would include to understand the reported, published and expected regulatory requirements in this segment such as having *in-vitro* and *in-vivo* evaluation studies of at least three formulations having different release rates. [77]. However, the impact of fabrication of such formulations on the intended quality target product profile (QTPP) of the drug product as well as generation such huge amount of data for CIDPs for any generic industry or academic research laboratories may not be feasible in terms of study duration and the humungous cost associated with it. Consequently, as an alternative approach, the researchers may utilize the existing data included in USFDA innovator summary basis of approval (SBOA) and integrate the same with their product development [71]. Additionally, integration of multiple biological data sources such as imaging of organ localization, efficacy in multiple species, pharmacokinetics, dose tolerability, acute and repeated toxicity profiles may help in improving the predictability of the developed models [218]. Importantly, inclusion of the innovator data requisites establishing Q1Q2Q3 similarity with innovator product and then integrating the *in-vitro* data with the *in -vivo* data from the SBOA or using literature available in the public domain exploring the PBPK/PBBM modelling for the formulation [55]. Additionally, it should be noted that attempts to establishing IVIVC/IVIVR have often been intended to gain mechanistic understanding of the product with aim to reduce the risk of bioequivalence failures and the approach may not suffice the regulatory requirements for obtaining biowaiver (like that observed in oral formulations) [219]. These studies would help to identify right biorelevant *in-vitro* tools for the test product and establish the QTPP. Later the developed PBPK/PBBM model for the test formulation needs be validated with appropriate studies to support the product development and bridging the same with the innovator product [220]. Further, such approaches may be utilized in prediction of multiple dose pharmacokinetics from single dose pharmacokinetic studies, dose escalation studies, establishing PK-PD correlation and justifying the QTPP for such products [221]. It would be pertinent to follow the above-mentioned steps for the as a guidance while including appropriate changes based on the type of the CIDP under consideration during their drug product development programmes [46]. It is important to note that there is no single established model for development of IVIVC for CIDP and choice of inclusion of particular data bases for the development of the IVIVC modelling should be made based upon the formulation, the intended therapeutic window as well as identification of the critical factors [222].

Understanding the behaviour of CIDPs after their administration has not been completely explored. As an alternative to reduce *in-vivo* preclinical studies a section of biopharmaceutical experts has propagated the usage of development of several simulation tools to mimic the *in-vivo* scenarios. Further, they have reported extremely poor correlation between animal models and human outcomes for subcutaneously/intramuscularly administered drugs. The various attempts to develop biorelevant *in-vitro* models for drugs being administered through subcutaneous and intramuscular routes have helped in gaining meaningful insights of *in-vivo* product performance (Table 5).

Further, it is important to understand the various approaches followed by various researchers in establishing the predictability of such formulations.

Shi et al. attempted to build in such an approach for the predictability of the Budenoside nanocrystalline inhalation product. The researchers evaluated the rat lung deposition pattern as well absorption from three formulations (micronized drug, nanocrystal drug and drug loaded hyaluronate microparticles) and correlated the same using GastroPlus™. The in-silico modelling of these formulations highlighted that the pulmonary drug solubility, the particle size and morphology of the formulations as well as permeability through the absorption barriers were the major factors affecting the absorption rate of the formulations [228].

Further, development of biorelevant IVIVC profiles may help in the evaluation and development of drug delivery platforms for potent drugs having unmet clinical needs. The immunosuppressant tacrolimus has been widely used in patients with organ transplants and present suitable candidates for development of CIDPs like microspheres and depot formulations [229]. Gao et al. developed IVIVC models incorporating the pathophysiological and physicochemical conditions associated with tacrolimus dosage. The researchers developed microsphere formulations and tested them using simulative biorelevant medium over the intended drug release period (7 days). The mechanistic model evaluated the effect of dissolution rate, mechanism and extent of degradation, diffusion rate from the intact/ degraded matrix to surrounding tissues as well as plasma and lymphatic drainage on tacrolimus therapeutic efficacy. The results indicated that evaluation of these parameters and their subsequent incorporation in the IVIVC models may help in the effective development of the appropriate drug delivery systems [230].

Additionally, IVIVC modelling may be used for understanding the mechanistic aspects of dissolution as well as quality tool for assessment of variability and discrimination in CIDP formulations. Andhariya et al. explored the variation in input values in manufacturing of PLGA microspheres in compositions like Lupron Depot™. The variation in physicochemical properties based on the changes in input parameters for peptide microspheres resulted in significant differences in the *in-vitro* release while presenting similar release profiles *in-vivo* release in rabbit

Table 5
List of *in-vitro* tools developed for better predictability of the CIDPs administered through subcutaneous and intramuscular routes.

Sr. No.	*In vitro* tool	Description	References
1.	SubCutaneous Injection Site SimulatOR (SCISSOR) from PION	SCISSOR N3 is the first instrument designed to simulate the stress conditions and environmental transitions that a biopharmaceutical, peptide or small molecule drug experiences when injected into a subcutaneous environment. These include chemical stresses - such as buffer composition, pH change and loss of excipients - and physical stresses - such as temperature and pressure changes. With that considered, there are also non-specific interactions with extracellular matrix components and aggregation events to contend with upon injection.	[223,224]
2.	The Rainbow R6 from PION	An *in-situ* fiber optic concentration monitoring system, is a powerful analytical instrument that correctly and accurately measures dissolution in real time. It is utilized for dissolution testing, flux assays, solubility studies and other applications requiring high accuracy and repeatability in concentration measurement. Rainbow R6 is equipped with up to 8 independent fiber optic channels with data acquisition of the UV Spectra (200–720 nm) to provide concentration measurements as fast as every 2 s.	[225,226]
3.	Muscle tissue homogenate-based drug release testing method	The muscle tissue (Porcine) was freeze-dried and subsequently pulverized for better handling and reproducibility. The tested microspheres were then incorporated together with the freeze-dried muscle tissue powder into a small assembly held together by agarose hydrogel, enabling that the microspheres are in direct contact with the muscle tissue, and at the same time, the small size of the assembly allows its placing into aqueous buffered release medium (simulating blood compartment), from which the samples can be conveniently taken and analysed using conventional techniques such as HPLC.	[227]
4.	*In vitro* release artificial matrices	Dialysis system consisting of Float-A-Lyzer$^{@}$ tubes filled with different extracellular matrices such as hyaluronic acid, agarose gel and collagen type I gel.	[223]

model. The *in-vivo* model presented lower burst release than *in-vitro* model owing to variable absorption profiles from the intramuscular injection site. The model exhibited good level A IVIVC for the developed formulations while being predicted of the Lupron Depot™. It also showed sensitivity and predictability of IVIVC of potent peptide depots while being capable of discrimination in response to changes in physicochemical properties of these products [231]. Similarly, the use of the IVIVC modelling was used for the prediction of the pharmacokinetic profile as well as clinically observed biodistribution of Foscan™ (Temoporfin nanocrystals) [232].

The improvements in PK profiles of clinically approved drugs may be facilitated using IVIVC. Electrosprayed microspheres with leuprolide were developed and evaluated for their PK profiles in the rats post subcutaneous administration. The PBPK model was developed and fitted with the clinical PK of Lucrin™ depot to assess the IVIVC for the new formulations. The drug from optimised formulation showed C_{max} and $AUC_{0\text{-}inf}$ of 4.01 ng/mL as well as 52.52 h·ng/mL respectively which was like that of USFDA approved product. The PPE (percent prediction error) of PK parameters suggested good correlation of the developed model. The new formulation showed similar PK profile like Lucrin depot while exhibiting reduction in initial burst profile and improved safety profiles [233].

Importantly, the development of the predictive biorelevant IVIVC methods may help in development of clinically effective generics to established CIDPs [234]. The USFDA has published detailed bioequivalence guidelines for the therapeutically active CIDPs (Table 6).

The developed CIDPs have presented characteristic mechanisms of drug release which help in the amelioration of the disease conditions. Development of effective dissolution profiles would help to create a correlation between the physiological conditions at the diseased site and the observed human pharmacokinetic profiles [136]. Such modelling will help in the establishment of appropriate tools for the prediction of the pharma-equivalence and effectiveness of the complex generic drug product in the intended disease [12]. Model integrated evidence (MIE) may be used as a further step to provide crucial information for generic drug approval. When MIE is combined with a suitable *in-vitro* BE assessment tool, the combination may serve as a suitable alternative to conducting superfluous and less sensitive *in-vivo* investigations in appropriate circumstances [235]. The extent to which virtual bioequivalence (VBE) simulations may be used is determined by the data available to qualify and validate the underlying model while being fitted to its intended purpose. MIE may be developed using VBE simulations as an aid for efficient regulatory decision makings by various agencies [236]. Additionally, artificial intelligence based PBPK model for IVIVC may help the generic formulation development with the aim of the assessment of the failure potential while conducting the comparative bioequivalence studies between the innovator product and its proposed generic [46].

5. Conclusion

PBPK models have proved as a useful integral tool in the development as well as life cycle management of long-acting injectable drugs with their potential to perform priori simulations. These QMM (quantitative methods and modelling) approaches may be considered as a knowledge management framework integrating scientific knowhow along with the existing physicochemical data, its stimulatory and real time dissolution profiles, PK, biodistribution as well as clinical responses. Such databases may help in evaluation of the comparative effectiveness between existing innovator and proposed generic drug products. Consequently, various regulatory agencies and pharmaceutical companies have been employing them for ensuring the safety as well as efficacy of the CIDPs.

Effectively, this knowledge database has presented various facets for drug development. The models have helped in finding useful correlations between the drug's physicochemical properties (permeability and partitioning) and its physiological and anatomical performance post-delivery through the CIDP. Importantly, the model assumptions and simulations should be carefully considered during the model building process with the components being in agreement with pharmacological conditions. Additionally, model fitting and validation using the demographic variability as well as conditions in diseased populations would improve the predictability of such databases. Further, IVIVC

Table 6
Bioequivalence guidelines for CIDPs by USFDA (The Bioequivalence recommendations for approved CIDPs have been assessed from https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm assessed on 12 March 2023).

CIDP	Molecule	Bioequivalence recommendations in general
Liposomes	➢ Doxorubicin HCl ➢ Amphotericin B ➢ Cytarabine ➢ Bupivacaine ➢ Vincristine sulfate ➢ Irinotecan hydrochloride ➢ Daunorubicin and Cytarabine	• Q1Q2 sameness • *In-vivo* PK bioequivalence studies: Single dose and or multiple dose healthy or patient population • *In-vitro* liposome size distribution study • *In-vitro* dissolution study • At least one batch of the Test product should be produced by the commercial scale process and be used in the *in-vivo* bioequivalence study. • Equivalent liposome characteristics including liposome composition, state of encapsulated drug, internal environment of liposome, liposome size distribution, number of lamellar, grafted PEG at the liposome surface, electrical surface potential or charge, and *in vitro* leakage rates comparable to the Reference Standard (RS).
Microspheres	➢ Leuprolide acetate ➢ Octreotide acetate ➢ Triptorelin pamoate ➢ Risperidone ➢ Naltrexone ➢ Olanzapine ➢ Exenatide synthetic	• Q1Q2 sameness • *In-vivo* PK bioequivalence studies: Single dose and or multiple dose: Patient Population • *In-vitro* drug dissolution study- Comparative or BE based on 90% of T50% for drug like Risperidone
Intramuscular Depot suspensions	➢ Paliperidone palmitate ➢ Aripiprazole salts ➢ Cabotegravir ➢ Cabotegravir; Rilpivirine	• Q1Q2 sameness • *In-vivo* PK bioequivalence studies: Single dose and or multiple dose steady state: Patient Population • *In-vitro* dissolution study
Subcutaneous Gels and Implants	➢ Leuprolide Acetate ➢ Lanreotide acetate ➢ Granisetron ➢ Buprenorphine	• Q1Q2 sameness • *In-vivo* PK bioequivalence studies: Single dose: Healthy or Patient Population • *In-vitro* dissolution study • Equivalent molecular, structural, and thermodynamic properties as the reference listed product for bio-waiver (Lanreotide) • Polymer composition, structure, degradation kinetics, excipient characterization details required (Granisetron)

models have served as useful guides to both regulatory agencies and pharmaceutical companies for product development as well as regulatory evaluations. Various applications of PBPK modelling including novel BE metrics research, PBPK models for systemic and locally acting products, complex and modified-release products, model-based BE assessment, post marketing evaluations, and risk-based evaluations have helped in the life cycle management of therapeutic agents. Thus, the development of appropriate PBPK models for IVIVC profiling of CIDPs not only provides a predictive tool for the *in-vivo* performance of the formulation but also is integral to the establishment of bioequivalence for attainment of desired therapeutic safety and efficacy in the target disease condition.

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CRediT authorship contribution statement

Amit Dabke: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Saikat Ghosh:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Pallavi Dabke:** Methodology, Visualization, Writing – original draft. **Krutika Sawant:** Project administration, Supervision, Writing – review & editing. **Ajay Khopade:** Project administration, Supervision.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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