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Mini review

In vitro – In vivo correlation in the development of oral drug formulation: A screenshot of the last two decades

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ABSTRACT

In vitro – in vivo correlation (IVIVC) allows prediction of the *in vivo* performance of a pharmaceutical product based on its *in vitro* drug release profiles and can be used to optimize formulations, set dissolution limits, reduce the number of bioequivalence studies during product development, and facilitate certain regulatory decisions. This review article aimed to assess papers published in the last two decades regarding the use of the IVIVC in the development of oral formulations, to demonstrate the scenario in this area, as well as to describe the main characteristics of the assessed studies. A systematic search of *PubMed* and *Web of Science* databases was conducted to retrieve articles reporting the use of the IVIVC in the oral formulation development in the period from 1998 to 2018. The qualified studies were abstracted regarding drug name, dosage form, BCS class, *in vitro* and *in vivo* data, level of IVIVC, number of formulations, presence of the validation and predictability. The discussion was supported by these data, which allowed to address broadly strengths and weaknesses in this area. Moreover, a large database has been described in this article containing different IVIVC models, with different substances, providing support to scientists interested in this area.

1. Introduction

Worldwide, the pharmaceutical industry and regulatory agencies have continuously worked to reduce the time for approval of a new pharmaceutical product, reduce the cost of development to maximize the return on investment, and to improve the access of the patients, especially for generic drug products. In the last two decades, the pharmaceutical industry has experimented and adopted several integrated and multidisciplinary approaches to achieve a more rational and assertive development flow. In the development of oral drug formulations, these efforts were mainly in the use of tools such as Quality by Design (QbD) (Yu et al., 2014; Pramod et al., 2016), Design of Experiments (DoE) (N. Politis et al., 2017), *In vitro – In vivo* Correlation (IVIVC) (Kaur et al., 2015), and the use of the Biopharmaceutical Classification System (BCS) in the adoption of biowaiver approaches to register some products (Davit et al., 2016).

The development and optimization of a pharmaceutical product involves varied levels of selection of excipients, processes, manufacturing equipment, development and validation of analytical methods to assess the *in vitro* performance and quality attributes, as well as expensive *in vivo* studies to asses efficacy and safety (Pramod et al., 2016). Considering that quantitative and/or qualitative changes in a formulation may affect drug release and its performance *in vivo*, impacting directly on its efficacy and safety (Yousefi et al., 2017), pharmaceutical development must be considered a complex process that requires a systematic approach based on multidisciplinary contributions. Moreover, with ever increasing pressures to reduce the timeline of product development, it is necessary an integrated work of scientists from the analytical, galenic, clinical and other pharma teams to ensure the success of pharmaceutical products in all stages of the development.

In this context, IVIVC has been used as a powerful tool for establishing a rational relationship between *in vitro* and *in vivo* characteristics. By definition, IVIVC is a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g. plasma drug concentration or amount of drug absorbed (González-García et al., 2015; Kaur et al., 2015; FDA, 1997). *In vitro* release is generally represented by dissolution profiles in biorelevant and/or bio-predictive media, and *in vivo* release is provided generally by pharmacokinetic studies. IVIVC constitutes an integral part of the development of a drug product, mainly for modified-release (MR) formulations, aiming to optimize prototypes, set dissolution limits, reduce the number of bioequivalence studies during the development and to support post-approval changes (components or composition,

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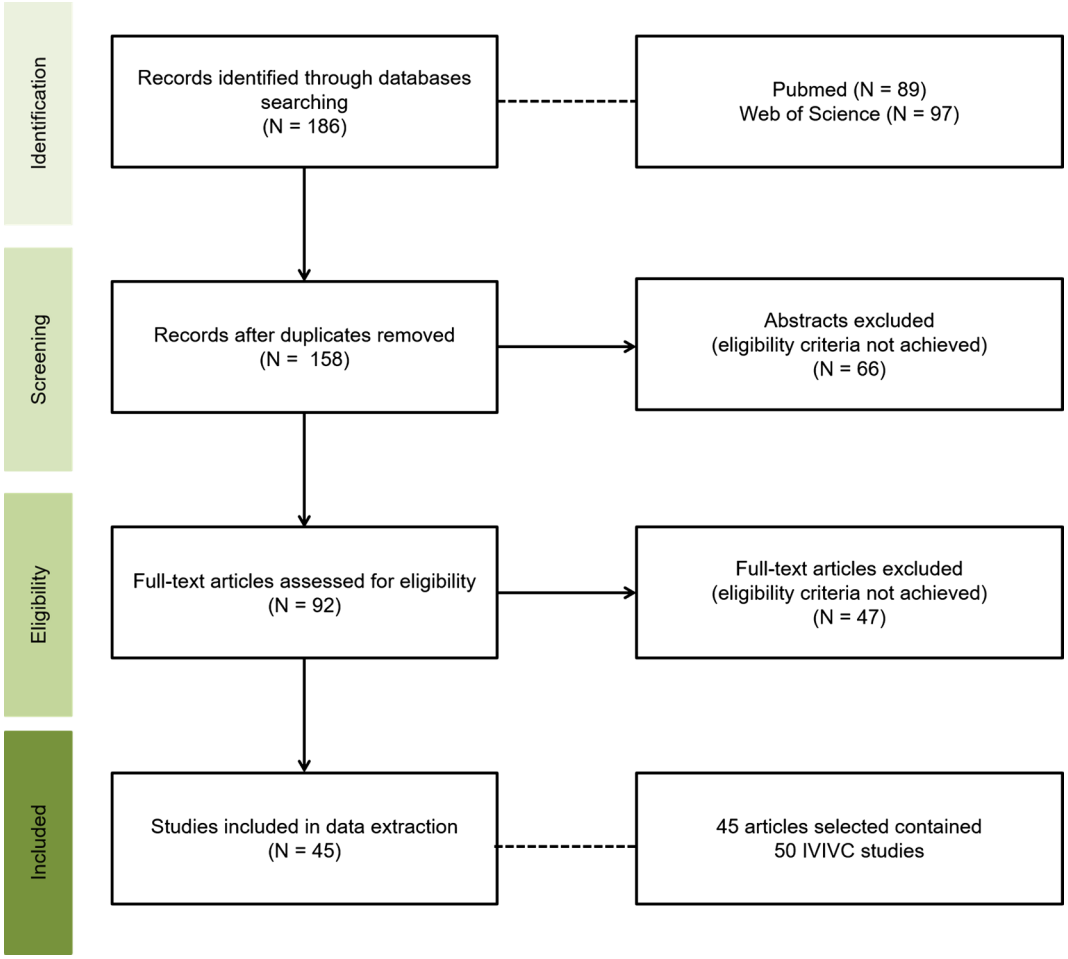

Fig. 1. PRISMA four-phase flow diagram for study retrieval and selection.

manufacturing site, scale-up/scale-down, manufacturing process or equipment) (Cardot et al., 2011).

Thus, the objective of this work was to assess how this tool has been used by scientists in the context of oral drug formulation development. For this purpose, papers published in the period from 1998 to 2018 related to the use of the IVIVC in the development of oral formulations were retrieved to compose a significant sample and demonstrate the scenario in this research field, as well as the main characteristics of these studies. Based on that, it was possible to carry out a broad discussion regarding the main concepts applied in the use of the IVIVC during the period searched. Finally, this article provides a large compilation of information on different drugs regarding the application of IVIVC, and it may be consulted by scientists interested in this approach for oral formulation development.

2. Methodology

2.1. Database search strategy

In April 2019, a systematic search of *PubMed* and *Web of Science* databases was conducted to retrieve all articles reporting IVIVC in the development of oral drug formulations considering the period from 1998 to 2018. Search terms including '*in vitro in vivo* correlation', 'oral dosage form', and 'product development' combined with the Boolean operator "AND", were applied for all database fields. Restrictions were applied to article language (only in English) and period (articles published from January 1998 to December 2018 were considered). The search was set to include the twenty-year period after the publication of the FDA Guidance for Industry 'Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In vitro/In vivo* Correlations' (FDA, 1997).

2.2. Eligibility criteria

The titles and abstracts of retrieved studies were firstly examined under a double check. In cases that it was not possible to identify the eligibility criteria only by evaluation of the title and abstract, the full text was evaluated for inclusion or rejection of the retrieved studies. Inclusion criteria were as follows: an article with original research, published from January 1998 to December 2018, in the English language, accessible in the database, and involving the application of IVIVC for development of oral drug formulations. The articles describing IVIVC application for non-oral formulations were rejected. Considering articles selected based on inclusion criteria, the full text was examined for an overall assessment and included in data extraction. In order to report numbers of studies screened, assessed for eligibility, and included in the review, a PRISMA four-phase flow diagram (Moher et al., 2009) of information was constructed through the different phases of systematic review.

2.3. Data extraction and analysis

The included articles were analyzed, and the following data extracted: drug/substance name, dosage form, BCS class of drug (when available in the article or consulted in the Drug Delivery Foundation database (available in http://www.ddfint.org/bcs-about), *in vitro* and *in vivo* data used for IVIVC, IVIVC level, number of formulations used in IVIVC, and presence of validation and predictability of IVIVC (internal

Table 1
Data extraction from the articles included involving IVIVC studies for oral formulations (N = 45 articles and 50 studies).

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
Alfuzosin hydrochloride	ER tablet	II	Data: fraction permeated Apparatus: USP II (paddle) at 50 rpm + dissolution/absorption simulating system. Medium: pH 2.0 and pH 6.8 Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method Design: PK study in beagle dogs (N = 6) under fasting condition.	A	One formulation (ER tablet marketed)	ND	ND	(Li, et al., 2018)
Aminophylline/ Theophylline	MR tablet	III/I	Data: fraction dissolved. Apparatus: USP II (paddle) at 50 rpm. Medium: pH 1.2 SGF without pepsin (SGF) (1 h) and pH 7.5 SIF without enzyme (2 – 8 h). Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method. Design: PK study in rabbits (N = 4).	A	Three tests and two reference formulations.	Internal validation	The %PEs of Cmax and AUC evaluated.	(Petrovic, et al., 2013)
Apremilast	ER tablet	IV	Data: fraction dissolved. Apparatus: USP II (paddle) at 50 rpm. Medium: pH 6.8 50 mM phosphate buffer. Volume: 900 mL.	Data: fraction absorbed. Deconvolution: numerical deconvolution and Wagner-Nelson method. Design: PK study in beagle dogs (N = 6) under fasting condition.	A	Two formulations: fast and slow.	Internal validation	The %PEs of Cmax and AUC evaluated.	(Tang, et al., 2016)
Arundic acid	Soft-gel capsule	ND	Data: fraction dissolved Apparatus: USP II (paddle). Media: 50 mM Na_2HPO_4 + 25 mM citric acid pH 8.0 and pH 6.8 dissolution medium + 2% SDS. Volume: 900 mL	Data: simulated fraction absorbed. Deconvolution: ND Design: plasma concentration data were deconvoluted by i.v. study.	A	Two formulations	Internal validation	The %PEs of Cmax and AUC evaluated.	(Nishimura, et al., 2007)
Capecitabine	ER tablet	I	Data: fraction dissolved (Higuchi modelling) Apparatus: USP II (paddle) at 50 rpm. Medium: water Volume: 900 mL	Data: 12 h *in vivo* release profile. Deconvolution: NA Design: PK study in patients (data from another article).	NA	One formulation	ND	ND	(Meulenaar, et al., 2014)
Capsaicin	Liposome	ND	Data: fraction dissolved. Apparatus: dialysis bag immersed in a single-neck flask and shaken at 70 rpm. Media: pH 7.4 phosphate buffer solution, pH 1.2 HCl solution and water. Volume: 100 mL	Data: absorbed *in vivo* input Deconvolution: ND Design: PK study in rats under fasting condition (N = 3).	A	One formulation	ND	ND	(Zhu, et al., 2015)
Carbamazepine	Nanodispersion	II	Data: fraction permeated. Apparatus: non-sink membrane permeation dissolution method. Media: Simulated gastric and intestinal fluids. Volume: 1 L	Data: cumulative AUC values. Deconvolution: Wagner-Nelson method. Design: PK study in in mice.	C	Three formulations: microamorphous, nanoamorphous, and nanocrystalline.	ND	ND	(Warnken, et al., 2018)
Cilostazol	IR tablet	II	Data: fraction dissolved in 4 h. Apparatus: USP IV (flow-through cell) apparatus closed-loop system. Medium: water (fasting condition) and 0.20% SLS (fed condition). Volume/flow: 20L at 4 mL/min.	Data: fraction absorbed in 4 h. Deconvolution: numerical deconvolution method. Design: bioavailability study in beagle dogs (N = 4) under fasting and fed condition.	C	Two formulations: wet-milled tablet and commercial tablet.	ND	ND	(Jinno, et al., 2008)

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Table 1 (*continued*)

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
Cyclosporine	Self-microemulsifying drug delivery contained in soft-gelatin capsule	II	Data: fraction dissolved Apparatus: USP II (paddle) apparatus at 50 rpm. Media: SGF without enzymes (pH 1.2), pH 4.5 phosphate buffer and SIF without enzymes (pH 6.8). Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method Design: PK study in male dog (N = 6 per group) under fasting condition.	A	Three formulations: test, reference I and reference II.	ND	ND	(Yang, 2010)
Diclofenac sodium	ER tablet	II	Data: fraction permeated. Apparatus: USP II (paddle) at 50 rpm + dissolution/absorption simulating system. Medium: pH 2.0 and pH 6.8 Volume: 900 mL	Data: fraction absorbed. Deconvolution: Wagner-Nelson or Loo-Riegelman methods (not specified). Design: PK study in beagle dogs (N = 6) under fasting condition.	A	One formulation: ER tablet marketed	ND	ND	(Li, et al., 2018)
Dipyridamole	MR tablet (floating osmotic pump system)	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: 0.1 N HCl solution Volume: 900 mL	Data: fraction absorbed. Deconvolution: ND. Design: bioavailability study in Beagle dogs (N = 6) under fasting condition.	A	One formulation: floating osmotic pump system.	ND	ND	(Zhang Z, 2009)
Emedastine difumarate	CR tablet	ND	Data: fraction dissolved. Apparatus: USP IV (flow-through cell) apparatus. Media: pH 1.2, 0–3 h and pH 6.8, 3 – 24 h. Volume/flow: 2.5 mL/h.	Data: fraction absorbed Deconvolution: Wagner-Nelson method. Design: data not showed.	A	Two formulations: CR tablet coated with different compositions)	ND	ND	(Morita, et al., 2003)
Etodolac	CR pellets	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 100 rpm. Media: phosphate buffer solution (pH 7.4). Volume: ND.	Data: fraction absorbed. Deconvolution: ND. Design: PK study in male beagle dogs (N = 6) under fasting condition.	A	One formulation: CR pellets	ND	ND	(Zhang, et al., 2018)
Felodipine	Nanocapsule	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: 40.0% v/v methanolic phosphate buffer pH 6.5. Volume: 250 mL.	Data: fraction absorbed. Deconvolution: Wagner-Nelson, GastroPlus mechanistic absorption, and numerical deconvolution. Design: PK study in Sprague Dawley rats (N = 6) under fasting condition.	A	One formulation (optimized formulation)	Internal validation	The %PEs of Cmax and AUC evaluated.	(Geroge, et al., 2017)
Fenofibrate	IR formulations	II	Data: fraction dissolved. Apparatus: custom-made biphasic dissolution-partition test (USP IV combined with USP II at 60 rpm). Media: FeSSIF-V2/octanol. Volume: 250 mL.	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: two PK study in human subjects under fasting and fed conditions.	A	Three formulations individually (capsule, nano-tablet and hot melt extrusion tablet).	ND	ND	(Xu, et al., 2018)
Fenofibrate	Capsule and suspension	II	Data: dissolution efficiency (%). Apparatus: USP II (paddle) at 75 rpm).	Data: oral bioavailability. Deconvolution: NA. Design: oral bioavailability	C	Three formulations (reference product, capsule and suspension prototypes)	ND	ND	(O'Shea, et al., 2017)

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Table 1 (*continued*)

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
			Medium: FaSSIF. Volume: 500 mL.	study in male Landrace pigs (N = 6) under fasting condition.					
Flurbiprofen	Lozenges (acting in oral cavity)	II	Data: mass loss of the lozenges. Apparatus: custom-made apparatus for simulating the oral cavity. Medium: simulated saliva fluid pH 6.8. Volume: saliva flow at 10 mL/min and artificial tongue at 180 dpm.	Data: mass loss of the lozenge after determined time of suction. Deconvolution: NA. Design: healthy volunteers (N = 12).	A	Two formulations (Prototype I and II)	ND	ND	(Tietz, et al., 2018)
Ginsenosides (NGR1, GRg1 and GRb1)	Bio-adhesive pellets	ND	Data: fraction dissolved. Apparatus: USP I (basket) apparatus. Medium: phosphate buffer pH 7.4. Volume: 500 mL.	Data: fraction absorbed. Deconvolution: numerical deconvolution. Design: PK study in Sprague Dawley rats (N = 6).	A	One formulation	ND	ND	(LI, et al., 2017)
Gliclazide	Push-pull osmotic pump tablet	II	Data: fraction dissolved (zero-order modelling) Apparatus: USP II (paddle) apparatus (with sinker) at 100 rpm. Medium: phosphate buffer pH 7.4 with NaCl. Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method Design: PK study in dogs (N = 6) under fasting condition	A	Reference and test formulations	ND	ND	(Tang, et al., 2013)
Glipizide	ER tablet	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: potassium phosphate buffer pH 6.8. Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method. Design: PK study in male pigs (N = 6).	A	One formulation (ER tablet marketed)	ND	ND	(Kulkarni, et al., 2012)
Indapamide hemihydrate	ER tablet	I	Data: fraction dissolved. Apparatus: USP I (basket) apparatus at 100 rpm. Medium: buffer solution pH 1.2, 4.5 and 6.8. Volume: 500 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method. Design: pilot and pivotal BE study (under fasting condition).	A (non-linear)	Three formulations (2 test and reference).	Internal validation	The %PEs of Cmax and AUC evaluated.	(Antovska, et al., 2017)
Isosorbide-5-mononitrate	SR tablet (monolithic osmotic pump tablet system)	I	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Media: water, 0.1 N HCl pH 1.2, and phosphate buffer solution pH 6.8. Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method Design: PK study in healthy male beagle dogs (N = 3 per group) under fasting condition.	A	2 formulations: test and the marketed SR tablet	ND	ND	(Duan, et al., 2009)
Isosorbide-5-mononitrate	ER tablet	I	Data: fraction permeated Apparatus: USP II (paddle) at 50 rpm + dissolution/absorption simulating system. Medium: pH 2.0 and pH 6.8 Volume: 900 mL	Data: fraction absorbed Deconvolution: Wagner-Nelson method Design: PK study in beagle dogs (N = 6) under fasting condition.	A	One formulation (ER tablet marketed)	ND	ND	(Li, et al., 2018)
Ketoconazole	Tablet	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm.	Data: Cmax. Deconvolution: NA. Design: bioequivalence study	C	2 formulations: test and reference.	ND	ND	(Viçosa, et al., 2009)

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Table 1 (*continued*)

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
			Media: buffer solution pH 4.5 without surfactant. Volume: 900 mL	in healthy adult volunteers (N = 28).					
Ketoprofen	Time-adjustable pulsatile release tablet	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 100 rpm. Media: pH 1.2 0.1 M HCl solution (acid phase) and pH 6.8 solution (basic phase). Volume: 250 mL (acid phase) and 750 mL (basic phase).	Data: fraction absorbed. Deconvolution: ND. Design: PK study in beagle dogs (N = 6) under fasting condition.	ND	One formulation	ND	ND	(Wang, et al., 2017)
Ketorolac tromethamine	Colon-targeted tablet	II	Data: fraction dissolved (Koresmeyer-Peppas model) Apparatus: USP I (basket) apparatus at 50 rpm. Medium: 2 h in 0.1 N HCl, 2 h in buffer pH 5.5 and phosphate buffer pH 7.4 up to 24 h. Volume: ND	Data: AUC value in each collect-time. Deconvolution: NA Design: PK study in healthy volunteers (N = 12) under fasting condition.	NA	One formulation: prototype of colon-targeted tablet	ND	ND	(Vemula & Veerareddy, 2013)
Lamivudine	Gastroretentive tablets (floating-bioadhesive formulation)	I	Data: % Dissolved, Log %Dissolved, MDT, T60%, T70%, T80%, T90%, Log T70% and Log T80%. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: SGF pH 1.2. Volume: ND	Data: % Absorbed, Log %Absorbed, MRT, Log Tmax, Log AUC, Log Cmax/AUC. Deconvolution: Wagner-Nelson method (for IVIVC level A). Design: PK study in rabbits (N = 6) under fasting condition.	A, B, C and multiple C.	Two formulations individually.	ND	ND	(Singh, et al., 2012)
Loxoprofen	ER tablet	I	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 100 rpm. Medium: 0.01 N HCl pH 2.0 and increased to pH 6.8. Volume: 750 mL (acid phase) and 1000 mL (basic phase).	Data: *in vivo* dissolution parameters obtained by POP-PK model. Deconvolution: NA Design: PK study in beagle dogs (N = 4 per group) under fasting condition.	A	Three formulations: fast, medium and slow.	Internal validation	The %PEs of Cmax and AUC evaluated.	(Kim, et al., 2017)
Metaxalone	IR tablet	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: pH 4.5 dissolution medium containing 0.5% NaCl with 0.2% SLS. Volume: 900 mL.	Data: direct plasma concentration (single step method). Deconvolution: NA. Design: bioequivalence study in healthy volunteers (N = 18) under fasting condition.	A	3 formulations: test A, test B, and reference.	Internal validation	The %PEs of Cmax and AUC evaluated.	(Vuletić, et al., 2018)
Metoclopramide hydrochloride	SR tablet	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 and 75 rpm. Media: pH 1.2, 4.5, 5.5, 6.8 and 7.4. Volume: 900 mL	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: PK study in healthy volunteers (N = 6) under fasting condition	A	Three formulations: fast, medium and slow.	Internal and external validation	The %PEs of Cmax and AUC evaluated.	(Narayanasamy & Shabaraya, 2017)
Metoprolol tartrate	ER tablet	I	Data: fraction permeated Apparatus: USP II (paddle) at	Data: fraction absorbed Deconvolution: Wagner-	A	One formulation (ER tablet marketed)	ND	ND	(Li, et al., 2018)

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Table 1 (*continued*)

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
			50 rpm + dissolution/absorption simulating system. Medium: pH 2.0 and pH 6.8 Volume: 900 mL	Nelson method Design: PK study in beagle dogs (N = 6) under fasting condition.					
Metoprolol tartrate	ER tablet	I	Data: fraction dissolved. Apparatus: USP I (basket) and II (paddle) apparatus at 150 and 50 rpm, respectively. Medium: phosphate buffer pH 6.8 Volume: ND	Data: fraction absorbed Deconvolution: numerical deconvolution approach. Design: bioavailabity study in healthy subjects (N = 9) under fasting condition.	A	Three formulations: slow, moderate and fast.	Internal validation	The %PEs of Cmax and AUC evaluated.	(Eddington, et al., 1998)
Niacin	ER tablet	I	Data: dissolution time-point. Apparatus: USP II (paddle) apparatus (speed not informed). Medium: phosphate buffer pH 6.8 Volume: ND	Data: Cmax, AUC and total urinary excretion (for parent drug and metabolite). Design: PK study in healthy volunteers (N = 36) under fasting condition.	Multiple C	Three different prototypes (varying HPMC percentage)	Internal validation	The %PEs of Cmax and AUC evaluated.	(Kesisoglou, et al., 2014)
Niacin	SR tablet	I	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: phosphate buffer pH 6.8 Volume: ND	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: PK study in healthy male volunteer subjects (N = 18) in fasting condition.	A	Three formulations: A, B and marketed product.	ND	ND	(Turner, et al., 2004)
Nifedipine	ER tablet	II	Data: fraction dissolved. Apparatus: USP III (reciprocating cylinder) at 12–16 dips/min. Medium: FaSSIF-V2 and FeSSIF-V2. Volume: 235 mL.	Data: fraction absorbed. Deconvolution: deconvolution-based approach using the Phoenix software. Design: unpublished *in vivo* data.	ND	Two formulations with different release mechanisms (osmotic-pump and matrix-type)	ND	ND	(Andreas, et al., 2016)
Olmesartan medoxomil	Solid and liquid self-nanoemulsifying tablet	II	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: SGF (pH 1.2) containing 0.5% SLS. Volume: 1000 mL	Data: fraction absorbed. Deconvolution: ND. Design: PK study in male Wistar rats (N = 6 per group).	A	Two formulations individually.	ND	ND	(Beg, et al., 2016)
Oxycodone hydrochloride	CR tablet	IV	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50–150 rpm. Medium: pH 6.8 phosphate buffer. Volume: 900 mL	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: PK study in healthy male volunteers (n = 18) under fasting condition.	A	One formulation.	ND	ND	(Kim, et al., 2015)
Pregabalin	Gastro-floating SR tablet	I	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus with sinker at 100 rpm. Medium: SGF pH 1.2 without pepsin. Volume: 900 mL.	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: PK study in male beagle dogs (n = 5) under fed condition.	A	One formulation	ND	ND	(Qin, et al., 2018)

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Table 1 (*continued*)

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
Propranolol hydrochloride	ER tablet	I	Data: fraction dissolved. Apparatus: USP apparatus I (basket) at 100 rpm. Medium: pH 1.2 varying to 6.8. Volume: 900 mL	Data: fraction absorbed. Deconvolution: numerical deconvolution approach. Design: PK study in male beagle dogs (N = 6) under fasting condition.	A	Two formulations: slow and fast.	Internal and external validation.	The %PEs of Cmax and AUC evaluated.	(Cheng, et al., 2014)
Ritonavir	Tablet	II	Data: fractional partition. Apparatus: custom-made biphasic dissolution partition test. USP IV apparatus (flow through cell) combined with USP II (dual paddle) apparatus at 60 rpm. Medium: aqueous/octanol. Volume: 200 mL of aqueous media and 200 mL of octanol.	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: mean plasma drug concentration − time profiles based on scientific literature.	A	One formulation	ND	ND	(Xu, et al., 2017)
Ritonavir	Tablet	II	Data: fractional partition. Apparatus: USP IV apparatus (flow through cell) combined with USP II (dual paddle) apparatus at 50 rpm. Medium: aqueous/octanol. Volume: 59 mL of aqueous media and 50 mL of octanol.	Data: Relative bioavailability and AUC. Deconvolution: NA Design: PK study in a dog model (data published in another article).	C	Three formulations: commercial generic products.	ND	ND	(Xu, et al., 2018)
Silybin	Capsule filled with calcium-phosphate microparticles	ND	Data: fraction dissolved. Apparatus: USP I (basket) apparatus with dialysis bag at 100 rpm. Media: phosphate buffer solution (pH 7.4) and HCl solution (pH 1.2). Volume: 900 mL	Data: fraction absorbed. Deconvolution: ND Design: PK study in male beagle dogs (N = 2) under fasting condition.	A	One formulation	ND	ND	(Zhu, et al., 2016)
Sinomenine	ER tablet	I	Data: fraction permeated. Apparatus: USP II (paddle) at 50 rpm + dissolution/absorption simulating system. Medium: pH 2.0 and pH 6.8. Volume: 900 mL	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: PK study in beagle dogs (N = 6) under fasting condition.	A	One formulation (ER tablet marketed)	ND	ND	(Li, et al., 2018)
Sulfur	Nanoparticle	NA	Data: fraction dissolved. Apparatus: ND. Media: gastric simulated HCl buffer (pH: 1.2; for 2 h) and intestine simulated phosphate buffer (pH: 6.8; for 6 h) Volume: ND	Data: fraction absorbed Deconvolution: ND. Design: PK study in female New Zealand white rabbits (N = 9) under fasting condition.	A	One formulation	ND	ND	(Choudhury, et al., 2013)
Tanshinone IIA	Capsule filled with SR pellets	ND	Data: percentage dissolved in 4, 6, 8, 10, 12, and 24 h. Apparatus: USP I (basket) apparatus at 100 rpm. Medium: distilled water containing 0.5% SDS. Volume: 900 mL.	Data: AUC_{4h}, AUC_{6h}, AUC_{8h}, AUC_{10h}, AUC_{12h} and AUC_{24h}. Deconvolution: NA Design: PK study in healthy male New Zealand rabbits (N = 6) under fasting condition.	C	One formulation	ND	ND	(Liu, et al., 2012)

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Table 1 (*continued*)

Drug/substance name	Dosage form	BCS Class*	*In vitro* data used for IVIVC/ *In vitro* methodology	*In vivo* data used for IVIVC/*In vivo* study	IVIVC level	Number of formulations used for IVIVC	Validation of the IVIVC	Predictability	Reference
Theophyline	ER tablet	I	Data: fraction permeated. Apparatus: USP II (paddle) at 50 rpm + dissolution/absorption simulating system. Medium: pH 2.0 and pH 6.8. Volume: 900 mL	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: PK study in beagle dogs (N = 6) under fasting condition.	A	One formulation (ER tablet marketed)	ND	ND	(Li, et al., 2018)
Tramadol hydrochloride	CR microparticle and IR formulation	I	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: initial 2 h in pH 1.2, next 2 h in pH 4.5, then 2 h in pH 6.8 and finally in pH 7.4 (phosphate buffer) for subsequent 18 h. Volume: 900 mL.	Data: fraction absorbed. Deconvolution: Wagner-Nelson method Design: PK study in healthy male human volunteers (N = 24) under fasting condition.	A	Three formulations individually (two CR and one IR formulation)	ND	ND	(Naeem Aamir, et al., 2011)
Tramadol hydrochloride	SR tablet	I	Data: fraction dissolved. Apparatus: USP II (paddle) apparatus at 50 rpm. Medium: acidic medium. Volume: ND.	Data: fraction absorbed Deconvolution: Wagner-Nelson method. Design: PK study in rabbits (N = 9) under fasting condition.	A	One formulation	ND	ND	(Kotta, et al., 2014)
Valsartan	Nanoparticles	II	Data: dissolution efficiency. Apparatus: USP II (paddle) at 50 rpm. Medium: HCl solution (pH 1.2) and acetate buffer (pH 4.0). Volume: 900 mL	Data: Cmax and AUC. Deconvolution: NA. Design: PK study in male Sprague-Dawley rats (N = 5 per group) under fasting condition.	C	Four formulations	ND	ND	(Kim & Baek, 2014)
Vincamine	Prolonged-release coated pellets	ND	Data: fraction dissolved. Apparatus: USP IV (flow-through cell) apparatus open-loop system. Medium: variable pH range (1.2, 4.5, 6.9 and 7.5). Volume and flow: ND.	Data: fraction absorbed. Deconvolution: Wagner-Nelson method. Design: comparative bioavailability study (N = 16) in human subjects.	A	Three formulations: two tests and reference.	ND	ND	(Emara, et al., 2000)

and/or external predictions).

3. Results

In total, 186 records were retrieved from the two databases searched, 89 from *Pubmed* and 97 from *Web of Science*. Within the articles retrieved, 28 were duplicated in the two databases. Then, 158 articles were assessed to meet the eligibility criteria under a double check for abstract and full-text. Finally, 45 studies (containing 50 IVIVC studies) were included in data extraction, as described in Fig. 1 (PRISMA four-phase flow diagram).

To demonstrate all relevant information from the included articles, Table 1 was designed to present the following data: name of drug/substance, dosage form, BCS class of drug, *in vitro* and *in vivo* data used for IVIVC, methodology applied for dissolution test or other used to assess the *in vitro* characteristics, deconvolution method used to obtain fraction absorbed (when applied), *in vivo* study design and population, IVIVIC level achieved (A, B, C, multiple C or D), number of formulations applied in the IVIVC and presence or absence of validation (internal and/or external) and predictability.

Glossary for Table 1: AUC: area under the curve, BCS: biopharmaceutics classification system, Cmax: maximum plasma concentration, CR: controlled-release, ER: extended-release, FaSSIF: fasted state simulated intestinal fluid, FeSSIF: fed state simulated intestinal fluid, HPMC: hydroxypropyl methyl cellulose, IR: immediate-release, IVIVC: *in vitro – in vivo* correlation, MR: modified-release, MDT: mean dissolution time, MRT: mean residence time, NA: not applied, ND: not described, PE: prediction error, PK: pharmacokinetic, SDS: sodium dodecyl sulfate, SGF: simulated gastric fluid, SIF: simulated intestinal fluid, SR: sustained-release, T50% (or TXX%): time to reach 50% (or XX %) of dissolution, Tmax: time to reach maximum plasma concentration, USP: United States Pharmacopoeia.

4. Data analysis and discussion

The aim of this work was to demonstrate a screenshot of the last two decades regarding the use of IVIVC for the development of oral drug formulations and to have a broad and critical analysis and discussion based on the scenario found. For this purpose, a systematic search was carried out to retrieve articles published from 1998 to 2018 related to use of this tool. Considering the results obtained in this review, the topics below are discussed, aiming to demonstrate the main characteristics of the studies selected and to provide a critical analysis on how this tool has been applied in the last twenty years.

4.1. Dosage form and biopharmaceutics classification system

Oral route is the most frequently used way of drug administration, as well as the most convenient, economic and preferred by patients (Viswanathan et al., 2017). In conventional oral drug products such as IR formulations (e.g. tablets and capsules), no deliberate efforts are made to modify the drug release rate. Thus, IR products generally result in relatively rapid drug absorption and onset of clinical effects. In the other hand, MR dosage forms are formulated to achieve a desired therapeutic objective or better patient compliance. Types of MR drug products include delayed-release (DR) (e.g. enteric-coated), extended-release (ER or XR), sustained-release (SR), controlled-release (CR), and others (Viswanathan et al., 2017; Shargel et al., 2012). These definitions may have slight variations between countries and regulatory agencies.

Biopharmaceutics classification system (BCS) is often used to predict the *in vivo* behavior of oral formulations, essentially based on drug solubility and intestinal permeability extension (Amidon et al., 1995). BCS class I drugs are highly permeably and soluble substances; therefore, they depend only on the release rate of the dosage form for dissolution on the gastro-intestinal (GI) fluids and, then, permeate intestinal or stomach mucosae. For a BCS class I drug contained in an IR dosage form, gastric emptying is the only limiting factor for drug absorption, which would not enable prediction of the *in vivo* behavior based on *in vitro* assays. Therefore, for this case, the acronym "IVIVC" (quantitative correlations) is inappropriate and the other acronym, as IVIVR (*in vitro in vivo* relationship – qualitative correlations), should be considered, since this approach only provides a formulation rank order based on dissolution profiles, and is not useful for regulatory purposes. In general, IVIVC for IR dosage forms is more difficult to be achieved (Qiu & Duan, 2017; FDA, 1997).

In addition to BCS class I, in the group of highly permeable substances, BCS class II are drugs with good permeability but with poor solubility. Thus, in this case, the dosage form plays a key role to improve drug solubility and to control the release rate to promote the best condition for dissolution and, consequently, permeability. Sub-classifications for BCS class II have been proposed recently (IIa, IIb and IIc) (Tsume et al., 2014), since these substances are highly dependent on the characteristics of the drug in the physiological pH range (acidic, basic or neutral drugs), formulation factors and luminal environment (e.g. presence of food). This approach considers BCS class IIa as weak acid drugs, with good solubility in the small intestine and low solubility in the acidic stomach pH, while BCS class IIb is the classification for weak base drugs with low solubility in the small intestine and good solubility in the acidic stomach pH. Finally, BCS class IIc should be considered neutral drugs as their solubility is not influenced by the physiological pH range (Tsume et al., 2014).

BCS classes III and IV drugs are poorly permeable, and this is related to molecule characteristics, with no regard to the formulation. Thereby, for these classes, any *in vitro* simulation aimed at predicting the *in vivo* behavior is generally more difficult or limited.

On the other hand, since only the dissolved drug in luminal fluids may permeate the mucosa at the absorptive sites of the GI tract, both the solubility of the drug and the release/dissolution rate of the dosage form are crucial for the *in vivo* input rate. Considering that release/dissolution is a limiting factor able to be simulated through *in vitro* tests (e.g. dissolution profiles), an IVIVC successful is expected mainly for BCS classes I and II, since for these classes drug permeability is not a limiting factor (Cardot & Davit, 2012). In this sense, Table 2 describes a relationship regarding the dosage form and probability to obtain a powerful IVIVC for each BCS class.

To understand whether IVIVC studies published in the literature

Table 2
Relationship between dosage form, BCS class and IVIVC probability.

Dosage form	BCS class	IVIVC probability	Justification
MR	I	High.	Release/dissolution rate is the limiting factor.
	II	High.	Release/dissolution rate is the limiting factor.
	III	Limited.	Permeability is the limiting factor.
	IV	Limited.	Permeability is the limiting factor.
IR	I	Limited.	Gastric emptying is the limiting factor.
	II	High.	Release/dissolution rate is the limiting factor.
	III	Limited.	Permeability is the limiting factor.
	IV	Limited.	Permeability is the limiting factor.

MR: modified release; IR: immediate release; BCS: biopharmaceutics classification system. IVIVC: *in vitro in vivo* correlation.

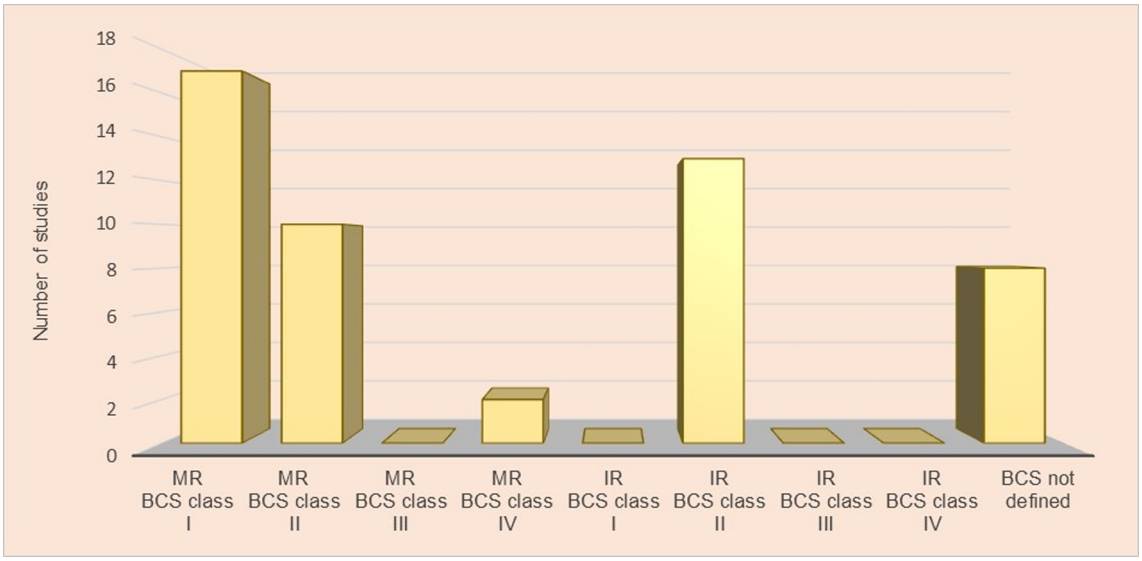

Fig. 2. Study distribution according to release dosage form and BCS class of drug (N = 50). BCS: biopharmaceutics classification system; MR: modified release; IR: immediate release.

(considering the period selected) match with the theoretical concepts to obtain a successful IVIVC, Fig. 2 was designed to show the distribution of dosage forms and BCS classes from the IVIVC studies assessed.

As demonstrated in Fig. 2, the MR dosage form has been the most applicable (54%) for IVIVC approaches, considering the articles assessed. In consensus with the IVIVC theoretical concepts (Qiu & Duan, 2017; Cardot & Davit, 2012; Kaur et al., 2015), BCS classes I (34%) and II (46%) have been the most usual classes used for IVIVC. Moreover, for IR dosage forms, only IVIVC studies with BCS class II drugs have been observed, and this is an important point that also matches with theoretical concepts described in the literature. In general, the articles assessed demonstrated that high permeability (BCS class I and II) drugs have been the main class applied for IVIVC approaches.

4.2. Dissolution media and apparatuses

For oral dosage form intended to drug absorption in GI tract, it is common to use dissolution media within the pH range of 1.2–6.8 to simulate the GI environment (stomach and intestine portions). Fasting and fed states also are important to set the adequate pH and dissolution media components (e.g. enzymes, salts, etc.) necessary to simulate these conditions. In addition, in the fed state, the delayed intragastrical dissolution caused by some food components may affect the absorption rates of drugs (especially poorly soluble drugs) and, subsequently, may influence its pharmacokinetics compared to the fasted state (Abrahamsson et al., 2004; Dressman et al., 2007). In this way, biorelevant and bio-predictive dissolution media for simulating stomach and small intestine, as well as conditions before and after meals, have been developed. The following examples may be cited: Simulated Gastric Fluid (SGF), Simulated Intestinal Fluid (SIF), Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF) (Nicolaides et al., 2001).

Among the retrieved articles, it was observed that the dissolution media in physiological pH range have been used as a single step or varying pHs in order to simulate different parts of GI tract (multiple steps). Single step dissolution medium was found in 24 studies (48%), while multiple steps approach was related in 13 of them (26%). Bio-predictive/bio-relevant media (SGF, SIF, FaSSIF and FeSSIF) were observed in 10 studies (20%) and water medium was related in 3 of them (6%). Even though single step approach has been found in the most of the studies and it could be related to the simplicity of this technique, multiple steps dissolution media in physiological pH range appeared in many studies, since this approach aims to simulate the different regions of the TGI tract and it could be more bio-predictive for some modified-release dosage forms (Li et al., 2018; Petrovic et al., 2013; Morita et al., 2003; Vemula & Veerareddy, 2013). The development and application of bio-predictive/bio-relevant media have been explored in the last two decades, mainly for a rational/assertive formulation development and, consequently, to save time and cost associated with pharmacokinetic and clinical studies (Klein, 2019; Klein, 2010).

Many articles have been published with different approaches regarding dissolution media and apparatuses to find the adequate condition to simulate the *in vivo* behavior for an oral dosage form. Conventional dissolution apparatuses such as USP I (basket) and USP II (paddle) are widely applied due to their practicality, availability in many laboratories, as well as the possibility to obtain expeditious results. However, in some cases, these apparatuses are not able to discriminate different formulations and to simulate conditions mimicking those *in vivo*. Thus, in some cases, USP III (reciprocating cylinder) and USP IV (flow-through cell) would be applied with rational protocols aiming to expose the dosage form to an environment potentially closer to that of the GI tract (Pezzini et al., 2015; Chevalier et al., 2009; Gao, 2009). USP IV has been widely recommended for poorly soluble drugs (Bhattachar et al., 2002), MR tablets (Andreas et al., 2015), and medical devices. Additionally, in the last years, non-conventional, custom-made and specific apparatuses have been developed to improve IVIVC approaches. TNO GI Model (TIM), a multi-compartmental model designed to realistically simulate conditions of the GI tract based on a computer simulation of the digestive conditions, is an example that demonstrates the advance of the dissolution apparatus in this area. Some systems have included a second stage in the apparatus, using an organic solvent or a membrane, for simulating the absorption process in the small intestine (Minekus, 2015).

Among the articles retrieved, the USP II (paddle) apparatus was the most applicable in the IVIVC studies assessed (52%, 26 of 50 studies) as shown in Fig. 3. Non-conventional or custom-made apparatuses were used in 24% of studies, followed by USP I (basket) in 14%, USP IV (flow-through cell) in 6% and USP III (reciprocating cylinder) in 2%.

These results demonstrated that the application of conventional basket (USP I) and paddle (USP II) apparatuses represents almost two thirds of the IVIVC studies assessed. As discussed previously, some characteristics allow these apparatuses to be widely applied for IVIVC, such as availability in many research laboratories and industries, easy handling, practicality and fast results. In many studies described in

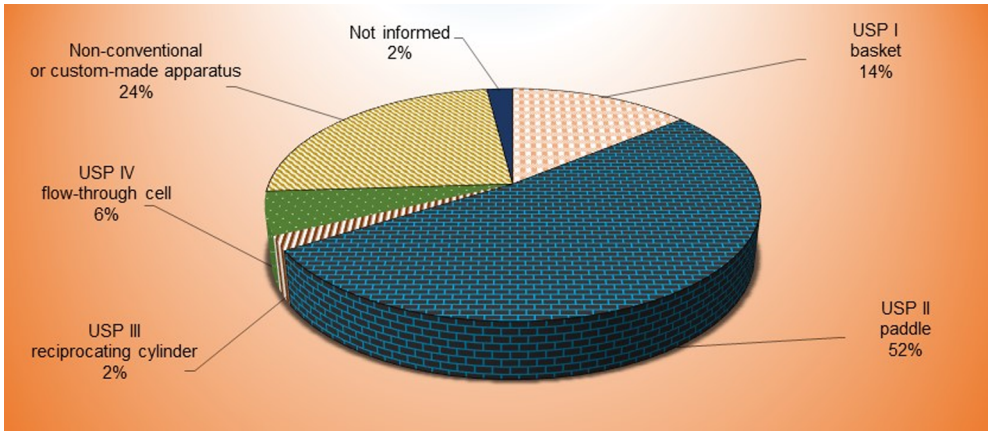

Fig. 3. Percentage distribution of dissolution apparatuses applied in the IVIVC studies retrieved (N = 50).

Table 1, it is possible to observe that the application of USP I and II is combined with dissolution media in the physiological pH range of GI tract. This approach has been used with physiological medium individually (Antovska et al., 2017), and as a combination of media with transition among physiological pH in the cube (e.g. acid phase for 1 h and basic phase for 24 h), mainly for MR formulations (Vemula & Veerareddy, 2013; Cheng et al., 2014).

Another point to be highlighted is the proportion (24%, 12 of 50 studies) of non-conventional and/or custom-made apparatuses applied for IVIVC. These systems are intentional changes made by scientists to mimic the *in vivo* condition. As examples, the article published by Li and collaborators described the application of a Drug Dissolution/Absorption Simulating System (DDASS) for IVIVC (Li et al., 2018); and the custom-made biphasic dissolution-partition test system, a combination of USP IV and II apparatuses, applied by Xu and collaborators in their works with different drugs (Xu et al., 2018; Xu et al., 2018; Xu et al., 2017).

By contrast, USP III and IV apparatuses were found only in 2 and 6% (Fig. 3), respectively, of the IVIVC studies assessed. It might indicate that these systems are not widely used either due to their unavailability in laboratories, or these methodologies are more complex and expensive than the others, since USP I and II are widely used also for quality control tests. Despite the low number of studies found with USP III and IV apparatuses, these systems have been extremely recommended for IVIVC approaches, mainly in the development of ER products (Andreas et al., 2015; Pezzini et al., 2015).

4.3. In vitro data

An important aspect in the development of pharmaceutical products is finding *in vitro* characteristics that reflect *in vivo* performance. Generally, the *in vitro* data used for an IVIVC are derived from curves obtained from dissolution tests performed in bio-predictive and biorelevant media. Recent advances in dissolution methodologies coupled with the availability of sophisticated modeling software enabled dissolution testing to be used for both the IVIVC and quality control approaches (Klein, 2019; Cardot & Davit, 2012; Gray, 2018).

To study the *in vitro* release kinetics of a dosage form, it is recommended that data obtained from *in vitro* drug release studies have results at least 85% of drug released/dissolved, twelve individual values (with adequate variability between cubes) and sufficient number of points to elucidate the dissolution curve shape. Having these data, modeling the dissolution profile curve to characterize the rate of drug release/dissolution is possible by using a mathematical model. Moreover, for IVIVC purposes, in cases where the timepoints of dissolution profile are not the same as those obtained *in vivo*, data modeling allows reaching the results calculated in other timepoints to construct a point-to-point relationship. Mathematical models such as Weibull, Higuchi, Korsemeyer-peppas among others, are usually applied for dissolution profile modeling (Costa & Sousa Lobo, 2001; Siepmann & Siepmann, 2013).

In face of the data extracted from IVIVC studies selected, 35 (70%) used data from dissolution profiles (represented by the fraction dissolved) for correlation with *in vivo* data, while 7 applied the permeated fraction, since they used a dissolution/absorption simulating system. In three of them, dissolution timepoints were used individually to construct a IVIVC level with pharmacokinetic parameters (Kesisoglou et al., 2014; Singh et al., 2012; Liu et al., 2012). Two of them used fractional partitioning (based on an octanol/water dissolution medium) as *in vitro* data to correlate with *in vivo* fraction absorbed (Xu, et al., 2017; Xu, et al., 2017); and, in two other studies, dissolution efficiency data was used to correlate with *in vivo* predictions (Xu, et al., 2018; Kim & Baek, 2014). Finally, only in one study applied the *in vitro* mass loss of the lozenges to correlate with *in vivo* mass loss after determined time of mouth suction (Tietz, et al., 2018).

In conclusion, based on IVIVC studies assessed for oral formulations, the main *in vitro* parameter, which has been used to correlate with *in vivo*, is the fraction dissolved obtained from dissolution tests. This type of correlation seeks to establish a link between *in vitro* and *in vivo* dissolution, which would be directly related to the *in vivo* input rate of a drug, mainly for highly permeable substances.

4.4. In vivo data

Pharmacokinetic studies are the way to elucidate the behavior of a drug in the body when administered through a dosage form (Derendorf & Meibohm, 1999). Indeed, some characteristics of these studies should be adequately selected to have reliable results for IVIVC purposes. Adequate sample size, design, population, and bioanalytical method are fundamental characteristics to perform a pharmacokinetic study and to have useful data. Subjects should be standardized as much as possible and acceptable to minimize intra and inter individual variation (Nishant, et al., 2011; ATKINSON, 2007).

Generally, concentration-time profile generated from a pharmacokinetic study is treated previously to the IVIVC approach to relate directly to the *in vitro* release rate. First, *in vivo* data are converted to fraction of dose absorbed or fraction absorbed 'Fa', to have the "pure" absorption process and, consequently, to be possible correlate directly with *in vitro* release (fraction dissolved). In other words, it is necessary to "remove" the elimination process of the absorption curve (initial phase after administration), since the *in vitro* assay (e.g. dissolution test) does not predict the *in vivo* elimination rate of a drug. For oral formulations, the traditional deconvolution/convolution-based approach is the most common methodology to establish an IVIVC level A.

Wagner–Nelson (Wagner & Nelson, 1964) and Loo-Riegelman (Wagner, 1975) are model-dependent methods based on one and two compartments, respectively. Wagner-Nelson has the great advantage of not requiring additional *in vivo* data beyond oral plasma profile, while the Loo–Riegelman method requires intravenous dosing data. Numerical deconvolution is a model-independent method that requires *in vivo* plasma data from an oral solution, or intravenous, as the unit impulse response, UIR. All three methods have limitations, but the requirement of additional data in addition to oral plasma data (from tablet or capsule) significantly limits the application of the Loo-Riegelman and numerical deconvolution methods (Langenbucher, 2003; Margolskee et al., 2016). Wagner-Nelson, Loo-Riegelman and numerical deconvolution are considered conventional methods and widely applied for IVIVC models. Additionally, the mechanistic absorption method, based on physiologically *in silico* tools such as GastroPlus™, has been used to predict oral drug absorption, since this approach allows to estimate separately the different processes that are involved in drug systemic absorption: dissolution, permeation, GI transit time, gut wall metabolism and first pass metabolism (Sjögren et al., 2013; Lin & Wong, 2017; Pathak et al., 2017). Among the IVIVC studies assessed (N = 50), the most frequently applied model for deconvolution was Wagner-Nelson (26 studies), followed by numerical deconvolution (6 studies), Loo-Riegelman (one study) and mechanistic absorption model using GastroPlus™ software (one study). For the remaining studies, deconvolution model was either not described, or it was not applied. Considering the distribution of deconvolution models found in this review work, the choice for Wagner-Nelson reflects that this model has been widely applied for IVIVC purposes and it would confirm that scientists, when possible, opted for a simpler and more practical model to deconvolute *in vivo* data.

Regarding the population applied for IVIVC purposes, Fig. 4 represents the distribution of *in vivo* models found in the assessed studies. As observed, dogs and humans have been the main models applied for IVIVC, responding for 19 and 14 studies assessed, respectively (N = 50). These categories were followed by rats (6), rabbits (5), and pigs (2). In 4 of them, the *in vivo* model was not declared.

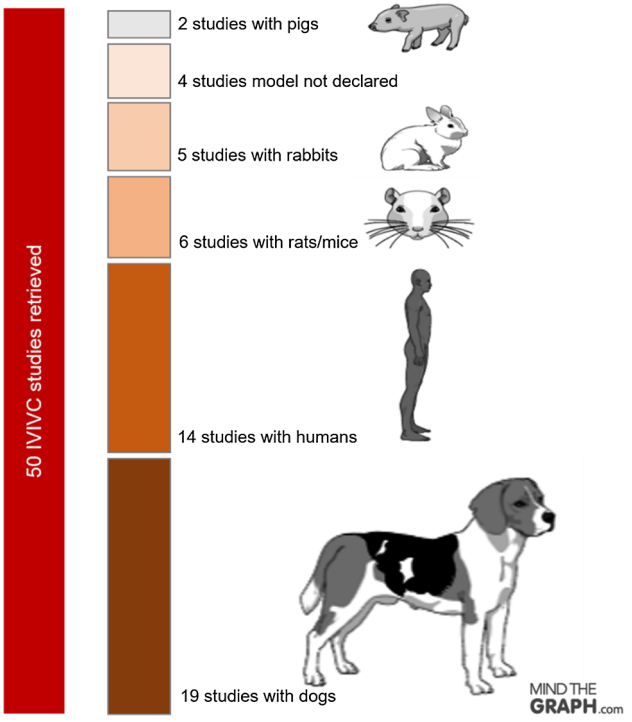

Fig. 4. Distribution of the *in vivo* models applied in the IVIVC studies retrieved (N = 50).

Unexpectedly, animal models (dog, rat, rabbit, and pig) represented 64% of the IVIVC studies assessed in the literature sampling assessed. Two main reasons may be discussed regarding this scenario. Firstly, the majority of IVIVC studies (published in literature) are being accomplished just for early formulation development, and not for regulatory purposes. Secondly, and in contrast, many studies with humans, with regulatory purposes and for clinical formulation development, are not published due to confidential and strategic reasons from the pharmaceutical industry, as well as lack of encouragement and/or interest of scientists for publication of the data. Other important reasons may be mentioned, such as high costs and large amounts of time to have a validated IVIVC in humans.

4.5. IVIVC level, number of formulations, validation and predictability

Levels A, B, and C IVIVC are clearly defined in some regulatory guidelines (EMEA, 1999; FDA, 1997). Level A, as a point-to-point correlation, represents the most informative class of correlation that considers complete *in vivo* and *in vitro* profiles. Based on FDA guidance (FDA, 1997), an IVIVC may be defined with a minimum of two formulations with different release rates (e.g. highest and lowest release rate formulations); three or more formulations with different release rates are recommended. In addition, the IVIVC should be evaluated to demonstrate its capacity to predict the *in vivo* performance of an oral drug formulation based on its *in vitro* dissolution characteristics and whether this model is maintained over a range of *in vitro* dissolution release rates and manufacturing changes (e.g. changes in excipients' proportion or manufacturing parameters). Predictability may be evaluated in two ways: internally or externally, depending on the intended application. Internal predictability is based on the initial data used to define the IVIVC model; in other words, it is based on a retrospective calculation of initial data. Differently, external predictability is assessed when an additional formulation (new dataset) is applied in the IVIVC model established (Cardot & Davit, 2012). In general, the combination of both internal and external assessments is recommended. For product development, to choose the best prototype for bioequivalence study, Cmax and AUC are essential parameters for testing IVIVC predictability. Moreover, these parameters must be assessed and established when IVIVC is applied for biowaiver in post-approval changes. Both internal and external predictabilities must be assessed after convolution process (application of *in vitro* data on IVIVC to obtain plasma concentration profile predicted), comparing the data observed versus data predicted. Average absolute percent prediction error (PE) between observed and predicted must not exceed 10% and individual PE for each formulation must not exceed 15%. If these criteria are not met, IVIVC is considered inconclusive, and should not be considered a surrogate for bioequivalence (FDA, 1997).

Fig. 5 demonstrates a schematic flow to establish a level A IVIVC, and its subsequent predictability assessments (internal and external).

Of the 50 studies applied in the data extraction (Table 1), 39 of them (78%) did not show any validation data and/or proof of predictability of the IVIVC. For these studies, only a point-to-point relationship between *in vitro* and *in vivo* data has been demonstrated. Although this approach (point-to-point relationship) is considered the highest IVIVC level to predict *in vivo* behavior though *in vitro* tests, a minimum number of formulations for validation and predictability evaluation should be considered to demonstrate if an IVIVC was constructed adequately. The findings of our work regarding the absence of validation and/or predictability assessment are consistent with the data published by Kaur et al. (2015). In this article, the authors reported a list of recurring common deficiencies related to IVIVC data in the abbreviated new drug application (ANDA) submissions based on FDA databases from 1996 to 2014. The list includes failure to assess external and/or internal predictability in the IVIVC model. In many cases, the model did not accurately predict plasma concentration profiles and pharmacokinetic parameters in the range of release rates tested.

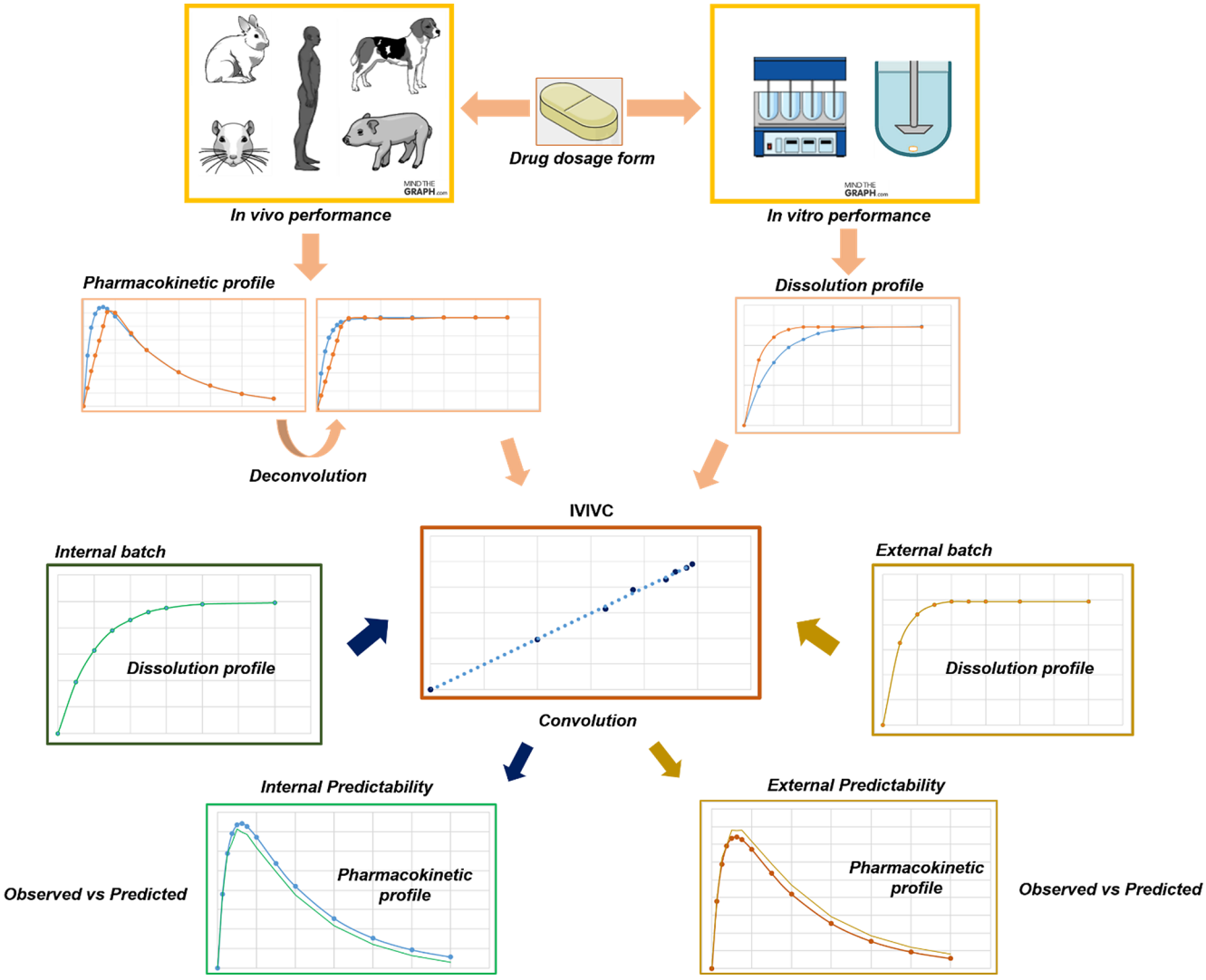

Fig. 5. Schematic flow to establish a level A IVIVC and its predictability assessments.

Considering the articles which showed validation data and/or proof of predictability of the IVIVC (11 of 50 studies examined), it is important to mention that most of them applied two or three formulations, with different release rates, for validation of IVIVC model. This approach is consistent with FDA guidance (FDA, 1997) that states IVIVC should be demonstrated consistently with two or more formulations with different release rates. Another relevant feature of those studies was the application of PE criteria between observed and predicted values in order to consider IVIVC model validated. Cmax and AUC parameters were considered in the predictability assessment as recommended by FDA guidance (FDA, 1997).

4.6. Distribution of articles published during the period assessed

To observe the distribution of articles published regarding the use of IVIVC for oral formulation development during the period assessed, Fig. 6 is presented.

Considering the last two years (2017 – 2018) of the period searched, it is possible to observe a significant growth in the number of publications of IVIVC studies for oral formulations. This fact might be related to the greater interest of scientists in the use of IVIVC for oral formulation development and in the publication of these data. In this way, if a constant growth in the number of publications of IVIVC studies is achieved in the next years, it can help not only academic scientists but also the pharmaceutical industry, which will be able to access more robust data.

5. Conclusion

Recent advances in the development of new methodologies that mimic GI conditions or other regions of the body has been observed, mainly with the development of multi-compartmental apparatuses that simulate environments and processes concomitantly (disintegration, dissolution and permeation). In the same sense, mathematical models for modeling have been implemented in the field of pharmacokinetics to create algorithms and applications in extrapolation of data to other populations or in specific pathological condition. In this context, IVIVC is currently supported by several tools that allow advancing in data correlation, as well as mimicking more accurately the conditions *in vivo* from *in vitro* assays/technologies.

Despite the observed advances of these tools, the sample of articles extracted from the two databases used in this review demonstrated that there are still very few published works with advanced technologies and that the application has been mainly in the early stage, and not for regulatory purposes. The following highlights have been described, based on discussion session, to summarize the main findings observed in the articles assessed:

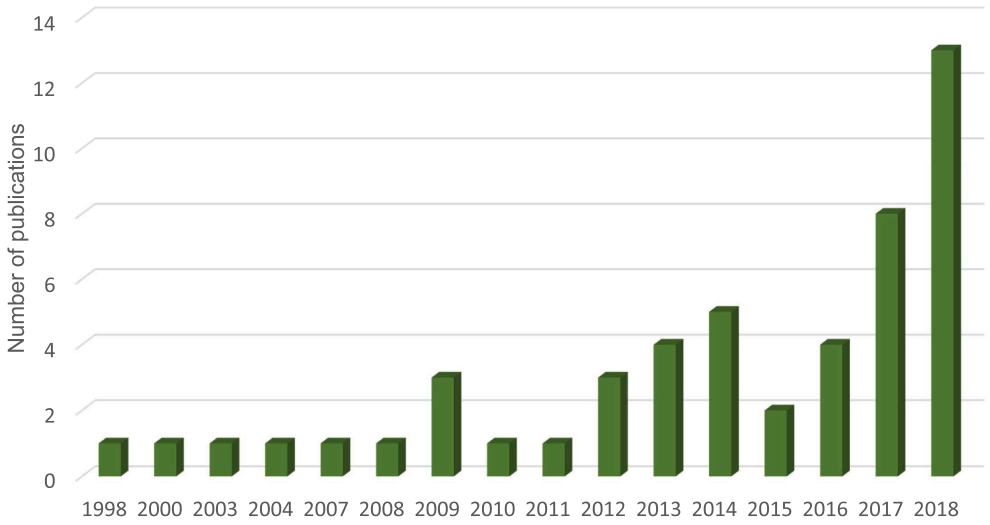

Fig. 6. Distribution of articles published regarding the use of IVIVC for oral formulation development during the period searched (1998–2018).

- MR dosage form has been the most applicable (54%) for IVIVC approaches;
- BCS classes I and II have been the most classes used for IVIVC;
- USP II (paddle) was the most (52%) applicable apparatus for IVIVC purposes;
- 70% of the IVIVC studies assessed used dissolution profile data, specifically fraction dissolved, for IVIVC approaches;
- Wagner-Nelson is the most frequently applied deconvolution model for IVIVCs (26 of 50 IVIVC studies);
- 78% of the IVIVC studies assessed did not show any validation and/or predictability data to prove the applicability of the IVIVC model; and
- The last two years (2017–2018) of the period searched showed a significant growth in the number of publications of IVIVC studies for oral formulations.

Based on the articles retrieved from both databases applied in our review, it was possible to gather a significant literature sample regarding the use of IVIVC in the development of oral formulations. Data analysis from retrieved articles showed the main characteristics of the studies, such as applied mathematical models, apparatus, main BCS classes, dosage forms, *in vivo* and *in vitro* models, among others. A discussion was completed based on these data, which allowed to address strengths and weaknesses in this area in a broad, comprehensive fashion. Additionally, a database of 45 different substances has been showed in this article and may serve as a consultation for researchers who intend to work with these drugs and dosage forms for IVIVC approaches.

Finally, this article contains an important screenshot of the use of IVIVC in the oral formulation development, as well as a view on trends and improvements needed in this area.

6. Perspectives

IVIVC is considered a tool of high potential to improve the success rate in bioequivalence studies and contributes to the registry applicants (e.g. pharmaceutical industry) to know precisely the quality attributes of their product for a rational/assertive development and possible post-approve changes. From this perspective, IVIVC approaches must be increasingly encouraged in R&D teams from pharmaceutical industries and research centers. Another important point to improve the use of this tool would be to create a harmonized and specific guideline. A possible way to do this may be to create a working group in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) to develop a guideline proposal for the evaluation of agencies around the world. Consequently, there would be an encouragement for teams to apply IVIVC in their product development, as well as harmonized concepts among the main regulatory agencies. Likewise, researchers must publish more articles in this area, so that a broad database would be available in the literature for consultation.

The ideal scenario for an IVIVC model is constructed based on a multidisciplinary team, very well-trained, with micro and macro views in pharmaceutical product development, as well as harmonized concepts for acceptability in different regulatory agencies. Galenic, analytical, quality assurance, clinical, biopharmaceutic, project management and business teams working together since the beginning of the project, and supported with tools such as IVIVC, QbD, DoE, etc., would bring significant time, cost and competitiveness to the product development process, promoting more pharmaceutical products on the market and greater access to medicines for the population. Therefore, the encouragement and initiatives in this area are extremely important, mainly from academic and pharmaceutical industry experts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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