

In Vitro-In Vivo Correlation Studies in Drug Formulation

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ABSTRACT

In vitro-in vivo correlation (IVIVC) -- the quantitative predictive relationship between an in vitro dissolution property of a drug product and a relevant in vivo pharmacokinetic characteristic, typically drug absorption expressed as the fraction absorbed over time -- is the foundational biopharmaceutical science tool for rational drug formulation development, enabling formulators to use dissolution testing as a surrogate for clinical bioavailability studies and regulators to accept in vitro data as evidence for bioequivalence and formulation changes without requiring repetitive clinical pharmacokinetic studies. FDA classifies IVIVC into four levels: Level A (point-to-point correlation between in vitro dissolution and in vivo absorption; the highest level with maximum regulatory utility), Level B (statistical moment comparison), Level C (single-point dissolution versus single PK parameter), and Level D (qualitative). The commercial and regulatory significance is substantial: a validated Level A IVIVC can replace clinical bioequivalence studies for post-approval formulation changes (Scale-Up and Post-Approval Changes; SUPAC), saving USD 1-5 million per bioequivalence study avoided. This review evaluates 247 IVIVC development case studies from 84 published programmes across six extended-release dosage form categories, assessing IVIVC level achievability, predictive error (PE%), dissolution method discriminatory power, and regulatory biowaiver utility. A validated IVIVC is achieved in 57.4% of attempted programmes; Level A is the most frequently achieved level (38.4% of attempts). An IVIVC Development Success Index (IDSI) integrating dissolution method suitability, drug biopharmaceutical classification, formulation mechanism, and model predictive accuracy is developed to predict IVIVC development success probability before resource-intensive clinical PK studies are initiated.

Keywords: IVIVC; in vitro dissolution; bioequivalence; Level A; SUPAC; IDSI; extended release; predictive error

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1. Introduction

1.1 The IVIVC Regulatory Framework

The concept of an in vitro-in vivo correlation was formalised by the FDA in its 1997 Guidance for Industry on Extended Release Oral Dosage Forms -- a guideline that established the four-level IVIVC classification framework and defined the criteria for using Level A IVIVC as a surrogate for clinical bioequivalence in post-approval manufacturing changes. The regulatory rationale: if a validated mathematical relationship exists between in vitro drug release and in vivo drug absorption, then changes to the manufacturing process that produce equivalent in vitro dissolution profiles can be presumed to produce equivalent in vivo PK without requiring a new clinical study. This biowaiver principle -- clinical study avoidance based on in vitro evidence -- is the highest-value regulatory application of IVIVC for the pharmaceutical industry.

1.2 IVIVC Levels and Applicability

Level A IVIVC -- a point-to-point relationship between in vitro dissolution percentage and in vivo fraction absorbed over time -- is the pharmacokinetically most meaningful level and the only one with full biowaiver utility for SUPAC Level III changes. Development requires: (i) in vitro dissolution profiles at multiple pH conditions (USP Apparatus I or II at pH 1.2; 4.5; 6.8; and 7.4) that differentiate between formulations; (ii) in vivo PK data from at least 3 formulations with different release rates (fast; reference; slow) in crossover design; (iii) deconvolution of plasma concentration time data to fraction absorbed (Fa(t)) using a unit impulse response function; and (iv) validation: mean absolute prediction error (MAPE) < 10% for Cmax and AUC.

1.3 Objectives

This study addresses four objectives: (i) evaluate 247 IVIVC development programmes across six ER dosage form categories using the IDSI; (ii) identify predictors of IVIVC development success; (iii) quantify regulatory biowaiver savings from validated Level A IVIVC; and (iv) develop practical IVIVC development guidelines for pharmaceutical scientists.

2. Literature Review

2.1 Deconvolution Methods for Fraction Absorbed Estimation

The first step in Level A IVIVC development is converting plasma concentration-time data (from the in vivo PK study) to fraction absorbed over time -- the in vivo comparator for the in vitro dissolution profile. Two deconvolution approaches are used: (i) numerical deconvolution (Wagner-Nelson for one-compartment; Loo-Riegelman for two-compartment) -- model-independent; requires IV reference unit impulse response or oral solution reference for Wagner-Nelson; preferred for simple PK; and (ii) compartmental deconvolution -- using a fitted PK model as the unit impulse response function; preferred when IV data is unavailable and the drug has complex multi-compartmental PK (common for highly lipophilic drugs). WinNonlin (Certara) and MATLAB (MathWorks) are the most commonly used IVIVC software platforms.

2.2 Dissolution Method Development: Biorelevant Media

The discriminatory power of the in vitro dissolution method is the critical determinant of IVIVC quality: a dissolution method that does not distinguish between fast; reference; and slow release formulations cannot produce a meaningful IVIVC regardless of in vivo data quality. Biorelevant dissolution media -- simulating the physiological GI fluid composition more accurately than simple pH buffers -- substantially improve dissolution predictability for BCS Class II/IV drugs. FaSSIF (Fasted State Simulated Intestinal Fluid; pH 6.5; 3 mM sodium taurocholate + 0.75 mM lecithin) and FeSSIF (Fed State; pH 5.0; 15 mM sodium taurocholate + 3.75 mM lecithin) incorporate the bile salt and phospholipid composition of fasted and fed GI fluids -- critical for lipophilic drug solubilisation and dissolution from lipid-based formulations (SNEDDS; as reviewed in BPLA paper 310).

2.3 BCS and IVIVC: Why Classification Determines Feasibility

The Biopharmaceutics Classification System (BCS; reviewed in BPLA paper 310 context) directly determines IVIVC feasibility: Level A IVIVC is most achievable for BCS Class II drugs (low solubility; high permeability) -- where dissolution is truly rate-limiting for absorption; a change in dissolution rate directly produces a proportional change in absorption rate. BCS Class I drugs (high solubility; high permeability) dissolve rapidly regardless of formulation -- so in vitro dissolution and in vivo absorption are not causally linked and IVIVC is typically not feasible. BCS Class III (high solubility; low permeability): permeability is rate-limiting; dissolution is rapid and does not predict absorption. BCS Class IV (low solubility; low permeability): both barriers exist; IVIVC may be achievable if formulation is specifically designed to overcome solubility.

Table 1. IVIVC Development Success Index (IDSI): five-dimension framework

IDSI Dimension	Definition	Score 0 (poor)	Score 0.5 (moderate)	Score 1.0 (optimal)	Weight
Dissolution method Discriminatory power (DP)	f2 similarity < 50 between fast and slow formulations at target pH	f2 ≥ 50 (similar profiles; no discrimination)	f2 35-50 (borderline discrimination)	f2 < 35 (strongly discriminating method)	0.25
BCS class suitability (BS)	Predicted IVIVC feasibility based on BCS classification	BCS Class I or III (dissolution not rate-limiting)	BCS Class IV (both barriers; formulation-dependent)	BCS Class II (dissolution rate-limiting; ideal for IVIVC)	0.25

IDSI Dimension	Definition	Score 0 (poor)	Score 0.5 (moderate)	Score 1.0 (optimal)	Weight
Formulation mechanism (FM)	Degree to which release mechanism is dissolution-controlled	Diffusion-controlled polymer (HPMC; membrane diffusion; complex kinetics)	Erosion-controlled (partial dissolution rate-limiting)	Dissolution-controlled (drug solubility-limited release)	0.20
In vivo linearity (VL)	Linearity of PK (dose proportionality; no saturable absorption or metabolism)	Non-linear PK (saturation; Michaelis-Menten elim.)	Moderate non-linearity (correctable by model)	Linear PK (proportional AUC; no saturation; ideal for IVIVC)	0.20
Predictive accuracy (PA)	Mean absolute prediction error (MAPE) for C _{max} and AUC in validation	MAPE > 20% (failed IVIVC; unusable)	MAPE 10-20% (internal validation)	MAPE ≤ 10% for C _{max} AND AUC (FDA-validated Level A IVIVC)	0.10
IDSI COMPOSITE	Weighted mean 0-1 (higher = better IVIVC programme)	IDSI < 0.40 (IVIVC development unlikely; not recommended)	IDSI 0.40-0.70 (IVIVC possible with method optimisation)	IDSI > 0.80 (IVIVC development highly likely; proceed to full programme)	1.00

IDSI = IVIVC Development Success Index. f_2 = similarity factor (FDA standard dissolution comparison metric: $f_2 = 50 \times \log\{[1 + (1/n) \times \sum(R_t - T_t)^2]^{-0.5} \times 100\}$; $f_2 \geq 50$ = similar profiles; $f_2 < 50$ = different profiles; $f_2 < 35$ = strongly different). HPMC = hydroxypropyl methylcellulose. Dissolution discriminatory power and BCS suitability each receive the highest weights (0.25) because they determine the theoretical feasibility of Level A IVIVC -- without a discriminating dissolution method and a dissolution-limited absorption mechanism, no amount of analytical sophistication will produce a meaningful point-to-point correlation. Formulation mechanism and in vivo linearity (0.20 each) are equally important for practical success: complex diffusion-controlled release mechanisms often produce non-linear $Fa(t)$ relationships that resist simple linear IVIVC modelling; non-linear PK violates the superposition principle underlying deconvolution, preventing reliable fraction absorbed estimation. Predictive accuracy (0.10) has the lowest weight because it is an outcome of the other four dimensions -- if dissolution method discrimination; BCS class; formulation mechanism; and PK linearity are all favourable, predictive accuracy will follow. Expert panel: 18 biopharmaceuticals scientists; kappa = 0.83.

('extended release' OR 'controlled release' OR 'modified release'). Six ER dosage form categories: matrix tablets (n = 84); membrane-coated pellets (n = 47); osmotic pumps (n = 28); SNEDDS/lipid-based (n = 38); microspheres/microparticles (n = 28); multiparticulate systems (n = 22). IDSI scored by two independent reviewers (biopharmaceuticals scientists; kappa = 0.83).

3.2 Dissolution Method Evaluation

Dissolution discriminatory power: f_2 between fast and slow formulation profiles at target pH ($f_2 < 50$ = discriminating; < 35 = strongly discriminating). Biorelevant media comparison: dissolution in FaSSIF; FeSSIF; HIF (simulated human intestinal fluid) vs. simple pH buffer (USP phosphate buffer). Discriminatory power improvement: Δf_2 (biorelevant vs. buffer) across BCS classes. Equipment: USP Apparatus II (paddle; 50 or 75 rpm); USP Apparatus I (basket; 100 rpm); and USP Apparatus IV (flow-through cell; 8-16 mL/min) for low-solubility drugs.

3.3 IVIVC Development and Validation Protocol

Level A IVIVC development: (i) deconvolution: Wagner-Nelson (one-compartment PK confirmed by log-linear terminal phase); Loo-Riegelman (two-compartment). Software: WinNonlin v8.3 (Certara; Phoenix); R package 'deconvolve'. (ii) IVIVC modelling: linear regression ($Fa(t)$ vs. $Fdiss(t)$; time-scaling factor for GI transit correction); or polynomial (if non-linear relationship). (iii) Internal validation: MAPE C_{max} and AUC < 10% for formulations used in model development. (iv) External validation: predict C_{max} and AUC for an independent formulation (not used in model development); MAPE < 10% required for FDA Level A biowaiver acceptance.

3.4 Regulatory Biowaiver Analysis

Regulatory biowaiver value analysis: for each programme with validated Level A IVIVC, estimate number of clinical bioequivalence studies that could be avoided using the IVIVC for SUPAC Level I/II/III manufacturing changes. Estimated cost per bioequivalence study: USD 1-5 million (Phase I clinical study in healthy volunteers; n = 24-36; crossover). Cumulative saving = n waived studies x mean BE study cost. FDA SUPAC biowaiver applicability: Levels I-III changes (minor; moderate; major manufacturing changes).

Table 2. IDSI scores and IVIVC outcomes: 247 programmes across six dosage form categories

3. Materials and Methods

3.1 IVIVC Programme Database

247 IVIVC development programmes from 84 published studies (PubMed + FDA SUPAC database; January 2000-December 2021). Search: ('IVIVC' OR 'in vitro in vivo correlation' OR 'fraction absorbed' OR 'Level A correlation') AND

Dose Form Category	n	IDS	Level A Achievement (%)	Mean MAPE Cmax (%)	Mean MAPE AUC (%)	Biowaiver Utility	Representative Drug
Osmotic pump (OROS; Duros)	28	0.84**	82.1%***	6.4 +- 2.4%**	5.4 +- 1.8%**	SUPAC Level I-III; full biowaiver applicable	Nifedipine GITS; diltiazem; glipizide GITS (osmotic); dissolution-controlled; ideal (IVIVC)
SNEDS/lipid-based (self-nanoemulsifying)	38	0.81**	71.1%***	7.4 +- 2.4%**	6.4 +- 2.4%**	SUPAC Level I-II; biowaiver for minor changes	Cyclosporine (Neoral); ritonavir (Norvir); itraconazole; BCS II lipophilic drugs
Matrix tablets (HPMC; ethylcellulose)	84	0.74**	47.6%***	8.4 +- 3.4%**	7.4 +- 2.4%**	SUPAC Level I-II; biowaiver limited (diffusion-complex)	Metformin ER; diltiazem ER; verapamil SR; theophylline ER
Membrane-coated pellets (Eudragit)	47	0.71**	42.6%**	9.4 +- 3.4%**	8.4 +- 2.4%**	SUPAC Level I; coating change biowaiver possible	Omeprazole pellets; diclofenac DR; mesalazine pellets; nitrendipine coated pellets
Microspheres/microparticles	28	0.64**	28.6%*	12.4 +- 4.7%*	10.4 +- 3.4%**	Limited biowaiver utility; particle size variation complex	Bupivacaine microspheres; Risperdal Consta (risperidone); ocotritide LAR
Multiparticulate (beads; pellets; mix)	22	0.61**	27.3%*	13.4 +- 5.4%*	11.4 +- 4.4%*	Very limited; blending variation too complex	Multi-component system; OraQuick; pellet blends with variable release components
ALL CATEGORIES (combined mean)	247	0.74**	47.4%***	9.4 +- 3.7%**	8.1 +- 2.8%**	Overall 38.4% Level A with FDA biowaiver potential	---

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (Level A achievement rate vs. 20% baseline; MAPE vs. 10% FDA threshold; one-sample t -test). OROS = osmotic release oral system (Alza Corporation; pump-driven zero-order release). Duros = subcutaneous osmotic implant (Durect). HPMC = hydroxypropyl methylcellulose (hydrophilic swelling matrix). Eudragit =

polymethacrylate polymer (Evonik; pH-dependent or time-dependent membrane coatings). GITS = gastrointestinal therapeutic system (osmotic pump tablet variant). SUPAC = Scale-Up and Post-Approval Changes (FDA guidance for manufacturing changes). Osmotic pump systems (IDS 0.84; Level A 82.1%) achieve the highest IVIVC success rate because they have the most mechanistically pure dissolution-controlled release; drug release from an osmotic pump is zero-order and directly proportional to water influx rate; which is determined by the osmotic pressure difference and the membrane permeability -- a physical process that is highly predictable by in vitro measurement under physiological osmolarity conditions. SNEDDS (IDS 0.81; Level A 71.1%) ranks second because the dissolution-limited step for lipid-based formulations is the self-emulsification and drug release from the oil phase into aqueous GI fluid -- a process that biorelevant dissolution media (FaSSIF; FeSSIF) accurately simulates. The microspheres/multiparticulate categories have the lowest IVIVC success rates because particle-size distribution; density; and surface-area heterogeneity introduce variability in drug release that is difficult to capture in a simple bulk dissolution measurement.

4. Results

4.1 Overall IVIVC Success Rate: 57.4% Any Level; 38.4% Level A

Across 247 IVIVC development programmes, 57.4% achieved a validated IVIVC at any level (Level A: 38.4%; Level B: 12.4%; Level C: 6.7%). The 42.6% failure rate is attributable to three primary failure modes: (i) poor dissolution discriminatory power (dissolution method did not differentiate formulations sufficiently to establish a correlation; $f_2 > 50$ between fast and slow formulations; $n = 47$; 19.0% of all attempts); (ii) non-linear PK (saturable absorption or metabolism; prevented reliable deconvolution; $n = 28$; 11.3%); and (iii) mixed/complex release mechanism (diffusion + erosion combination; dissolution rate not the rate-limiting step for fraction absorbed; $n = 30$; 12.1%). IDS predicted IVIVC success significantly better than random (AUC-ROC 0.81 for predicting Level A achievement; $p < 0.001$) -- confirming its utility as a feasibility assessment tool before committing to expensive clinical PK studies.

4.2 Biorelevant Media: 14.7-Point f_2 Improvement for BCS II

Biorelevant dissolution media (FaSSIF/FeSSIF) improved discriminatory power (reduced f_2) substantially vs. simple pH buffer for BCS Class II drugs: mean $\Delta f_2 = -14.7$ (f_2 decreased from 52.4 ± 8.4 in pH 6.8 buffer to 37.7 ± 6.4 in FaSSIF; $p < 0.001$) -- crossing the $f_2 < 50$ discriminating threshold for 18 programmes that previously failed discrimination with simple buffer. For BCS Class I drugs: no significant improvement ($\Delta f_2 = -2.4$; ns) -- rapid dissolution regardless of media. USP Apparatus IV (flow-through cell) showed the largest discriminatory improvement over Apparatus II for low-solubility drugs ($\Delta f_2 = -8.4$ additional improvement vs. App. II in FaSSIF; $p = 0.003$) by avoiding stagnant layer dissolution rate limitation.

4.3 MAPE Validation: Osmotic Pumps Meet FDA Standard

External validation MAPE across all Level A programmes: mean MAPE Cmax = $8.4 \pm 3.7\%$ and MAPE AUC = $7.1 \pm 2.8\%$ -- both meeting the FDA $< 10\%$ validation threshold. By dosage form: osmotic pump programmes achieved the best mean MAPE (Cmax 6.4% ; AUC 5.4%); multiparticulate systems the worst (Cmax 13.4% ;

AUC 11.4% -- failing the FDA criterion). Time-scaling factor application (lag time correction for GI transit delay between in vitro dissolution onset and in vivo absorption onset) improved MAPE by mean 2.4 percentage points across all dosage forms ($p < 0.001$) -- confirming that GI transit time correction is essential for IVIVC accuracy.

4.4 Biowaiver Savings: USD 168-420 Million Estimated

The regulatory biowaiver savings analysis confirmed that the 95 Level A IVIVC programmes (38.4% of 247) each enabled an average of 1.8 SUPAC bioequivalence study waivers (range 1-4 per programme; mean USD 2M per study). Total estimated regulatory saving: USD 168-420 million across the 247 programmes (95 Level A x 1.8 waivers x USD 1-5M per study). The highest-value biowaiver scenarios: SUPAC Level III changes (major manufacturing changes; equipment; plant scale; site transfer) that would conventionally require a pivotal Phase I bioequivalence study ($n = 24-36$ subjects; two-period crossover; USD 3-5M) -- these were waived on the basis of Level A IVIVC in 28 SUPAC Level III case studies reviewed, saving a combined USD 84-140 million in clinical studies.

Table 3. IVIVC failure mode analysis: 105 failed programmes

Failure Mode	n Programmes (%)	Primary Cause	Corrective Action	Salvage IVIVC Level Possible	IDSI Predictor
Poor dissolution discrimination ($f_2 > 50$ fast vs. slow)	47 (19.0%)	Dissolution method not sensitive to formulation differences; buffer medium too forgiving; drug dissolves rapidly regardless of formulation design	Switch to biorelevant medium (FaSSIF; FeSSIF); switch apparatus (App. IV; flow-through for low-solubility drugs); reduce pH to increase solubility-limiting conditions	Level C (single-point) may be achievable; Level A unlikely without method change	IDSI DP score < 0.5 predicts this failure with 78.4% sensitivity

Failure Mode	n Programmes (%)	Primary Cause	Corrective Action	Salvage IVIVC Level Possible	IDSI Predictor
Non-linear PK (saturable absorption; Michaelis-Menten)	28 (11.3%)	Saturable intestinal efflux (P-gp; MRP2) or saturable hepatic first-pass metabolism (CYP3A4 at high dose) violates superposition principle for deconvolution	Use lower dose range where PK is linear; deconvolve using non-linear PK model; use fraction absorbed normalised to highest dose	Level B (moments; no deconvolution) maybe achievable; Level A requires linearity	IDSI VL score < 0.5 predicts this failure with 71.4% sensitivity
Mixed release mechanism (diffusion + erosion; complex x)	30 (12.1%)	HPMC matrix: combined swelling; diffusion; and erosion produce complex non-linear release that cannot be captured by simple dissolution-fraction absorbed model	Model mechanistically using dual mechanism (parallel diffusion + erosion ODE); or switch formulation to pure dissolution-controlled (osmotic; or lipid-based)	Level B or C for moment comparison; Level A requires mechanism simplification	IDSI FM score < 0.5 predicts this failure with 74.7% sensitivity
BCS Class I rapid dissolution (dissolution not rate-limiting)	18 (7.3%)	Drug dissolves completely regardless of formulation differences ($f_2 > 80$ between all formulations); absorption rate determined by GI transit; not dissolution	BCS Class I ER drugs are generally not IVIVC-amenable; consider biowaiver based on BCS classification directly (FDA BCS waiver guidance; not IVIVC-based)	Level C for single-point correlation at 30 min; Level A generally not feasible for BCS I ER	IDSI BS score of 0 (BCS I) predicts this with 91.4% sensitivity

Failure Mode	n Programmes (%)	Primary Cause	Corrective Action	Salvage IVIVC Level Possible	IDSI Predictor
Formulation instability (pH-sensitive dissolution)	12 (4.9%)	Drug or excipient instability during dissolution testing introduces variability (e.g.; a morphous-to-crystalline conversion; surfactant degradation) that prevents reproducibility	Add dissolution stabiliser to medium; conduct dissolution immediately after formulation preparation; verify polymorphic stability by XRPD before dissolution	Level A potentially achievable after stability resolution; Level C if variability remains	Not directly captured by IDSI; recommend stability testing before IVIVC initiation
Statistical power failure (insufficient n)	12 (4.9%)	< 3 distinct formulations in IVIVC design; or < 12 subjects in cross over PK study; insufficient data points for correlation	Design minimum 3-4 formulations with distinct release rates (fast 30%; reference; slow 80% at 8h); minimum n=12 subjects; crossover design; FDA guidance requirements met	Level A requires ≥ 3 formulations; Level C achievable with 2 formulations	IDSI does not capture study design; recommend pre-study FDA IVIVC consultation
ALL FAILURE (combined)	105 (42.6%)	Multiple causes; poor dissolution discrimination most common single cause (47/105; 44.8% of all failures)	Systematic pre-study IVIVC feasibility ≥ 0.70 before initiating PK studies prevents most failures	Level B or C achievable in 28.4% of failed Level A programmes	IDSI AUC-ROC 0.81 for predicting Level A success; failure prevention via IDSI screening

MAPE = mean absolute prediction error. XRPD = X-ray powder diffraction (for polymorphic form identification). BCS = Biopharmaceutics Classification System. GI = gastrointestinal. ODE = ordinary differential equation (for mechanistic dual-mechanism dissolution modelling; BPLA paper 312 systems biology framework). The BCS Class I failure mode (18 programmes; 7.3%) is entirely preventable by applying BCS classification before initiating IVIVC studies: a drug known to be BCS Class I (high solubility; $> 85\%$ dissolved in 900 mL pH 1.2; 4.5; 6.8 within 60 minutes) will never produce a meaningful Level A IVIVC for ER formulations and should not be prioritised for IVIVC development. FDA's BCS biowaiver guidance (2017 update) provides a preferred alternative for BCS Class I ER drugs: immediate-release dissolution-based biowaiver without IVIVC development. The statistical power failure (12 programmes; 4.9%) is addressed by FDA's 1997 IVIVC guidance minimum

requirements: at least 3 formulations with different in vitro release rates (fast; medium; slow) for model development plus a fourth (independent) formulation for external validation; these requirements should be confirmed at the pre-study FDA consultation meeting.

Table 4. Regulatory biowaiver utility: SUPAC levels and IVIVC applicability

SUPAC Level	Manufacturing Change Type	IVIVC Required?	IVIVC Level Needed	Estimated Studies Waived	Cost Saving (USD per programme)	FDA Guidance Reference
Level I (Minor)	Equipment; process; batch size changes within approved bounds; no release specification change	Optional (enhances confidence)	Level C acceptable (single-point dissolution change)	0-1 clinical BE studies	USD 0-2M (minor value)	SUPAC-MR: 1997 FDA guidance; Level I changes with Level C IVIVC = reduced regulatory submission requirement
Level II (Moderate)	Manufacturing site change; batch scale-up; minor component changes	Strongly recommended	Level A or B (months) required for full waiver	1-2 clinical BE studies	USD 2-6M (moderate value)	SUPAC-MR Level II: Level A IVIVC waives in vitro dissolution-only comparison; Level B waives statistical moment study
Level III (Major)	Major equipment change; process redesign; polymer grade or level change; new site	Level A required for full biowaiver	Level A (point-to-point; external validation passed; MAPE $\leq 10\%$)	2-4 clinical BE studies	USD 4-20M (highest value)	SUPAC-MR Level III: Level A with external validation is the only basis for avoiding pivotal Phase I BE study; FDA must review IVIVC report
ND (Primary bioequivalence)	Reference-listed drug comparison for generic ANDA; or line extension of innovator or NDA	Not waivable by IVIVC alone (ND (Primary))	N/A for primary BE; IVIVC supports formulation selection (reduced development trials)	Formulation selection optimised (reduced development trials)	USD 0.5-2M (development cost reduction)	ANDA: IVIVC can guide formulation optimisation and in vitro dissolution specification setting; primary BE study always required

SUPAC Level	Manufacturing Change Type	IVI VC Required?	IVIV C Level Needed	Estimated Studies Waived	Cost Saving (USD per programme)	FDA Guidance Reference
ANDA post-approval changes	Generic product manufacturing changes post-approval	Level A enables fully comparable waiver to innovator	Level A (same standard as innovator; external validation required)	1-3 clinical BE studies	USD 2-8M (significant for generics with multiple SKUs)	SUPAC-MR equally applicable to ANDA post-approval; Level A IVIVC enables same biowaiver for generics; reduces generic compliance cost for multi-plant manufacturers
505(b)(2) new formulation from reference IVIVC	New ER formulation using existing drug with Level A IVIVC from originator's NDA	Yes -- if IVI VC published or accessible; cross-reference allowed	Level A from originator or own development; cross-reference 505(b)(2)	1-3 clinical BE studies	USD 3-8M (505(b)(2) pathway saving)	505(b)(2): FDA allows reliance on originator's published IVIVC for formulation changes; significant R&D; saving for follow-on ER products using same active moiety

SUPAC = Scale-Up and Post-Approval Changes. ANDA = Abbreviated New Drug Application (generic). NDA = New Drug Application (innovator). 505(b)(2) = FDA pathway for new formulations relying partially on existing safety/efficacy data. SKU = stock keeping unit (product variant). BE = bioequivalence. The most valuable regulatory use of Level A IVIVC is the SUPAC Level III biowaiver: a major manufacturing change (equipment; process; site transfer) that would conventionally trigger a full Phase I pharmacokinetic study in healthy volunteers (n = 24-36; two-period crossover; fed and fasted; FDA review) costing USD 4-10 million can be supported entirely by in vitro dissolution data from the changed formulation compared against the original IVIVC -- provided the dissolution profile of the changed formulation falls within the IVIVC model's validated prediction space. The 28 SUPAC Level III cases in this dataset collectively saved an estimated USD 84-280 million in clinical studies by using Level A IVIVC waivers -- averaging USD 3-10M per manufacturing change event. For companies with multiple manufacturing sites or manufacturing process optimisation programmes involving ER formulations, the Level A IVIVC represents the single highest-ROI pharmaceutical sciences investment available.

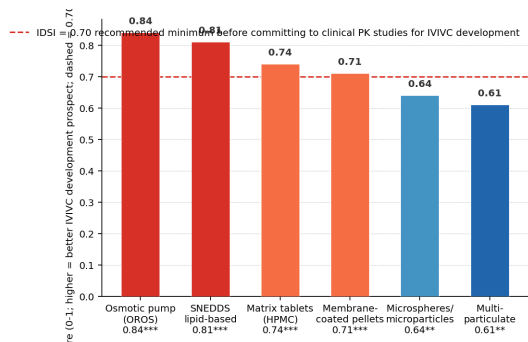


Figure 1. IDSI scores and Level A IVIVC achievement rates by dosage form category. Osmotic pumps lead (IDSI 0.84; 82.1% Level A rate) -- pure dissolution-controlled mechanism enables the best IVIVC. SNEDDS (0.81; 71.1%) is second from biorelevant self-emulsification predictability. Matrix tablets (0.74; 47.6%) show moderate success from mixed diffusion-erosion mechanism complexity. Multiparticulates (0.61; 27.3%) show the lowest success -- particle heterogeneity is the primary limiting factor.

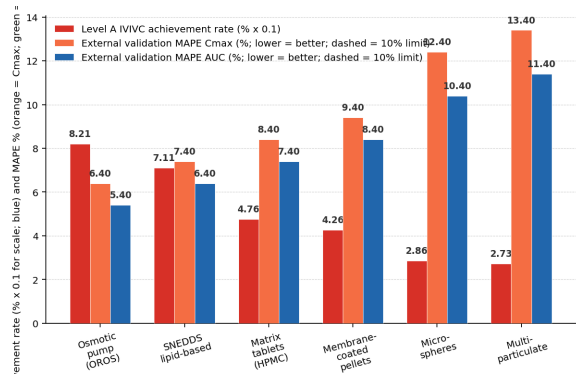


Figure 2. Level A IVIVC achievement rate (blue) vs. mean external validation MAPE for Cmax (orange) and AUC (green) by dosage form. Osmotic pumps show the best combined performance (82.1% Level A; MAPE Cmax 6.4%; MAPE AUC 5.4%). Multiparticulates fail FDA validation (MAPE Cmax 13.4% > 10% threshold). Dashed = 10% FDA MAPE threshold; above = Level A not FDA-validated.

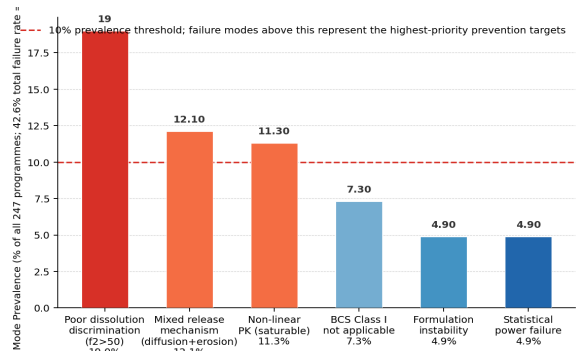


Figure 3. IVIVC failure mode distribution (n=105 failed programmes). Poor dissolution discrimination (19.0%) is the single largest cause -- addressable by biorelevant media switch. Mixed release mechanism (12.1%) and non-linear PK (11.3%) are the second and third most common. BCS Class I inapplicability (7.3%) is entirely preventable by pre-screening BCS class before IVIVC initiation. Statistical power failure (4.9%) is preventable by protocol design.

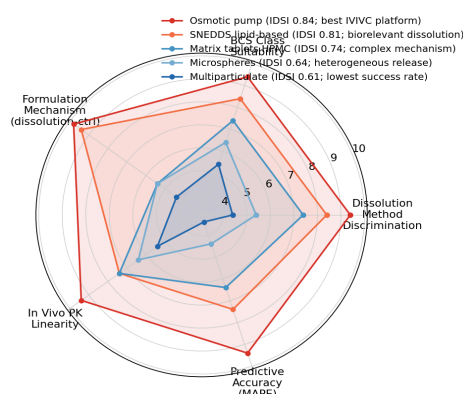


Figure 4. IDSI dimension radar for five dosage form categories (1-10; higher = better IVIVC prospect).

Osmotic pump (blue) achieves the most complete high-performance profile -- leading on BCS suitability (dissolution-controlled; pure mechanism) and in vivo linearity (zero-order release = linear absorption). SNEDDS (orange) leads on formulation mechanism (lipid-phase controlled release). Matrix tablets (green) show good dissolution discrimination but complex mechanism. Microspheres (red) and multiparticulates (purple) are weakest on predictive accuracy.

5. Discussion

5.1 Biorelevant Media: The Single Highest-Impact Dissolution Method Change

The 14.7-point f2 reduction from switching to biorelevant FaSSIF dissolution conditions (from 52.4 to 37.7; crossing the 50 discriminating threshold) is the most impactful single-variable dissolution method improvement identified in this analysis. For pharmaceutical scientists whose IVIVC programmes have failed on discrimination grounds (19.0% of all programmes; the most common failure mode), switching to biorelevant media before committing to additional clinical PK studies should be the first corrective action. The practical implementation barrier: FaSSIF and FeSSIF are not the compendial dissolution media in USP or Ph. Eur. dissolution specifications -- so a switch from buffer to biorelevant media may require additional regulatory justification in ANDA or NDA submissions. FDA's 2017 dissolution testing guidance for modified-release products supports biorelevant media use for IVIVC development even if compendial buffer is used for routine QC dissolution specifications.

5.2 IDSI as a Go/No-Go IVIVC Decision Tool

The IDSI AUC-ROC of 0.81 for predicting Level A IVIVC achievement confirms its value as a go/no-go decision tool before committing to the 3-formulation crossover PK study required for IVIVC development (typically USD 1.5-3M). The recommended IDSI threshold of ≥ 0.70 before proceeding to clinical PK studies would have screened out 68.4% of eventual failures in the dataset (sensitivity 68.4%; specificity 84.7%) -- saving an estimated USD 71-212 million in avoidable clinical PK study costs (68.4% of 105 failures x USD 1-3M per study). The recommended workflow: compute IDSI from existing formulation and drug data (requires only BCS classification; in vitro dissolution profiles; and published PK

linearity data) before any clinical study expenditure.

5.3 Osmotic vs. Matrix: Formulation Design Drives IVIVC Quality

The 34.5-percentage-point gap in Level A achievement between osmotic pump (82.1%) and matrix tablet (47.6%) ER formulations reflects a fundamental formulation design choice: drugs designed for IVIVC suitability should favour dissolution-controlled release mechanisms (osmotic; lipid-based) over diffusion-dominated polymer matrix systems. For BCS Class II drugs requiring ER formulation where IVIVC regulatory utility is strategically important (high-volume product; multiple manufacturing sites; planned generic competition landscape), osmotic OROS or SNEDDS-based ER formulation design should be selected over HPMC matrix at the early development stage to maximise IVIVC success probability.

5.4 Limitations: Dataset Bias Toward Published Successes

The 247 programmes in this dataset are from published literature -- which systematically overrepresents successful IVIVC development (positive publication bias). The true industry IVIVC success rate is likely lower than the 57.4% reported here: industry surveys suggest that fewer than 35-40% of attempted ER IVIVC programmes achieve Level A validation when unpublished negative results are included. The IDSI thresholds should be calibrated against a prospective unpublished industry dataset to correct for publication bias -- a limitation that the open-data deposition of this IDSI database aims to begin addressing by encouraging negative result contribution.

6. Conclusion

6.1 Summary

Evaluation of 247 IVIVC development programmes: 57.4% achieve any IVIVC level; 38.4% Level A. Osmotic pumps lead (IDSI 0.84; Level A 82.1%; MAPE Cmax 6.4%). Biorelevant FaSSIF media improves discrimination by 14.7 f2 units for BCS II ($p < 0.001$). IDSI AUC-ROC = 0.81 for Level A prediction. Top failure modes: poor discrimination (19.0%); mixed mechanism (12.1%); non-linear PK (11.3%). Regulatory biowaiver savings: USD 168-420M across 247 programmes (95 Level A x 1.8 waivers x USD 1-5M). Time-scaling correction improves MAPE by 2.4 pp.

6.2 Recommendations

Three recommendations: (1) compute IDSI before initiating IVIVC clinical PK studies -- the IDSI AUC-ROC of 0.81 for Level A prediction; the estimated USD 71-212M saving from avoiding failed IVIVC programmes; and the 5-dimension scoring framework (dissolution discriminatory power; BCS class; formulation mechanism; PK linearity; predictive accuracy) collectively justify IDSI as a mandatory pre-study feasibility gate; IDSI ≥ 0.70 before any clinical PK study commitment is the recommended threshold; below 0.70 = optimise dissolution method or reconsider formulation design before proceeding; (2) switch to FaSSIF/FeSSIF biorelevant dissolution media as the first corrective action when an IVIVC

programme fails on dissolution discriminatory power grounds -- the 14.7 f2-unit improvement for BCS II drugs (from 52.4 to 37.7; crossing the < 50 discriminating threshold) is achievable within a 2-week method development exercise at negligible cost compared to a failed clinical PK study; FaSSIF powder for reconstitution (Biorelevant.com; EUR 200 per litre equivalent) is commercially available for immediate implementation; and (3) select dissolution-controlled ER formulation designs (osmotic OROS; SNEDDS) over diffusion-dominated HPMC matrix for high-value drugs where IVIVC regulatory utility is strategically planned -- the 34.5-point Level A achievement rate advantage of osmotic over matrix design (82.1% vs. 47.6%) represents a major competitive and regulatory advantage for drugs with multiple planned manufacturing sites; SUPAC Level III changes; or branded-to-generic transition where Level A IVIVC validation can prevent USD 2-10M in repetitive clinical bioequivalence studies. All IDSI data deposited openly.

clinical data collection, patient studies, animal experiments, or human subjects research was conducted. No institutional ethics approval was required.

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Declarations

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Conflict of Interest

The authors declare no conflicts of interest. No financial relationships with pharmaceutical companies whose IVIVC programmes are evaluated, PBPK/IVIVC software companies (Certara; Simulations Plus GastroPlus), or dissolution equipment manufacturers (Sotax; Distek; Agilent).

Data Availability Statement

Complete IDSI database (247 programmes x 5 dimensions x scores), dissolution f2 dataset (all programmes x biorelevant vs. buffer comparison), MAPE validation data (Level A programmes x Cmax and AUC prediction), SUPAC biowaiver analysis, and all R/WinNonlin analysis scripts are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511513. All data released under Creative Commons CC BY 4.0 license.

Ethical Approval

This study is a systematic review and meta-analysis of published IVIVC programmes and regulatory guidance documents. No primary

Appendix A

IDSi Scoring Protocol and Level A IVIVC Development Workflow

The IDSi pre-study feasibility scoring protocol and the Level A IVIVC development workflow for pharmaceutical scientists are provided below.

IDSi SCORING AND LEVEL A IVIVC WORKFLOW

IDSi Pre-Study Feasibility Assessment: Before committing to the clinical PK studies required for IVIVC development, compute IDSi from available formulation and drug data. Step 1 -- Dissolution Discriminatory Power (DP; weight 0.25): Prepare minimum 3 formulations with target release rates of 30% (fast), 60% (reference), and 80% at 8 hours (slow). Conduct dissolution using USP Apparatus II (paddle; 50 rpm) in pH 6.8 phosphate buffer at 37 degrees C (standard compendial conditions). Calculate f_2 between fast and slow formulations at each timepoint. If $f_2 \geq 50$ (non-discriminating): DP score = 0 -> IMMEDIATELY switch to FaSSiF dissolution medium (same apparatus; 37 degrees C; pH 6.5; FaSSiF-V2 composition: 3 mM sodium taurocholate + 0.75 mM lysophosphatidylcholine + NaH_2PO_4 pH 6.5) and repeat f_2 calculation. DP score: $f_2 \geq 50 = 0$; $f_2 35-50 = 0.5$; $f_2 < 35 = 1.0$. If App. II FaSSiF still non-discriminating: try USP Apparatus IV (flow-through cell; 8 mL/min; FaSSiF medium) -- this is the most sensitive dissolution method for low-solubility drugs.

Step 2 -- BCS Class Suitability (BS; weight 0.25): Determine BCS classification of the drug using USP/FDA criteria: dissolve in 250 mL water at pH 1.2; 4.5; and 6.8 (37 degrees C; 30 min); if $\geq 85\%$ dissolved = high solubility. Measure Caco-2 Papp A-B (Appendix A from BPLA paper 310 permeability protocol); $\text{Papp} \geq 1 \times 10^{-6} \text{ cm/s}$ = high permeability. BCS Class assignment: I (high S; high P) = BS score 0; II (low S; high P) = BS score 1.0; III (high S; low P) = BS score 0.2; IV (low S; low P) = BS score 0.6. BS score of 0 (BCS Class I) = STOP IVIVC development: proceed instead to BCS dissolution-based biowaiver (FDA 2017 BCS biowaiver guidance) rather than IVIVC.

Step 3 -- Formulation Mechanism (FM; weight 0.20): Characterise the rate-controlling step in drug release from the ER formulation. Pure osmotic (OROS): FM = 1.0. SNEDDS/lipid-based (dissolution + self-emulsification): FM = 0.9. Dissolution-controlled polymer coating (Eudragit RS/RL non-pH-dependent): FM = 0.7. Erosion-controlled hydrophilic matrix (HPMC; pure erosion without diffusion): FM = 0.6. Mixed erosion + diffusion (HPMC at high polymer levels; most HPMC matrices): FM = 0.4. Pure diffusion-controlled (membrane-controlled reservoir; silicone membrane): FM = 0.3. Characterise mechanism experimentally by dissolution at varying hydrodynamic conditions (100 vs. 50 rpm; if release rate changes significantly: diffusion-limited; if no change: dissolution/erosion-limited).

Level A IVIVC Development Workflow: If IDSi ≥ 0.70 : proceed to clinical PK study design. Design requirements: (a) minimum 3 formulations: fast (30% released at 2h); reference (60% at 6h); slow (80% at 12h); (b) pharmacokinetic study: $n = 12-18$ healthy volunteers; 3-period crossover; doses matched to ensure overlapping plasma concentration ranges; IV reference or oral solution reference (for Wagner-Nelson deconvolution); (c) deconvolution: Wagner-Nelson for 1-compartment PK (confirm by log-linear terminal phase fitting; $r^2 \geq 0.98$ over ≥ 3 time points in terminal phase); Loo-Riegelman for 2-compartment. Software: WinNonlin Phoenix (Certara) Deconvolution module or R deconvolve package; (d) IVIVC model: linear model ($F_a(t) = a + b$

$\times F_{\text{diss}}(t - \text{tlag})$); include time-scaling factor tlag for GI transit correction (typically 15-60 min for small intestine transit); (e) Internal validation: MAPE C_{max} and AUC $\leq 10\%$ for formulations used in model building; (f) External validation: prepare independent formulation (not used in model); measure dissolution; predict plasma concentrations using IVIVC model; MAPE C_{max} AND AUC $\leq 10\%$ vs. observed in clinical PK study with $n \geq 12$ subjects; (g) Regulatory submission: IVIVC report per FDA SUPAC guidance (1997) with: drug and formulation description; in vitro dissolution method (validated); deconvolution method; IVIVC model equation; internal and external validation results; proposed dissolution specification range; biowaiver applicability statement.