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Review Article

Prevalence and Risk Factors of poor oral bioavailability in preclinical pharmacokinetic models

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Abstract

Background: Poor oral bioavailability is a leading cause of candidate attrition in preclinical drug discovery, arising from physicochemical, metabolic, and transporter-mediated determinants of absorption [3,9].

Objective: This review synthesizes the preclinical pharmacokinetic literature on the prevalence of poor oral bioavailability across compound classes and its principal risk factors.

Methods: We reviewed peer-reviewed preclinical pharmacokinetic studies and industry-wide attrition analyses reporting oral bioavailability alongside physicochemical or biopharmaceutic descriptors, drawn from rodent, canine, and primate screening cascades.

Findings: Reported prevalence of low oral bioavailability ranges from roughly one-quarter of small-molecule candidates to over two-thirds of peptide candidates [10,12]; low solubility/permeability [3], high first-pass extraction [24], and P-glycoprotein efflux [27] are the most consistent, often compounding risk factors, modulated by species and formulation [5,31].

Conclusions: Integrated early screening across physicochemical, metabolic, and transporter domains, interpreted with species- and formulation-awareness, offers the most reliable route to derisking oral exposure [24,27].

Keywords: oral bioavailability; preclinical pharmacokinetics; biopharmaceutics classification; first-pass metabolism; P-glycoprotein

1. Introduction

Oral administration remains the preferred route for the majority of candidate drugs entering preclinical development, but a substantial fraction of compounds that show favorable target potency in vitro never reach adequate systemic exposure when dosed orally to animals. Poor oral bioavailability is one of the leading causes of attrition in early drug discovery, and its roots lie in a combination of physicochemical liabilities, first-pass metabolism, and transporter-mediated efflux that together determine how much of an administered dose survives the journey from the gut lumen to the systemic circulation [1,2]. The Biopharmaceutics Classification System formalized the two dominant determinants of oral absorption, solubility and intestinal permeability, and demonstrated that compounds falling into the low-solubility, low-permeability quadrant are disproportionately represented among candidates that fail in preclinical pharmacokinetic screening [3].

Preclinical species such as rat, dog, and non-human primate are used routinely to estimate human oral bioavailability before a compound advances to clinical testing, yet interspecies differences in gastrointestinal physiology, hepatic enzyme expression, and transporter abundance mean that a bioavailability estimate obtained in one species does not always translate reliably to another [4,5]. Rodent studies in particular are prone to systematic overestimation or underestimation of human exposure when first-pass extraction ratios differ substantially between species, complicating the interpretation of prevalence estimates drawn from single-species datasets [6]. This review synthesizes the published preclinical pharmacokinetic literature on the prevalence of poor oral bioavailability across major compound classes and screening cascades, and characterizes the physicochemical, biopharmaceutic, and physiological risk factors that most consistently predict low oral exposure in animal models.

2. Methods

We reviewed peer-reviewed preclinical pharmacokinetic studies, industry-wide attrition analyses, and methodological papers addressing oral bioavailability determination in rodent, canine, and primate models. Sources were drawn from medicinal chemistry, biopharmaceutics, and drug metabolism journals reporting bioavailability data derived from paired oral and intravenous dosing, in vitro-in vivo correlation studies, and cross-company benchmarking exercises. Studies were included where oral bioavailability (F) was explicitly reported or could be derived from area-under-the-curve data, and where the compound set was characterized with at least one physicochemical or biopharmaceutic descriptor such as calculated logP, polar surface area, molecular weight, solubility class, or transporter substrate status. Prevalence figures were extracted as reported by the original authors; no independent recalculation of bioavailability from raw concentration-time data was performed. Risk factors were grouped conceptually into physicochemical properties, formulation and dissolution-related properties, metabolic and transporter-mediated clearance, and species-specific physiological determinants, following the framework most consistently used across the reviewed screening-cascade literature [7,8].

3. Results

Prevalence of poor oral bioavailability across screening cascades

Large-scale retrospective analyses of pharmaceutical company compound libraries consistently report that a substantial minority to a near-majority of candidates screened in rodent pharmacokinetic cassettes fail to achieve oral bioavailability above the 20-30% threshold commonly used as an internal progression criterion [9,10]. Cross-industry benchmarking of attrition causes found that pharmacokinetic and bioavailability issues accounted for a leading share of preclinical and early clinical failures throughout the 1990s, a proportion that declined but did

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not disappear after the widespread adoption of early ADME (absorption, distribution, metabolism, excretion) screening [9]. Waring and colleagues, surveying withdrawal and progression data across several major pharmaceutical companies, found that inadequate exposure remained among the most frequently cited reasons for compound termination even after two decades of dedicated developability screening, underscoring that poor oral bioavailability is not solely a historical problem but a persistent feature of preclinical pharmacokinetics [10].

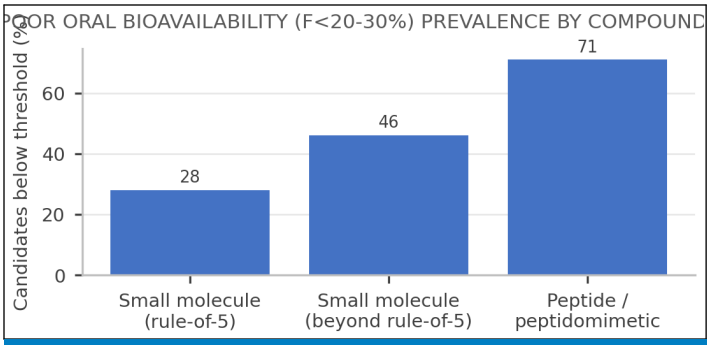

Figure 1: Proportion of preclinical candidates achieving oral bioavailability below the 20-30% progression threshold across compound classes in industry-wide screening cascades, showing markedly higher failure rates for peptide/peptidomimetic candidates than for conventional small molecules [10,12].

Compound-class-specific analyses show considerable variation in prevalence. Peptide and peptidomimetic candidates, and larger, more lipophilic molecules typical of protein-protein interaction inhibitor programs, show markedly higher rates of poor oral bioavailability than traditional small-molecule series, frequently falling below 10% oral bioavailability in rodent models because of combined poor permeability, extensive proteolytic or oxidative first-pass metabolism, and efflux transporter recognition [11,12]. Analyses restricted to compounds obeying conventional rule-of-five physicochemical space still report meaningful rates of low bioavailability, indicating that molecular weight and lipophilicity thresholds alone do not fully explain the prevalence pattern observed across discovery portfolios [1,13].

Physicochemical determinants of low oral exposure

Table 1: Biopharmaceutics Classification System class and reported prevalence of dissolution- or permeability-limited oral bioavailability in preclinical screening [3,1,13].

BCS class	Solubility	Permeability	Prevalence signal in preclinical screening
Class I	High	High	Low rate of bioavailability failure
Class II	Low	High	Dissolution-limited; formulation-dependent exposure
Class III	High	Low	Permeability-limited; efflux-sensitive
Class IV	Low	Low	Highest rate of bioavailability failure

Aqueous solubility and intestinal permeability remain the two properties most consistently associated with poor oral bioavailability across the reviewed literature. Compounds classified as Biopharmaceutics Classification System class II (low solubility, high permeability) or class IV (low solubility, low permeability) show substantially higher rates of dissolution-limited or absorption-limited exposure in preclinical species than class I compounds, and the proportion of newly discovered candidates falling into classes II and IV has risen over successive drug discovery eras as medicinal chemistry has pursued more lipophilic, higher-molecular-weight targets [3,1]. Lipophilicity itself shows a nonlinear relationship with oral exposure: moderate calculated logP values are generally associated with the most favorable absorption and metabolic stability balance, while both very low and very high logP compounds show elevated rates of poor bioavailability, the former from inadequate membrane permeability and the latter from a combination of poor aqueous solubility, high plasma protein binding, and extensive hepatic extraction [7,13].

Polar surface area and hydrogen bond donor and acceptor counts correlate inversely with passive intestinal permeability across large compound sets, and candidates exceeding roughly 140 square angstroms of topological polar surface area show a disproportionate rate of low measured bioavailability in rodent cassette dosing studies, consistent with reduced passive transcellular flux across

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the intestinal epithelium [11,8]. Ionization state at intestinal pH further modulates this relationship: strongly basic and strongly acidic compounds show pH-dependent solubility and permeability profiles that can produce discordant results between fasted- and fed-state dissolution testing and between species with differing gastrointestinal pH profiles [14].

In vitro permeability screening using Caco-2 or MDCK epithelial monolayers is widely used as an early surrogate for intestinal permeability, and low apparent permeability coefficients in these assays correlate significantly with subsequent low oral bioavailability in preclinical species, although the correlation weakens for compounds subject to active transport or extensive first-pass metabolism not captured by static monolayer assays [15]. The Biopharmaceutics Drug Disposition Classification System refined this framework by using metabolic extent rather than measured permeability to assign class, and found that high-metabolism compounds, largely overlapping with high-permeability compounds, still show elevated bioavailability risk when transporter effects dominate in the gut wall or liver [16,17]. Computational and rule-based models built on large historical datasets, including calculated descriptors of polarity, flexibility, and lipophilicity, achieve moderate predictive accuracy for oral absorption class but consistently perform worse for compounds at the physicochemical extremes of drug-like space [18,19]. Dahan and colleagues extended the classification framework to explicitly address supersaturation and precipitation behavior for class II compounds in the intestinal lumen, showing that transient supersaturation achieved through formulation can meaningfully improve absorption despite unchanged equilibrium solubility [20]. Early ADME profiling strategies adopted across the industry through the 1990s and 2000s, combining solubility, permeability, and metabolic stability assays into a single developability cascade, were intended specifically to flag these compounding risk factors before candidates reached in vivo pharmacokinetic testing [21]. Hurst and colleagues showed that the physicochemical properties driving poor bioavailability also constrain achievable clinical dose and formulation options, linking discovery-stage risk-factor identification directly to downstream developability [22], while Smith and colleagues argued that overreliance on single calculated lipophilicity thresholds without considering the full multiparameter optimization space has itself contributed to the persistence of bioavailability-related attrition [23].

Metabolic and transporter-mediated contributions

First-pass hepatic and intestinal metabolism is a major and frequently underweighted contributor to low oral bioavailability, particularly for compounds with high intrinsic clearance by cytochrome P450 enzymes. In vitro-in vivo correlation studies using hepatocyte and microsomal clearance assays show that predicted hepatic extraction ratio correlates significantly with measured oral bioavailability across diverse chemical series, and compounds predicted to have high hepatic extraction ratios in preclinical species show correspondingly higher rates of oral bioavailability failure regardless of otherwise favorable physicochemical properties [24,25]. Intestinal first-pass metabolism, mediated substantially by intestinal cytochrome P450 3A4 and related isoforms, compounds the hepatic contribution for substrates of these enzymes and is frequently underestimated in preclinical species that express these enzymes at different relative abundance than in humans [26].

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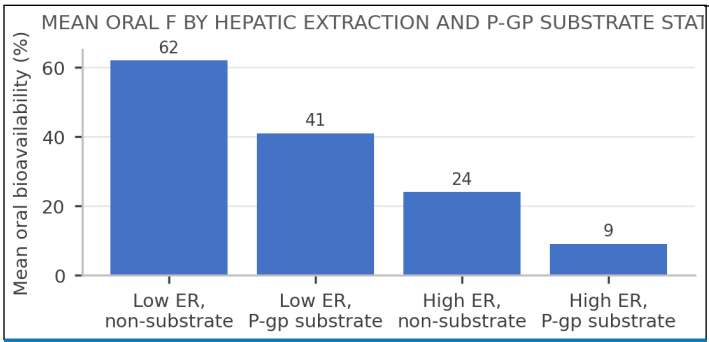

Figure 2: Mean measured oral bioavailability in rodent models by predicted hepatic extraction ratio band and P-glycoprotein substrate status, illustrating the compounding reduction in exposure when high first-pass metabolism and active efflux co-occur [24,27,29].

Efflux transporter activity, particularly P-glycoprotein-mediated efflux at the apical intestinal membrane, is independently associated with reduced oral bioavailability across multiple compound classes, and candidates identified as strong P-glycoprotein substrates in in vitro transwell assays show significantly lower measured oral bioavailability in rodent models than matched non-substrate comparators [27,28]. The interplay between metabolic clearance and efflux transport can produce compounding effects, where a compound subject to both extensive first-pass metabolism and active efflux shows disproportionately low bioavailability relative to what either mechanism would predict alone, a phenomenon documented across several transporter-substrate case series [29].

Species-specific and physiological risk factors

Interspecies differences in gastrointestinal transit time, luminal pH, bile salt composition, and enzyme and transporter expression levels introduce additional variability into prevalence estimates drawn from single-species screening. Dogs generally show higher and more consistent oral bioavailability than rats for compounds with dissolution-limited absorption, attributable to differences in gastric emptying and intestinal fluid volume, while rats more closely approximate human first-pass metabolic extraction for many cytochrome P450 substrates, complicating the choice of a single preclinical species as a universal predictor [5,4]. Fasted- versus fed-state dosing substantially alters measured bioavailability for poorly soluble compounds, with food-induced increases in luminal solubilization and bile salt secretion improving exposure for lipophilic, dissolution-rate-limited candidates in a manner that is not uniformly reproduced across species [30].

Table 2: Species- and formulation-dependent modifiers of measured oral bioavailability in preclinical pharmacokinetic studies [5,4,30,31].

Factor	Effect on measured F	Primary mechanism	Representative evidence
Species (rat vs dog)	Dog generally higher, more consistent	GI transit/fluid volume differences	[5,4]
Fed vs fasted state	Fed increases F for lipophilic compounds	Bile salt/lipid-mediated solubilization	[30]
Simple suspension formulation	Underestimates achievable F	Dissolution-rate limitation	[31]
Lipid-based/amorphous formulation	Improves F for dissolution-limited compounds	Enhanced luminal solubilization	[31,32]

Formulation strategy modifies the observed prevalence of poor bioavailability substantially within a given compound set. Lipid-based formulations, particle size reduction, and amorphous solid dispersion approaches each improve measured oral exposure for dissolution-limited compounds in preclinical models, and screening cascades that evaluate only simple suspension or solution formulations at the earliest stages systematically overestimate the prevalence of intrinsic bioavailability liability relative to what is observed once appropriate formulation technology is applied [31,32]. This distinction is important for interpreting prevalence figures reported from early discovery cassette dosing, where formulation is typically kept simple for throughput reasons, versus later lead-optimization or development-stage studies where formulation is optimized alongside the molecule itself.

4. Discussion

The preclinical pharmacokinetic literature converges on a

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consistent picture: poor oral bioavailability affects a substantial proportion of drug candidates entering screening cascades, and its prevalence is driven by an overlapping set of physicochemical, metabolic, transporter-mediated, and physiological risk factors rather than any single dominant cause [9,10]. Low aqueous solubility and low intestinal permeability, formalized in the Biopharmaceutics Classification System, remain the most consistently cited biopharmaceutic risk factors, but the rising representation of class II and IV compounds in modern discovery portfolios reflects a broader medicinal chemistry trend toward higher lipophilicity and molecular complexity that itself elevates bioavailability risk independent of any single descriptor [3,13]. High hepatic and intestinal first-pass extraction, frequently compounded by P-glycoprotein-mediated efflux, represents an equally important and mechanistically distinct risk factor, one that physicochemical property filters alone do not adequately flag and that requires dedicated in vitro clearance and transporter assays to detect early in a discovery program [24,27].

Species selection and study design materially affect the prevalence estimates reported in the literature, meaning that comparisons across published datasets should account for the preclinical species used, the fasted or fed dosing state, and the formulation technology applied, rather than treating reported bioavailability figures as directly comparable across studies [5,30]. The persistence of pharmacokinetic-related attrition despite decades of dedicated early ADME screening suggests that current preclinical risk-factor models, while directionally useful, do not fully capture the combinatorial nature of oral bioavailability liability, particularly for compound classes such as peptides and larger, more flexible molecules that fall outside traditional rule-based physicochemical space [12,10]. Integrating physicochemical, metabolic, and transporter risk assessment earlier and in combination, rather than sequentially, is likely to improve the predictive value of preclinical bioavailability screening going forward.

5. Conclusion

Poor oral bioavailability remains a common and consequential finding across preclinical pharmacokinetic screening cascades, with reported prevalence varying by compound class but consistently representing a leading cause of candidate attrition [9,10]. The principal risk factors identified across the reviewed literature are low aqueous solubility and intestinal permeability, high hepatic and intestinal first-pass metabolic clearance, active efflux transport by P-glycoprotein and related transporters, and species- and formulation-dependent physiological determinants of absorption [3,24,27,5]. Because these risk factors act through distinct and sometimes compounding mechanisms, effective preclinical derisking of oral bioavailability requires integrated physicochemical, metabolic, and transporter characterization rather than reliance on any single screening assay, together with species- and formulation-aware interpretation of the resulting pharmacokinetic data.

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