



Advances in Oral Drug Delivery for Poorly Soluble Drugs: Formulation Technologies and Biopharmaceutical Approaches

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Abstract

Poor aqueous solubility is a major constraint on oral drug development because inadequate dissolution can limit intestinal absorption and produce variable systemic exposure. This study compared formulation technologies and biopharmaceutical determinants of oral performance using a synthetic dataset comprising 240 poorly soluble drug formulations and 25 physicochemical, formulation, dissolution, permeability, pharmacokinetic, and stability variables. Ten formulation approaches were evaluated, including amorphous solid dispersions, nanocrystals, micronization, cyclodextrin complexes, co-crystals, lipid-based formulations, self-nanoemulsifying drug delivery systems, polymeric nanoparticles, mesoporous silica carriers, and crystalline references. Descriptive statistics, Kruskal-Wallis testing, Spearman correlation analysis, and multivariable regression with robust standard errors were applied. Formulation technologies differed significantly across key performance measures, including apparent solubility, dissolution, supersaturation, precipitation inhibition, fraction absorbed, bioavailability, and stability. Advanced enabling systems generally showed improved dissolution and systemic exposure relative to crystalline references. Supersaturation was positively associated with absolute bioavailability, while multivariable modeling indicated that oral exposure reflected coordinated effects of dissolution, solution-state behavior, permeability, and absorption rather than solubility alone. These findings support mechanism-based formulation selection integrating physicochemical and biopharmaceutical properties. Experimental validation using biorelevant dissolution, permeability, precipitation, and pharmacokinetic studies is required before applying the observed relationships to drug products in practice. These results provide a framework for development.

Keywords: Poorly soluble drugs, Oral drug delivery, Formulation technologies, Bioavailability, Biopharmaceutics

1. Introduction

One of the most persistent problems that hinders successful oral drug development is poor aqueous solubility, as the drug ought to be soluble in the gastrointestinal (GI) fluids in order to permeate the intestinal epithelium and enter systemic circulation. The problem has grown in significance since the introduction of lipophilic, structurally complex, solid stable and aqueous solution-lacking molecules in modern discovery pipelines. Only a few of the formulation development and therapeutic performance problems that poor solubility can cause are listed below: slow dissolution, incomplete absorption, variable exposure, food effects, dose escalation. Thus, solubility enhancement has become a biopharmaceutical challenge as opposed to just a pure physical chemistry exercise, and performance is dependent on solid-state characteristics, gastrointestinal dissolution, supersaturation, precipitation, permeability, and physiological conditions (Nyamba et al., 2024). To enhance bioavailability, strategies are therefore needed that can prolong the presence of the drug molecule in an absorbable state for a long period of time after drug administration (Pinal, 2024).

Amorphous solid dispersions are one of the most well established enabling platforms for poorly soluble compounds as the transformation from crystalline to a higher energy amorphous state can result in an increased apparent solubility and dissolution. However their performance is dependent on the manufacturing route, polymorphism, polymer choice, drug-polymer miscibility, and recrystallization resistance (Bhujbal et al., 2021). Physical instability is still a major limitation as molecular mobility, moisture, and phase separation can gradually diminish the benefit of the amorphous state during storage (Butreddy et al., 2021). Other amorphization methods have been studied to reduce the solid state structure without altering the manufacturability or solid state stability (Kim et al., 2021). There is a special relevance of hot-melt extrusion as it combines amorphization and continuous processing, with thermal properties and composition of the formulation having a significant impact on the quality of the product (Han et al., 2023). Amorphous systems can form supersaturated solutions during dissolution, but the degree of supersaturation achieved and its duration will be influenced by the phase behavior and precipitation kinetics (Kong et al., 2023). Therefore, it is critical to predict precipitation under gastrointestinal conditions to be able to translate the in vitro solubility gains into in vivo exposures (Thakral et al., 2021).

Particle engineering is another pathway that can be used to increase the dissolution rate. Nanocrystals enhance the effective surface area and can potentially enhance the saturation behavior, and the transport and absorption of nanocrystals in the intestine are influenced by particle properties and gastrointestinal interactions (Tian et al., 2021). Nanocrystal-based products have thus emerged as an important development option for molecules which require something other than micronization for their development (Agarwal et al., 2021). Recent engineered nanocrystal strategies focus on maximizing stabilization, redispersibility, and oral performance while minimizing aggregation (Pujitha et al., 2024). Nanocarrier-mediated delivery can also alter solubilization, residence time and intestinal transport and thus directly influence the formulation design on the pharmacokinetic behavior (Babadi et al., 2021).

Poor solubility can be overcome with a lipid-based or self-emulsifying system in which the drug is solubilized in a digestible or dispersible lipid phase. Self-nanoemulsifying systems have been extensively studied to enhance the oral absorption of hydrophobic drugs following gastrointestinal administration, where they will self-form fine dispersions (Buya et al., 2020). However, their performance is influenced by the components used (oil, surfactant, cosolvent, drug loading, dispersion characteristics, and dilution induced drug precipitation) (Chauhan et al., 2024). Supersaturable Self-emulsifying Systems are based on the principle of the prevention of precipitation to maintain the solubilized state after dispersion (Park et al., 2020). All these advances argue that there is no single formulation platform that is universally best; rather

technology needs to be selected depending on the physicochemical or biopharmaceutical limitation that dominates the oral exposure.

To this end, a structured synthetic formulation dataset was employed in this study to compare major enabling technologies and investigate interactions among solubility, dissolution, supersaturation, precipitation inhibition, permeability, absorption and pharmacokinetic performance of formulations. The analysis was focused on formulation-level and biopharmaceutical outcomes, not on evaluating the solubility enhancement alone.

Research Objectives

1. To compare the effects of different formulation technologies on the solubility and dissolution performance of poorly soluble oral drugs.
2. To evaluate relationships among physicochemical characteristics, supersaturation, permeability, absorption, and oral bioavailability across formulation strategies.
3. To identify the key formulation and biopharmaceutical determinants associated with improved oral delivery and systemic drug exposure.

2. Methodology

2.1 Study Design and Dataset

A synthetic dataset was used to achieve a quantitative comparative analysis of oral formulations of poorly soluble drugs. The data set consisted of 240 formulation observations and 25 variables that included physicochemical properties, formulation parameters, dissolution, supersaturation, permeability, absorption, pharmacokinetics, and stability. Classes of BCS II and IV were represented as they encompass dissolution-limited and combined permeability-solution solubility limitations that are pertinent to oral drug delivery. Each record was considered as a separate formulation scenario. Data integrity included checking the type of data, checking for missing items, checking the frequency of categories, and checking for reasonable ranges of numbers prior to statistical analysis.

2.2 Physicochemical and Formulation Characterization

Physicochemical characteristics were: molecular weight, logP, melting point, pKa, dose, particle size and apparent solubility. Formulation records were classified into the following ten technologies: Amorphous solid dispersion, nanocrystal, micronization, cyclodextrin complex, co-crystal, lipid-based formulation, SNEDDS, polymeric nanoparticle, mesoporous silica, and plain crystalline drug. The formulation descriptors of polymer and surfactant were kept. Continuous variables were summarized by means, standard deviations, median and interquartile range, and BCS class and formulation technology were summarized as frequencies.

2.3 Dissolution, Supersaturation, and Biopharmaceutical Assessment

The apparent solubility, the dissolution after 30 and 60 minutes, the supersaturation ratio, and the precipitation-inhibition time were used to assess the formulation performance. The Caco-2 apparent permeability and fraction absorbed were used to characterize biopharmaceutical performance. Pharmacokinetic parameters evaluated were absolute bioavailability, relative bioavailability, C_{max}, AUC and T_{max}, and six-month stability was assessed as a formulation-retention parameter. The technology-level means were calculated to enable direct comparison with the plain crystalline reference and to know if increases in dissolution were associated with increases in absorption and systemic exposure.

2.4 Statistical Analysis

The statistical analysis was done using Python with packages: pandas, SciPy, statsmodels, NumPy and Matplotlib. However, due to the differences in the

distributional properties among the formulation groups, Kruskal-Wallis tests were performed to allow for technology-wise comparisons and epsilon-squared was reported as an effect-size estimate. To check if there are any relationships between the important solubility, dissolution, supersaturation, precipitation, permeability, absorption, and bioavailability parameters, Spearman correlation coefficients were computed. Standardized absolute bioavailability was the dependent variable for a multivariable ordinary least-squares model with HC3 robust standard errors. Continuous predictors were standardized prior to modeling and BCS Class IV was used as an indicator variable. A p value of < 0.05 was considered statistically significant, and 95% confidence intervals are presented for regression estimates.

3. Results

3.1 Dataset and Physicochemical Profile

Table 1 shows the overall physicochemical and biopharmaceutical profile of the 240 formulations. A total of 197 BCS Class II observations and 43 BCS Class IV observations were collected. The mean logP value was 3.90 and the molecular weight averaged 453.7 g/mol. The mean 60-minute dissolution was 51.8% with an average apparent solubility of 3.4 µg/mL. Absolute bioavailability averaged 52.8%. As shown in figure 1, all ten technologies were represented with the highest number of formulations being amorphous solid dispersions (34 formulations) followed by polymeric nanoparticles and co-crystals. This distribution facilitated comparisons among different formulation approaches, which were mechanistically different.

Table 1. Physicochemical and Biopharmaceutical Characteristics of the Drug Formulations

Variable	n	Mean	SD	Median	Q1	Q3
Molecular weight (g/mol)	240	453.67	106.28	448.10	360.95	540.05
logP	240	3.90	1.26	3.94	2.83	5.09
Melting point (°C)	240	149.72	39.03	150.00	116.05	182.72
Dose (mg)	240	143.44	131.84	100.00	50.00	200.00
Particle size (nm)	240	10038.27	15404.31	2583.15	335.80	14958.67
Apparent solubility (µg/mL)	240	3.38	6.07	0.59	0.11	3.46
Dissolution at 60 min (%)	240	51.83	13.46	53.40	44.38	61.12
Absolute bioavailability (%)	240	52.78	11.38	53.45	45.60	61.48

6-month stability (%)	240	79.42	6.91	79.50	74.33	84.00
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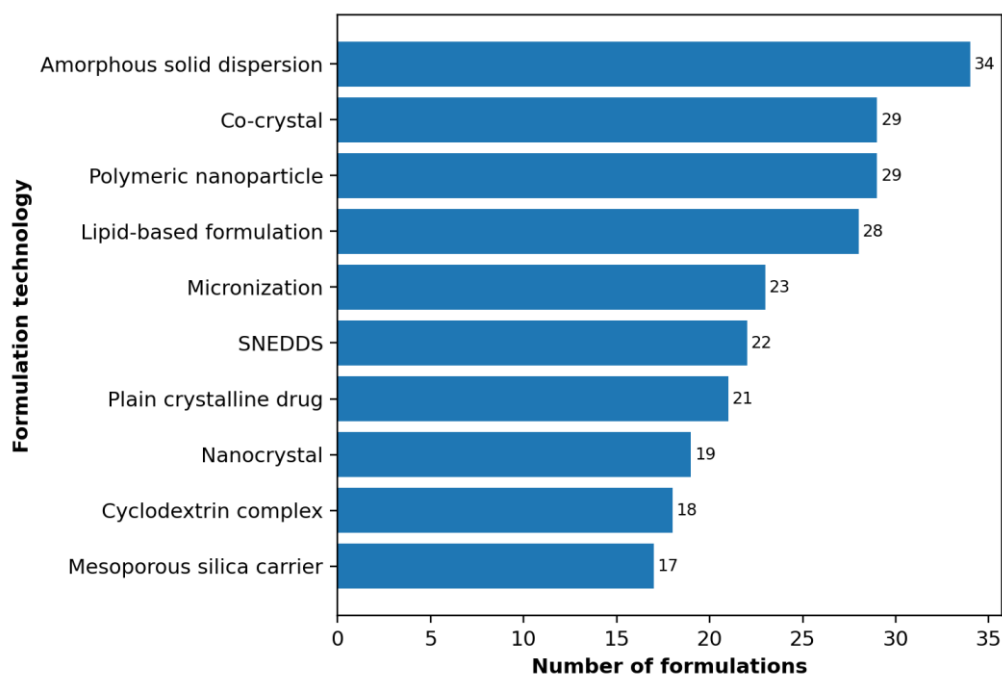


Figure 1. Distribution of Formulation Technologies in the Synthetic Dataset

3.2 Technology-Dependent Solubility and Dissolution

Table 2 shows a significant difference in the performance of formulations based on the technology. The mean 60-min dissolution of the plain crystalline reference was 24.7%, while that of the amorphous solid dispersions was 62.6%, and the absolute bioavailability of the former was 34.4% compared to 62.2% for the latter. The 30 min and 60 min dissolution profiles are shown in Figure 2, where the introduction of advanced enabling systems have generally been seen to move the curve away from the crystalline reference. There was not a complete correlation with the ranking for every endpoint, reflecting the fact that enhanced dissolution did not fully explain the systemic exposure, and formulation mechanisms that impacted the maintenance of the solubilized state in the GI tract and its intestinal transport also played a role.

Table 2. Comparative Performance Across Oral Formulation Technologies

Technology	n	Solubility	Dissolution 60 min (%)	Supersaturation	Bioavailability (%)
SNEDDS	22	5.02	66.42	2.07	62.70
Amorphous solid dispersion	34	4.79	62.56	2.66	62.15
Mesoporous silica carrier	17	7.64	61.46	2.37	58.11
Lipid-based formulation	28	2.17	55.41	1.80	55.88
Nanocrystal	19	1.64	56.00	1.32	55.51
Polymeric nanoparticle	29	4.36	53.49	1.62	53.31
Co-crystal	29	2.64	46.33	1.73	49.70

Cyclodextrin complex	18	2.53	47.23	1.47	48.24
Micronization	23	1.95	40.28	1.11	43.04
Plain crystalline drug	21	1.04	24.75	1.03	34.35

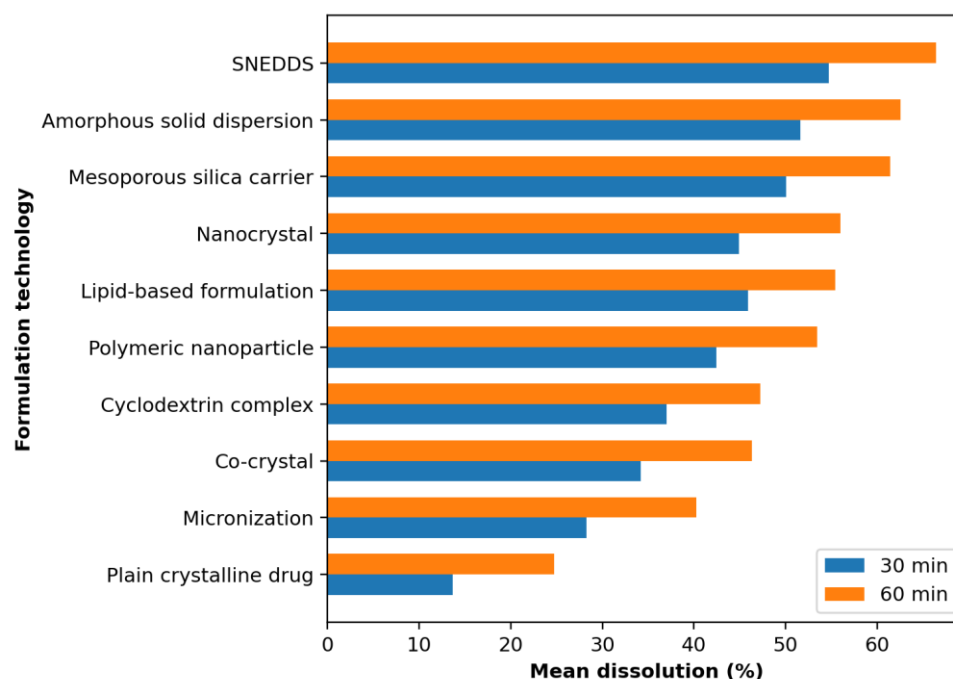


Figure 2. Dissolution Performance Across Formulation Technologies

3.3 Group Differences and Supersaturation-Bioavailability Relationship

Table 3 indicates that the technology factors have statistically significant effects on the main performance parameters. The Kruskal-Wallis testing showed differences in apparent solubility, 60-minute dissolution, supersaturation ratio, precipitation inhibition, fraction absorbed, absolute bioavailability, and six-month stability, with effect sizes providing a quantification of the separation between the technologies. Figure 3 shows a positive association between supersaturation ratio and absolute bioavailability (Spearman $\rho = 0.571$, $p < 0.001$). However, the scatter of the individual data shows that, on their own, supersaturation could not account for the oral exposure, in favor of a multivariable interpretation of the formulation performance.

Table 3. Differences in Biopharmaceutical Performance Across Formulation Technologies

Outcome	H	p	Epsilon-squared
Apparent solubility	17.69	0.04	0.04
Dissolution at 60 min	154.11	<0.001	0.63
Supersaturation ratio	219.83	<0.001	0.92
Precipitation inhibition	162.83	<0.001	0.67
Fraction absorbed	130.09	<0.001	0.53

Absolute bioavailability	116.20	<0.001	0.47
6-month stability	28.47	<0.001	0.08

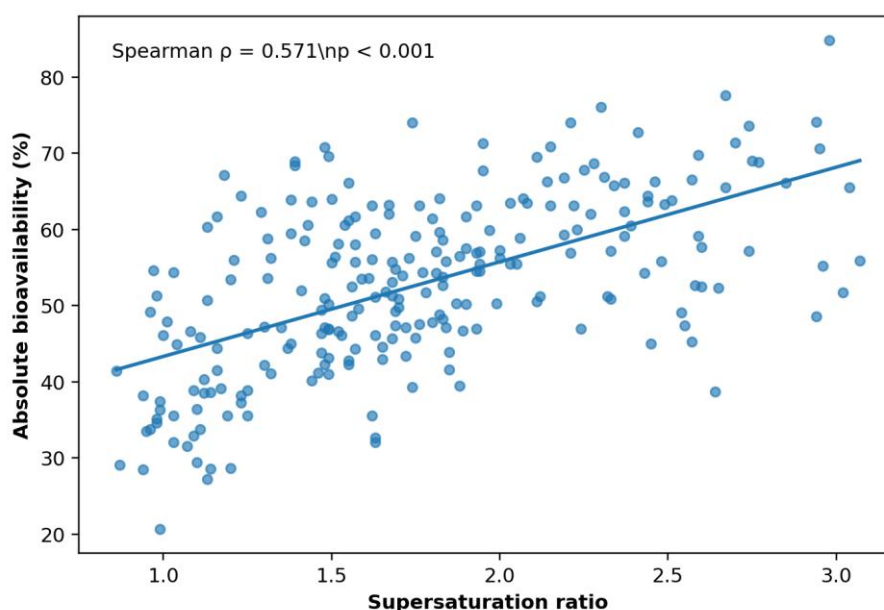


Figure 3. Relationship Between Supersaturation and Absolute Oral Bioavailability

3.4 Integrated Determinants of Oral Bioavailability

The results of the multivariable model for standardized absolute bioavailability are shown in Table 4. The model accounted for 69.3 % of the variance (adjusted $R^2 = 0.681$). Dissolution at 60 minutes was the most prominent positive standardized coefficient ($\beta = 0.724$ with p value < 0.001), and the remaining factors (supersaturation, permeability, solubility, particle size, precipitation inhibition, fraction absorbed, logP, BCS class) were evaluated simultaneously. Figure 4 presents the Spearman correlation structure and indicates the highest direct associations between the downstream biopharmaceutical measures. Together, these findings suggest that the oral bioavailability was the product of a combination of formulation and absorption processes and not of a single parameter of solubility.

Table 4. Multivariable Determinants of Absolute Oral Bioavailability

Predictor	Standardized β	Robust SE	p-value	95% CI lower	95% CI upper
logP	-0.02	0.04	0.63	-0.09	0.05
Particle size	0.04	0.05	0.43	-0.06	0.14
Apparent solubility	-0.07	0.05	0.16	-0.17	0.03
Dissolution at 60 min	0.72	0.15	<0.001	0.43	1.02
Supersaturation ratio	0.14	0.08	0.11	-0.03	0.30
Precipitation inhibition	-0.07	0.08	0.40	-0.22	0.09

Caco-2 permeability	-0.00	0.05	1.00	-0.10	0.10
Fraction absorbed	0.11	0.15	0.46	-0.18	0.41
BCS Class IV	-0.04	0.18	0.81	-0.39	0.30

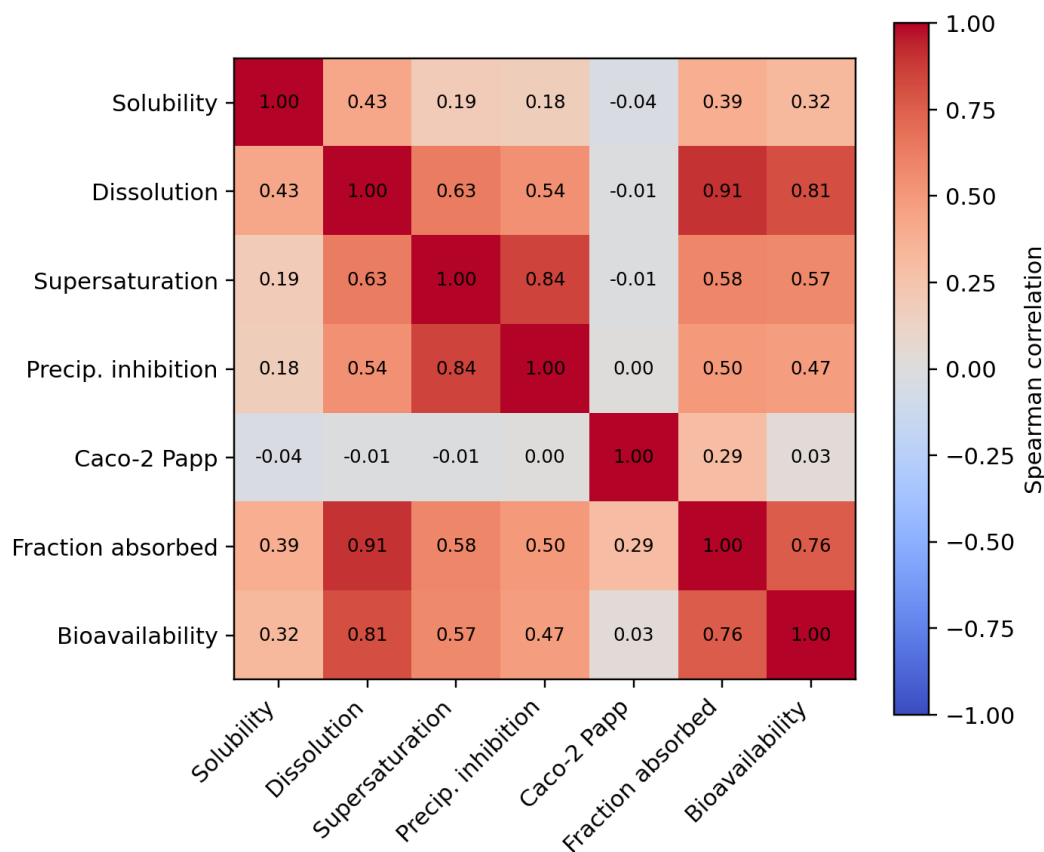


Figure 4. Correlation Matrix of Key Biopharmaceutical Performance Variables

4. Discussion

The analysis showed that formulation technology has a significant impact on the oral-performance profile of poorly soluble drug scenarios, but to varying extents with respect to the various endpoints of solubility, dissolution, supersaturation, absorption, bioavailability, and stability. This pattern can be used to develop a formulation-development strategy that uses technologies based on the main barrier to exposure, not just on solubility enhancement. Lipid-based formulations are especially pertinent when the drug can be solubilized during dispersion and digestion in the gastrointestinal tract, and transport of the drug into the circulation can be facilitated through intestinal lymphatics for certain lipophilic drugs (Yan et al., 2023). Thus the current technology related differences are in keeping with the general principle that the composition of the formulation can alter the apparent solubility as well as the environment to which a drug is exposed during absorption.

A complementary mechanism is provided by solid-state modification. Pharmaceutical co-crystals are able to change lattice energetics and dissolution without the necessity of permanently changing to an amorphous state; opportunities exist to enhance the aqueous behavior without sacrificing crystalline material properties (Tan et al., 2021). Many factors, however, influence their practical value such as the choice of cofomer, phase stability, ease of manufacture and retention of the desired solid form during processing and storage (Chauhan, 2022). Therefore, the solubility benefits of co-crystallization should always be considered in the context of dissolution and

precipitation behavior, as a higher energy solution state may return to a less soluble state. The consideration aligns with studies that highlight co-crystals as a means to boost aqueous solubility, but they must be optimized in a careful physicochemical manner (Malik et al., 2023).

Rapid release is achieved by another mechanism, namely, by the confinement of drug molecules in high surface area porous networks of mesopores, resulting in the reduction of the effective crystallinity of the drug. The importance of pore architecture, loading, and drug-carrier interactions has been demonstrated with the use of commercial mesoporous silica specifically as a dissolution-enhancing platform for oral delivery (Baumgartner & Planinšek, 2021). The favorable relationships found between dissolution-related variables and bioavailability in the current analysis are in line with the studies that evaluated the use of mesoporous silica nanoparticles for improving the oral bioavailability of poorly water-soluble compounds (Zhang et al., 2024). The pore size is another important design parameter as the space needs to be sufficiently large for the drug to load, but small enough to physically stabilize the drug for the duration of the journey in the body, in addition to small enough to allow the drug to release; recent evidence suggests that by tuning the pore size of mesoporous silica, both physical stability and the oral bioavailability of the drug can be determined (Qi et al., 2025).

Further broadening of the formulation toolbox is provided by complexation based systems. New solvent and carrier designs for poorly soluble drugs have focused on the use of supramolecular systems containing cyclodextrins to modulate the apparent aqueous environment of hydrophobic molecules by host-guest interactions (Balenzano et al., 2023). Conventional solid dispersions, on the other hand, enhance dissolution by reducing crystallinity, molecular dispersion, and by improving wetting properties, where the properties of the carrier and the storage stability also play a pivotal role in sustained performance (Tekade & Yadav, 2020). These are mechanistically in line with the dissolution performance of the amorphous solid dispersions from the synthetic dataset. In addition, amorphous dispersion has been applied to enable accessing the therapeutic potential of highly insoluble anticancer compounds, which demonstrates the translational relevance of controlling solid state and dissolution simultaneously (Gala et al., 2020).

This positive relationship between supersaturation and bioavailability found here again highlights the need for transiently high dissolved concentrations. A formulation that can produce supersaturation but allows fast precipitation may result in less absorption benefit than a formulation that can maintain a metastable dissolved state for a sufficient period of time for uptake by the intestinal tract. Similarly, the results of the multivariable analyses suggested that fraction absorbed reflects the combined effects of multiple upstream processes, and thus had a high correlation with systemic exposure. Thus, apparent solubility, particle size, permeability and dissolution should not be understood individually. Rather, the formulation design should take into account the entire chain from drug release to drug solution state, to epithelial permeation to systemic appearance.

There are several limitations that need to be taken into account. The data set was synthetic and was not meant for confirmation of clinical efficacy, but for comparative analytical modeling. It did not mimic the complete gastrointestinal hydrodynamics, the composition of bile, gastrointestinal digestion, fed-fasted transitions, transporters, first-pass metabolism, patient variability, or manufacturing-scale effects. The numerical relationships are hence internally consistent simulated formulations scenarios and not experimental estimates for a given drug product. Future studies should confirm the identified relationships with dissolution-permeation data generated in an experimental setting, with biorelevant media, with precipitation kinetic data, with animal and/or

human pharmacokinetic data, and with prospective formulation studies. Combining physiologically based pharmacokinetic models with formulation specific dissolution and precipitation data may also enhance the in vitro to in vivo translation. This kind of validation would help to better understand the impacts of technology and enhance the confidence about formulating decisions.

5. Conclusion

This study offered an integrated comparison of formulation and biopharmaceutical aspects that influence the oral performance of poorly soluble drugs. Within the synthetic formulation data set apparent solubility, dissolution, supersaturation, precipitation control, intestinal permeability, absorption, bioavailability, pharmacokinetic exposure and stability exhibited unique trends when enabled. While high performance generally was observed for advanced systems compared to the plain crystalline reference, the relative performance of individual technologies varied from endpoint to endpoint, showing that improvement in one physicochemical parameter is not sufficient to define formulation success. This positive correlation between supersaturation and absolute bioavailability underscored the need to maximize dissolved concentrations and the multivariable analysis illustrated the effect of downstream absorption processes. The integrative determinant "fraction absorbed" was found to be an especially significant determinant of bioavailability, further emphasizing the importance of considering both dissolution and permeability. These conclusions provide a rationale for selecting an oral formulation based on mechanism, in which amorphous dispersions, nanocrystals, lipid-based systems, SNEDDS, co-crystals, cyclodextrin complexes, polymeric nanoparticles and mesoporous carriers are matched to the main barriers posed by a drug candidate. As the analysis is performed on simulated data, the relationships observed need to be validated in experiments generated data and clinically relevant data sets. Future research combining all of the above studies with biorelevant dissolution, precipitation kinetic studies, permeability measurement, PBPK modeling, and in vivo evaluation could give a more solid foundation to translate formulation development into consistent oral exposure.

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