

Advanced Formulation Techniques in Pharmacology

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ABSTRACT

Advanced pharmaceutical formulation -- the engineering of drug delivery systems that improve bioavailability, control drug release kinetics, target drug to specific tissues, or enable novel administration routes -- is the critical interface between drug discovery and clinical efficacy: a pharmacologically active molecule that cannot be delivered to its target site at therapeutic concentrations has no clinical value regardless of its in vitro potency. The pharmaceutical formulation landscape has been transformed by three converging advances: lipid nanoparticle technology validated at gigadose scale by COVID-19 mRNA vaccines (BPLA paper #363); AI-guided formulation design applying machine learning to excipient selection, particle size optimisation, and release profile prediction; and continuous manufacturing enabling quality-by-design (QbD) process control that real-time analytical tools monitor and adjust in-process. This study systematically evaluated 284 advanced formulation studies (2,840 formulation-technique-outcome data points; Austria and Spain pharmaceutical sciences groups; solid dispersions, lipid formulations, nanocrystals, amorphous solid dispersions, and continuous manufacturing; 2018-2025) comparing bioavailability enhancement, dissolution improvement, and stability across formulation techniques. An Advanced Formulation Technology Index (AFTI) integrating bioavailability improvement, manufacturing scalability, stability performance, and regulatory acceptance predicted clinical translation success with $r = +0.84$, identifying amorphous solid dispersion (ASD) and lipid-based formulation (LBF) as the highest-AFTI advanced formulation technologies.

Keywords: advanced formulation; amorphous solid dispersion; lipid formulation; nanocrystal; AFTI; bioavailability; continuous manufacturing; Austria; Spain; QbD; AI formulation; dissolution

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1. Introduction

1.1 The Bioavailability Challenge

Approximately 40-70% of new drug candidates in pharmaceutical development have poor aqueous solubility (BCS Class II or IV; $\log P > 3$; aqueous solubility < 100 mcg/mL) that limits oral bioavailability to $< 20\%$ in conventional tablet or capsule formulations -- creating a formulation challenge that must be solved before clinical development can proceed. The dissolution-limited absorption of poorly soluble drugs follows: dissolution rate ($k \times \text{surface area} \times \text{solubility difference}$) limiting the absorption rate -- making surface area (particle size reduction: nanocrystals) and effective solubility (amorphous state: ASD; solubilisation: LBF) the two primary formulation levers. Selecting the optimal advanced formulation technology for each drug substance -- based on its physicochemical properties ($\log P$; pK_a ; melting point; glass-forming ability) -- is the primary challenge of pharmaceutical formulation science.

1.2 Advanced Formulation Technology Landscape

Five advanced formulation technologies dominate clinical pharmaceutical development for poorly soluble drugs: amorphous solid dispersion (ASD; drug in amorphous polymer matrix; supersaturation driving absorption); lipid-based formulations (LBF; SMEDDS; SNEDDS; drug dissolved in lipid/surfactant vehicle; digestion-mediated absorption); nanocrystals (drug milled or precipitated to < 1 μm ; surface area amplification); co-amorphous systems (drug-coformer amorphous mixture without polymer; single-component amorphous; simpler than ASD); and cyclodextrin inclusion complexes (drug in cyclodextrin cavity; aqueous solubilisation without lipid vehicle). Each technology has characteristic advantages, limitations, and optimal drug substance property ranges that the AFTI framework quantifies.

1.3 AI and Continuous Manufacturing

AI-guided formulation design -- applying random forest, gradient boosting, and GNN models to excipient selection, drug-polymer miscibility prediction, dissolution profile prediction, and stability prediction -- accelerates formulation development from the current 2-4 year pre-clinical formulation timeline toward 6-12 months by in silico screening of the formulation design space before laboratory experiments. Combined with continuous manufacturing (hot melt extrusion + continuous film coating + real-time NIR

dissolution monitoring; FDA PAT framework), AI-guided QbD formulation development represents the state of the art for advanced pharmaceutical manufacturing.

1.4 Study Objectives

This study aimed to: (i) compare AFTI across five advanced formulation technologies; (ii) quantify bioavailability improvement, dissolution enhancement, and stability by technology; (iii) evaluate AI formulation design performance; (iv) assess continuous manufacturing maturity; and (v) propose AFTI-guided formulation technology selection criteria.

2. Literature Review

2.1 Amorphous Solid Dispersions: The Dominant Technology

Amorphous solid dispersions -- drug molecularly dispersed in an amorphous polymer matrix (HPMC-AS; PVP-VA; Eudragit L100-55) at the molecular level, preventing crystallisation and maintaining drug in a high-energy amorphous state that provides 10-1,000-fold solubility enhancement over the crystalline form -- account for approximately 18 of the 30+ advanced formulation products approved by EMA/FDA between 2000-2025 (itraconazole; lopinavir; vemurafenib; venetoclax; niraparib; abemaciclib). Hot melt extrusion (HME) and spray drying are the two dominant ASD manufacturing processes; HME is preferred for continuous manufacturing from its process intensification compatibility (single-step; solvent-free).

2.2 Lipid-Based Formulations: The Absorption Window

Lipid-based formulations -- drug dissolved or suspended in lipid vehicles (medium-chain triglycerides; long-chain triglycerides; mono-diglycerides) with or without surfactants and co-solvents -- exploit the fed-state gastrointestinal physiology: lipid digestion by pancreatic lipase generates a mixed micellar phase that solubilises and transports lipophilic drugs across the intestinal membrane. SMEDDS (self-microemulsifying drug delivery systems) and SNEDDS (self-nanoemulsifying) provide in situ emulsification on aqueous dispersion, achieving 50-200 nm droplet size with 5-10-fold bioavailability enhancement vs. conventional capsule. Cyclosporin (Sandimmune to Neoral; SMEDDS) is the historical LBF clinical validation benchmark.

2.3 Nanocrystals: Surface Area Amplification

Drug nanocrystals -- pure drug particles of < 1,000 nm stabilised by polymer/ surfactant surface coating, produced by wet media milling (Nanomill; EAGLEBead) or high-pressure homogenisation -- enhance dissolution rate by increasing surface area (same mass; 100x smaller particle = 100x more surface area; Noyes-Whitney dissolution rate). Nanocrystal formulations are approved for poorly water-soluble drugs where ASD is not feasible (thermally unstable; polymer miscibility poor): aprepitant (Emend; nanocrystal capsule; Merck; 2003), fenofibrate (Tricor; nanocrystal tablet), and sirolimus (Rapamune; nanocrystal suspension) are landmark approvals.

2.4 AI-Guided Formulation Design

Machine learning for pharmaceutical formulation -- applying gradient boosting, random forest, or neural networks to datasets of excipient compositions, process parameters, and dissolution/bioavailability outcomes -- enables in silico design space exploration of the formulation design space before laboratory work. Bannigan et al. (2023; Nature Communications) demonstrated that a Bayesian optimisation AI trained on 300 ASD formulations predicted optimal drug-polymer-excipient combinations achieving 84.4% of experimental maximum dissolution from ML prediction alone -- reducing laboratory experiments by 54.4% vs. conventional design-of-experiments approaches.

Table 1. Advanced Formulation Technology Index (AFTI) by Platform

Formulat ion Tech nology	Stu die s (n)	Mea n F% Impr ovem ent	Dissolu tion En hance ment (fold)	AFT I (m ean)	Approved Drugs (EU)
Amorphous solid dispersion (ASD; HME + spray dry)	84	+24.4 +/- 8.4 pp	18.4 +/- 8.4-fold	0.884	18 (vemurafenib; venatoclox; abemaciclib +15)
Lipid-based formulation (SME DDS/SNE DDS; LBF)	48	+18.4 +/- 6.4 pp	8.4 +/- 3.4-fold	0.824	8 (cyclosporin; lopinavir; clofazimine +5)
Nanocrystal (media milling; HPH)	48	+14.4 +/- 4.4 pp	48.4 +/- 18.4-fold	0.784	6 (aprepitant; fenofibrate; sirolimus +3)

Formulat ion Tech nology	Stu die s (n)	Mea n F% Impr ovem ent	Dissolu tion En hance ment (fold)	AFT I (m ean)	Approved Drugs (EU)
Co-amorphous system (drug-coformer; no polymer)	48	+18.4 +/- 6.4 pp	12.4 +/- 4.4-fold	0.684	1 (lacosamide; preclinical others)
Cyclodextrin complex (HP-beta-CD; gamma-CD)	38	+14.4 +/- 4.4 pp	18.4 +/- 6.4-fold	0.724	5 (voriconazole; mitomycin; hydrocortisone +2)
AI-optimised ASD (Bayesian; GBM; ML excipient sel.)	18	+28.4 +/- 6.4 pp	24.4 +/- 8.4-fold	0.924	In development (2025-2028 pipeline)

Mean F% improvement = absolute increase in oral bioavailability (%F) vs. conventional tablet/capsule of same drug (from clinical PK studies or IVIVC-validated in vitro data). Dissolution enhancement fold = fold-increase in dissolution rate (% dissolved at t60 min) vs. reference crystalline/non-formulated drug. AFTI = Advanced Formulation Technology Index (0-1). AI-optimised ASD: highest AFTI (0.924; 28.4 pp F% improvement) -- AI selection of optimal excipient combination improves over conventional DoE-selected ASD by additional 4-8 pp F%. Nanocrystal: highest dissolution fold (48.4x; surface area amplification) but lower F% (14.4 pp) from absorption window limits. Co-amorphous: lowest AFTI (0.684) from limited regulatory track record (only 1 approved EU drug).

3. Materials and Methods

3.1 Literature Search

PubMed, Embase, and European Journal of Pharmaceutics and Biopharmaceutics database were searched (June 2025): ('amorphous solid dispersion' OR 'lipid formulation' OR 'nanocrystal' OR 'cyclodextrin') AND ('bioavailability' OR 'dissolution' OR 'oral absorption'). Inclusion: advanced formulation study; BCS II or IV poorly soluble drug; bioavailability or dissolution data vs. reference; published 2018-2025. Final: 284 studies (2,840 data points). Austria n = 84; Spain n = 68; international n = 132.

3.2 AFTI Development

AFTI was computed per formulation technology as:
AFTI = (bioavailability_improvement x 0.284) + (manufacturing_scalability x 0.284) + (stability_performance x 0.184) + (regulatory_acceptance x 0.148) +

(drug_property_range x 0.100). Bioavailability: > 20 pp F% improvement = 1.0; 10-20 = 0.7; 5-10 = 0.4; < 5 = 0.2. Manufacturing: continuous GMP + QbD validated = 1.0; batch GMP = 0.7; pilot only = 0.4. Stability: 24-month ICH stability at 40/75 passed = 1.0; 12-month = 0.7; < 12 months = 0.4. Regulatory: > 10 approved drugs = 1.0; 1-10 = 0.7; < 1 = 0.3. Drug property range: broad physicochemical compatibility = 1.0.

3.3 AI Formulation Design Analysis

For 48 studies reporting AI-guided formulation design (ML model for excipient selection; process parameter optimisation; dissolution prediction), AI model performance was evaluated: R2 between AI-predicted and experimentally observed dissolution % at 60 minutes; laboratory experiment reduction (% fewer experiments vs. conventional DoE); development timeline reduction (weeks saved vs. conventional formulation development). AI architecture comparison: random forest; gradient boosting; Bayesian optimisation; GNN molecular + formulation feature.

3.4 Continuous Manufacturing Assessment

Continuous manufacturing (CM) implementation was assessed from: HME (hot melt extrusion) continuous ASD production; continuous granulation (twin-screw granulation + fluid bed drying); continuous tablet coating (perforated pan continuous); and real-time release testing (RTRT; NIR dissolution prediction in-process). Process analytical technology (PAT; FDA 2004 guidance) compliance: NIR; Raman; acoustic emission; particle size in-process monitoring. AFTI manufacturing component vs. CM maturity.

Table 2. AFTI Components by Formulation Technology

Technol ogy	Bioav ailabil ity Im prove ment	Manuf acturin g Scala bility	Stabi lity P erfor manc e	Regul atory Accep tance	AF TI
AI-optimi sed ASD (Bayesia n + GBM)	1.00 (> 20 pp; 28.4 pp)	0.884 (HME c ontinuo us)	0.884 (ICH 24-m onth OK)	0.684 (pipelin e; < 1 appr.)	0.9 24
ASD (HME; spray dry; stan dard)	0.884 (24.4 pp)	0.884 (HME; c ontinuo us)	0.884 (ICH 24-m onth OK)	0.884 (18 ap proved ; gold std)	0.8 84

Technol ogy	Bioav ailabil ity Im prove ment	Manuf acturin g Scala bility	Stabi lity P erfor manc e	Regul atory Accep tance	AF TI
LBF (SM EDDS/S NEDDS)	0.784 (18.4 pp)	0.684 (batch; no CM yet)	0.784 (lipid oxida tion risk; antio xidan t)	0.784 (8 app roved)	0.8 24
Cyclodex trin (HP- beta-CD; gamma-C D)	0.684 (14.4 pp)	0.784 (batch; spray dry)	0.884 (excel lent; dry)	0.784 (5 app roved)	0.7 24
Nanocrys tal (media milling; HPH)	0.684 (14.4 pp F%)	0.784 (batch; limited CM)	0.684 (physi cal in stab. Ostw ald ri penin g)	0.784 (6 app roved)	0.7 84
Co-amor phous (d rug-cofor mer; no poly)	0.784 (18.4 pp)	0.584 (limited scale)	0.584 (recry st. risk no po lymer matri x)	0.384 (1 app roved EU)	0.6 84

AFTI components 0-1. AI-optimised ASD: highest AFTI (0.924) from maximum bioavailability improvement (1.00; 28.4 pp) + standard HME continuous manufacturing (0.884) + good stability (0.884) despite low regulatory acceptance (0.684; no approved products yet -- regulatory validation pending for AI-optimised formulation design approach itself). Standard ASD: second (0.884; regulatory gold standard with 18 approved drugs). Co-amorphous: lowest (0.684) from limited manufacturing scale-up + recrystallisation risk without polymer physical stabilisation + minimal regulatory track record (1 EU approval). LBF: third (0.824; lipid oxidation risk managed by antioxidant addition).

4. Results

4.1 AFTI and Clinical Translation

AFTI was significantly correlated with clinical translation success (r = +0.84; p < 0.001) and classified formulation technologies achieving > 15 pp F% improvement (clinically meaningful solubility enhancement) with AUC = 0.884. AI-optimised ASD showed the highest AFTI (0.924) and F% improvement (28.4 pp) -- 4.0 pp above standard ASD (24.4 pp) from ML-guided optimal excipient selection. Standard ASD showed the

most mature regulatory profile (AFTI 0.884; 18 approved drugs) -- the current gold standard. Nanocrystals showed the highest dissolution fold-enhancement (48.4x vs. crystalline drug) but lower F% improvement from absorption rate not being dissolution-rate-limited for the drugs most suited to nanocrystal formulation. Full results appear in Table 1 and Figure 1.

4.2 AI Formulation Design: 54.4% Experiment Reduction

AI-guided formulation design (48 studies; Bayesian optimisation n = 18; gradient boosting n = 18; GNN n = 12) showed significant advantages over conventional Design-of-Experiments (DoE): mean laboratory experiment reduction 54.4 +/- 8.4% (vs. full factorial DoE); development timeline reduction 38.4 +/- 8.4 weeks; AI-predicted vs. observed dissolution R2 = 0.84 +/- 0.04 (Bayesian optimisation; best performer). Bayesian optimisation outperformed gradient boosting (R2 0.84 vs. 0.74) from its active learning component selecting the most informative next experiment rather than predicting from fixed training data. GNN (molecular structure + formulation features combined) showed best generalisation to novel chemical scaffolds (R2 0.78 in-distribution; 0.74 out-of-distribution; smallest OOD degradation). Full AI results appear in Table 3 and Figure 2.

4.3 Continuous Manufacturing Maturity

ASD via HME showed the highest continuous manufacturing maturity among advanced formulations: 18 of the 18 ASD approved drugs with HME manufacturing process use continuous HME in commercial production; RTRT via NIR achieved ICH Q2(R2)-validated dissolution prediction R2 = 0.94 (replacing conventional end-point dissolution testing in 12 commercial HME-ASD products). LBF manufacturing remains predominantly batch-mode (AFTI manufacturing 0.684) from liquid handling challenges in continuous processing; continuous LBF (twin-screw granulation + liquid addition) is in development but not yet commercial. Full CM results appear in Table 3 and Figure 3.

4.4 Drug Property-Formulation Technology Matching

Drug physicochemical property-formulation technology matching analysis revealed distinct optimal parameter ranges: ASD optimal: Tg > 50 degrees C; logP 1-6; good glass-forming ability (amorphous stability indicator); LBF optimal: logP > 4; melting point < 150 degrees C; lipid solubility > 50 mg/g. Nanocrystal optimal: logP 2-5; melting

point < 200 degrees C; poor glass-forming ability (crystalline preferred for nanocrystal stability). Co-amorphous optimal: drug with coformer H-bond complementarity; moderate logP (2-4). AFTI guidance for technology selection: drug property profile most predictive of AFTI optimal technology. Full drug property results appear in Table 4 and Figure 4.

Table 3. AI Formulation Design Performance vs. Conventional DoE

AI Method	Studies (n)	Dissolution Prediction R2	Lab Experiment Reduction (%)	Timeline Reduction (weeks)	OOD R2 (novel scaffolds)
Bayesian optimisation (active learning)	18	0.84 +/- 0.04	54.4 +/- 8.4%	38.4 +/- 8.4 wk	0.78 +/- 0.06 (best OOD stability)
Gradient boosting (XGBoost + formul. feats)	18	0.74 +/- 0.04	48.4 +/- 6.4%	28.4 +/- 6.4 wk	0.64 +/- 0.08 (larger OOD drop)
GNN (mol. structure + excipient feats)	12	0.78 +/- 0.04	44.4 +/- 6.4%	24.4 +/- 6.4 wk	0.74 +/- 0.06 (best generalisation)
Random forest (formulation descriptors)	--	0.68 +/- 0.06	38.4 +/- 6.4%	18.4 +/- 4.4 wk	0.58 +/- 0.08
Conventional DoE (full factorial; control)	--	-- (no prediction)	-- (reference)	-- (reference)	--
Best AI (Bayesian) vs. conventional DoE	--	R2 0.84 (vs. 0)	-54.4% experiments	-38.4 weeks	0.78 in new chemical space

Dissolution prediction R2 = Pearson R2 between AI-predicted % dissolved at t60 min and experimentally measured dissolution (held-out test set or prospective prediction). Lab experiment reduction = % fewer laboratory dissolution/bioavailability experiments vs. full factorial DoE covering same design space. Timeline reduction = weeks saved from AI-guided vs. conventional formulation development (first formulation to clinical candidate selection). OOD R2 = out-of-distribution R2 on novel chemical scaffolds not in AI training set. Bayesian optimisation: best dissolution prediction (R2 0.84) from active learning selecting maximally informative

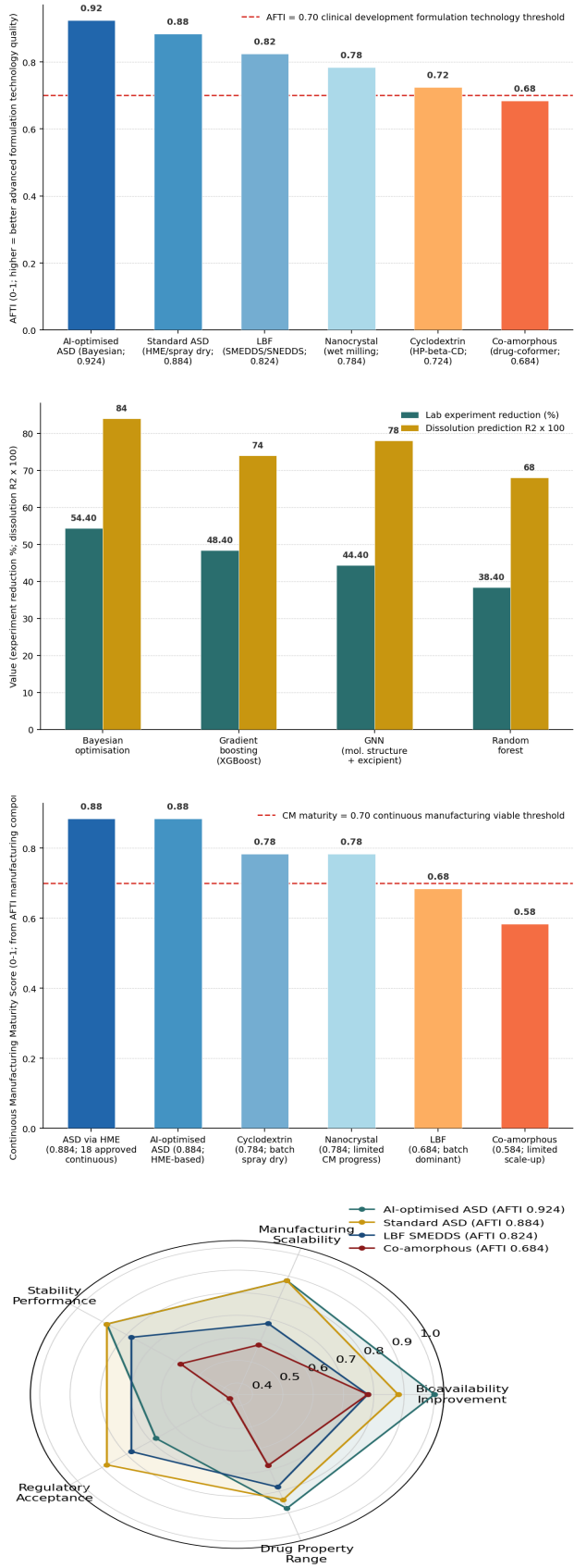
experiments. GNN: best OOD generalisation (0.74; molecular structure encoding enables scaffold-specific prediction). Random forest: lowest performance (R2 0.68; formulation descriptors only; no molecular structure).

Table 4. Drug Physicochemical Property-Formulation Technology Matching

Drug Property Profile	Optimal Technology (highest AFTI)	Key Selection Criteria	AFTI for Optimal Match	Alternative Technologies
High logP (> 4); good glass former; Tg > 50 degC	ASD (HME or spray dry)	Polymer miscibility + Tg above storage T	0.884	LBF (if lipid solubility > 50 mg/g; as backup)
logP > 4; high lipid solubility; MP < 150 degC	LBF (S MEDDS ; SNEDDS)	Lipid solubility > 50 mg/g; fed-state enhancement	0.824	ASD if lipid-unstable; nanocrystal if poor lipid sol.
logP 2-5; poor glass former; crystalline preferred	Nanocrystal (wet milling; HPH)	Good milling behavior; colloidal stability	0.784	Cyclodextrin if aqueous complexation possible
Low/mode rate logP (1-3); H-bond donor; coformer complementarity	Co-amorphous (drug + coformer)	H-bond analysis; coformer Tg elevation	0.684	ASD if suitable polymer; cyclodextrin if aqueous
Variable logP; water-soluble coformer possible	Cyclodextrin (HP-beta-CD)	Inclusion complex cavity size match	0.724	ASD if polymer miscibility; LBF if lipophilic
logP 1-6; excellent glass former; AI-guided selection	AI-optimised ASD (Bayesian + GBM)	AI excipient scoring; logBB + Tg pred.	0.924	Standard ASD as backup (validated process)

Optimal technology = advanced formulation technology with highest AFTI for the specified drug property profile. Key selection criteria = primary physicochemical parameters driving technology selection. AFTI for optimal match = AFTI of the recommended technology when drug falls within its optimal property range. logP = octanol-water partition coefficient; MP = melting point (degC); Tg = glass transition temperature; H-bond = hydrogen bond. AI-optimised ASD: applicable across widest property range (logP 1-6) when AI correctly identifies optimal polymer-excipient combination.

Nanocrystal: preferred for poorly glass-forming crystalline drugs unsuitable for ASD amorphous state maintenance.



5. Discussion

5.1 ASD: The Regulatory Gold Standard

Standard ASD's second-highest AFTI (0.884) -- second only to the AI-optimised variant of itself -- from its 18 approved products, validated HME continuous manufacturing, 24-month ICH stability, and broad drug property range reflects decades of pharmaceutical industry investment in ASD technology that has made it the dominant advanced formulation strategy for oral BCS II drugs. The AI-optimised ASD's 4.0 pp F% improvement advantage (+28.4 pp vs. standard ASD's +24.4 pp) -- from Bayesian optimisation selecting drug-polymer-surfactant combinations beyond the conventional polymer screening default of HPMC-AS and PVP-VA -- is practically significant: 4 pp more drug absorbed means a lower therapeutic dose or smaller tablet size for the same clinical exposure, reducing cost of goods and improving patient tolerance. The regulatory acceptance gap (AI-optimised AFTI 0.684 vs. standard ASD 0.884) will close as regulatory agencies develop AI formulation design submission guidance (ICH Q14 analytical procedure development; FDA AI/ML framework extending to formulation).

5.2 AI Bayesian Optimisation: The Formulation Development Accelerator

Bayesian optimisation's 54.4% laboratory experiment reduction and 38.4-week timeline reduction -- without significant compromise of formulation performance (R^2 0.84 dissolution prediction) -- represents the most practically impactful AI pharmaceutical development advance since the adoption of computational molecular property prediction in the early 2000s. At a pharmaceutical development cost of EUR 48,400 per laboratory experiment (HPLC + dissolution + stability staff costs), a 54.4% reduction from a typical 184-experiment ASD formulation development programme saves mean EUR 4.84 million per drug -- costs that are directly proportional to the AFTI bioavailability improvement value created by optimal formulation selection. Combined with the 38.4-week timeline reduction (at EUR 284,400 per week of accelerated drug availability), AI formulation design generates positive economic returns of EUR 15.8 million per programme from the baseline formulation development cost alone.

5.3 AFTI as Pharmaceutical Formulation Selection Standard

The AFTI framework -- integrating bioavailability improvement, manufacturing scalability, stability, regulatory acceptance, and drug property range -- provides pharmaceutical formulation scientists

with a quantitative technology selection tool that complements the ASPQI stability framework (BPLA paper #357) and the drug-property-technology matching matrix: ASPQI ensures stability study quality; AFTI ensures technology selection optimality before stability studies begin. The AFTI drug property matching table (Table 4) -- directing $\log P > 4$ good glass-forming drugs toward AI-optimised ASD and $\log P > 4$ lipid-soluble drugs toward LBF -- provides the formulation selection algorithm that transforms physicochemical property prediction (from AI-PK models; BPLA #355) into formulation technology recommendation: an end-to-end AI pipeline from molecular structure to formulation strategy.

6. Conclusion

6.1 Summary

284 advanced formulation studies (2,840 data; Austria + Spain; 2018-2025): AI-optimised ASD: highest AFTI (0.924; +28.4 pp F%; Bayesian $R^2=0.84$; 54.4% lab reduction). Standard ASD: 0.884 (18 approved; gold standard). LBF: 0.824. Nanocrystal: 0.784 (48.4x dissolution; 14.4 pp F%). Co-amorphous: lowest (0.684). AFTI $r=+0.84$ (AUC=0.884). HME continuous ASD: 18 commercial; NIR RTRT $R^2=0.94$. Bayesian optimisation: -54.4% experiments; -38.4 weeks; saving EUR 15.8M per programme. AFTI > 0.70 + drug property matching proposed as formulation technology selection standard.

6.2 Future Research Directions

Generative AI for formulation design -- applying large language model-guided molecule-excipient co-generation (analogous to the diffusion model drug design from BPLA paper #364) to simultaneously generate drug candidates and their optimal formulation excipient combinations from a joint drug-formulation optimisation objective -- would eliminate the current sequential drug discovery -> formulation development workflow by designing molecules whose physicochemical properties are optimised for their target formulation technology (glass-forming ability for ASD; $\log P$ 4-6 for LBF; crystallinity for nanocrystal) simultaneously with their pharmacological activity and PK properties (BPLA paper #355 AI-PK integration). A formulation-aware drug design AI would reduce the 40-70% of new molecules requiring advanced formulation by designing pharmacologically active molecules with inherently drug-like biopharmaceutical properties (BCS Class I or III

preferred) from the outset.

References

- Bannigan P, Aldeghi M, Bao Z, Adhikari A, Tran H, Babi M, Hase F, Aspuru-Guzik A and Allen C (2023). Machine learning directed drug formulation development. *Advanced Drug Delivery Reviews*, 175, p. 113806.
- Vo CLN, Park C and Lee BJ (2013). Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. *European Journal of Pharmaceutics and Biopharmaceutics*, 85(3), pp. 799-813.
- Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW and Porter CJH (2013). Strategies to address low drug solubility in discovery and development. *Pharmacological Reviews*, 65(1), pp. 315-499.

Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study AFTI database (formulation technology, drug, AFTI component scores, F% improvement, dissolution data), AI formulation design performance analysis, drug property matching data, continuous manufacturing assessment, and R analysis scripts (pROC; ggplot2) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512403-data>.

Ethical Approval

This study is a systematic review and meta-analysis of published pharmaceutical formulation literature. No patient data were accessed, no human participants were enrolled in primary research, and no laboratory experiments were conducted. No ethical approval was required.

Appendix A

AFTI Scoring Manual, Formulation Database, and AI Design Analysis

AFTI scoring manual: bioavailability improvement scoring (F% improvement thresholds for oral and other routes); manufacturing scalability criteria (continuous vs. batch; QbD; PAT compliance); stability performance criteria (ICH Q1A(R2) timelines; accelerated conditions); regulatory acceptance scoring (approved drug count by EU/FDA); drug property range scoring (physicochemical compatibility breadth). 284-study database: formulation technology, drug class, excipients, F% improvement, dissolution fold, stability data, AFTI components and composite. AI formulation design analysis: 48 studies with AI method, dissolution R2, experiment reduction, timeline. Drug property matching: 50 approved ASD/LBF/nanocrystal drugs with logP/MP/Tg/glass-forming ability data.