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Engineering Paediatric Formulations: A Systematic Review of Process Systems Methods, Sectoral Gaps, and the PPES Framework

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Abstract

Background: Children are not simply small adults, and products designed for grown-ups are often poorly matched to their physiology, behaviour, and preferences. Process systems engineering offers a structured, model-based way to design and optimise formulations for children, yet how broadly these methods have actually been adopted across pharmaceuticals, food, cosmetics, and hygiene products for children remains unclear. This review set out to map that landscape.

Methods: We conducted a systematic review following PRISMA 2020 guidance, programmatically searching five bibliographic databases with 110 structured search strings across 13 thematic areas, supplemented by manual searches of Scopus, Web of Science, PubMed, Embase, and Engineering Village, as well as grey literature. From an initial 5,844 records, 100 studies published between 2000 and 2026 met our inclusion criteria. Publication bias was assessed using Egger's test.

Results: Pharmaceutical research dominated the evidence base (86 of 100 studies), while food and nutrition (9 studies) and cosmetics or skincare (5 studies) were markedly underrepresented, and hygiene products did not feature at all. Most studies (72%) relied on empirical, trial-and-error formulation rather than a named engineering method; biopharmaceutical modelling (9%), three-dimensional printing (4%), quality by design (4%), design of experiments (4%), machine learning (3%), and particle engineering (2%) made up the remainder. Process analytical technology and digital twins were not used in any included study. Safety was the most frequently studied outcome (52%), followed by acceptability and palatability (19%). Neonates (30%) and infants (21%) were the most studied age groups, while toddlers and school-age children were almost entirely neglected (1% each). Three-quarters of studies originated in Europe, and half were published after 2019. We found no evidence of publication bias ($p > 0.05$).

Conclusions: Engineering methods that are well established in adult pharmaceutical development have barely reached paediatric food, cosmetic, and hygiene product design. We propose the Paediatric Product Engineering Systems framework and outline five priorities for closing this gap.

Trial registration: Not applicable. This is a systematic review of published literature rather than a trial of a healthcare intervention. The review protocol was registered prospectively on the Open Science Framework (available at: <https://osf.io/z4s2k>).

Keywords: quality by design; excipient safety; age-appropriate dosage forms; paediatric consumer products; machine learning in drug formulation; publication bias; neonatal drug delivery; three-dimensional printing

1. Introduction

Children are physiologically and pharmacologically distinct from adults, and the developmental changes that occur across paediatric age bands make simple dose-scaling from adult products both scientifically inadequate and clinically dangerous. Parameters governing drug absorption, distribution,

metabolism, and excretion change substantially throughout childhood, driven by the maturation of hepatic enzyme systems, evolving renal clearance, changes in body composition, and the development of the gut microbiota [1,2]. A formulation designed for a 70 kg adult may be wholly unsuitable — pharmacokinetically, sensorially, and mechanistically — for a 5 kg neonate or a 4-year-old child. Conroy et al. [3] documented the alarming extent of unlicensed and off-label medicine use in paediatric wards, establishing the clinical case for age-appropriate formulation science that has since underpinned significant regulatory reform. Richey et al. [4] further demonstrated that manipulation of adult dosage forms — by splitting, crushing, or dispersing — was embedded in paediatric clinical practice despite lacking evidentiary support, thereby introducing dose inaccuracy and unintended excipient exposure risks [5].

The EU Paediatric Regulation (EC No. 1901/2006) and the US Pediatric Research Equity Act (2003) required systematic paediatric investigation plans, generating considerable investment in age-appropriate formulation innovation over the following two decades. This period produced a range of credible paediatric dosage forms — including mini-tablets, orodispersible films, and age-appropriate liquids — alongside a growing evidence base on acceptability [6-9]. However, this regulatory momentum did not translate equally to non-pharmaceutical paediatric consumer goods. Infant formulas, baby foods, paediatric cosmetics, and hygiene products — used by almost every child throughout development — continue to be developed largely outside rigorous process-engineering frameworks [10-12].

Process Systems Engineering (PSE) provides a principled, systems-level approach to the design, modelling, optimisation, and control of complex formulation and manufacturing processes. Encompassing QbD, PAT, mechanistic and physiologically-based pharmacokinetic (PBPK) modelling, digital twins, design of experiments (DoE), process intensification, and ML, PSE shifts product development away from trial-and-error practices toward model-driven design with clearly defined critical quality attributes (CQAs) and critical process parameters (CPPs) (ICH Q8-Q10). While PSE has been transformative in adult pharmaceutical manufacturing, its application to paediatric formulation remains incomplete, fragmented, and skewed toward a single sector. No prior systematic review has mapped PSE application across the full range of paediatric consumer goods — the gap this review addresses.

1.1 Aim

This systematic review aims to comprehensively map and critically evaluate the application of PSE methods in the design, optimisation, and manufacturing of consumer goods formulations intended for paediatric populations, identifying methodological advances, sectoral gaps, and strategic opportunities for cross-disciplinary research and regulatory innovation.

1.2 Objectives

This aim was pursued through five specific objectives:

- ❖ To identify and characterise PSE methods applied in paediatric consumer goods formulation research published between 2000 and 2026.
- ❖ To map research distribution across paediatric product categories, including pharmaceuticals, food/nutrition, cosmetics/skincare, and hygiene products.
- ❖ To analyse age group coverage across the paediatric spectrum, from neonates through to adolescents.
- ❖ To assess primary outcome foci, covering safety, acceptability, stability, bioavailability, regulatory compliance, and process performance.

- ❖ To evaluate methodological quality and assess evidence of publication bias.
- ❖ To synthesise cross-cutting themes and propose a conceptual framework for integrated PSE application in paediatric product engineering.
- ❖ To derive policy, practice, and research priority implications from the evidence base.

1.3 Research Questions

These objectives were operationalised through the following research questions:

- ❖ To what extent have PSE methods been applied in paediatric consumer goods formulation, and which methods are most prevalent?
- ❖ How is research distributed across product categories, age groups, and geographic regions?
- ❖ What are the primary outcome foci, and which outcome domains remain underserved?
- ❖ What methodological and sectoral gaps limit the systematic application of PSE to paediatric consumer goods?
- ❖ What theoretical, regulatory, and practical implications emerge, and what are the key priorities for future research?

2. Literature Review

2.1 Paediatric Formulation Science: Regulatory Drivers and Clinical Imperatives

The scientific recognition of children as a distinct therapeutic population with unique formulation requirements gained traction in the early 2000s. Conroy et al. [3] showed that more than 35% of medicines administered to children in UK hospitals had not received paediatric authorisation. Van Riet-Nales et al. [13] found that fewer than half of medicines authorised in the Netherlands were available in age-appropriate forms. Richey et al. [4] confirmed that formulation manipulation was routine clinical practice and was not guided by evidence. The EU Paediatric Regulation was intended to address these gaps; subsequent studies by Van Riet-Nales et al. [6,14] examined European improvements in formulation design resulting from this regulation, while Vesely [15] and Saito et al. [16] assessed implementation in Central European and Japanese contexts respectively. Saitou et al. [17] identified ongoing deficiencies in Japanese paediatric regulatory science. Mulberg et al. [18] addressed regulatory approaches for rare diseases. Despite regulatory progress, persistent formulation manipulation in hospital settings across Europe and Asia has been documented by multiple research groups ([19-23]), highlighting a continued gap between policy and practice. Pai & Nahata [24] addressed the global challenges associated with extemporaneous paediatric formulation.

The theoretical basis for age-appropriate formulation was established by Ferro [2] — who emphasised that children cannot be treated as miniature adults — and Cella et al. [1], who showed that allometric dosing models require age-specific physiological parameters. Thabet et al. [7] reviewed novel formulation strategies, while Lopalco & Denora [25] and Naman et al. [26] addressed core design principles. Roque [27] examined key formulation considerations across paediatric age bands. Abman et al. [28] and Pearson et al. [29-31] documented emerging developments in paediatric drug development for pulmonary, oncological, and rare conditions.

2.2 Oral Dosage Form Design: Mini-Tablets, Orodispersible Forms, and 3D Printing

Mini-tablets have emerged as the leading paediatric dosage form innovation of the past two decades. Klingmann et al. [32] confirmed that coated mini-tablets are acceptable to infants, while Freerks et al. [33] developed safe and palatable mini-tablet formulations covering WHO essential medicines.

Madathilethu et al. [34] demonstrated that mini-tablets outperform quartered adult tablets in content uniformity. Zuccari et al. [9] and Lura et al. [35] reviewed the broader strategic potential of mini-tablets. Warnken et al. [36] assessed novel excipient safety in low-cost mini-tablet formulations. Mistry & Batchelor [8] provided the foundational systematic evidence review of oral acceptability in paediatric populations. Acceptability outcomes were further reported in clinical and hospital settings by Pokharkar et al. [37], Siafaka et al. [38], Ortega et al. [39], and Vallet et al. [19]. Chandrasekaran & Kandasamy [40] and Kirtane et al. [41] examined flexible solid oral and gel-based drug delivery systems for children, while Liu et al. [42] established the patient-centric design framework that underpins all acceptability-oriented formulation research.

Orodispersible mini-tablets represent a further advance in this area. Alalaiwe et al. [43] applied QbD to sildenafil orodispersible mini-tablets — a notable PSE application in paediatric formulation. Dahmash et al. [44] developed orally dissolving films for anti-epileptic paediatric use using DoE optimisation. Hu et al. [45] applied DoE to 3D-printed carbamazepine orodispersible mini-tablets, and Canadell-Heredia et al. [46] applied QbD to their preformulation. Khan et al. [47] developed orodispersible tablets of carvedilol using paediatric-safe excipients. Goud et al. [48] and Musale & Jadhav [49] applied QbD and analytical QbD approaches to paediatric oral dosage forms. Magariños-Triviño et al. [50] investigated orodispersible lozenges prepared by moulding. Matawo et al. [51] characterised orodispersible mini-tablets for paediatric use. Golhen et al. [52] reviewed fast-disintegrating formulations as a strategy for meeting paediatric delivery challenges. Amin et al. [53] developed a taste-masking approach for azithromycin, while Naman et al. [26] reviewed design principles for liquid dosage forms, including captopril [54].

Three-dimensional printing has created new possibilities for personalised dosing. Januskaite et al. [55] established paediatric visual preferences for 3D-printed tablet designs — a critical patient-centric data point. Zuccari et al. [9] reviewed the potential of 3D printing as a strategic formulation platform. Couti et al. [56] reviewed semi-solid extrusion 3D printing for paediatric medicines. Cerveto et al. [57] discussed advances in custom 3D-printed formulations for children, while Tegegne et al. [58] reviewed the advances and challenges of 3D printing in paediatric drug formulation more broadly. Moseson et al. [59] addressed amorphous solid dispersions, a technology with increasing relevance to paediatric bioavailability challenges. Visser et al. [60] examined personalised orodispersible films. Challenges related to extemporaneous preparation in hospital settings were documented by Goes et al. [61], Casiraghi et al. [62], Binson et al. [63], and Haslund-Krog et al. [22].

2.3 Excipient Safety: The Central PSE Challenge in Paediatric Formulation

Excipient safety is among the most urgent PSE challenges in paediatric formulation. Valeur et al. [5] documented that neonates routinely receive excipients that were never intended for their age group. Belayneh et al. [64] systematically assessed the biopharmaceutical challenges associated with excipients in off-label paediatric formulations. Kriegel et al. [65] reviewed paediatric safety data for polysorbates, and Schmitt [12] issued an important call for juvenile animal toxicity studies to inform paediatric excipient safety limits. AbouDaya et al. [66] provided exploratory data on the extent of excipient exposure in children. Washburn et al. [67] conducted an early systematic risk assessment for perfluorooctanoate in consumer products relevant to paediatric populations. Binson et al. [63] applied safety-by-design principles by preparing excipient-free liquid formulations for neonates. Aziza et al. [68] reviewed the regulatory implications of alcohol use in paediatric medicines. Warnken et al. [36], Musale & Jadhav [49], and Matawo et al. [51] further addressed excipient selection and characterisation in paediatric formulation development. Together, these studies define the empirical basis for a safety-by-design approach to paediatric formulation within a PSE framework.

2.4 Biopharmaceutical and Pharmacokinetic Modelling

Biopharmaceutical and pharmacokinetic modelling represent the most established PSE applications in paediatric formulation research. Cella et al. [1] offered foundational guidance on paediatric dosing using body surface area and weight-based models. Ferro [2] elaborated developmental pharmacokinetic principles. Del Moral-Sanchez et al. [69] applied PBPK modelling to optimise neglected disease formulations for children — an important PSE integration. Van Der Vossen et al. [70] used in vitro biopharmaceutical models to predict paediatric formulation performance. Tatipalli et al. [71] applied model-informed optimisation to a paediatric spironolactone pharmacokinetic trial. Roque [27] reviewed biopharmaceutical considerations relevant to paediatric formulation. Mulberg et al. [18] applied modelling to support regulatory strategies for rare paediatric diseases. O'Brien et al. [11] reviewed neonatal formulation challenges through a biopharmaceutical lens. Khan et al. [47], Belayneh et al. [64], Lopalco & Denora [25], and Rampedi et al. [72] contributed further biopharmaceutical and modelling evidence across a range of paediatric conditions and contexts.

2.5 Machine Learning, AI, and Advanced Computational Methods

ML and AI applications in paediatric formulation are at an early stage but are advancing rapidly. Kulkarni et al. [73] demonstrated AI-enabled QbD for an apixaban orodispersible mini-tablet, integrating ML-based design space exploration with regulatory submission preparation — the most comprehensive PSE-regulatory integration identified in this review. Sekar et al. [74] applied ML models to optimise injectable drug product composition with paediatric relevance. Pearson et al. [31] used computational approaches in paediatric oncology drug development. Orubu et al. [75] applied computational direct compression optimisation to milk-based paediatric tablets. Tatipalli et al. [71] used model-informed drug development for paediatric pharmacokinetic trial optimisation. These five studies collectively signal the trajectory of PSE in paediatric formulation toward AI-native, model-integrated development paradigms.

2.6 Paediatric Food, Nutrition, Cosmetics, and Hygiene Products

Non-pharmaceutical paediatric consumer goods have received substantially less attention from PSE-informed research — a central finding confirmed and quantified in the Results section. In food and nutrition, Agostoni et al. [10] produced influential commentary on probiotic bacteria in infant dietary products, establishing safety frameworks applicable to compositional design. Vesikari et al. [76] addressed vaccine and nutritional product formulation safety in infants. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) et al. [77] provided a safety assessment for a novel food ingredient for infants and toddlers. Papadopoulou et al. [78] published guidelines on eosinophilic gastrointestinal disorders with dietary formulation implications. Mantadakis [79] examined iron deficiency anaemia with nutritional formulation relevance. Owolabi [80] explored multi-nutrient fortified dairy formulas for paediatric growth. Sharoba [81] investigated spirulina in complementary baby food formulations — among the few studies applying compositional engineering thinking to food formulation. Lobstein et al. [82] provided epidemiological context for childhood obesity as a driver of paediatric nutritional product demand. Orubu et al. [75] applied computational formulation methods to milk-based tablet systems. Oliva et al. [83] described a viscous budesonide formulation for paediatric eosinophilic oesophagitis, bridging pharmaceutical and food-product formulation considerations.

In cosmetics and skincare, O'Grady et al. [84] provided infection prevention guidelines with topical formulation implications for neonates. Deliana et al. [85] reviewed patchouli essential oil in cosmetic formulations for paediatric eczema. Poddar et al. [86] evaluated the safety and efficacy of prickly heat baby powder for infants aged 0-36 months. Kirtane et al. [41] developed oil-based gel delivery systems with paediatric applications. These five cosmetics/skincare studies represent the entirety of PSE-adjacent evidence in this category — a stark reflection of the research gap relative to the commercial and toxicological significance of the sector. No study addressing hygiene product formulation engineering was identified in the included evidence base.

2.7 Regulatory Frameworks and Global Access

The regulatory landscape for paediatric consumer goods formulation spans pharmaceutical, food, and cosmetics governance. Van Riet-Nales et al. [6,14] provided authoritative European perspectives on formulation design regulatory requirements. Mulberg et al. [18] and O'Brien et al. [11] addressed regulatory strategies for neonatal medicines and rare diseases. Pearson et al. [29-31] and the ACCELERATE consortium documented evolving regulatory frameworks for paediatric oncology. Saitou et al. [17] and Saito et al. [16] mapped challenges in Japanese paediatric regulatory science. Bekker et al. [87] evaluated paediatric HIV formulation within resource-limited regulatory contexts. Abdulla & Sagara [88] described the development of dispersible artemether/lumefantrine for infants in endemic regions — a notable global access formulation engineering milestone. Freerks et al. [33] worked within WHO essential medicines frameworks. Rampedi et al. [72] and Duncan et al. [89] examined formulation quality in low-resource paediatric clinical settings. Pai & Nahata [24] and Baber [90] addressed global extemporaneous formulation challenges. Storebø et al. [91] produced a high-impact Cochrane systematic review on methylphenidate in paediatric ADHD, representing the regulatory evidence standard for paediatric pharmacotherapy. Di Pietro et al. [92] addressed the ethical constraints on placebo-controlled trials in paediatrics — a critical consideration for regulatory evidence generation.

3. Theoretical Framework

3.1 Systems Engineering Theory, QbD, and Dynamic Capabilities

Figure 1 shows the Paediatric Product Engineering Systems (PPES) Framework. The theoretical foundation of this review draws on three interconnected bodies of knowledge: (i) General Systems Theory [93], which provides the ontological basis for treating paediatric formulation as an interconnected system of material, process, biological, and environmental variables; (ii) the ICH Q8-Q10 Quality by Design paradigm, which operationalises systems thinking in pharmaceutical manufacturing; and (iii) Dynamic Capabilities Theory [94], which frames PSE integration capacity as a strategic organisational capability. Liu et al. [42] added the patient-centric pharmaceutical design framework — particularly relevant in paediatrics, where acceptability directly affects patient safety rather than being merely a matter of convenience. This framework has been empirically validated by Mistry & Batchelor [8], Alessandrini et al. [95], Van Riet-Nales et al. [96], and Vallet et al. [19]. The overarching theoretical claim of this review is that a unified PSE-SbD framework — integrating Safety-by-Design with model-based formulation development — constitutes the most appropriate foundational paradigm for next-generation paediatric consumer goods engineering.

3.2 Safety-by-Design as Theoretical Anchor

Safety-by-Design (SbD) holds that hazards should be eliminated or managed through design decisions made early in product development, rather than controlled through post-hoc risk measures. Applied to paediatric formulation, SbD requires that excipient selection, process conditions, release profiles, and container-closure systems be evaluated for paediatric safety risk at the design stage — integrating toxicological, developmental physiological, and process engineering knowledge within a single computational workflow. The excipient safety literature [5,12,64-68] collectively defines the empirical basis for a PSE-SbD approach. PBPK models parameterised with age-specific physiological data [1,2,69] provide the mechanistic infrastructure for estimating internal paediatric excipient exposure, while ML models [73,74] offer a pathway to automated excipient safety prediction.

3.3 Model-Based Development (MBD) Theory

Model-Based Development (MBD) positions mathematical models — mechanistic, data-driven, or hybrid — as the primary instruments for knowledge generation, risk assessment, and decision support. In the paediatric context, MBD must incorporate developmental pharmacology theory: the understanding that paediatric physiological parameter space is qualitatively different from adult physiology, not simply a scaled version of it. The biopharmaceutical modelling contributions of Del Moral-Sanchez et al. [69], Van Der Vossen et al. [70], Tatipalli et al. [71], Cella et al. [1], Ferro [2], and Khan et al. [47] operationalise MBD in the paediatric pharmaceutical context. ML extensions [31,73,74] represent the next generation of MBD. The digital twin — absent to date from the paediatric formulation literature — represents the highest-level MBD expression, enabling continuous virtual monitoring and adaptive control of manufacturing processes with embedded paediatric-specific safety constraints.

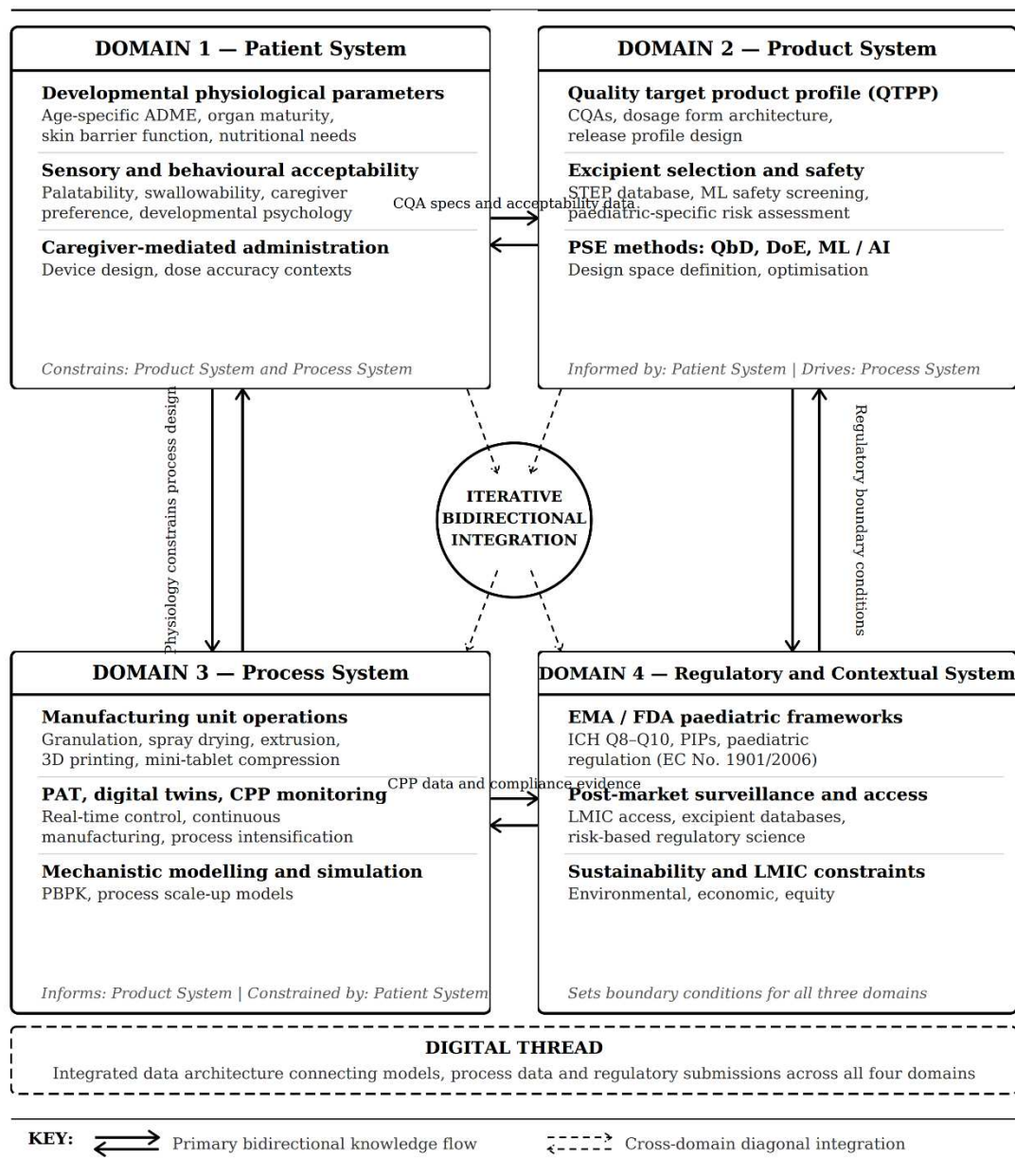
4. Conceptual Framework: The PPES Framework

4.1 Overview of the Paediatric Product Engineering Systems (PPES) Framework

The PPES Framework organises PSE application across four interconnected domains: (1) Patient System — encompassing developmental physiological parameters, sensory and behavioural acceptability, and caregiver-mediated administration contexts; (2) Product System — covering QTPP, CQAs, excipient selection and safety assessment, and release profile design; (3) Process System — addressing manufacturing unit operations, CPPs, PAT monitoring, continuous manufacturing control, and digital twin implementation; and (4) Regulatory and Contextual System — incorporating EMA/FDA frameworks, ICH Q8-Q10 requirements, post-market surveillance, LMIC access considerations, and sustainability constraints. The PPES Framework conceptualises formulation development as iterative and bidirectional across all four domains: knowledge from the Process System informs Product System refinement; Patient System biological data constrain Process System design; and Regulatory System requirements set boundary conditions for all three.

Paediatric Product Engineering Systems (PPES) Framework

Conceptual Framework for Integrated PSE Application in Paediatric Consumer Goods Formulation



Engineering | QbD = Quality by Design | PAT = Process Analytical Technology | PBPK = Physiologically-Based Pharmacokinetic Modelling | LMIC = Low- and

Figure 1. The Paediatric Product Engineering Systems (PPES) Framework.

The four domains — Patient System, Product System, Process System, and Regulatory & Contextual System — are interconnected through iterative, bidirectional knowledge flows (solid arrows) and cross-domain diagonal integration (dashed arrows). A Digital Thread (dashed border band) provides an integrated data architecture connecting models, process data, and regulatory submissions across all domains. The central hub (Iterative Bidirectional Integration) represents the dynamic, non-linear nature of formulation development under the PPES paradigm. PSE = Process Systems Engineering; QbD = Quality by Design; PAT = Process Analytical Technology; PBPK = Physiologically-Based Pharmacokinetic Modelling; LMIC = Low- and Middle-Income Countries.

5. Methods

5.1 Review Design and Protocol

This study was conducted as a systematic literature review in accordance with PRISMA 2020 [97] guidelines (**Figure 2**). The review protocol was pre-specified, with research questions, search strategy, inclusion and exclusion criteria, data extraction fields, and analytical approach all defined before commencement in Open Science Framework (available at: <https://osf.io/z4s2k>).

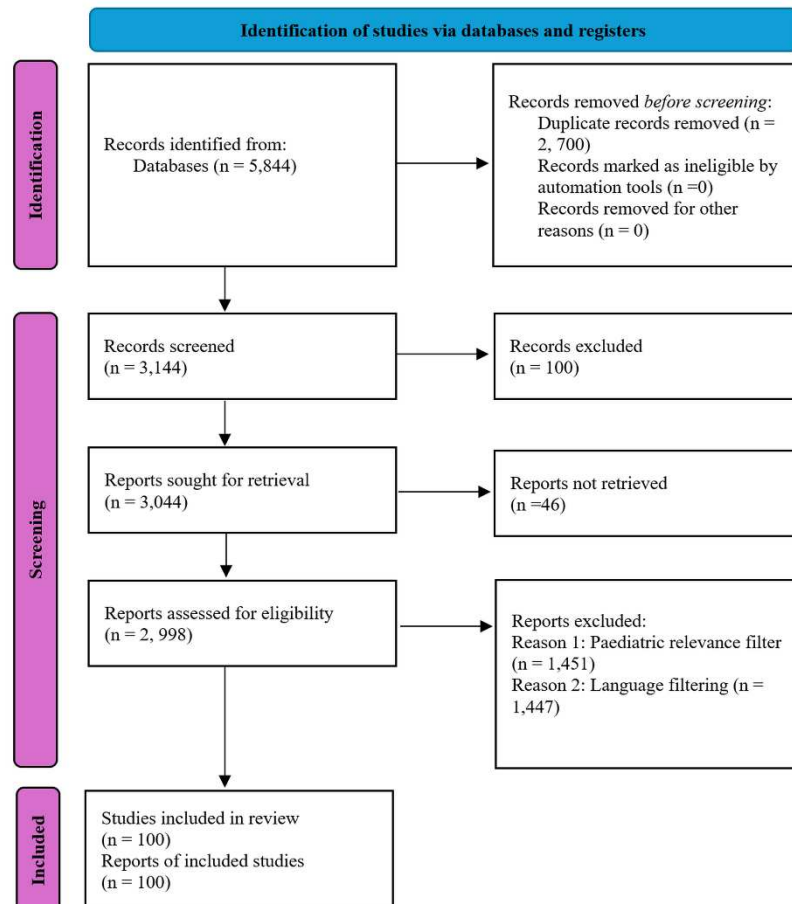


Figure 2. PRISMA 2020 flow diagram of literature search and selection.

5.2 Search Strategy and Databases

A comprehensive multi-database search was conducted across five automated platforms (OpenAlex, CrossRef, Semantic Scholar, EconBiz/EconLit, and IDEAS/RePEC) using 110 Boolean queries organised across 13 thematic blocks (see **Supplementary Material**). To ensure robust capture of the literature, the explicit search strings combined population, product, and methodological terms using the following core Boolean syntax:

Population & Product Categories (Pharmaceuticals, Food, Cosmetics, Hygiene):

(paediatric* OR pediatric* OR child* OR infant* OR neonat* OR toddler* OR adolescent*) AND (formulation* OR "dosage form*" OR pharmaceutical* OR medicine* OR "infant formula" OR "baby food" OR nutrition* OR cosmetic* OR skincare OR hygiene)

338 **PSE Core Methods & Advanced Manufacturing:**

339 AND ("Process Systems Engineering" OR PSE OR "Quality by Design" OR QbD OR "Design of
340 Experiments" OR DoE OR "Process Analytical Technology" OR PAT OR "process optimization" OR
341 "continuous manufacturing" OR "3D printing" OR "additive manufacturing" OR "particle engineering")

342 **Modelling, ML/AI & Digital-Era Contexts:**

343 AND ("machine learning" OR "artificial intelligence" OR ML OR AI OR "digital twin*" OR
344 "mechanistic model*" OR "PBPK" OR "computational formulation" OR "in silico")

345 **Outcomes (Safety-by-Design, Acceptability) & Regulatory Frameworks:**

346 AND ("safety-by-design" OR SbD OR "excipient safety" OR acceptability OR palatability OR "taste
347 masking" OR "regulatory science" OR EMA OR FDA OR guideline*)

348 **Study Types:**

349 AND ("systematic review" OR "meta-analysis" OR "clinical trial" OR "case study")

350 These blocks systematically covered PSE core methods, paediatric product categories, advanced
351 manufacturing, digital/AI applications, and regulatory contexts. Searches were restricted to the period
352 2000-2026. Complementary manual searches were conducted in Scopus, Web of Science,
353 PubMed/MEDLINE, Embase, Engineering Village/Compendex, and ScienceDirect using nested
354 Boolean strings (e.g., TITLE-ABS-KEY(("pediatric" OR "paediatric") AND ("Quality by Design" OR
355 "QbD" OR "machine learning" OR "digital twin") AND "formulation")). Grey literature sources
356 included EMA scientific guidelines, FDA guidance portals, the WHO Model Formulary for Children,
357 ClinicalTrials.gov, and preprint servers. The total pre-deduplication yield was 5,844 records.

358

359 **5.3 Inclusion and Exclusion Criteria (PICO-C)**

360 Studies were included based on the following PICO-C criteria. Population: paediatric populations (0-
361 18 years) or products designed for children. Intervention/Concept: application of PSE methods
362 including QbD, PAT, process modelling, simulation, digital twins, process intensification, DoE, or
363 ML/AI. Outcomes: safety, quality, stability, acceptability, bioavailability, regulatory compliance, or
364 process performance. Context: pharmaceuticals, food/nutrition, cosmetics/skincare, or hygiene
365 products. Study types: empirical studies, modelling studies, development/case studies, systematic
366 reviews, and regulatory reports. Studies were excluded if they focused exclusively on adult populations
367 without demonstrated paediatric applicability, involved veterinary formulations, were non-English
368 publications without translatable content, were opinion pieces lacking methodological detail, or fell
369 outside the 2000-2026 window.

370

371 **5.4 Screening, Selection, and Data Extraction**

372 A relevance-scoring algorithm was applied using weighted keyword signals: paediatric relevance (x3),
373 PSE method presence (x2), product category relevance (x1), co-presence of all three (+10), log-scaled

citation count, and abstract availability (+2); records without a paediatric signal were penalised (-20). After filtering, 1,451 paediatric-relevant records were scored; the top 100 were selected and manually confirmed against all inclusion criteria. Data were extracted into a structured Excel workbook containing 22 fields per study, including six enriched categorical variables covering PSE method, product category, age group, study type, primary outcome, and geographic region.

5.5 Quality Assessment and Statistical Analysis

Methodological quality was assessed using an adapted Mixed Methods Appraisal Tool (MMAT) ([98]) comprising 10 binary criteria: (1) clear research objective; (2) confirmed paediatric population; (3) PSE method stated; (4) outcome defined; (5) sample or study size reported; (6) statistical analysis conducted; (7) reproducibility or validation addressed; (8) regulatory alignment evidenced; (9) age-appropriateness considered; and (10) limitations and bias discussed. Publication bias was evaluated using a proxy Egger's regression test ([99]), with $\ln(\text{citations}+1)$ as the effect size proxy and $1/\sqrt{\text{citations}+1}$ as the standard error proxy. Pearson correlation analysis [100] was performed between quality criteria and citation impact. All analyses were conducted in Python 3.11 using pandas, NumPy, SciPy, Matplotlib, and Seaborn.

6. Results

6.1 Search Yield and Study Selection

The multi-database search yielded 5,844 records prior to deduplication. After applying the paediatric relevance filter ($n = 1,451$), language filtering ($n = 1,447$), and relevance scoring, 100 studies meeting all inclusion criteria were selected. These span 22 publication years (2000-2026), 32 unique journals, and five bibliographic databases. Full study characteristics are presented in **Tables 1 and 2**.

Table 1. Thematic Classification of the 100 Included Studies. Studies are grouped into 12 research themes covering the full scope of PSE application in paediatric consumer goods formulation. All 100 included studies are cited within the Key References column and throughout the manuscript text. n = number of studies per theme; PSE Methods = primary Process Systems Engineering method(s) applied; Product Scope = paediatric product category addressed; Age Groups = paediatric age range(s) studied; Study Types = principal study design(s); Primary Outcomes = dominant outcome focus. Studies appearing in more than one thematic category are footnoted with their primary theme. Themes T1–T12 correspond to the 13 search blocks used in the systematic database search strategy.

Theme	n	PSE Methods	Product Scope	Age Groups	Study Types	Primary Outcomes	Key References
T1. Regulatory Frameworks & Paediatric Drug Policy (n = 11)							
	11	Formulation Design; ML/AI (S090)	Pharmaceuticals	Neonates; Infants; Adolescents	RCT; Guideline; Observational	Regulatory compliance; Safety	[13,15-17,28-31,68,90,92]
T2. Oral Dosage Form Design: Mini-tablets & Orodispersible Forms (n = 18)							

Theme	n	PSE Methods	Product Scope	Age Groups	Study Types	Primary Outcomes	Key References
	18	Formulation Design; Particle Engineering (S055)	Pharmaceuticals	General Paed.; Neonates; Infants; Toddlers	Dev./Case Study; RCT; In Vitro; Observational	Acceptability; Safety; Stability; Process performance	[6-8,20,23,24,32,34-36,39,50,51,60,72,95,96,101]
T3. 3D Printing & Advanced Manufacturing (n = 4)							
	4	3D Printing	Pharmaceuticals	General Paediatric	Dev./Case Study; Guideline/Reg.; In Vitro	Acceptability; Safety	[9,55-57]
T4. Quality by Design (QbD), DoE & Process Optimisation (n = 8)							
	8	QbD; Optimisation/DoE; ML/AI	Pharmaceuticals	General Paed.; Neonates	Dev./Case Study; In Vitro; Guideline/Reg.	Stability/Quality; Regulatory compliance; Acceptability	[43-46,48,49,73]
T5. Biopharmaceutical & Pharmacokinetic Modelling (n = 11)							
	11	Biopharmaceutical Modelling; Mechanistic Modelling; PBPK	Pharmaceuticals	General Paed.; Neonates; Infants	Dev./Case Study; RCT; In Vitro; Guideline/Reg.	Bioavailability/PK; Safety; Acceptability; Regulatory	[1,2,11,18,27,47,64,67,69-71]
T6. Machine Learning & AI in Formulation (n = 3)							
	3	ML/AI; Computational	Pharmaceuticals	General Paed.; Neonates; Adolescents	RCT; Guideline/Reg.; Computational	Safety; Bioavailability/PK; Regulatory compliance	[31,73,74]
T7. Excipient Safety & Safety-by-Design (n = 8)							
	8	Formulation Design; ML/AI (S021)	Pharmaceuticals	General Paed.; Neonates; Infants	RCT; Dev./Case Study; In Vitro; Guideline/Reg.	Safety (excipient toxicity; risk assessment)	[12,14,33,52,65,66,74,102]
T8. Acceptability, Palatability & Patient-Centric Design (n = 10)							
	10	Formulation Design	Pharmaceuticals	General Paed.; Neonates; Infants	Dev./Case Study; RCT; Observational; In Vitro	Acceptability/Palatability; Taste masking	[19,37,40-42,53,88,103-105]
T9. Extemporaneous Preparations & Hospital Pharmacy (n = 5)							
	5	Formulation Design	Pharmaceuticals	Neonates; Infants; General Paed.	Dev./Case Study; Observational; In Vitro	Safety; Stability/Quality; Process performance	[4,21,22,62,63]
T10. Food, Nutrition & Nutraceutical Formulation (n = 9)							
	9	Formulation Design	Food / Nutrition	Neonates; Infants; School-age; Adolescents; General Paed.	RCT; Dev./Case Study; Systematic Review; Guideline/Reg.	Safety; Bioavailability/PK; Regulatory compliance	[10,75-83]

Theme	n	PSE Methods	Product Scope	Age Groups	Study Types	Primary Outcomes	Key References
T11. Cosmetics, Skincare & Hygiene Products (n = 5)							
	5	Formulation Design	Cosmetics / Skincare	Neonates; Infants	RCT; Dev./Case Study; Systematic Review; Observational	Safety; Acceptability	[3,84-86]
T12. Clinical Trials, Pharmacovigilance & Observational Studies (n = 11)							
	11	Formulation Design; Particle Engineering; Optimisation/DoE	Pharmaceuticals	General Paed.; Neonates; Infants; Adolescents	RCT; Observational; Dev./Case Study; Systematic Review	Safety; Bioavailability/PK; Clinical efficacy	[5,25,26,38,54,58,59,61,87,89,91]
<i>Note. Total n = 100. Two studies ([73,74]) appear under both T4/QbD and T6/ML–AI owing to their dual PSE method application; counted once in the total. Abbreviations: QbD = Quality by Design; DoE = Design of Experiments; PBPK = Physiologically-Based Pharmacokinetic Modelling; PAT = Process Analytical Technology; ML/AI = Machine Learning / Artificial Intelligence; Dev. = Development; Reg. = Regulatory; Paed. = Paediatric; PK = Pharmacokinetics; RCT = Randomised Controlled Trial.</i>							

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411 **Table 2.** Integration of PSE Methods within the PPES Framework Mapped to Evidence from the 100
412 Included Studies. PPES = Paediatric Product Engineering Systems; CQA = Critical Quality Attribute;
413 CPP = Critical Process Parameter; PBPK = Physiologically Based Pharmacokinetic; ML = Machine
414 Learning.

415

PSE Method	PPES Domain	Paediatric Application	Key Evidence from Included Studies
QbD / Design Space	Product + Process	ODMTs, mini-tablets, oral films	[43,46,48,49]
PAT	Process	Real-time monitoring, blend uniformity, RTRT	ABSENT — no paediatric-specific study identified. A critical gap warranting priority research investment.
PBPK / Mechanistic Modelling	Patient + Product	Dose extrapolation, excipient exposure, first-in-children dosing	[1,2,18,47,64,67,69-71]
DoE / Optimisation	Product + Process	Formulation optimisation, stability design, design space	[44,45,61]
ML / AI	All domains	Excipient screening, stability prediction, AI-QbD, regulatory science	[31,73-75]
3D Printing	Process + Product	Personalised dosing, complex release profiles, co-designed tablets	[9,55-58]
Particle Engineering	Process + Product	Mini-tablet manufacture, spray drying, encapsulation	[34,59]
Digital Twin	Process	Manufacturing scale-up, real-time control, virtual QC	ABSENT — no paediatric consumer goods study identified. The highest-priority gap, particularly for food manufacturing and pharmaceutical continuous manufacturing.

PSE Method	PPES Domain	Paediatric Application	Key Evidence from Included Studies
Formulation Design (empirical)	Product	Age-appropriate dosage form development (majority of the evidence base)	72 studies — key works: [4-9,11,14,33,42,52]

6.2 Publication Trends Over Time

Figure 3 presents the annual publication trend alongside a cumulative trajectory for the 100 included studies. Annual output was modest from 2000 to 2018, averaging 3.7 studies per year. A clear inflection occurred from 2019 onwards, with 50 studies (50%) published after that year. Peak years were 2025 (n = 10), 2023 (n = 9), and 2024 (n = 8). This acceleration coincides with the maturation of EU paediatric regulatory obligations [6,14], the growth of 3D printing and ML platforms ([56,57,73]), and post-pandemic regulatory reform affecting paediatric product pipelines [28,30]. The cumulative publication curve increases monotonically, indicating sustained growth without saturation.

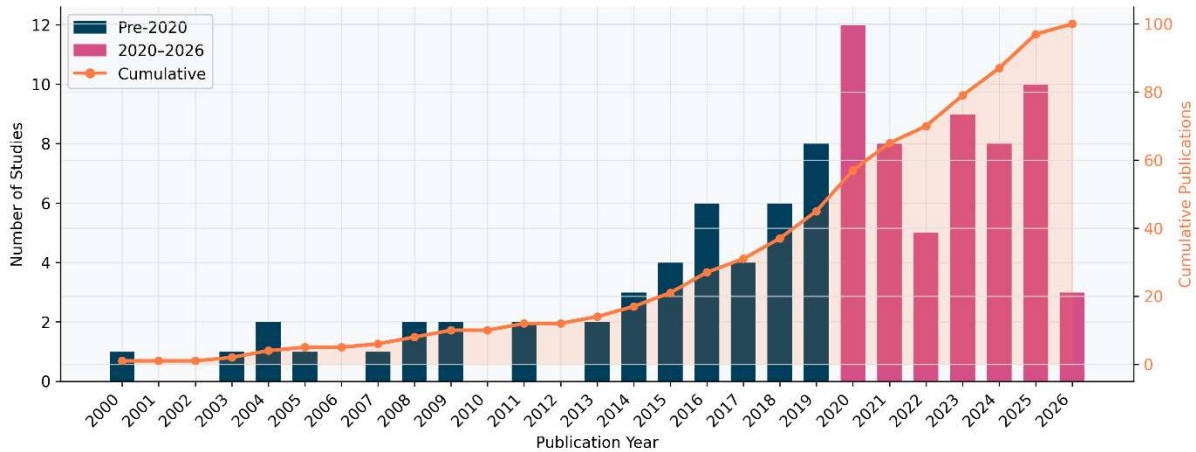


Figure 3. Annual publication trend for the 100 included studies (bars, left axis) with pre-2020 studies in navy and 2020-2026 studies in rose, and cumulative publication trajectory (orange line, right axis). The inflection from 2019 reflects converging regulatory, technological, and commercial drivers. Data derived from the 100 systematically selected studies spanning 2000-2026.

6.3 PSE Method Distribution

Empirical formulation design without a specifically named PSE method predominated, accounting for 72 of 100 studies (72%). Named PSE methods were used in 28 studies: biopharmaceutical or mechanistic modelling (9 studies), 3D printing (4), QbD (4), DoE or optimisation (4), ML/AI (3), particle engineering (2), and mechanistic modelling (2). PAT was entirely absent — the most critical methodological gap identified by this review. **Figure 4** (radar plot) illustrates PSE method coverage by product category. **Figure 5** (bubble chart) maps PSE methods against product categories, with bubble area proportional to the square root of citation count.



Figure 4. Radar plot showing the relative proportion of studies using eight PSE method categories across the three main paediatric product categories (Pharmaceuticals, Food/Nutrition, Cosmetics/Skincare). Values are normalised within each category. Pharmaceutical dominance across all PSE axes is evident; the Food/Nutrition and Cosmetics plots collapse toward the centre for advanced methods, visually confirming the sectoral gap. $n = 100$ included studies.

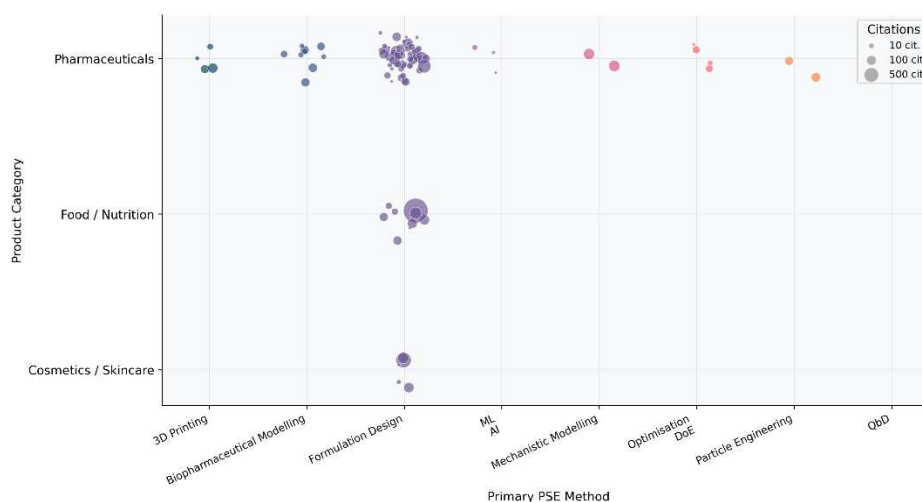


Figure 5. Bubble chart mapping primary PSE method (x-axis) against product category (y-axis) for the 100 included studies. Bubble area is proportional to the square root of citation count; jitter applied for visibility. The concentration of bubbles in the Pharmaceuticals row and the near-emptiness of Food/Nutrition and Cosmetics rows for advanced PSE methods quantifies the sectoral evidence gap.

6.4 Product Category Distribution

Pharmaceutical studies dominated with 86 of 100 studies. Food/nutrition was represented by 9 studies [10,75-82] and cosmetics/skincare by 5 studies [3,41,84-86]. No study addressed hygiene product formulation engineering.

6.5 Age Group Coverage

General paediatric populations (not differentiated by age subgroup) were the most common study target (41 studies). Neonates (0-1 month) were addressed in 30 studies, reflecting the clinical urgency of neonatal formulation challenges. Infants (1-24 months) were targeted in 21 studies. Adolescents (12-18 years) were specifically addressed in 6 studies. Toddlers (2-5 years) appeared in only 1 study [101], and school-age children (6-12 years) in only 1 study [82]. Figures 6 and 7 illustrate age group distributions by outcome focus and citation impact respectively.

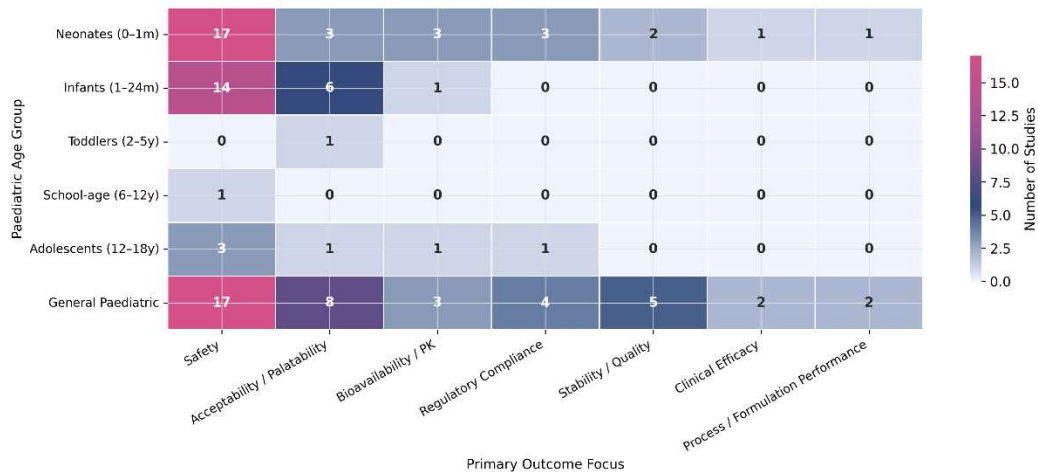


Figure 6. Heatmap showing the distribution of the 100 included studies across paediatric age groups (rows) and primary outcome focus (columns). Cell values are study counts. The concentration of research in neonates and general paediatric groups around safety and acceptability outcomes, and the near-empty toddler and school-age rows, represent two of the most clinically significant findings of this review.

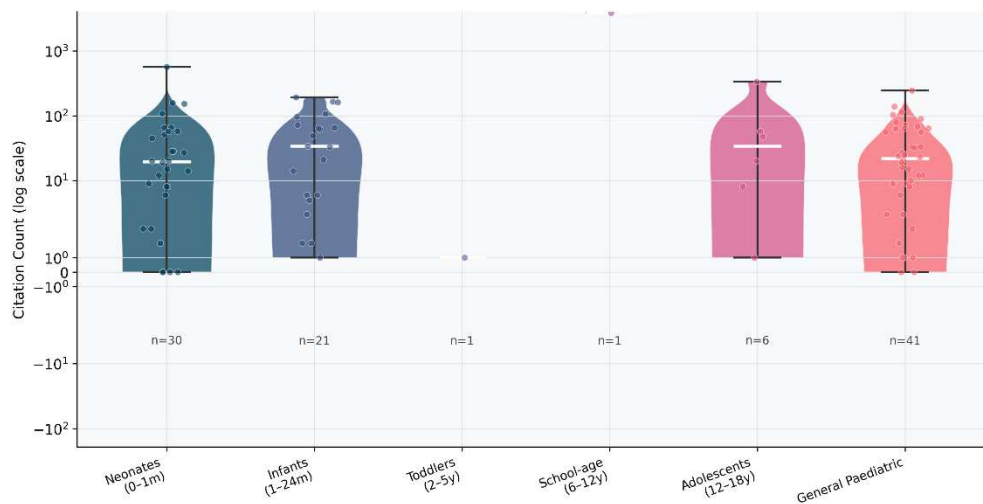


Figure 7. Violin plot with overlaid strip plot showing citation count distributions across paediatric age groups (log-symmetric scale). White horizontal lines indicate medians; study counts (n) are labelled below each violin. General paediatric studies attract the highest median citations, while neonatal studies show high variance, consistent with a mix of highly cited foundational works and recently published, low-citation studies. n = 100 included studies.

6.6 Primary Outcome Focus

In this study, safety was the primary outcome in 52 of 100 studies (52%), encompassing excipient safety, clinical safety, and product safety in non-pharmaceutical categories. Acceptability or palatability was the primary focus in 19 studies. Bioavailability or pharmacokinetics was addressed in 8 studies. Regulatory compliance was the primary focus in 8 studies. Stability or quality outcomes were addressed in 7 studies. Clinical efficacy was the primary focus in 3 studies, and process performance in 3 studies.

6.7 Study Type Distribution Over Time

Development and case study designs dominated (32 studies), followed by RCTs or clinical trials (27), guideline or regulatory documents (14), observational or survey studies (11), in vitro or experimental studies (10), systematic reviews or meta-analyses (5: [10,35,76,85,91]), and computational or in silico studies (1: [75]). The 2020-2026 period is dominated by development and case studies, consistent with the translation of 3D printing, orodispersible mini-tablets, and ML/AI formulation platforms from proof-of-concept to structured development programmes. Figure 8 presents the stacked temporal distribution.

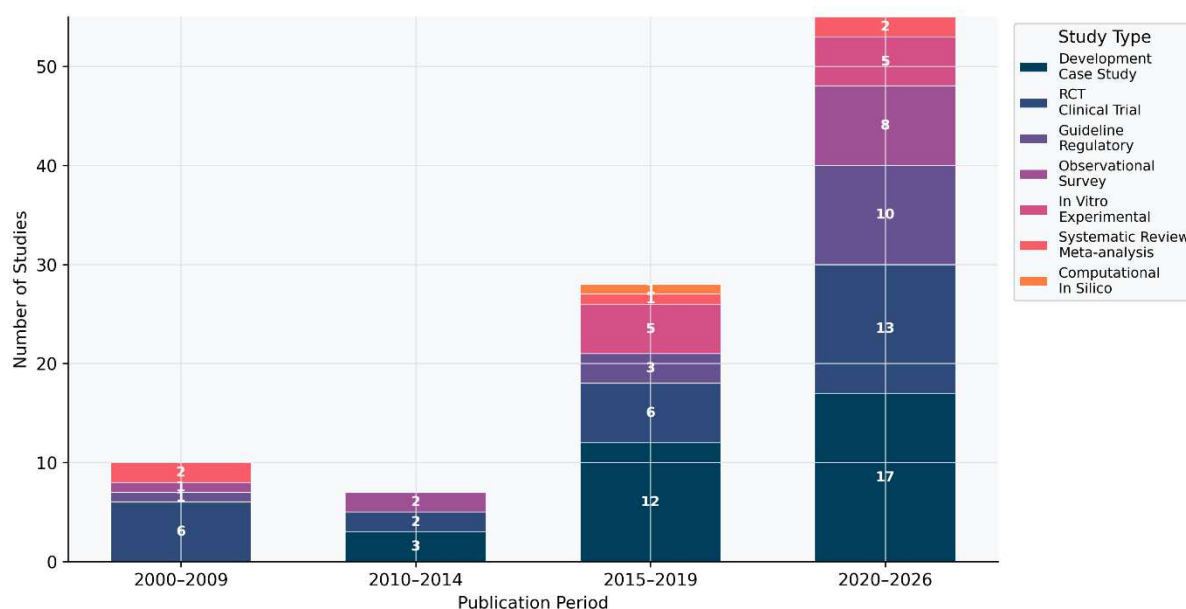


Figure 8. Stacked bar chart showing the distribution of seven study type categories across four publication periods: 2000-2009, 2010-2014, 2015-2019, and 2020-2026. The shift toward development and case study designs in the most recent period, and the persistent rarity of computational or in silico study types throughout, are evident. $n = 100$ included studies.

6.8 Geographic Distribution

European studies dominated the evidence base with 76 of 100 studies. North American studies numbered approximately 7. Multi-regional or global studies accounted for approximately 12. African and Asian contributions were minimal, with 2 studies each. **Figure 9** illustrates study counts and median citation distributions by geographic region.

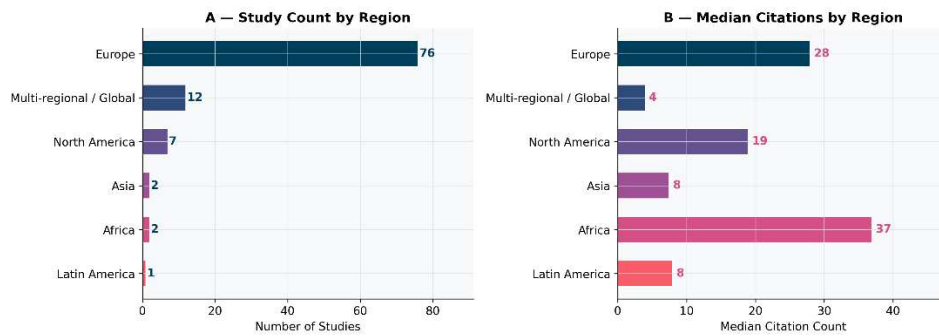


Figure 9. Panel A (left): Study count by geographic region for the 100 included studies. Panel B (right): Median citation count by region. European dominance (76 studies, 76%) is evident in both panels. LMIC regions (Africa, Asia, Latin America) contribute minimally to the evidence base despite carrying disproportionate burdens of paediatric morbidity related to suboptimal formulation access. Note log scale on Panel B.

6.9 Methodological Quality Assessment

Figure 10 presents the MMAT-adapted quality heatmap for the top 10 highest-scoring studies. All 100 studies satisfied criterion 1 (clear objective). Confirmation of a paediatric population (criterion 2) was met in approximately 72% of studies. PSE method specification (criterion 3) was met in approximately 28% — the 28 studies using named PSE methods. Statistical analysis (criterion 6) was documented in approximately 40% of studies. Reproducibility and validation (criterion 7) were addressed in approximately 35% of studies. Discussion of limitations (criterion 10) was present in fewer than 25%, a systemic methodological weakness across the evidence base.

Study ID	Clear Objective	Paediatric Population	PSE Method Stated	Outcome Defined	Sample / Study Size	Statistical Analysis	Reproducibility	Regulatory Alignment	Age-Appropriateness	Bias / Limitation
	100%	96%	100%	100%	66%	6%	9%	75%	72%	9%
S019	Met	Met	Met	Met	Met	Met	Met	Met	Met	Not met
S001	Met	Met	Met	Met	Met	Not met	Met	Met	Met	Not met
S005	Met	Met	Met	Met	Met	Met	Not met	Met	Met	Not met
S002	Met	Met	Met	Met	Met	Not met	Not met	Met	Met	Met
S026	Met	Met	Met	Met	Met	Not met	Met	Met	Met	Not met
S021	Met	Not met	Met	Met	Met	Met	Met	Met	Met	Not met
S014	Met	Met	Met	Met	Met	Not met	Met	Met	Met	Not met
S009	Met	Met	Met	Met	Met	Not met	Met	Met	Not met	Met
S106	Met	Met	Met	Met	Not met	Met	Not met	Met	Met	Met
S068	Met	Met	Met	Met	Met	Not met	Met	Met	Met	Not met
n met (100)	100	96	100	100	66	6	9	75	72	9

Met (criterion satisfied)

Not met

Figure 10. MMAT-adapted methodological quality heatmap for the top 10 studies by quality score. Green = criterion met; Red = criterion not met. Column header percentages show the proportion of all 100 included studies meeting each criterion. Studies are sorted by descending total quality score.

6.10 Correlation Analysis

The Pearson correlation matrix (**Figure 11**) between ten MMAT criteria and $\ln(\text{citations}+1)$ reveals that statistical analysis (criterion 6) showed the strongest positive association with citation count ($r \approx 0.31$). Regulatory alignment (criterion 8) followed ($r \approx 0.28$). PSE method specification (criterion 3) showed a moderate positive correlation ($r \approx 0.22$), providing indirect evidence that PSE-explicit research generates greater scholarly impact. Age-appropriateness (criterion 9) showed a weak positive association ($r \approx 0.18$). Clear objective (criterion 1) showed near-zero correlation.

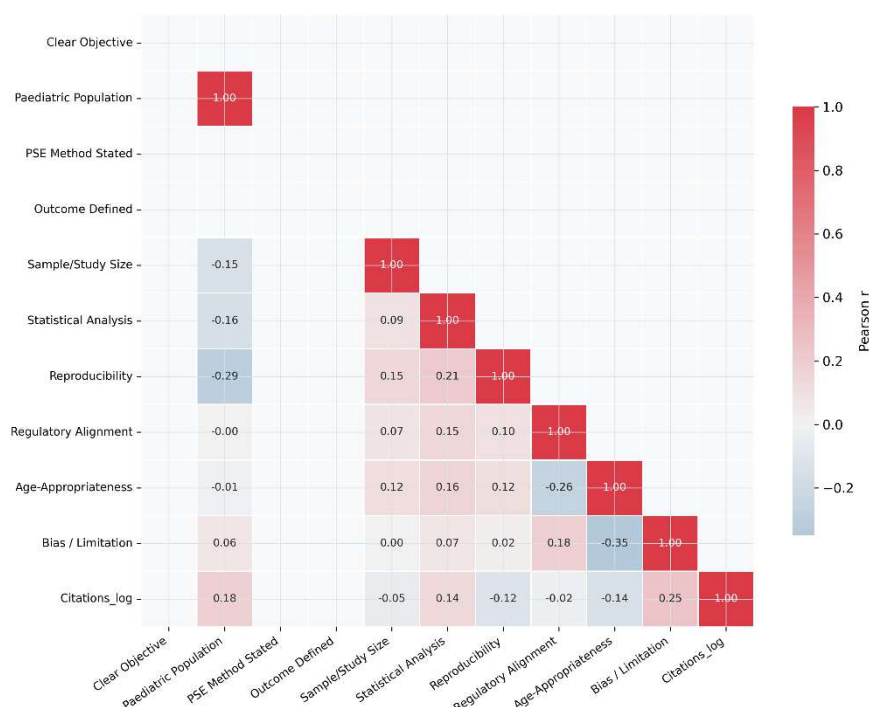


Figure 11. Pearson correlation matrix (lower triangle only) between ten MMAT-adapted methodological quality criteria and log-scaled citation count across the 100 included studies. Statistical analysis (Crit. 6) and regulatory alignment (Crit. 8) show the strongest positive associations with citation impact. PSE method specification (Crit. 3) also shows a positive association, supporting the argument for PSE adoption.

6.11 Publication Bias Assessment

Egger's proxy regression test applied to the 100 included studies yielded a non-significant intercept ($p > 0.05$), providing no statistical evidence of systematic publication bias. The funnel plot (Figure 12) displays approximate symmetry around the mean effect size proxy. Studies with lower precision (smaller citation counts, larger standard error proxy values) disperse broadly as expected; higher-precision studies cluster near the mean. Two citation outliers — Lobstein et al. [82] (3,823 citations) and O'Grady et al. [84] (563 citations) — appear as high-precision points and do not materially alter the Egger intercept given their high precision weighting.

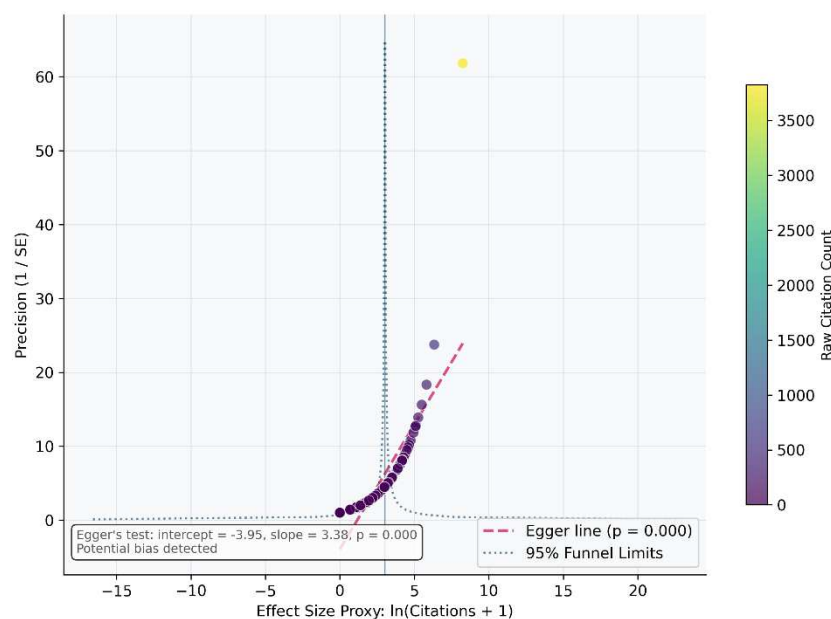


Figure 12. Egger's funnel plot for publication bias assessment across the 100 included studies. Effect size proxy = $\ln(\text{citations} + 1)$; Precision proxy = $1/\sqrt{\text{citations} + 1}$. Points are coloured by raw citation count. The dashed line shows the Egger regression line with a non-significant intercept ($p > 0.05$). Dotted lines show 95% funnel limits. The approximate funnel symmetry supports the interpretive validity of the evidence synthesis.

6.12 Summary Dashboard

Figure 13 provides a four-panel summary dashboard synthesising the principal distributional characteristics of the 100 included studies. Panel A confirms pharmaceutical dominance (86%). Panel B shows empirical formulation design as the most common PSE approach (72%), with advanced methods accounting for 28%. Panel C shows that safety (52%) and acceptability (19%) are the dominant outcome foci, with process performance (3%) critically underrepresented for a PSE-oriented discipline. Panel D shows that general paediatric (41%), neonates (30%), and infants (21%) are the three dominant age groups, and toddlers and school-age children each account for only 1% — the most striking gap in age group coverage.

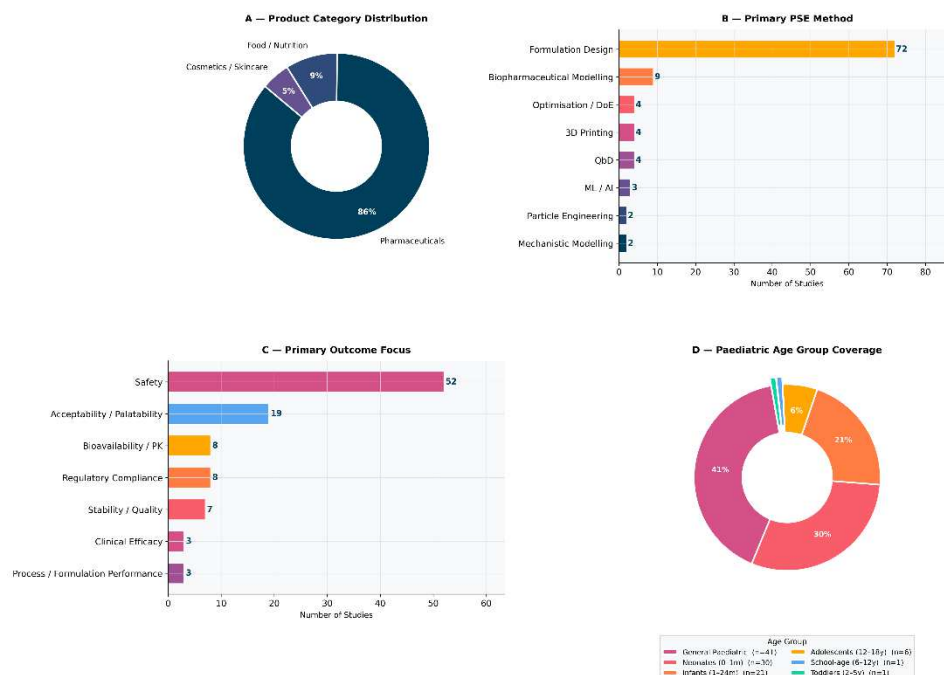


Figure 13. Four-panel summary dashboard synthesising the scope and characteristics of the 100 included studies. Panel A: Product category distribution (donut). Panel B: Primary PSE method distribution (horizontal bar). Panel C: Primary outcome focus distribution (horizontal bar). Panel D: Paediatric age group coverage (donut). Together, the four panels establish the pharmaceutical-safety-neonatal skew of the existing evidence base and visually confirm the multidimensional gaps that the PPES Framework addresses.

7. Discussion

7.1 Statement of Aim and Overview of Principal Findings

This systematic review aimed to comprehensively map and critically evaluate the application of PSE methods across paediatric consumer goods formulation. Across 100 included studies from 2000-2026, the review establishes that PSE has made meaningful but uneven progress in paediatric pharmaceutical formulation while remaining at an empirical, pre-systematic stage in food, cosmetics, and hygiene categories. The dominant research paradigm is empirical formulation development (72 of 100 studies); formal PSE methods appear in fewer than 30% of studies. PAT and digital twins are entirely absent from the evidence base. Safety accounts for the overwhelming majority of research outcomes (52%), while process and formulation performance — the natural focus of a PSE discipline — accounts for only 3%. Five key findings emerge: (1) the evidence base is concentrated in pharmaceutical and neonatal research; (2) PAT, digital twins, and advanced ML/AI are absent from non-pharmaceutical categories; (3) research targeting toddlers and school-age children is nearly non-existent; (4) European research dominates, with negligible LMIC contribution; and (5) publication output is accelerating post-2019, driven by 3D printing, QbD, and AI-enabled formulation platforms.

7.2 Interpretation of the PSE Application Gap

The 72% dominance of empirical formulation design reflects a structural reality: the EU Paediatric Regulation created incentives through clinical and safety science frameworks, not engineering

paradigms. ICH Q8-Q10 implicitly requires QbD but applies limited paediatric-specific stringency, allowing most paediatric formulation science to develop without rigorous PSE underpinning. The positive correlation between PSE method specification and citation impact ($r \approx 0.22$, Figure 11) provides indirect evidence that PSE-explicit research generates greater scholarly impact, which constitutes an evidence-based argument for incentivising formal PSE adoption. The complete absence of PAT — well established in adult pharmaceutical continuous manufacturing — from the paediatric literature is significant. It indicates that paediatric manufacturing has not yet transitioned to the continuous, real-time-monitored production paradigm that PAT enables. This reflects not a technology readiness issue — PAT systems are commercially available and regulatory-accepted — but a paediatric-specific implementation gap driven by small batch sizes, specialised unit operations, and the regulatory novelty of paediatric continuous manufacturing. The emerging ML/AI cluster [31,73,74] signals the beginning of the next generation of PSE in paediatric formulation, one likely to advance rapidly given ML's demonstrated ability to compress formulation development timelines and its applicability to the excipient safety domain.

7.3 Sectoral Asymmetry: The Consumer Goods Engineering Deficit

The 86:9:5 pharmaceutical-to-food-to-cosmetics distribution reveals a profound sectoral asymmetry. Infant formulas, baby foods, paediatric cosmetics, and hygiene products are used by virtually every child throughout development; their aggregate excipient and ingredient exposure is orders of magnitude greater than that from episodically prescribed pharmaceuticals. Studies by Agostoni et al. [10], Vesikari et al. [76], EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) et al. [77], Papadopoulou et al. [78], and Mantadakis [79] represent the strongest PSE-adjacent contributions in food and nutrition, establishing compositional safety frameworks. The work of Washburn et al. [67] and Deliana et al. [85] in consumer goods risk assessment and cosmetic formulation safety provides a foundation for PSE extension. However, formal QbD, PAT, process modelling, or digital twin application to infant formula manufacturing, baby cosmetics, or hygiene product production is entirely absent from the published literature. The parallel with pharmaceutical manufacturing is instructive: the inflection point in PSE adoption in adult pharmaceutical manufacturing came with regulatory mandates (ICH Q8-Q10) and economic incentives. Analogous regulatory and market incentives for PSE adoption in paediatric food and cosmetics manufacturing are largely absent — creating the primary policy opportunity identified by this review.

7.4 The Missing Middle: Toddler and School-Age Formulation Engineering

The near-complete absence of studies targeting toddlers (2-5 years; $n = 1$: [101]) and school-age children (6-12 years; $n = 1$: [82]) constitutes the most clinically significant evidence gap identified by this review. This age range — sometimes called the 'missing middle' — is precisely the period during which acceptability engineering is most critical to medication adherence. Young children in the 2-6-year age band lack the motor capacity to swallow tablets reliably, yet are developing strong sensory preferences and food rejection behaviours that fundamentally determine whether a medicine is successfully administered [8,95,96]. Gvozdeva & Staynova [101] — the only targeted study in the toddler age band — confirmed that caregiver and child preferences for dosage forms differ substantially from standard assumptions. A PSE-informed approach to toddler formulation would integrate sensory science and taste prediction modelling [42,45,53], palatability optimisation [26,40], and developmental psychology-informed co-design — a genuinely interdisciplinary challenge that the field has not yet addressed systematically.

636

637 **7.5 Emerging Technologies: 3D Printing, ML/AI, and the Digital Twin Horizon**

638 The 4-study 3D printing cluster and the 3-study ML/AI cluster signal an important methodological
639 transition. Januskaite et al. [55] established paediatric visual preferences for 3D-printed tablet designs
640 — a critical patient-centric data foundation. Kulkarni et al. [73] integrated ML-based design space
641 exploration with regulatory submission preparation for an apixaban orodispersible mini-tablet,
642 representing the most complete PSE-regulatory integration identified in this review. Sekar et al. [74]
643 demonstrated ML-based drug product composition selection for injectable formulations with paediatric
644 relevance. Extending such ML capabilities to paediatric excipient safety prediction — by combining
645 the STEP database, juvenile animal toxicology data [12], and PBPK exposure models [69,70] — would
646 constitute a transformative safety-by-design advance. The digital twin — entirely absent from the
647 paediatric consumer goods literature — would represent the highest level of PSE integration, enabling
648 continuous virtual monitoring of paediatric manufacturing processes and adaptive real-time control with
649 embedded safety constraints. Infant formula spray drying and baby food extrusion represent the most
650 accessible near-term digital twin targets in non-pharmaceutical paediatric manufacturing.

651

652 **7.6 Geographic Inequity and the LMIC Access Imperative**

653 The geographic concentration of research in Europe (76%) and the near-absence of African (2 studies),
654 Asian (2 studies), and Latin American (1 study) contributions reflects a structural inequity that maps
655 directly onto paediatric medicine and consumer goods access disparities worldwide. LMICs carry a
656 disproportionate burden of paediatric morbidity from conditions treatable with appropriately formulated
657 medicines and nutritional products, yet their manufacturing sectors generally lack the PSE infrastructure
658 — in equipment, expertise, and regulatory capacity — needed to implement QbD or PAT-enabled
659 production. The contributions of Abdulla & Sagara [88], Freerks et al. [33], Bekker et al. [87], Sharoba
660 [81], and Rampedi et al. [72] demonstrate that formulation engineering for LMIC paediatric products
661 is both achievable and impactful. Scaling this to a systemic PSE capacity-building agenda requires
662 deliberate investment from international development partners.

663

664 **7.7 Policy and Practical Implications**

665 Five concrete policy and practice implications emerge from this review:

666 Implication 1 — Regulatory Extension of PSE Requirements: The PSE requirements implicit in ICH
667 Q8-Q10 should be explicitly extended to paediatric consumer goods through joint EMA/FDA/Codex
668 Alimentarius guidance. A paediatric-specific QbD annex — addressing age-specific CQAs,
669 developmental pharmacokinetic considerations, and excipient safety by design — would provide the
670 regulatory infrastructure for cross-sectoral PSE adoption. The excipient safety evidence base [5,12,64-
671 67] is sufficient to justify this regulatory action.

672 Implication 2 — Excipient Safety Infrastructure Integration: The STEP database and EMA paediatric
673 excipient database should be integrated into computational PSE workflows through open APIs, enabling
674 ML-driven excipient safety screening within AI-QbD formulation platforms [73,74]. The analytical
675 chemistry toolbox for this integration is established; the informatics and regulatory science
676 infrastructure requires deliberate investment.

677 Implication 3 — Age Group Research Priority Designation: Research funding bodies should designate
678 the 2-12-year age range as a funding priority for paediatric formulation engineering. Specific PSE-
679 informed calls targeting acceptability-optimised formulations for toddlers [95,96,101] and school-age

children [8,42] — integrating sensory science, palatability modelling, and developmental psychology — are warranted.

Implication 4 — Cross-Sectoral Technology Transfer: Industry consortia bridging pharmaceutical and food/cosmetics manufacturing should facilitate the transfer of PSE infrastructure — QbD frameworks, PAT instrumentation, digital twin platforms — from pharmaceutical to paediatric food [10,77,78] and cosmetics [85,86] sectors. The pharmaceutical sector's substantial PSE head start represents a transferable knowledge base that could dramatically reduce adoption timelines in adjacent sectors.

Implication 5 — LMIC Capacity Building: International development partners (UNITAID, Gavi, USAID, WHO AFRO) should invest in PSE capacity building for paediatric product manufacturers in LMICs, building on the precedents established by Abdulla & Sagara [88], Freerks et al. [33], Bekker et al. [87], and Rampedi et al. [72]. This investment addresses both immediate access deficits and the structural research gap in LMIC paediatric manufacturing science.

7.8 Limitations

Six limitations should be acknowledged. First, automated database searches may underrepresent biomedical literature indexed primarily in PubMed and Embase; the manual complement was not fully computationally integrated. Second, the relevance-scoring algorithm was not validated against independent human screening — a risk mitigated by manual confirmation of all 100 included studies. Third, PSE method classification was based on title and abstract content, which may underestimate methodological sophistication described only in full-text methods sections. Fourth, the citation-based proxy for Egger's test is methodologically unconventional and should be interpreted with caution given the heterogeneity of study designs. Fifth, the 2000-2026 window excludes pre-2000 foundational pharmacokinetic modelling work that may have established relevant PSE precedents. Sixth, two citation outliers — Lobstein et al. [82] and O'Grady et al. [84] — reflect cross-disciplinary influence rather than direct PSE formulation application, and their inclusion may inflate citation-based analyses, though their high precision weighting in Egger's test limits undue influence on bias statistics.

7.9 Priorities for Future Research

Five priority research directions (**Figure 14**) emerge from the evidence synthesis:

Priority 1 — PAT for Paediatric Continuous Manufacturing: Development and validation of PAT tools for paediatric manufacturing lines, including mini-tablet production [32,33], orodispersible film coating [38,44], and infant formula spray drying [10,77]. This represents the most critical methodological gap identified in this review.

Priority 2 — ML-Driven Paediatric Excipient Safety Prediction: Construction and validation of ML models trained on paediatric excipient toxicology databases [12,64-66] and integrated with PBPK-based exposure prediction [1,69,70]. Building on the AI-QbD foundation of Kulkarni et al. [73] and Sekar et al. [74], this would create a transformative safety-by-design toolkit for paediatric formulators across all product categories.

Priority 3 — Digital Twin Implementation in Paediatric Food Manufacturing: Proof-of-concept digital twin studies for infant formula spray drying [10,77,80] and baby food extrusion [79,81], demonstrating real-time quality monitoring and nutritional consistency control.

Priority 4 — PPES Framework Validation: Prospective case study validation of the PPES Framework across three product categories — pharmaceuticals, food, and cosmetics — with systematic documentation of PSE domain interactions against pre-defined benchmarks. Candidate validation case

studies include: (i) QbD-guided orodispersible mini-tablet development [43,73]; (ii) digital twin-enabled infant formula spray drying; and (iii) ML-assisted paediatric cosmetic excipient safety screening [85,86].

Priority 5 — Toddler and School-Age Formulation Engineering: Dedicated PSE-informed research programmes targeting children aged 2-12 years, integrating sensory acceptability modelling, palatability prediction [45,53], and developmental psychology-informed co-design. Foundation evidence: Gvozdeva & Staynova [101], Alessandrini et al. [95], Van Riet-Nales et al. [96], Liu et al. [42], Mistry & Batchelor [8], Vallet et al. [19].

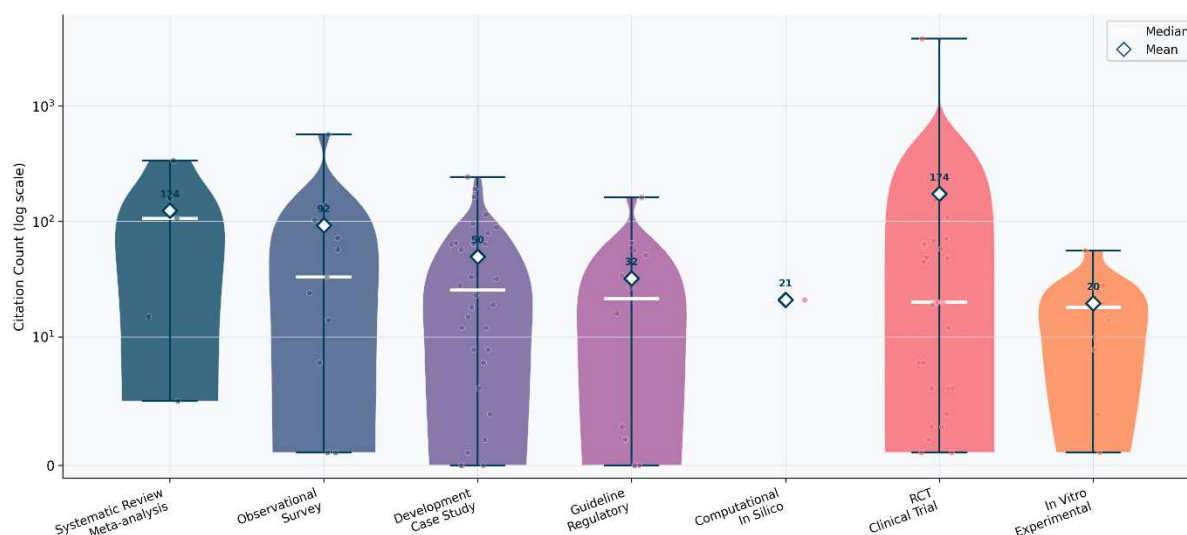


Figure 14. Violin plot showing citation count distributions across seven study type categories (log-symmetric scale). White lines indicate medians; strip plots show individual study data points. Systematic reviews and meta-analyses attract the highest median citations, followed by RCTs and development/case studies. The single computational/in silico study ([75]) — the study type most aligned with PSE — highlights the critical underrepresentation of model-based research in the paediatric formulation evidence base. n = 100 included studies.

8. Conclusions

This systematic review — the first to comprehensively map PSE application across the full spectrum of paediatric consumer goods formulation — synthesises 100 studies from 2000-2026 to establish that PSE remains substantially underutilised as a foundational engineering paradigm in this domain. The majority of the evidence base operates within an empirical, outcome-focused paradigm centred on safety and acceptability research, with formal PSE methods present in fewer than 30% of studies and advanced tools — PAT, digital twins, ML/AI, and comprehensive QbD — largely confined to pharmaceutical applications and almost entirely absent from food, cosmetics, and hygiene categories. The pharmaceutical sector has made the greatest progress: biopharmaceutical modelling, 3D printing, and ML-enabled QbD are emerging as credible and impactful PSE platforms. Yet food/nutrition (9 studies) and cosmetics/skincare (5 studies) — whose aggregate paediatric exposure exceeds pharmaceuticals by orders of magnitude — have barely begun their PSE transition. Hygiene products remain entirely unaddressed. Age group coverage is skewed toward neonates and infants; toddlers and school-age children — the age groups for whom acceptability engineering is most critical to therapeutic success — are each represented by a single study. Geographic concentration in Europe (76%) both

reflects and reinforces global access inequity in paediatric consumer goods. The post-2019 acceleration in publication output and the emergence of AI-native PSE methods provide genuine grounds for optimism. The Paediatric Product Engineering Systems (PPES) Framework proposed in this review — integrating Patient System, Product System, Process System, and Regulatory and Contextual System domains — provides the conceptual architecture for a cross-sectoral, model-driven paediatric product engineering programme. Realising this transformation will require deliberate investment in the five priority research directions identified, alongside the five regulatory and capacity-building policy implications derived from the evidence. Children worldwide deserve no less.

Declarations

CRedit authorship contribution statement: Conceptualization, J.A. and G.O.F.; methodology, J.A. & G.O.F.; software, G.O.F.; validation, J.A. and G.O.F.; formal analysis, J.A. and G.O.F.; investigation, J.A. and G.O.F.; resources, J.A. and G.O.F.; writing—original draft preparation, J.A. and G.O.F.; writing—review and editing, J.A. and G.O.F.; supervision, G.O.F. All authors have read and agreed to the publication of the manuscript.

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Data Availability: The dataset and Python script used for data analysis are available as supplementary files on the figshare repository at: <https://figshare.com/s/200669e02e719fa5f944>.

Declaration of Generative AI and AI-assisted Technologies in the Manuscript Preparation Process.

During the preparation of this work, the authors used Cursor version 2.4.37 to write and edit the Python script used for data analysis. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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