Advances in Pediatric Drug Formulations

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Article Info

ISSN (online): 3049-0421
Volume: 02
Issue: 06
November-December 2025
Received: 06-09-2025
Accepted: 04-10-2025
Published: 02-11-2025
Page No: 01-08

Abstract
The development of safe, effective, and age-appropriate medicinal products for the pediatric population presents a multifaceted challenge arising from immature physiological systems, complex pharmacokinetic variability, swallowing limitations, and historically insufficient clinical data. Children are not small adults; their gastrointestinal pH, enzymatic activity, body composition, and renal function differ substantially from adult benchmarks and evolve continuously from birth through adolescence. This review aims to comprehensively examine current advances in pediatric drug formulation technologies with emphasis on pharmaceutical strategies that improve tolerability, dose accuracy, and therapeutic compliance across all pediatric age groups as classified by ICH E11(R1). Key formulation technologies discussed include age-appropriate liquid and solid oral dosage forms, multiparticulate systems, orodispersible tablets, and modified-release platforms. Emerging innovations such as nanotechnology-based drug delivery, three-dimensional (3D) printing, and personalized medicine approaches are evaluated for their clinical applicability and translational potential. Therapeutic applications encompass the management of infectious diseases, chronic conditions including asthma and epilepsy, and vaccine delivery. Regulatory frameworks from the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are critically reviewed alongside excipient safety considerations unique to pediatric patients. This review underscores the imperative for cross-disciplinary collaboration between formulators, clinicians, and regulatory bodies to accelerate the development of child-friendly medicines that fulfill unmet medical needs while adhering to rigorous safety and quality standards.

Keywords: Pediatric drug delivery, Age-appropriate formulations, Taste masking, Modified release, Multiparticulate systems, Pediatric pharmacotherapy

1. Introduction

The global pediatric population encompasses approximately 2.4 billion individuals spanning neonates to adolescents, representing a clinically heterogeneous cohort with distinct physiological, pharmacokinetic, and developmental characteristics [1]. Despite this demographic significance, the majority of medications used in children remain unlicensed or off-label, a consequence of inadequate formulation development historically targeting adult populations [2, 3]. Off-label prescribing not only raises safety concerns—such as dosing errors and exposure to unsuitable excipients—but also compromises therapeutic outcomes in vulnerable patients [4].

Regulatory mandates, including the U.S. Pediatric Research Equity Act (PREA), Best Pharmaceuticals for Children Act (BPCA), and the European Union Paediatric Regulation (EC 1901/2006), have substantially accelerated pediatric drug development in recent decades [3, 30]. Nevertheless, significant formulation gaps persist, particularly for neonates and infants in whom the physicochemical barriers to conventional dosage forms are most pronounced [5].

Pediatric drug formulation is inherently complex due to the wide age range encompassed by this population—from premature neonates with body weights below 1 kg to adolescents approaching adult physiology. Age-related changes in gastrointestinal motility, absorptive surface area, hepatic metabolizing enzyme expression, and renal clearance demand that formulation scientists adopt dynamic, developmentally informed strategies [12, 14]. Furthermore, palatability, dosage form acceptability, and ease of administration are pivotal determinants of adherence in pediatric patients [8, 10].

This review synthesizes current advancements in pediatric drug formulation, from conventional liquid and solid systems to emerging nanotechnology-based platforms and additive manufacturing, with particular focus on age-appropriateness, clinical applicability, and the evolving regulatory landscape.

2. Pediatric Drug Formulation Considerations

2.1. Age-Related Physiological Differences

The ontogenic development of gastrointestinal physiology profoundly influences drug absorption in neonates and infants. Gastric pH is near-neutral at birth, gradually decreasing to adult values by approximately two years of age [12]. Gastric emptying time is prolonged in neonates, resulting in delayed Tmax for orally administered drugs. Intestinal permeability and transporter expression, including P-glycoprotein and organic anion-transporting polypeptides, are significantly lower in early life [14]. These developmental factors necessitate age-stratified dosing and formulation design.

Body composition also changes markedly with age; neonates possess a higher proportion of total body water (approximately 85% of body weight) compared with adults (~60%), affecting the volume of distribution of hydrophilic drugs. In contrast, reduced plasma protein binding in neonates due to lower albumin concentrations and competing endogenous ligands may increase free drug fractions, heightening pharmacodynamic effects [11, 14].

2.2. Pharmacokinetics and Pharmacodynamics

Cytochrome P450 (CYP) enzyme activity undergoes significant postnatal maturation. CYP3A7, the predominant isoform in fetal liver, declines sharply after birth while CYP3A4 and CYP2C9 expression increases progressively [12]. This isoform transition alters the metabolic clearance of numerous drugs, including anticonvulsants, antibiotics, and immunosuppressants, necessitating formulations that accommodate dose flexibility across developmental stages [13]. Renal drug elimination is also immature in neonates, with glomerular filtration rate reaching adult values only by six to twelve months of age.

2.3. Acceptability and Compliance

Palatability and ease of administration are critical dimensions of pediatric formulation design. Children exhibit a heightened sensitivity to bitter taste compared to adults, mediated through a greater density of bitter-sensitive TAS2R taste receptors and a relatively immature sweet taste habituation [8, 19]. Liquid formulations requiring large volumes or unpleasant organoleptic properties are frequently rejected. Acceptability studies employing age-appropriate behavioral and hedonic assessment tools—including the facial hedonic scale and the Pediatric Oral Medicine Observer Scale—are now integral to formulation development programs [18].

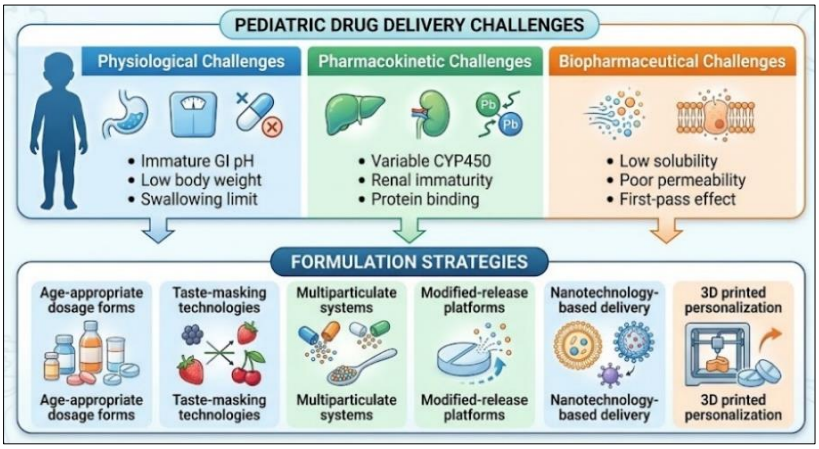

Fig 1: Schematic overview of key pediatric drug delivery challenges and corresponding pharmaceutical formulation strategies adopted to address them

3. Conventional Pediatric Dosage Forms

3.1. Liquid Formulations

Oral liquid preparations—solutions, suspensions, syrups, and drops—constitute the cornerstone of pediatric pharmacotherapy in neonates and infants, offering dose flexibility and ease of administration [5, 6]. However, their formulation presents significant challenges including physicochemical stability of drug substances in aqueous environments, microbial contamination risk, and the inclusion of potentially harmful excipients such as propylene glycol, benzyl alcohol, and parabens [2].

Furthermore, accurate dose measurement by caregivers using non-standardized measuring devices introduces a clinically significant risk of dosing error; oral syringes are now recommended over spoons as the delivery device of choice [7].

Suspensions are employed for water-insoluble drugs but present challenges of dose non-uniformity due to particle sedimentation if not adequately resuspended before administration. Controlled flocculation, use of appropriate suspending agents (e.g., xanthan gum, microcrystalline cellulose),

and inclusion of clear patient information are critical formulation and packaging considerations [6].

3.2. Solid Dosage Adaptations

Conventional tablets and capsules are generally unsuitable for children under six years due to swallowing difficulties and choking risk [5]. Extemporaneous preparation—crushing tablets or opening capsules to mix with food or liquid—is widespread but compromises dose accuracy, stability, and may alter the drug release profile of modified-release formulations [6]. The pharmaceutical industry has responded with purpose-designed solid forms including dispersible tablets, effervescent granules, and sprinkle capsules as transitional strategies pending dedicated pediatric formulation development.

3.3. Limitations of Conventional Approaches

Extemporaneous compounding, though frequently employed in hospital settings, lacks standardization, is susceptible to preparation errors, and is subject to limited shelf-life data [3]. The WHO has highlighted these inadequacies through its "Make Medicines Child Size" initiative, underscoring the global imperative for industry-sponsored pediatric formulation development underpinned by robust regulatory guidance [2, 4].

Table 1: Age classification and formulation considerations per ICH E11(R1) guidelines

Age Group	ICH E11 Classification	Key Formulation Challenges	Preferred Dosage Forms
Preterm neonates	Gestational age <37 wk	Sterility, low volumes, osmolality control	IV infusion, oral drops
Term neonates (0–28 d)	Neonates	GI immaturity, enzyme deficiency, renal limitations	Oral liquid, rectal
Infants (1–23 mo)	Infants and toddlers	Swallowing reflex developing, palatability	Oral liquids, mini-tablets, suppositories
Young children (2–5 yr)	Children (2–5 yr)	Dose accuracy, taste aversion, choking risk	Chewable tablets, ODTs, sprinkle capsules
Older children (6–11 yr)	Children (6–11 yr)	Tablet swallowing ability, adherence	Small tablets, ODTs, chewable, liquids
Adolescents (12–17 yr)	Adolescents	Adult-like PK but body-weight variability	Conventional tablets/capsules, patches

Table 2: Common pediatric dosage forms and their characteristics

Dosage Form	Age Suitability	Key Characteristics	Limitations
Oral solutions/syrups	All ages, esp. neonates	Easy dose titration, rapid absorption	Stability issues, excipient load, bulky
Suspensions	Infants–children	Suitable for insoluble drugs	Dose uniformity, resuspendability concerns
Dispersible tablets	≥6 months	Accurate dosing, portable, stable	Requires water preparation
Mini-tablets (2–3 mm)	≥6 months	Flexible dosing, MR coating possible	Manufacturing complexity, cost
Orodispersible tablets	≥2 years	No water needed, rapid dissolution	Fragile, hygroscopic, taste must be masked
Chewable tablets	≥2 years	Accepted palatability, portable	Requires adequate dentition, taste challenge
Granules/multiparticulates	≥6 months	Flexible dosing, controlled release	Uniformity validation, swallowing technique
Rectal suppositories	Neonates–toddlers	Useful when oral route compromised	Variable absorption, acceptability issues
Transdermal patches	Older children–adolescents	Bypasses GI, sustained delivery	Skin irritation, limited drug candidates

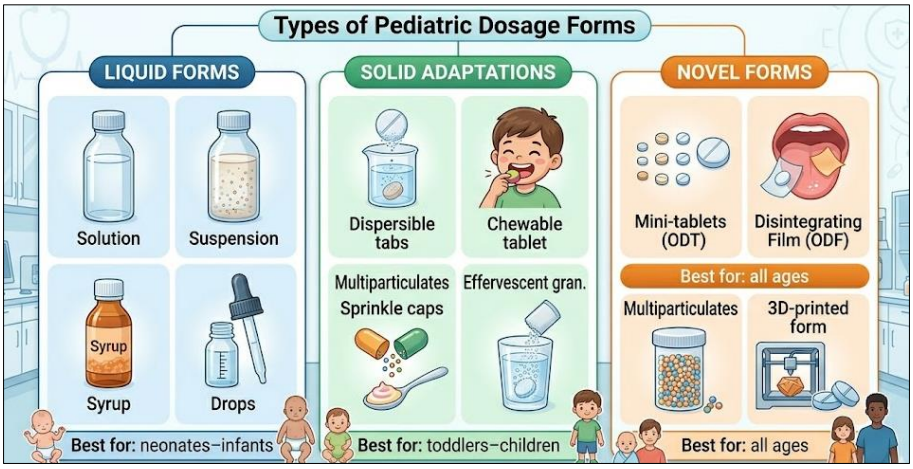

Fig 2: Classification of pediatric dosage forms by physical state and developmental suitability, illustrating the spectrum from conventional liquid preparations to novel solid-based systems

4. Advances in Pediatric Drug Formulations

4.1. Taste-Masking Technologies

Given the heightened bitterness sensitivity of children, taste masking remains one of the most technically demanding aspects of pediatric formulation development [8, 9]. Polymer film coating of drug particles using materials such as Eudragit® E100, hydroxypropyl methylcellulose (HPMC), or ethylcellulose physically separates the drug from taste receptors in the oral cavity [9]. Microencapsulation using fluid-bed coating technology provides a scalable and reproducible approach to achieve uniform particle coverage. Ion-exchange resin complexation—employing agents such as Amberlite™ IRP69—offers simultaneous taste masking and modified drug release by ionic binding of drug to the resin

matrix [19]. Cyclodextrin complexation has gained traction as a dual-purpose technology that enhances drug solubility while reducing bitter taste perception through molecular encapsulation [20]. Hot-melt extrusion (HME) enables the production of solid dispersions in which the drug is molecularly dispersed within a polymer matrix, effectively reducing the concentration of free drug available for taste receptor interaction [26]. Comprehensive evaluation of taste-masking efficacy employs both electronic tongue (e-tongue) technology and trained human taste panels in age-appropriate cohorts [9].

Table 3: Taste-masking techniques and technologies used in pediatric drug formulations

Technique	Mechanism	Examples	Advantages
Coating (film/microencapsulation)	Physical barrier over drug particles	Eudragit®, HPMC, ethylcellulose	Durable, scalable, MR potential
Sweeteners and flavoring	Sensory modulation of taste perception	Sucralose, aspartame, strawberry flavor	Simple, cost-effective
Ion-exchange resins	Ionic binding of drug to resin	Cholestyramine, Amberlite™ IRP69	Sustained release + taste masking
Cyclodextrin complexation	Molecular encapsulation	β-CD, HP-β-CD	Solubility enhancement + masking
Hot-melt extrusion	Drug-polymer solid dispersion	Kollidon® VA64, Soluplus®	Continuous process, solvent-free
Fluid bed coating	Spray coating of particles	HPMC, Surelease®	Uniform coating, scalable
Lipid-based systems	Encapsulation in lipid matrix	Glyceryl behenate, beeswax	Masks bitter drugs effectively
3D printing (inkjet/FDM)	On-demand drug deposition	PVA, PLA, Eudragit® filaments	Personalized dosing, novel shapes

4.2. Modified and Controlled Release Systems

Controlled-release (CR) formulations offer therapeutic benefits in pediatric populations by reducing dosing frequency and minimizing peak-related adverse effects, thereby improving adherence and quality of life for children with chronic conditions [15]. Matrix tablets, reservoir systems, and osmotic pump technologies have been adapted for pediatric use, often through size reduction. The particular challenge in pediatric CR formulations is ensuring that release mechanisms remain robust across the broader pH range encountered in the immature GI tract [13].

Extended-release granules and pellets coated with pH-dependent polymers are frequently incorporated into sprinkle formulations, allowing caregivers to open capsules and administer the contents in soft food without compromising the release profile—provided the food vehicle is correctly chosen [15]. Validation of this "sprinkle" approach requires *in vitro* and *in vivo* studies confirming the integrity of the coating system under relevant food conditions.

4.3. Multiparticulate Systems

Multiparticulate systems—including pellets, mini-tablets, microparticles, and granules—represent a significant advance in pediatric formulation science due to their inherent dose flexibility, reduced intra- and inter-subject variability in gastric emptying, and compatibility with modified-release coating technologies [16, 17]. Mini-tablets of 2–3 mm diameter have been extensively studied and demonstrated to be swallowable by infants as young as six months of age in prospective clinical studies [16, 17]. The therapeutic advantage of mini-tablets is further augmented by the capacity to coat individual units with different polymer systems to achieve pulsatile, extended, or pH-dependent release profiles within a single dosage unit [15].

4.4. Orodispersible and Chewable Dosage Forms

Orodispersible tablets (ODTs) and orodispersible films (ODFs) rapidly dissolve or disintegrate in the oral cavity without the need for water, making them particularly suitable for children aged two years and above, as well as patients with dysphagia [22]. ODTs are manufactured via freeze-drying, direct compression with superdisintegrants, or wet granulation, and must satisfy disintegration time requirements (typically <30 seconds per Ph.Eur. standards) [22]. A critical prerequisite for ODT and ODF acceptability is effective taste masking, as complete drug dissolution in the oral cavity directly exposes taste receptors.

Orodispersible films, fabricated from cellulosic or polyvinyl alcohol (PVA)-based polymer matrices via solvent casting or hot-melt extrusion, offer additional advantages of dose precision, portability, and ease of administration [22]. Their thin structure facilitates rapid drug absorption through the buccal mucosa for selected drugs, bypassing hepatic first-pass metabolism. Chewable tablets, widely accepted in older children, require robust palatability and texture optimization alongside sufficient mechanical strength to prevent premature crumbling during handling [10].

5. Emerging Technologies

5.1. Nanotechnology-Based Delivery

Nanotechnology-based drug delivery systems—including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanosuspensions, and dendrimers—offer transformative potential for pediatric pharmacotherapy by enhancing solubility, enabling targeted delivery, and facilitating controlled drug release [21, 29]. Polymeric nanoparticles fabricated from biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA) enable sustained drug release over days to weeks following a single administration, significantly reducing dosing burden in chronic pediatric conditions. SLNs, composed of physiologically tolerated lipid matrices, demonstrate favorable safety profiles relevant to pediatric use [21].

Liposomal formulations, already approved for adult indications (e.g., liposomal amphotericin B), have demonstrated utility in pediatric infectious disease management, providing reduced nephrotoxicity compared with conventional amphotericin B formulations [29]. Despite promising preclinical data, the clinical translation of nanotechnology platforms to pediatric patients faces significant hurdles including regulatory uncertainty regarding nanoparticle safety, limited long-term toxicology data in developing organ systems, and manufacturing scalability [21].

5.2. Three-Dimensional Printing in Pediatrics

Three-dimensional (3D) printing—encompassing fused deposition modeling (FDM), inkjet printing, stereolithography (SLA), and selective laser sintering (SLS)—represents a paradigm-shifting approach to personalized pediatric drug formulation [23, 24, 25]. The capacity to fabricate dosage forms with defined geometries, drug concentrations, and release profiles on a patient-specific basis addresses the fundamental challenge of dose flexibility across pediatric age groups. FDM printing utilizes thermoplastic polymer filaments loaded with drug substance to produce tablets of customizable shape and dimension, with drug release modifiable through infill geometry [23].

The first FDA-approved 3D-printed pharmaceutical product—levetiracetam (Spritam®)—employs a proprietary inkjet-based ZipDose® technology producing highly porous tablets with rapid disintegration, directly applicable to pediatric epilepsy management [24, 25]. Despite this landmark approval, widespread clinical implementation of 3D printing in pediatrics remains constrained by regulatory gaps in quality standards for point-of-care manufacturing, printer validation, and in-process quality control [25].

5.3. Personalized Medicine Approaches

Personalized or precision medicine approaches leverage pharmacogenomic profiling, physiologically based pharmacokinetic (PBPK) modeling, and therapeutic drug monitoring (TDM) to individualize dosing regimens and formulation selection for pediatric patients [13, 28]. PBPK models incorporating developmental parameters—organ maturation, ontogenic enzyme expression, body composition changes—enable prediction of drug exposure across pediatric age groups prior to clinical studies, facilitating rational formulation design [13]. Pharmacogenomics-informed prescribing is increasingly relevant in pediatric oncology and transplantation, where CYP2C19, CYP2D6, and TPMT polymorphisms substantially influence drug metabolism and therapeutic outcomes [28].

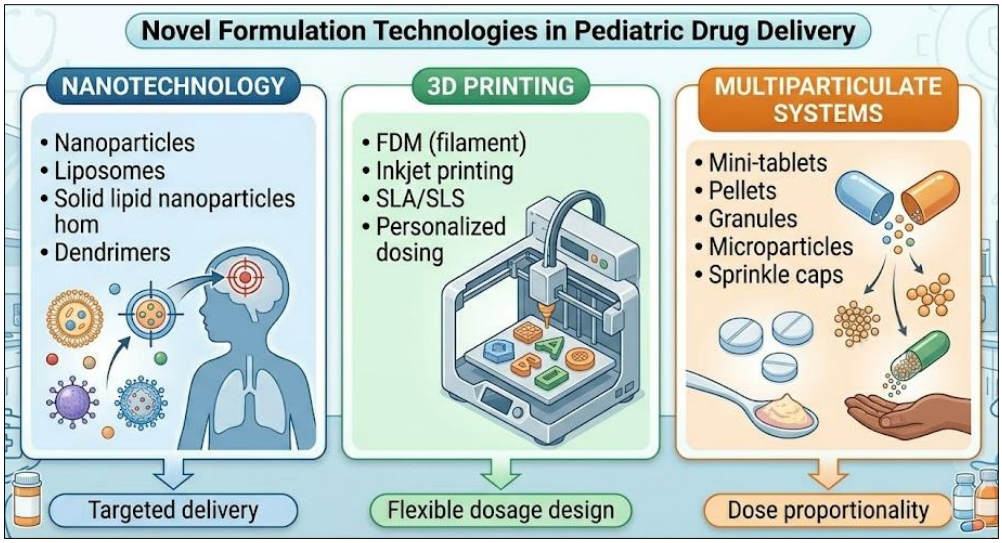

Fig 3: Overview of novel pharmaceutical technologies applied to pediatric drug delivery, encompassing nanotechnology platforms, three-dimensional printing methodologies, and multiparticulate systems

6. Therapeutic Applications

6.1. Infectious Diseases

Pediatric infectious diseases—including HIV/AIDS, tuberculosis, malaria, and bacterial infections—represent a major driver of pediatric formulation development globally. The WHO pediatric antiretroviral (ARV) program has catalyzed the development of dispersible, fixed-dose combination (FDC) ARV tablets suitable for infants and young children, incorporating drugs such as lopinavir/ritonavir and abacavir/lamivudine [27]. Taste-masked dispersible tablets and granule-filled sachets have significantly improved antiretroviral delivery in resource-limited settings where cold-chain-dependent liquid formulations present logistical challenges [27]. Cyclodextrin-based formulations of ciprofloxacin have been developed specifically for pediatric urinary tract infections, combining solubility enhancement with effective taste masking [20].

6.2. Chronic Conditions

Epilepsy management in children benefits substantially from modified-release formulations that reduce seizure breakthrough associated with peak-trough drug concentration fluctuations. Lamotrigine dispersible tablets and levetiracetam oral solution represent approved pediatric-specific formulations, while the 3D-printed levetiracetam ODT demonstrates the potential of additive manufacturing in this therapeutic area [24]. Asthma pharmacotherapy in young children has advanced through the development of ciclesonide and fluticasone dry powder inhalers with low resistance devices optimized for pediatric inspiratory flow rates, alongside montelukast chewable tablets for prophylactic management [5].

6.3. Vaccines and Biologics

Vaccine formulation for pediatric populations demands consideration of antigen stability, adjuvant safety, administration volume, and immunogenicity across developmental stages. The shift toward combination vaccines has reduced the number of injections required in early childhood immunization schedules, improving adherence. Emerging intranasal and oral vaccine platforms, including oral poliovirus vaccine and live attenuated rotavirus vaccines, exemplify age-appropriate biological formulations that circumvent injection-related pain and needle-phobia [3, 30]. Monoclonal antibody formulations for pediatric oncology and inflammatory diseases are increasingly being

reformulated as subcutaneous injection devices or age-appropriate oral biologics to reduce hospitalization burden.

7. Regulatory and Safety Considerations

7.1. Pediatric Regulatory Frameworks

The regulatory landscape for pediatric medicines has been transformed over the past two decades. In the United States, the BPCA and PREA mandate pediatric studies for new molecular entities affecting pediatric populations, while the FDA's Pediatric Advisory Committee (PAC) provides specialized scientific evaluation of pediatric data submissions [3, 30]. In Europe, the EMA's Paediatric Committee (PDCO) requires the submission of a Pediatric Investigation Plan (PIP) for all new medicines, ensuring that formulations suitable for children are developed concurrently with adult products [2, 4].

The ICH E11(R1) guideline provides harmonized global guidance on clinical investigation in pediatric populations, emphasizing the importance of studying formulations across all six age subgroups [4]. The EMA reflection paper on formulations of choice for the pediatric population provides specific pharmaceutical guidance on preferred dosage forms and excipient acceptability thresholds for different age groups [2].

7.2. Safety and Excipient Concerns

The safety of pharmaceutical excipients in pediatric formulations deserves particular scrutiny, as many established excipients for adult medicines have not been systematically evaluated in children [3]. Benzyl alcohol, associated with "gasping syndrome" in neonates at high doses, is contraindicated in neonatal formulations. Propylene glycol, widely used as a solvent in oral liquids, accumulates in neonates due to immature alcohol dehydrogenase activity, potentially causing metabolic acidosis. Sorbitol, a common sweetener, can induce osmotic diarrhea in young children when administered in quantities exceeding 0.5 g/kg/day [5, 6]. The European Paediatric Formulation Initiative (EuPFI) and the Safety and Toxicity of Excipients for Paediatrics (STEP) database provide comprehensive resources for excipient risk assessment in pediatric formulation development.

8. Challenges and Future Perspectives

8.1. Manufacturing Challenges

The commercial manufacture of pediatric dosage forms presents distinct challenges compared with adult medicine production. Small batch sizes necessitated by limited market size, tight particle size control for multiparticulate systems, and the requirement for specialized coatings and taste-masking processes elevate manufacturing complexity and cost [1, 5]. Continuous manufacturing technologies, including continuous granulation and coating systems, offer potential efficiency gains for pediatric formulation production while enhancing process consistency and real-time quality assurance [26].

8.2. Clinical Translation

The clinical translation of novel pediatric formulation technologies from proof-of-concept to regulatory approval requires extensive acceptability studies, pharmacokinetic bridging studies, and age-appropriate clinical trials that present significant logistical and ethical challenges [18, 30]. Physiologically based pharmacokinetic (PBPK) modeling and *in vitro*–in vivo correlation (IVIVC) methodologies are increasingly accepted by regulatory authorities as tools to reduce the extent of *in vivo* pediatric studies required, accelerating the clinical development pathway [13].

8.3. Future Innovations

Future innovations in pediatric drug delivery will likely converge on the intersection of digital health technologies, precision medicine, and advanced manufacturing. Smart drug delivery systems incorporating sensor-based compliance monitoring, digitally embedded dosage forms, and AI-driven dose optimization algorithms represent nascent but promising directions [28]. The integration of microfluidics with 3D printing may enable on-demand production of patient-specific dosage forms at the point of care, transforming the hospital pharmacy model for inpatients. Expansion of the approved pediatric excipient database through systematic toxicological evaluation and integration with computational safety models will facilitate formulation innovation [2].

Table 4: Advantages and limitations of pediatric drug delivery systems

Delivery System	Advantages	Limitations
Nanoparticle systems	Targeted delivery, improved bioavailability, controlled release	High manufacturing cost, limited long-term safety data in children
Liposomes	Biocompatible, encapsulates hydrophilic and lipophilic drugs	Short shelf life, scale-up challenges, cold-chain requirements
Solid lipid nanoparticles	Improved stability, scalable, low toxicity carrier	Drug leakage on storage, particle size variability
Mini-tablets	Flexible dosing, coatable for MR, age-appropriate size	Requires validated swallowing studies in each age group
3D-printed dosage forms	Precise dosing, personalized geometry, novel drug combinations	Regulatory unclear, limited large-scale reproducibility
Orodispersible films	Thin, portable, no water needed, good compliance	Drug loading limitation, mechanical fragility
Transdermal systems	Non-invasive, bypasses hepatic first pass, sustained release	Limited to lipophilic, low-MW drugs; skin permeability varies by age
Multiparticulate systems	Dose flexibility, reduced food effects, modified release possible	Complex manufacturing, bead uniformity critical for dosing accuracy

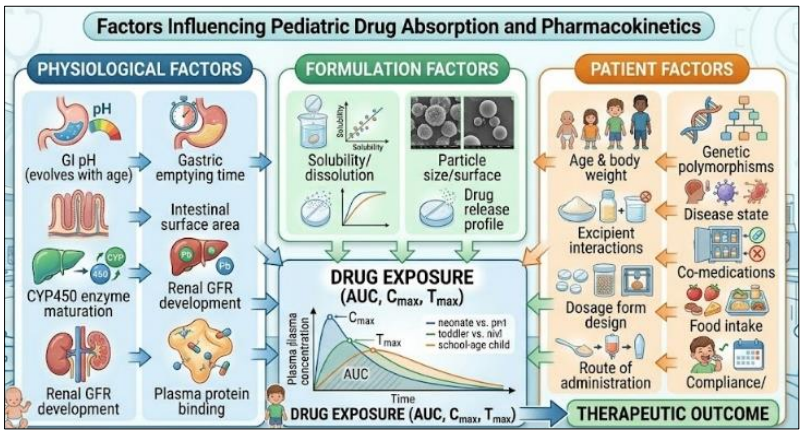

Fig 4: Multifactorial determinants of pediatric drug absorption and pharmacokinetics, illustrating the interplay between physiological maturation, formulation design parameters, and patient-specific factors

9. Conclusion

Advances in pediatric drug formulation have fundamentally expanded the therapeutic armamentarium available to clinicians managing disease in children across all developmental stages. The transition from extemporaneous compounding and off-label adult formulations toward purpose-designed, age-appropriate dosage forms—encompassing dispersible tablets, mini-tablets, multiparticulate systems, orodispersible films, and modified-release platforms—represents a critical maturation of the field underpinned by strengthened regulatory frameworks in both the United States and Europe.

Emerging technologies including nanotechnology-based delivery systems, three-dimensional printing, and personalized medicine platforms hold transformative promise for further individualizing pediatric pharmacotherapy, addressing residual unmet needs particularly in rare diseases and neonatal medicine. The continued application of PBPK modeling, acceptability science, and innovative taste-masking technologies will be essential to bridging the gap between technological innovation and clinical implementation.

Sustained progress in this discipline demands cross-disciplinary collaboration between pharmaceutical scientists, clinical pharmacologists, pediatric clinicians, regulators, and patient advocacy communities. As the global burden of pediatric disease continues to evolve, the development of safe, effective, and child-friendly medicines remains an ethical and scientific imperative that the pharmaceutical community is increasingly well-equipped to address.

References

1. Breitkreutz J, Boos J. Paediatric and geriatric drug delivery. Expert Opin Drug Deliv. 2007;4(1):37–45.
2. European Medicines Agency. Reflection paper: formulations of choice for paediatric population. EMA/CHMP/PEG/194810/2005. London: EMA; 2006.
3. U.S. Food and Drug Administration. Pediatric Drug Development: Guidance for Industry. Silver Spring, MD: FDA; 2018.
4. International Council for Harmonisation. ICH E11(R1): Clinical investigation of medicinal products in the pediatric population. Geneva: ICH; 2017.
5. Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014;134(2):361–372.
6. Standing JF, Tuleu C. Paediatric formulations – getting to the heart of the problem. Int J Pharm. 2005;300(1–2):56–66.
7. Walsh J, Bickmann D, Breitkreutz J, Chariot-Goulet M. Delivery devices for the administration of paediatric formulations. Int J Pharm. 2011;415(1–2):272–281.
8. Mennella JA, Beauchamp GK. Optimizing oral medications for children. Clin Ther. 2008;30(11):2120–2132.
9. Pein M, Preis M, Eckert C, Kiene FE. Taste-masking assessment of solid oral dosage forms – a merger of approaches. Int J Pharm. 2014;465(1–2):239–254.
10. Liu F, Ranmal S, Batchelor HK, *et al*. Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. Drugs. 2014;74(16):1871–1889.
11. Abdel-Halim MS, Bhattacharyya GK. Pediatric pharmacokinetics: developmental changes and therapeutic implications. Clin Pharmacokinet. 2019;58(5):577–593.
12. Kearns GL, Abdel-Rahman SM, Alander SW, *et al*. Developmental pharmacology – drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157–1167.
13. Reppas C, Karatza E. Physiologically based pharmacokinetic modelling in pediatric drug development. Eur J Drug Metab Pharmacokinet. 2010;35(3–4):91–97.
14. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. Br J Clin Pharmacol. 2015;79(3):395–404.
15. Stoltenberg I, Breitkreutz J. Orally disintegrating mini-tablets (ODMTs) – a novel solid oral dosage form for paediatric use. Eur J Pharm Biopharm. 2011;78(3):462–469.
16. Spomer N, Klingmann V, Stoltenberg I, *et al*. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child. 2012;97(5):389–393.
17. Klingmann V, Spomer N, Lerch C, *et al*. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. J Pediatr. 2013;163(6):1728–1732.
18. Ranmal SR, O'Brien F, Lopez F, *et al*. Methodologies for assessing the acceptability of oral formulations among children and older adults. Drug Discov Today. 2018;23(5):1092–1108.

19. Klingmann V. Palatability and taste-masking in paediatric medicines. Expert Opin Drug Deliv. 2020;17(9):1249–1262.
20. Thi THH, Azaroual N, Flament MP. Characterisation and *in vitro* evaluation of cyclodextrin complexes of ciprofloxacin for the treatment of paediatric infectious diseases. Eur J Pharm Biopharm. 2009;72(3):214–220.
21. Charbe NB, Pardhi DM, McCarron PA, *et al*. Nano-sized drug delivery platforms: targeting strategies in paediatric pharmacotherapy. Biomed Pharmacother. 2017;90:637–652.
22. Preis M, Woertz C, Kleinebudde P, Breitkreutz J. Oromucosal film preparations: classification and characterization methods. Expert Opin Drug Deliv. 2013;10(9):1303–1317.
23. Goyanes A, Buanz ABM, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. Int J Pharm. 2014;476(1–2):88–92.
24. Awad A, Trenfield SJ, Gaisford S, Basit AW. 3D printed medicines: a new branch of digital healthcare. Int J Pharm. 2018;548(1):586–596.
25. Alhnan MA, Okwuosa TC, Sadia M, *et al*. Emergence of 3D printed dosage forms: opportunities and challenges. Pharm Res. 2016;33(8):1817–1832.
26. Passerini N, Albertini B, Gonzalez-Rodriguez ML, *et al*. Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation. Eur J Pharm Sci. 2002;15(1):71–78.
27. Nwoye CI, Ogboaka IB. Antiretroviral therapy in children: current status and future perspectives. Paediatr Drugs. 2016;18(6):431–442.
28. Primorac D, Bach-Rojecky L, Vadunec D, *et al*. Pharmacogenomics at the base of precision medicine: challenges and perspectives in rare diseases. Pharmgenomics Pers Med. 2020;13:57–65.
29. Moulari B, Béduneau A, Pellequer Y, Lamprecht A. Nanoparticle targeting to inflamed tissue of the gut. Eur J Pharm Biopharm. 2008;69(2):498–505.
30. Zajicek A, Barrett JS, Ni L, *et al*. The National Institutes of Health and the Best Pharmaceuticals for Children Act: a new process for drug development. Pediatrics. 2013;131(5):e1591–e1601.