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A Formulation Strategies for Paediatric Medication: Challenges, Approaches and Future Directions

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Abstract: *Despite major progress in ensuring the safety and effectiveness of pharmaceuticals, the development of medicines specifically suitable for children continues to be one of the most complex areas of drug development. Children are not simply smaller versions of adults; their rapidly changing physiology, growth patterns, and behavioural characteristics require specially tailored formulation approaches. This review focuses on the diverse strategies involved in the design of paediatric medicines that meet the physiological, developmental, and practical needs of patients from infancy through adolescence.*

Current regulatory requirements and guidance issued by international agencies such as the WHO, EMA, and FDA are discussed, along with key paediatric-specific physiological factors including variations in gastric pH, enzyme maturity, organ development, and body composition. The review further outlines formulation approaches for different dosage forms such as oral liquids, solid oral preparations, dispersible tablets, advanced taste-masked systems, and alternative drug delivery routes.

Special attention is given to the selection and safety evaluation of excipients using modern risk-assessment approaches, as well as methods used for palatability evaluation and the importance of accurate dosing devices. Key aspects of manufacturing, stability, and quality assurance are also highlighted, together with recent advancements such as microencapsulation and nanoparticulate drug delivery systems. By examining practical case examples and existing research limitations, this review aims to provide scientifically grounded guidance for researchers, formulators, clinicians, and regulatory authorities involved in paediatric medicine development. In addition, future perspectives focusing on innovative technologies, patient-centred formulation design, and globally harmonized regulatory frameworks are outlined to help address the continuing lack of age-appropriate medicines for children worldwide.

Keywords: paediatric formulations, taste masking, excipient safety, dosage forms, palatability, regulatory guidelines, drug delivery, nanoparticles, pharmaceutical development, age-appropriate medicine

I. INTRODUCTION

1.1 Background and Clinical Significance

The development and availability of appropriate pharmaceutical formulations for children represents one of the most critical yet underserved areas in modern therapeutics[1][2].

Globally, children represent approximately 20–25% of the population, yet fewer than 10% of registered medications have been specifically formulated and marketed for paediatric use[1]. This disparity has profound consequences: healthcare providers are frequently compelled to modify adult formulations through extemporaneous compounding (tablet crushing, capsule opening, suspension preparation) to treat paediatric patients, a practice associated with significant risks including dosing inaccuracy, formulation instability, masking failure, reduced bioavailability, and inadvertent exposure to inappropriate excipients[3][4].

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The term "therapeutic orphans" has been used to describe children who lack access to safe, appropriate, and labelled medications[2]. This situation emerged historically due to multiple factors: perceived liability concerns regarding paediatric drug testing, limited commercial incentives owing to smaller market sizes, incomplete understanding of developmental physiology and pharmacokinetics in children, and a legacy assumption that adult formulations could be simply dose-adjusted for children[1][3]. The consequences of this therapeutic gap have been well-documented: prolonged disease suffering, suboptimal treatment outcomes, preventable hospitalizations, medication errors, and in some tragic instances, preventable deaths[5][6].

1.2 Regulatory Evolution and Current Drivers

Medications and formulations specifically designed for paediatric populations[11].

1.3 Scope and Objectives of This Review

This review examines the scientific, regulatory, and practical landscape of paediatric formulation development. Specifically, we address: (1) regulatory frameworks and age- group definitions; (2) physiological and developmental factors unique to children that impact formulation design; (3) evidence-based formulation design principles and strategies across multiple dosage forms; (4) contemporary excipient safety evaluation and selection frameworks; (5) palatability and acceptability assessment; (6) dosing accuracy and administration devices; (7) manufacturing, stability, and quality control considerations; (8) real-world case studies illustrating successful formulation strategies;
(9) persistent gaps and unmet needs; and (10) future technological and regulatory directions. The target audience includes pharmaceutical scientists, formulators, regulatory specialists, clinical pharmacists, and paediatricians involved in medicine development and selection.

II. REGULATORY AND POLICY CONTEXT

Age Group	Age Range	Formulation Considerations
Preterm Newborn	<37 weeks gestation	Limited oral ability; parenteral, topical preferred; minimal excipient safety data
Term Newborn	0–27 days	Very limited oral administration; gastric immaturity; minimal excipient tolerance
Infant	28 days–<2 years	Emerging oral ability; liquid/semi-solid forms preferred; highly sensitive to excipients
Toddler/Young Child	2–5 years	Mixed oral-motor skills; growing ability to handle small tablets/granules; taste sensitivity remains high
Child	6–11 years	Improved swallowing; can handle larger tablets; better taste discrimination
Adolescent	12–17 years	Near-adult swallowing ability; varied preferences; approaching adult physiological parameters

Table 1: Regulatory age group definitions and formulation requirements

III. PAEDIATRIC-SPECIFIC PHYSIOLOGIC AND DEVELOPMENTAL CONSIDERATIONS

3.1 Overview

Paediatric populations are not simply "small adults." Children undergo profound physiological maturation affecting drug absorption, distribution, metabolism, and excretion. Additionally, cognitive and motor development directly influences formulation acceptability. Understanding these factors is essential for rational formulation design.

3.2 Age-Related Gastrointestinal Physiology

3.2.1 Gastric pH and Buffer Capacity

Neonates and young infants present markedly different gastric pH compared to older children and adults[15]. At birth, gastric pH averages 6–8 in term newborns; by age 3–4 weeks, pH drops toward adult levels (1.5–3.5)[15]. This

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elevation in neonatal pH affects the dissolution and bioavailability of acid-labile drugs and pH-dependent formulations. For example, penicillins, cephalosporins, and enteric-coated formulation design, generally making immediate-release or more predictable modified- release strategies preferable[15].

3.2.3 Intestinal Enzyme Development

Brush border enzyme activity (particularly alkaline phosphatase, peptidases, and carboxyl esterases) develops progressively after birth[16]. This has significant implications for prodrugs and for drugs metabolized by intestinal enzymes. For example, chloramphenicol prodrugs and certain beta-lactam esters are metabolized differently in infants versus older children, affecting bioavailability and potential for systemic toxicity[16]. Formulation scientists must consider intestinal enzyme- dependent metabolism when selecting active pharmaceutical ingredients and designing modified-release formulations targeting specific intestinal regions.

3.3 Hepatic and Renal Function Maturation

3.3.1 Phase I and Phase II Metabolism

Hepatic cytochrome P450 enzyme activity is substantially reduced at birth and develops unevenly over the first years of life[17][18]. CYP3A4 (which metabolizes a large proportion of medicines) reaches ~50% of adult activity by 1–3 months of age and ~100% by age 6–12 months[17]. CYP2D6, CYP2C9, and other isoenzymes mature on different timelines[17]. This developmental variation in hepatic metabolism means that dose adjustments based on body weight or surface area alone are insufficient; age-appropriate adjustments are often necessary[17][18]. Formulation design must account for the possibility that first-pass metabolism is reduced in infants, potentially leading to unexpectedly high systemic concentrations if adult-like formulations are used[18].

Phase II metabolism (glucuronidation, sulfation, acetylation) is also significantly reduced in infants, increasing the risk of drug and metabolite accumulation[18]. This was historically a factor in "Gray Baby Syndrome" associated with chloramphenicol in neonates[5]. Formulation choices should avoid or minimize compounds requiring rapid Phase II metabolism in the paediatric population.

3.3.2 Renal Function Development

Glomerular filtration rate (GFR) at birth is approximately 20–30 mL/min/1.73m² in term newborns (compared to 90–140 mL/min/1.73m² in adults)[19]. GFR increases rapidly to adult levels by 3–12 months of age[19]. This immature renal function prolongs drug elimination and increases accumulation risk for renally cleared drugs. Formulations of renally eliminated drugs require careful consideration of dose and dosing interval[19]. Additionally, immature tubular secretion means drugs normally cleared by active renal transport are cleared more slowly in infants[19].

3.4 Body Composition and Volume of Distribution

Infants have a higher total body water content (70–75%) compared to adults (50– 60%)[20]. This increased extracellular fluid volume affects the volume of distribution for hydrophilic drugs, often requiring higher weight-adjusted doses to achieve therapeutic concentrations[20]. Conversely, infants have lower adipose tissue content, reducing the volume of distribution for lipophilic drugs[20]. These compositional changes evolve progressively through childhood, stabilizing toward adult proportions by adolescence[20].

3.5 Swallowing Ability and Oral Motor Development

3.5.1 Developmental Stages of Swallowing

Coordinated swallowing emerges gradually during infancy. Premature infants may have weak or uncoordinated swallowing reflexes; coordination improves during weeks 32–36 of gestation[21]. Term newborns (0–3 months) can swallow but often reflexively suckle; swallowing is not yet volitional or reliable. By 4–6 months, infants begin to accept semi- solid foods and can handle some liquid formulations with assistance[21]. By 1–2 years (toddler stage), most children can drink from a cup and take oral medications, although fine motor control remains developing[21]. By

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3–5 years, children can reliably take oral medications in appropriate dosage forms; by 6+ years, most can swallow tablets if appropriately sized[21].

3.5.2 Formulation Implications

These developmental milestones directly determine formulation appropriateness. Premature and term newborns (0–6 months) generally cannot reliably take oral liquid formulations; nasogastric administration or alternative routes (parenteral, rectal) are often necessary[21]. Infants (6–24 months) can handle liquid formulations but often refuse unpalatable tastes, necessitating strong flavor masking[21]. Toddlers and young children (2–5 years) can take liquid or semi-solid formulations reliably and may be able to handle dissolvable or small solid dosage forms if properly designed[21]. Older children (6–11 years) can generally accept larger tablets and various solid dosage forms[21].

3.6 Taste Perception and Palatability Sensitivity

3.6.1 Developmental Taste Changes

Taste perception changes markedly across development. Neonates and infants have heightened sensitivity to bitter and sour tastes, with strong innate aversions[22]. Sweetness preference also emerges early, but excessive sweetness can be rejected[22]. Umami (savory) perception develops gradually[22]. By 2–4 years, taste discrimination becomes more sophisticated, but bitter aversion remains strong, often persisting into adolescence[22]. This heightened bitter sensitivity in young children makes taste masking critical for formulations containing bitter-tasting drugs.

3.6.2 Adherence and Acceptability Issues

Unpalatable taste is cited as a leading cause of non-adherence in paediatric patients[22] [23]. Studies show that up to 90% of patients (adults and children) express resistance to taking medications due to poor taste[13]. In children, taste-related refusal can lead to doses being missed, underdosed, or administered inconsistently, compromising therapeutic efficacy[23]. This is particularly problematic for chronic conditions (asthma, diabetes, ADHD, infections) requiring sustained adherence.

IV. FORMULATION DESIGN PRINCIPLES AND STRATEGIES

4.1 Overview and Hierarchical Approach

Dose flexibility: Enables precise dose adjustment based on individual patient weight or age Ease of administration: Can be delivered via syringe, spoon, or incorporated into food/drink Acceptability: Better accepted by young children compared to solid dosage forms Swallowability: Suitable across all paediatric age groups

Consequently, liquid formulations remain the primary dosage form for children under 6 years and are widely used in older children[24][25].

4.1.2 Formulation Challenges and Stability Strategies

Oral liquid formulations present significant formulation and commercial challenges[24] [25]:

Solubility and Crystallization: Many drugs have poor aqueous solubility. Formulators employ multiple strategies to enhance solubility[25]:

pH adjustment: Optimizing pH to maximize the ionized (soluble) form of the drug Use of cosolvents: Propylene glycol, ethanol, sorbitol (though excipient safety concerns apply; see Section 5)

Complexation: Cyclodextrins, particularly hydroxypropyl-β-cyclodextrin (HPβCD),

enhance solubility and may also contribute to taste masking[25]

Micellar systems and lipid-based formulations: For lipophilic drugs, incorporation into micelles, self-emulsifying drug delivery systems (SEDDS), or lipoidal excipients improves solubility[25] are often employed. However, suspensions require careful control of particle size, density, and rheology to maintain uniform dose over shelf life[25]. Common approaches include:

Surfactant selection: Non-ionic surfactants (polysorbates, lecithin) typically better tolerated than ionic surfactants

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Thickening agents: Microcrystalline cellulose (Avicel), xanthan gum, bentonite improve suspension stability; however, thickening agents affect taste and mouthfeel pH buffering: Maintaining optimal pH reduces drug degradation and particle aggregation Chelation: Inclusion of chelating agents (e.g., disodium edetate for iron-containing suspensions) prevents metal-catalyzed oxidation

Chemical Stability and Degradation: Liquid formulations are exposed to aqueous hydrolysis, oxidation, photodegradation, and enzymatic degradation. Mitigation strategies include[25]:

Antioxidants (ascorbic acid, sodium metabisulfite, butylated hydroxytoluene) to prevent oxidative degradation

Chelating agents to sequester trace metals catalyzing oxidation Headspace oxygen minimization during manufacturing and storage Light-protective packaging (amber glass, opaque bottles) Appropriate pH optimization to minimize hydrolytic degradation

Microbial Growth and Preservation: Aqueous liquid formulations are susceptible to microbial contamination and growth. Preservatives are typically required[24]:

Parabens (methyl-, propyl-, butylparaben) are widely used but have emerging safety concerns (see Section 5)

Benzoic acid and sodium benzoate are effective in acidic formulations but less suitable for neutral/alkaline systems

Sorbic acid offers an alternative but may affect taste

Newer preservatives under investigation include phenoxyethanol and combinations of naturally derived preservatives (though efficacy and regulatory status vary globally) Taste Masking and Flavor Engineering: Given the heightened bitter sensitivity in children, taste masking is often essential. Approaches include[24][25]:

Flavor addition: Sweet, fruity, or other child-appealing flavors (e.g., cherry, orange) mask (discussed in Section 4.5) pH adjustment: Raising pH can reduce perceived bitterness of certain drugs

Co-precipitation with cyclodextrins: HPβCD complexation improves both solubility and taste

4.2 Solid Oral Alternatives:

Dispersible Tablets, ODTs, Mini-Tablets, Granules, and Sprinkle Formulations

4.2.1 Rationale and Advantages

While oral liquids remain the gold standard for very young children, solid oral alternatives offer significant advantages[26]:

Dose flexibility: Mini-tablets, granules, and sprinkle capsules allow cumulative dosing for precise weight-adjusted doses

Stability: Solid dosage forms are more chemically and microbiologically stable than liquids

Palatability: Solid formulations can avoid liquid-based excipients (cosolvents, preservatives) that may impart unpleasant taste or smell

Convenience: Solid formulations are easier to transport, store (room temperature), and dispense than liquids

Manufacturing economy: Reduced need for specialized equipment compared to some liquid formulations

Regulatory agencies increasingly recognize these advantages and encourage development of solid alternatives for paediatric use[12][14].

4.2.2 Dispersible Tablets (DTs)

Definition and Characteristics: Dispersible tablets (DTs) disintegrate in water within 3 minutes (per USP specification) to form a suspension suitable for administration to children who cannot swallow tablets[26]. Key characteristics include:

Easy dispersion in water or applesauce, with or without heating

Maintained dose accuracy upon dispersion (critical for narrow-therapeutic-index drugs) Acceptable taste after dispersion (flavor added during manufacture or as recommended vehicle)

Sufficient mechanical strength to survive manufacturing, packaging, and storage without breaking water penetration

Minimal or no binder, or use of highly water-soluble binders

Lubricants (silica, magnesium stearate) at minimal levels to avoid interfering with disintegration

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Taste-masking agents (cyclodextrins, polymers, coatings) for bitter drugs

Advantages and Limitations:
Advantages: Simple to use (add water, disperse, administer), adequate for most drugs not requiring absolute dose accuracy, room-temperature stable
Limitations: Larger tablet size than immediate-release tablets (if not optimized); palatability depends on vehicle; not suitable for all drugs (e.g., those requiring gastric protection or those unstable in neutral/alkaline pH)

4.2.3 Orodispersible Tablets (ODTs)
Definition and Characteristics: ODTs (also called orally disintegrating tablets or mouth- dissolving tablets) disintegrate rapidly in the oral cavity (typically within 30 seconds to 2 minutes) without requiring water[26][27]. They are particularly attractive for paediatric use as they address the dual challenges of swallowing difficulty and acceptability[27].
Formulation Technologies: Multiple technologies enable ODT formulation[27]:
1. Lyophilization (freeze-drying): The drug is dissolved or suspended, then freeze- dried in the tablet mold, creating a highly porous tablet that rapidly absorbs saliva and disintegrates. Advantages include very rapid disintegration and excellent porosity; limitations include brittleness, difficulty achieving consistent content uniformity for low-dose drugs, and high manufacturing costs.
2. Direct Compression with Effervescent Agents: Effervescent tablets use CO_2- generating compounds (citric acid, sodium bicarbonate) to create porosity and promote rapid disintegration. The chemical reaction between saliva moisture and effervescent agents drives disintegration within 30–60 seconds. Limitations include: CO_2 gas may be uncomfortable for some children; formulation moisture sensitivity requires protective packaging; and taste may be affected by acidic pH from citric presses) but can employ standard tablet formulation approaches. The small size means that fill weight variation is relatively lower than expected, and compression force must be carefully controlled to ensure adequate tablet hardness without breaking during capsule filling or chewing[26][28].
Regulatory Acceptance: Regulatory agencies (EMA, FDA) have increasingly settings

Formulation Approaches: Granules are typically formed by[29]:
Wet granulation followed by screening and drying (often spray-dried) Direct compression of individual granule units
Agglomeration of microparticles (e.g., taste-masked drug particles coated with binders and packaged into loose granule form)
Administration: Granules are typically mixed with applesauce, jam, or small amount of liquid immediately before administration. Regulatory guidance emphasizes the need for patient instructions on appropriate vehicles to maintain dose accuracy[12].

4.2.6 Sprinkle Formulations and Capsule-Based Systems
Concept: Sprinkle formulations employ capsules (typically size 2 or 3) filled with small pellets, granules, or coated particles that can be opened and sprinkled onto soft food (applesauce, pudding) for administration to children unable to swallow capsules[28][30]. The capsule provides protection during storage and handling; sprinkle administration enables dose flexibility and circumvents the swallowing barrier[30].

Formulation Strategies: Sprinkle formulations typically employ[30]:
Microbeads or pellets: Small coated particles (0.5–1.5 mm) that are individually processed and then filled into capsules. Individual pellets are often enterically coated or taste-masked; this approach maintains dose integrity even if a child doesn't consume
Capsule selection: Gelatin or plant-based (hypromellose) capsules, with consideration of vegetarian/religious preferences

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Advantages and Limitations:

Advantages: Addresses swallowing difficulties; dose flexibility through partial capsule use or multiple capsules; maintains physical separation of individual units if patient compliance is imperfect; increasingly well-accepted by regulators

Limitations: Requires patient/caregiver instruction on proper administration (e.g., not chewing pellets, which defeats taste masking); more complex and costly manufacturing; not appropriate for liquid-soluble formulations

4.3 Modified-Release and Controlled-Release Formulations

4.3.1 Appropriateness in Paediatrics

Modified-release formulations (sustained-release, extended-release, delayed- release/enteric-coated) are used in paediatric populations but require careful consideration[31]:

Appropriate Indications:

Drugs requiring sustained therapeutic levels (e.g., methylphenidate, theophylline) where multiple daily doses would impair compliance

Drugs causing gastric irritation (NSAIDs, potassium) where delayed-release formulations reduce adverse effects

Drugs where extended-release improves efficacy (e.g., retinoid-based acne treatments)

Concerns in Paediatric Populations:

Unpredictable GI physiology: As noted in Section 3.2, infant gastric emptying and intestinal motility are variable and age-dependent, making sustained-release behavior unpredictable[31]

Dose flexibility limitations: Extended-release formulations typically cannot be divided or adjusted, limiting their utility when weight-based dosing is necessary[31] Risk of dose-dumping: If a child bites or breaks an extended-release formulation, sudden drug release may occur, risking toxicity[31] in development, regulatory harmonization, and capacity building will progressively narrow the "therapeutic orphan" gap, ensuring that children worldwide have access to safe, effective, acceptable medicines specifically designed for their unique needs.

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