Review Article

Nanoemulsions in Pediatric Drug Delivery: Formulation Strategies, Therapeutic Applications, Safety, and Future Perspectives

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ABSTRACT

Pediatric patients have distinctive pharmacokinetic, physiological, developmental, and acceptability requirements that make conventional adult formulations difficult to use safely and effectively. Nanoemulsions are submicron dispersions of oil and aqueous phases stabilized by surfactants and, when appropriate, cosurfactants. Their large interfacial area, capacity to solubilize lipophilic compounds, and flexibility across oral, topical, nasal, pulmonary, ocular, and parenteral routes make them attractive for pediatric drug delivery. This review summarizes the rationale for nanoemulsions in children, formulation and characterization considerations, representative pediatric applications, and major safety and translational barriers. Particular attention is given to dose flexibility, palatability, excipient selection, bioavailability enhancement, and age-related physiological differences. Available evidence includes promising preclinical studies and a limited number of pediatric-focused formulation investigations, including nanoemulsions or self-nanoemulsifying systems of vitamin D3, stiripentol, amphotericin B, and bedaquiline. However, most evidence remains formulation- or animal-based rather than derived from pediatric clinical trials. Successful translation will require child-appropriate excipients, robust stability and manufacturing controls, age-specific pharmacokinetic evaluation, and systematic safety assessment. Nanoemulsions therefore represent a promising but still emerging platform for pediatric medicines rather than a universally applicable solution.

Key words: Nanoemulsion, pediatric drug delivery, pediatric formulation, bioavailability, lipid-based delivery, nanomedicine, excipient safety

Children are not simply small adults. Growth and maturation alter gastrointestinal physiology, body composition, enzyme and transporter activity, hepatic metabolism, renal elimination, and the ability to accept different dosage forms. Consequently, an appropriate pediatric medicine must consider age, body size, developmental stage, route of administration, dose flexibility, swallowability, and palatability rather than relying only on weight-based modification of an adult product [1,2]. Inadequate age-appropriate formulations can lead to manipulation of adult dosage forms, inaccurate dosing, poor adherence, and unnecessary exposure to unsuitable excipients [3,4].

Poor aqueous solubility is an additional challenge because many contemporary active pharmaceutical ingredients have limited dissolution and variable oral absorption. Lipid-based delivery systems can maintain poorly soluble drugs in a solubilized state and may improve intestinal dissolution, absorption, and, for selected compounds, lymphatic transport [5,6]. Nanoemulsions are particularly interesting because they provide a large interfacial area and can be adapted to different routes and dosage forms. Reviews of nanoemulsion technology describe improved solubilization, bioavailability, and flexibility in formulation and manufacturing [7-9].

For pediatric use, however, the value of a nanoemulsion depends on more than nanoscale droplet size. The composition must be safe for the intended age group, the formulation must be physically and chemically stable, and the finished product must be practical for children and caregivers. Recent pediatric nanomedicine reviews emphasize that translation has progressed more slowly in children than in adults because developmental physiology and pediatric-specific formulation requirements complicate extrapolation from adult products [10,11]. This review therefore focuses on how nanoemulsions may address pediatric drug-delivery needs while critically considering their limitations and translational requirements.

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2. PEDIATRIC DRUG-DELIVERY CHALLENGES RELEVANT TO NANOEMULSIONS

Age-appropriate dosage forms should permit accurate administration of small and sometimes rapidly changing doses. Infants and younger children may be unable to swallow conventional tablets or capsules, whereas older children may still reject medicines because of unpleasant taste, texture, or smell. Palatability is closely linked to adherence, and excipient toxicity may also differ between children and adults [3,12]. Liquid formulations can provide dosing flexibility but may require preservatives, sweeteners, flavoring agents, cosolvents, or other excipients that need careful assessment in young patients [2,13].

Physiological maturation can influence the performance of lipid-based systems. Gastric pH, gastric emptying, intestinal transit, bile secretion, intestinal surface area, and expression of metabolic enzymes and transporters change during development. These factors may alter drug solubilization, digestion of lipid excipients, absorption, and systemic exposure. Therefore, formulation performance observed in adults or adult animal models cannot automatically be assumed to apply across pediatric age groups [10,14].

Nanoemulsions can potentially address some of these challenges by presenting the drug in a pre-solubilized lipid environment, supporting liquid or semisolid dosage forms, and enabling incorporation of flavoring or viscosity modifiers when justified. Nevertheless, they should not be viewed as a substitute for age-appropriate product design. A nanoemulsion that improves dissolution but contains poorly characterized or excessive surfactant concentrations may create a new safety problem. Pediatric development must therefore balance pharmaceutical performance, palatability, dose accuracy, and excipient safety.

3. NANOEMULSIONS: FORMULATION PRINCIPLES AND CHARACTERIZATION

Nanoemulsions are kinetically stable dispersions of two immiscible liquids, commonly oil-in-water (O/W) or water-in-oil (W/O), stabilized by interfacial agents. They are distinct from thermodynamically stable microemulsions, although terminology is sometimes used inconsistently in the literature [7,8]. Droplet dimensions commonly fall within the nanometer range, and the small droplets provide a high interfacial area that can improve dispersion and apparent solubilization of poorly water-soluble drugs. The formulation is nevertheless thermodynamically unstable and requires adequate control of droplet formation, interfacial properties, and storage conditions [7,9].

Formulation begins with selection of the oil phase according to drug solubility, digestibility, route, and safety. Medium-chain and long-chain lipids, vegetable oils, and other pharmaceutically acceptable lipids may be considered. Surfactants reduce interfacial tension and stabilize droplets, while cosurfactants may improve interfacial flexibility and emulsification. For pediatric products, the choice and concentration of every excipient should be justified using available age-specific safety information rather than simply adopting concentrations from adult formulations [12,15].

High-energy methods include high-pressure homogenization, microfluidization, and ultrasonication, whereas low-energy approaches include spontaneous emulsification and phase-inversion methods. High-energy techniques can provide reproducible small droplets but may require substantial energy and process control; low-energy approaches can be attractive for certain compositions but are highly dependent on formulation composition and phase behavior [7-9]. For translation, the selected process should be scalable and capable of consistently producing the desired critical quality attributes.

Typical characterization includes droplet size, polydispersity index, zeta potential, pH, viscosity, drug content, morphology, in-vitro release, and physical and chemical stability. For oral lipid-based systems, additional studies of digestion and drug precipitation can be informative because lipid digestion changes the colloidal environment encountered in the intestine [16]. Stability testing should evaluate creaming, flocculation, coalescence, phase separation, drug degradation, and changes in droplet size under intended storage conditions. The final product should also be evaluated for dose uniformity and ease of administration.

4. APPLICATIONS OF NANOEMULSIONS IN PEDIATRIC DRUG DELIVERY

4.1 Oral delivery and bioavailability enhancement

Oral delivery is the most attractive route for many pediatric chronic and outpatient therapies because it is non-invasive and convenient. Nanoemulsions can enhance the apparent solubility and dissolution of lipophilic drugs and may promote absorption by maintaining drug in a dispersed or solubilized state. Lipid digestion can generate colloidal structures that facilitate drug transfer toward the intestinal membrane, while selected lipids may influence lymphatic transport and presystemic metabolism [5,6,16]. These mechanisms are particularly relevant to pediatric drugs with poor aqueous solubility, provided that the formulation is compatible with developmental gastrointestinal physiology.

Pediatric-focused studies illustrate this potential. A self-nanoemulsifying system containing stiripentol, an antiepileptic used in pediatric care, was investigated to improve oral bioavailability and pharmacokinetic performance [17]. More recently, an infant-friendly self-nanoemulsifying formulation of amphotericin B produced nanoscale droplets rapidly after

dispersion in water, demonstrating a possible strategy for reformulating an important drug commonly used off-label in pediatric practice [18].

A vitamin D3-loaded nanoemulsion was also developed specifically with children with autism in mind; the optimized formulation showed improved oral exposure compared with plain vitamin D3 in the reported experimental model [19]. These studies are encouraging but should not be interpreted as evidence of established clinical efficacy in children.

4.2 Anti-infective and tuberculosis applications

Infectious diseases represent an important target for pediatric nanomedicine because treatment may be limited by poor solubility, unpleasant dosage forms, variable exposure, and the need for prolonged therapy. Nanoemulsions can provide a vehicle for lipophilic anti-infective agents and may facilitate formulation into child-friendly liquid systems. A recent study developed bedaquiline nanoemulsions for potential pediatric treatment of multidrug-resistant tuberculosis using quality-by-design principles. The optimized system showed nanoscale droplets, acceptable physicochemical characteristics, and improved formulation properties, although further pharmacological and clinical evaluation remains necessary [20].

The broader pediatric nanomedicine literature also includes lipid-based systems for infectious diseases, but evidence specific to nanoemulsions remains limited [10,11]. Consequently, the major opportunity is not simply to produce smaller particles, but to develop formulations that deliver a reproducible dose, remain stable during storage, have acceptable palatability, and provide predictable exposure across pediatric age groups.

4.3 Topical and transdermal delivery

The skin offers an important route for children who have difficulty swallowing medicines or require local therapy. Nanoemulsions can enhance drug partitioning and penetration because of their small droplets, large interfacial area, and ability to solubilize selected compounds. Reviews of topical and transdermal nanoemulsions describe improved drug release and skin permeation compared with conventional systems [21,22].

Potential pediatric applications include dermatological infections, inflammatory skin disorders, wound management, and selected systemic therapies. However, pediatric skin is developmentally different, particularly in premature infants and young neonates, and greater permeability may increase systemic exposure. Formulations should therefore be designed specifically for the intended age group, with careful attention to surfactant irritation, drug potency, application area, repeated dosing, and accidental ingestion or transfer to caregivers.

4.4 Nasal, pulmonary, ocular, and other routes

Nanoemulsions can also be engineered for nasal, pulmonary, and ocular administration. Nasal systems are of interest because the nasal mucosa offers a non-invasive route that may provide rapid systemic absorption and, for selected compounds, potential nose-to-brain transport. Pulmonary nanoemulsions may be relevant to local treatment of respiratory diseases, whereas ocular formulations can potentially improve retention and drug solubilization. General nanoemulsion reviews support the versatility of these routes [8,9], but pediatric-specific clinical evidence remains sparse. In young children, device compatibility, dose delivery efficiency, airway anatomy, ocular tolerability, and caregiver technique are as important as the formulation itself.

5. SAFETY AND REGULATORY CONSIDERATIONS

Safety is the central issue in pediatric nanoemulsion development. A nanoemulsion contains substantially more interfacial surface area than a conventional emulsion, and the biological response depends on droplet characteristics as well as the identity and concentration of surfactants, cosurfactants, oils, preservatives, and other excipients. Pediatric formulation guidance emphasizes that excipients considered acceptable in adults are not automatically appropriate for children, particularly neonates and infants [12,15].

Excipients require assessment for developmental toxicity, hepatic and renal effects, hypersensitivity, gastrointestinal tolerance, and cumulative exposure when the medicine is administered repeatedly. The risk-benefit assessment should be age-specific and should consider the total daily exposure from all medicines. Evidence continues to highlight gaps in pediatric excipient safety data, reinforcing the need for transparent databases and better age-specific evidence [23].

Nanomedicine pharmacokinetics also require special attention. Changes in absorption, distribution, metabolism, and excretion during development can alter the relationship between formulation characteristics and systemic exposure. Pediatric nanomedicine research therefore benefits from population pharmacokinetic modeling, physiologically based pharmacokinetic approaches, and appropriately designed age-stratified studies [14]. Importantly, improved bioavailability is not inherently beneficial if it increases exposure beyond the intended therapeutic range.

Regulatory translation requires control of critical material attributes and critical process parameters, validated analytical methods, reproducible manufacturing, and stability data. For nanoemulsions, droplet size distribution, drug loading, phase behavior, microbial quality, and changes during storage can all influence product performance. Quality-by-design approaches can help identify formulation and process variables systematically, as demonstrated in recent pediatric-relevant

bedaquiline work [20]. Clinical development should ultimately demonstrate not only formulation quality but also age-appropriate pharmacokinetics, safety, acceptability, and therapeutic benefit.

6. CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Despite strong formulation potential, the pediatric nanoemulsion field remains at an early translational stage. A major limitation is the imbalance between the large number of laboratory nanoemulsion studies and the small number of pediatric clinical investigations. Many published systems are tested in adult animals or in vitro, and the relevance of their excipient concentrations, gastrointestinal behavior, and pharmacokinetics to children is uncertain [10,14].

Future development should prioritize age-stratified formulation design rather than a single product for all children. Infant, preschool, school-age, and adolescent populations may require different concentrations, dosage volumes, excipient exposures, devices, and sensory characteristics. Child-centered formulation development should involve caregivers and patients when appropriate, particularly for taste, administration time, dosing devices, and packaging.

Advanced formulation approaches may combine nanoemulsions with taste masking, solidification, mucoadhesion, or controlled-release strategies. Quality-by-design and design-of-experiments methods can reduce formulation complexity and improve robustness. Computational modeling and artificial intelligence may eventually help predict drug-excipient compatibility and optimize formulations, but these approaches should complement rather than replace experimental and clinical validation. The most important research priority is to connect physicochemical optimization with clinically meaningful outcomes such as dose accuracy, adherence, pharmacokinetic predictability, and safety.

CONCLUSION

Nanoemulsions offer a versatile platform for pediatric drug delivery because they can improve the solubilization and absorption of poorly water-soluble drugs and can be adapted to several routes of administration. Pediatric-focused studies involving vitamin D3, stiripentol, amphotericin B, and bedaquiline illustrate the potential of this approach. Nevertheless, nanoemulsion development for children must extend beyond droplet-size optimization. Age-appropriate excipient selection, palatability, dose flexibility, stability, scalable manufacturing, pharmacokinetic evaluation, and long-term safety are essential for successful translation. At present, nanoemulsions should be regarded as a promising emerging technology requiring stronger pediatric clinical evidence before broad therapeutic adoption.

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