Breakthroughs in Solubility Optimization for Pediatric Drug Formulations

Mays Fadhil Mohammed-Kadhum *, Ghaidaa S. Hameed *, Zainab H. Mahdi**
**Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq*
***Department of pharmaceutics, College of Pharmacy, Applied science private university, Amman, Jordan*

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Corresponding Author email:
mays_fadel@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0009-0007-9538-7728

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Abstract:

Formulating drugs for pediatric patients is more complex than for adults due to the diversity within this group. Solubility of active pharmaceutical ingredients (APIs) presents specific challenges, since children have unique physiological traits—smaller stomach volume and immature digestive systems—that affect absorption, metabolism, and overall drug effectiveness.

Oral formulations must consider drug sensitivity, swallowing difficulties, and compliance. Taste, ease of administration, and patient acceptance strongly influence therapeutic outcomes and safety. Ensuring children take medication as directed is often as important as the formulation itself.
To address these issues, solubility enhancement technologies have advanced

Keywords: Pediatric population, Techniques, Dosage form, Excipients, Solubility.

اختراقات في تحسين الذوبان في تركيبات أدوية الأطفال

ميس فاضل محمد كاظم*، غيداء سليمان حميد*، زينب حسن مهدي**
**قسم الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق*
***قسم الصيدلانيات، كلية الصيدلة، جامعة العلوم التطبيقية الخاصة، عمان، الأردن*

الخلاصة:

على عكس البالغين، فإن صياغة الأدوية للمرضى الأطفال أكثر تعقيدًا من البالغين بسبب التنوع داخل هذه المجموعة. عندما يتعلق الأمر بذوبان المكونات الصيدلانية النشطة (APIs)، فإن تطوير الأدوية للمرضى الأطفال يواجه مجموعة محددة من التحديات. يتمتع الأطفال الصغار بخصائص فسيولوجية محددة، مثل حجم المعدة المنخفض والأنظمة الهضمية التي لم تنضج تمامًا، والتي يمكن أن يكون لها تأثير على طريقة امتصاص الأدوية، وكيفية استقلابها، ومدى فعاليتها بشكل عام. بالإضافة إلى ذلك، عند تطوير التركيبات الفموية، من الضروري مراعاة مجموعة متنوعة من الجوانب، بما في ذلك حساسية الدواء، وصعوبة بلع الأقراص، ودرجات متفاوتة من امتثال المريض. لها تأثير على كل من النتائج العلاجية وسلامة العلاج. هناك عدد من العناصر التي تلعب دورًا مهمًا في تحديد ما إذا كان المرضى الأطفال سيتناولون أدويتهم وفقًا للتوجيهات أم لا. تشمل هذه الاعتبارات طعم الدواء ومدى سهولة تناوله.
ومن أجل حل هذه التحديات، تم تنفيذ التطورات في تقنيات تحسين الذوبان، مما أدى إلى زيادة التوافر البيولوجي وفعالية الأدوية المخصصة للأطفال. وقد أحرز هذا المجال تقدماً هائلاً بفضل استخدام العديد من الاستراتيجيات، بما في ذلك تقليل حجم الجسيمات، واستخدام المستحلبات الصلبة، ودمج المواد الخافضة للتوتر السطحي، واستخدام الأشكال غير المتبلورة. وقد ظهرت تقنية النانو،

على وجه الخصوص، كخيار قابل للتطبيق، لأنها تمكن من توليد جزيئات دوائية بحجم النانو والتي تظهر قابلية ذوبان أكبر ومعدلات ذوبان أسرع. وهذا بدوره يؤدي إلى تحسين الامتصاص لدى مرضى الأطفال. وعلاوة على ذلك، ساهمت المواد المساعدة وطرق التوصيل المطورة حديثًا، مثل الليبوزومات والسيكلوديكسترين، في تعزيز الذوبان، وبالتالي ضمان أن الأدوية ليست آمنة فحسب، بل إنها فعالة أيضًا للاستخدام لدى مرضى الأطفال.

الكلمات المفتاحية: الاطفال، التقنيات، الشكل الدوائي، الاضافات، الذوبانية.

Introduction

Pediatric formulation development poses distinct problems and opportunities in the pharmaceutical sciences. In contrast to adults, Children need individualized pharmaceutical treatments based on their physiological and developmental needs. Children are more sensitive to bitter tastes; hence taste masking is necessary. Research is complicated by regulatory issues and the need for precise dosing based on body weight and age. The lack of pediatric-specific clinical trials and the need for safe and effective formulations for different age groups are major barriers [1]. Pediatric patients range from premature infants to teenagers with differing metabolic rates, organ development, and taste preferences. Oral, rectal, parenteral, transdermal, nasal, and pulmonary administration are available for liquid and solid formulations. The majority of formulations are oral [2]. Due to their existing knowledge, oral solid drug delivery systems are the pharmaceutical industry's preferred formulation for long-term stability, supply chain simplicity, and cheap manufacturing costs. Traditional solid formulations may be inadequate for dysphagia, especially in children, and have limited dosage flexibility [3]. Consumers or providers break, chew, or crush hard API tablets to make them easier to swallow, which may affect drug dissolution and absorption. This increases the risk of inaccurate dosing and APIs' unpleasant taste, which can lead to hospitalization, higher healthcare costs, and death [4]. Oral liquids: solutions, suspensions, syrups, elixirs, and emulsions. These formulations are suitable for children who can not consume oral solids. The dosage volume of a liquid formulation determines its palatability, dose measurement, and stability [5].

Pediatric dosage formulation has changed significantly. Initial administration of adult medications to children caused dose accuracy and safety issues. Pediatric-specific formulations become necessary over time. Initially, plant extracts and unprocessed mixes were used, but tablets and capsules were popular in the 19th century. Despite these advances, pediatric formulations were overlooked, resulting in off-label adult medication use in children [6].

Recent developments in pediatric medication formulation have prioritized the development of dose forms that are suitable for different age groups, easily tolerated, and adaptable. Conventional pills must be divided into four or more halves for smaller children. Newborns and infants cannot receive enough dosage. The correct dosing regimen is difficult to determine. Pharmacy-compounded capsules typically lack bulk and content homogeneity. Orally dissolving tablets, mini-tablets, and multi-particle systems have improved medicine administration and child adherence. Research and collaboration are needed to provide more effective and economical pediatric formulations [7, 8]. The future outlook for pediatric dosage forms appears favorable due to technological developments. Customized drug delivery systems are possible using 3D

printing (such as Fused Deposition Modeling, Stereolithography, and Selective Laser Sintering) and nanotechnology [9].

The Best Pharmaceuticals for Children Act (BPCA) and Paediatric Development Equity Act (PREA) have encouraged pharmaceutical corporations to invest in pediatric medication development. Quality by Design (QbD) frameworks should improve pediatric drug safety and efficacy [10]. Thus, pediatric-friendly dosage formulations that are easy to administer, especially orally, are possible. Child-friendly administration methods and elegant dosage forms are becoming more important in dosage form development [11].

This paper explores the difficulties encountered in developing pediatric dosage forms and strategies for formulating medications with low water solubility. It also delineates the essential factors to be considered in the formulation process for the pediatric demographic.

Oral drug delivery system

While intravenous administration of drugs is frequently the most reliable and precise method of drug delivery, it is not always comfortable, practical, or acceptable for the pediatric population. Consequently, oral drug delivery is commonly utilized and generally favored in practice, especially in outpatient, home, and school environments. More than 60% of widely used small-molecule drugs intended for commercial use are administered orally [12]. The oral route is favored over other routes of administration due to its ability to be self-administered, ease of production, and lower cost. In addition, the oral route is the preferred method for healthcare providers and patients [13]. Solubility is crucial in attaining the desired concentration of drugs in the systemic circulation to elicit the intended pharmacological response. A primary challenge in developing new chemical entities is their limited aqueous solubility [14].

The efficacy of any oral drug formulation in children depends on its capacity to overcome the chemical, physical, mechanical, and biological obstacles presented by the developing gastrointestinal (GI) tract. In typical conditions, nearly all structural components of the mature adult gastrointestinal tract are present in the term newborn; however, significant functional variations exist that are physiologically and clinically relevant to pediatric medication absorption [15].

Palatability has become a crucial component in formulation development to guarantee the acceptability of medications by children (the quality aspect of Paediatric Investigation Plan PIP) [16]. Adults may overcome their inherent dislike of swallowing a bitter pill, however, young children cannot make that informed choice. The bitter taste, in particular, persists longer than other flavors and cannot be easily masked by the addition of other flavors. Consequently, an unpleasant flavor must be encapsulated to make it unnoticeable [17].

When developing oral pediatric drug products, several critical factors must be thoroughly studied, including the dosage form, the issue of fixed versus customized doses, the potential combination of active pharmaceutical ingredients (APIs), the selection of excipients, and the flavor profile [18]. Furthermore, the precise age of the pediatric patients, the particular illnesses requiring treatment, and the distinct cultural and therapeutic contexts must be considered. Dosage forms that enable the administration of various doses and are suitable for children of different ages are beneficial for addressing a wide array of children's demands. The Paediatric Regulation aims to create formulations and preparations that will be made and regulated industrially[19].

Pediatric oral dosage forms must be suitable for the child's age. Liquid oral dose forms, including syrups, solutions, and suspensions, are suitable for newborns (0–28 days), infants (1 month to 2 years), young preschool children (2–5 years), children (6–11 years), and teenagers (12–18 years)[20]. Conversely, powders, granules, pellets, tablets, and capsules administered in their original form are generally considered unsuitable or inappropriate for very young patients.

Standard-sized pills or capsules are unsuitable for children. Breaking down pills is frequently inaccurate and unsuitable for coated tablets, as functional coatings, such as those for taste masking, would be damaged. Minitablets with a diameter of 2 mm are suitable for children aged 6 months and older [21].

The range of pharmaceutical excipients for pediatric medication formulations is restricted. When selecting an excipient, it is essential to evaluate not only its technological features and properties but also safety, treatment duration, and potential side effects such as allergies and sensitization. In pediatric formulations, the concentration of excipients should be minimized to the greatest extent feasible. Delivering contemporary and high-quality pharmaceuticals for children without access to the complete excipient spectrum can pose a barrier [22].

Advantages and disadvantages of oral route of administration

Oral administration is typically favored for pediatric formulations due to various advantages [23]:

1. Convenience: Oral drugs are simple to deliver and entail fewer difficulties than parenteral approaches (e.g., injections).
2. Non-invasive: Oral delivery alleviates the pain and suffering linked to injections or infusions.
3. Adherence: Oral formulations are more readily accepted by children and caregivers, resulting in improved compliance.

Nonetheless, oral administration has its drawbacks:

1. Delayed Onset: Oral formulations typically exhibit a longer time to efficacy relative to intravenous formulation.
2. Variable Absorption: Factors including gastric pH, enzymatic activity, and gastric emptying might influence drug absorption, complicating dose optimization.

Paediatric formulation

Desirable characteristics of oral pediatric formulations

In the development of oral pediatric formulations, it is important to evaluate numerous factors to guarantee that the formulation meets the needs of both the pediatric patient and the carer, while also considering the restrictions of available resources. As seen in Table 1 and Figure 1, these considerations include attributes on the formulation, the end-user (kid and carer), and the resources accessible for production and administration.

Table 1: Desirable characteristics of oral pediatric formulations, adapted from [24, 25]

Formulation	• Obtain sufficient bioavailability • Uniformity of dosage and appropriateness/adaptability to the intended age • Minimal, non-toxic excipients • Consistent (during storage, usage, and across many geographic climates) • Acceptable (ideally with a neutral flavor) • Offer safety, accuracy, and dependable dosage delivery
End-user needs	• Little effect on lifestyle, characterized by minimal dosing and accessibility • Acceptable to end-users (patients, carers, and healthcare professionals) in diverse socio-cultural settings • Supports patient abilities (e.g. swallowing capacity, coordination for administration) • Simple and convenient to administer (ideally ready-to-use, else necessitating minimal handling)
Resource dependencies	• Rapidly provided with an appropriate administration device (if necessary) and clear usage instructions • Continuously available and accessible to patients • Cost-effective (encompassing manufacturing and procurement expenses) • commercially viable

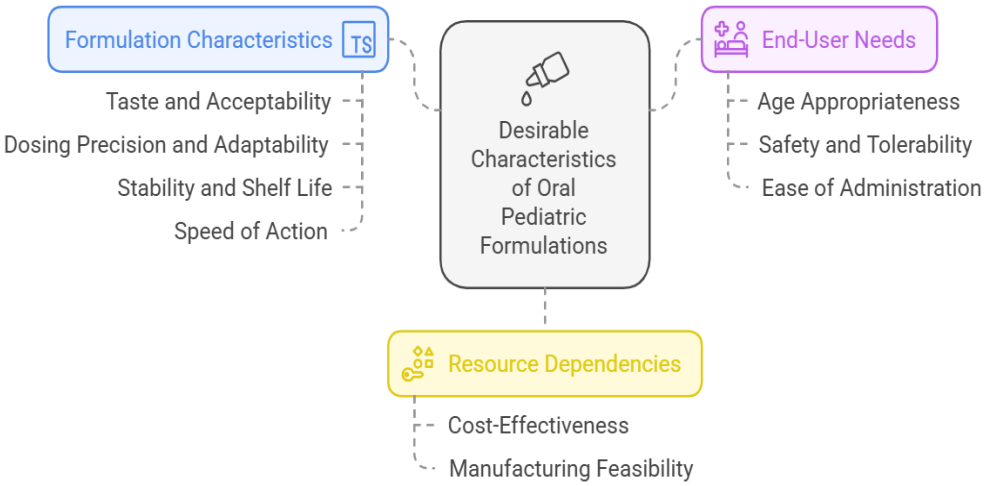

Figure 1: Desirable characteristics of oral pediatric formulations

Pediatric formulations for different age groups

The appropriateness of dosage forms is essential for guaranteeing the suitability of pediatric formulations for different age groups. Pediatric patients necessitate dosage formulations specifically tailored to meet their physiological unique characteristics and developmental stages. Below are many essential issues to propose [26, 27]:

1. **Swallowing:** Young children frequently have challenges in ingesting tablets or capsules. Liquid formulations, chewable tablets, and dispersible tablets are more appropriate for this age group.

2. **The accuracy of dose:** Pediatric patients necessitate exact dose to prevent underdosing or overdosing. Liquid formulations provide precise dosage measurement, which is crucial for guaranteeing the safety and efficacy of the treatment.
3. **Flavor and Acceptability**: Children exhibit increased response to the taste of drugs.

4. **Flavoring agents and sweeteners:** are frequently used in pediatric formulations to enhance palatability and promote adherence.

5. **Excipients' Safety:** The inactive components of pharmaceuticals, referred to as excipients, must be deemed safe for pediatric use. Certain excipients utilized in adult formulations may be inappropriate for pediatric applications owing to potential toxicity or intolerance.

6. **The ease of administration:** is essential for pediatric patients. Administration of dosage forms that are user-friendly, such as syrups or orally disintegrating tablets, can enhance compliance with the specified treatment schedule.

The problem of the lack of appropriate formulations available for pediatric

The absence of suitable formulations for pediatric patients is a considerable concern in healthcare. Numerous drugs utilized in adults are not offered in appropriate dosage forms for pediatric patients, resulting in difficulties in safely and effectively giving the necessary dosages. Here are some points to be considered [28, 29]:

1. **Dosage Forms**: Pediatric patients often require distinct dosage forms compared to adults, including liquids, chewable tablets, or dissolvable formulations. However, several drugs are exclusively offered in adult formulations, requiring off-label use or compounding, which may be less precise and safe.

2. **Excipients:** The inactive components of medicinal products, referred to as excipients, might influence the acceptability and safety of pediatric formulations. Identifying appropriate excipients that are safe for pediatric use presents a problem.

3. **Stability and storage**: Pediatric formulations must exhibit stability under diverse conditions and possess a feasible shelf life. Ensuring the stability of liquid formulations is essential for their efficacy.

4. **Regulatory and Financial Support**: Increased financing and regulatory support are necessary to promote the development of pediatric-specific formulations. Existing rules and funding possibilities frequently fail to satisfy the need for pediatric drugs.

5. **The heterogeneity** in weight and clinical features among the pediatric population has also changed. To address the significant individual diversity, pharmacological formulations must be customized for newborns, babies, children, and adolescents.

Professional and nonprofessional carers frequently must divide adult formulations and combine them with food or beverages to administer an appropriate dose for an individual child [30]. For intravenous formulations with elevated concentrations, successive dilutions may be required. All these adjustments result in supplementary dosing mistakes. Occasionally, pharmacists would construct "extemporaneous" formulations according to a medical prescription for a specific patient [31]. While this likely enhances reproducibility to some extent, fully tested formulations suitable for usage remain far. Furthermore, the procedures and guidelines for extemporaneous formulations vary among pharmacists and countries, hence increasing the potential for further uncertainties or errors [32].

Everyone involved, including society, healthcare providers, the pharmaceutical industry, regulatory agencies, and academics, has increasingly recognized the significance of this issue [33]. The formulation science seeks to align with the regulatory framework for formulations and pediatric pharmacological assessment. European legislation and similar legislative measures require that producers of new pharmaceuticals execute a Paediatric Investigation Plan (PIP) as a component of their marketing application strategy [34]. Consequently, these regulations urge companies to create pediatric formulations for novel substances hitting the market that may be utilized for children. Likewise, regulatory bodies recognized the necessity of updating their rules for excipients and recommended formulations for specific subpopulations due to newly emerging facts, opposing perspectives, or unfeasible requirements [35].

Proposed methods include tablets that may be segmented into smaller portions, "waffles," and minitablets, which are more suitable for children to consume. Alternatives encompass orodispersible tablets that dissolve in the oral cavity upon saliva contact, multi-particulate systems within a single capsule for dose modification, and fast-dissolving films containing active components [36].

Challenges in the development of pediatric dosage form

Pediatric patients are a diverse and highly susceptible population, and drug development is difficult since dosages and formulations must be unified, which adds to the complexity of the problem [37]. Administering pharmacological treatments to children can provide significant challenges due to differences in their capacity to swallow dose forms, age-related compliance, and dosing regimen factors, including dose accuracy, flexibility, frequency, mode of administration, dosage form, compatibility and stability of substances, appropriateness and regulatory aspects of excipients, susceptibility to formulation-related toxicity, acceptability and taste preferences [38]. Furthermore, it is essential to note that how a drug is processed and its effects on the body can vary significantly depending on the age, weight (due to continuous change in body weight), and the childs physiology [39]'. As a result, pediatric medications need to be adjusted in size as the child grows, requiring flexible dosing and different ways of administration. It may not be possible to create a single product that is suitable for all the different groups of people, as seen in Figure 2, including preterm newborn

newborns, term newborn infants (0–8 days), infants and toddlers (1 month–2 years), preschool children (2–5 years), school children (6–11 years), and teenagers (12–16/18 years). Among all patients, this age group demands the highest degree of flexibility in dosing [40].

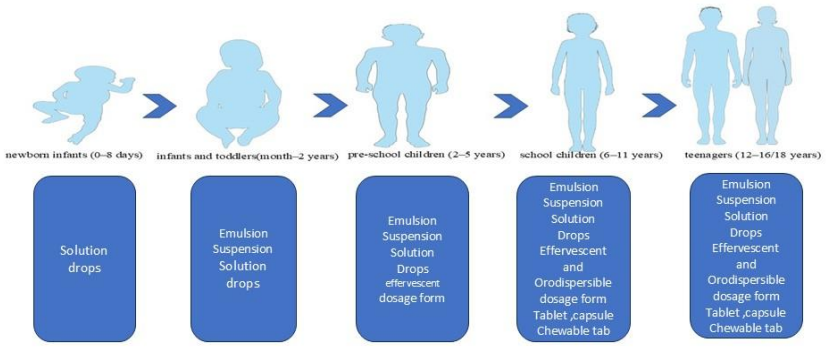

Figure 2: Pediatric population categorized by age group with their suitable oral dosage form

Commonly available pharmacological formulations are not specifically designed for pediatric use. As a result, pharmacists in hospitals or caregivers at home need to modify them to acquire the correct dosage. Specifically, they crush tablets and mix them into food without taking into account the potential impact of alterations in pH, viscosity, fat, and sugar levels on the drug's bioavailability, which is not mentioned in the product's summary of characteristics (SmPC), which is a binding document that offers detailed information regarding a pharmaceutical product [41]. Healthcare workers must comprehend the safe and effective use of drugs. The SmPC encompasses information regarding therapeutic indications, dosage and administration methods, contraindications, warnings, precautions, potential side effects, and drug interactions [42]. The practice of off-label drug usage, which involves using a medication for a purpose other than what it is approved for, needs more oversight and quality control compared to licensed medicinal products. This practice has the potential to adversely impact the outcome of the disease [43].

Although there have been notable improvements in pediatric preparations in recent years, the previously mentioned issues continue to pose important challenges for

pharmaceutical technology. Additionally, they can be enhanced with unique technology to ensure the drug is delivered as intended [44]. Oral administration is commonly used for solid, dispersed, and liquid dosage forms, although the solid form is preferred since it offers more stability and convenience for patients to carry around [45]. Due to their ongoing and incomplete organ development, pediatric patients may necessitate using distinct oral drug delivery systems (DDSs) tailored to their specific dose and administration needs. Alongside the issue, an opportunity is emerging to develop advanced pharmaceutical manufacturing technology to create customized preparations for children [46].

As seen in Figure 3, the considerations related to the development of a pediatric-friendly dosage form encompass formulation, physiological, and regulatory aspects, which are further discussed in the subsequent sections.

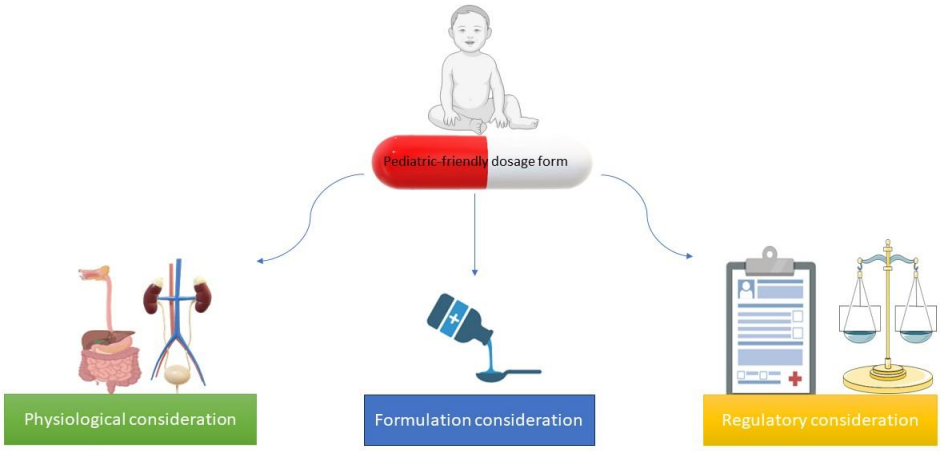

Figure 3: Consideration associated with the preparation of a pediatric-friendly dosage form

Formulation consideration

Several formulation-related issues contribute to pediatric patient non-adherence. Understanding the composition of formulation components is essential for ensuring the production of a safe, palatable, and efficient pediatric formulation. Excipients refer to inert components, including in pharmaceutical formulations, and are intended to be safe for human consumption. These include taste, odor, mouthfeel (viscosity, grittiness), and appearance [47].

Nevertheless, several chemicals considered safe for adults may not be appropriate for children, particularly infants and newborns, due to their physiological characteristics and age-related development of tissue functions. In addition, the insufficiency of child-friendly formulations leads to non-compliance with the recommended drug regimen in children, therefore decreasing the therapeutic efficacy. Dosing devices like spoons and oral syringes can also affect young patients' and caregivers' acceptance

and adherence [48]. Figure 4 illustrates considerations for pediatric formulation.

I. **Active pharmaceutical ingredient API**: The API's physiochemical properties and palatability characteristics might guide the approach to formulating a drug for children. A comprehensive evaluation of the reliability of using the BCS classification as a biopharmaceutic risk assessment method, together with the potential advantages and disadvantages of using a clinical enabling formulation compared to the commercial formulation in the clinic, should be conducted at an early stage of the development program [49].

II. **Excipient:** Paediatric formulations require excipients to preserve their quality and enhance the acceptance among pediatric patients. A classification of the essential excipients established based on their function in the formulation, noting the potential negative impacts on the pediatric population:

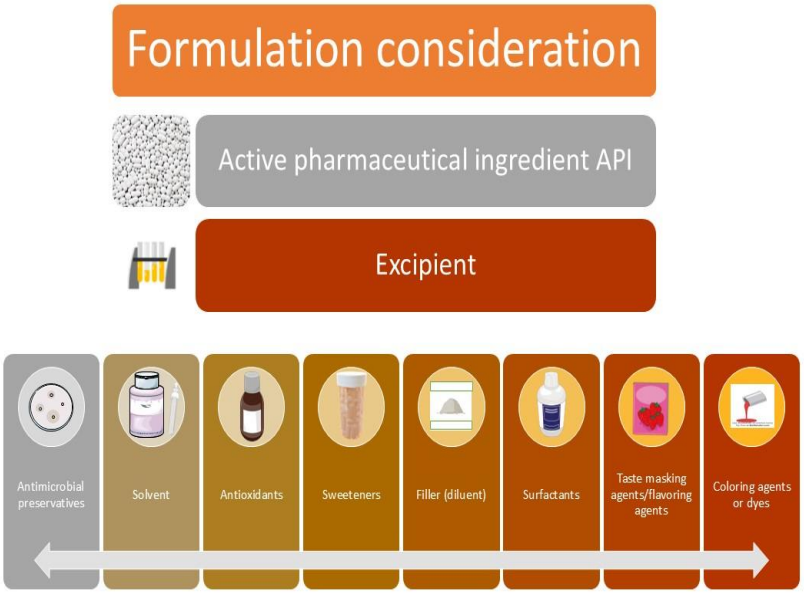

Figure (4): pediatric formulation consideration

A. Antimicrobial preservatives

Preservatives are a category of additives that inhibit the rapid growth of microorganisms. They prevent the breakdown of the active ingredient and any potential modification of the sensory properties of the end product [50]. The American Academy of Paediatrics advises against using preservatives in pharmaceutical preparation for children under three years old since these children have not yet reached suitable physiological and metabolic development levels [51]. The incomplete development of this component may result in the deposition of preservatives in the liver, therefore heightening the likelihood of cardiovascular failure, as well as causing non-specific responses or even allergic reactions. The use of preservatives in children under three years of age is not prohibited but should be limited to urgent circumstances [52].

Major preservatives of concern are benzoates, parabens, and benzalkonium chloride. Benzyl alcohol is a bacteriostatic preservative utilized in oral formulations. The mortality of neonates has been characterized by the administration of an oral solution containing benzyl alcohol. Benzyl alcohol syndrome is a documented condition in neonates, contraindicated for preterm infants and newborns [53].

A previous study conducted by Attebäck Met. al. developed oral liquids containing naloxone and propranolol for pediatric use. Sodium benzoate was selected as the microbiological preservative; oral solutions containing sodium benzoate demonstrated adequate preservation capabilities during storage for a duration of up to 28 days [54].

B. Solvent

Despite water being the most often utilized solvent in a liquid formulation, the majority of active pharmaceutical ingredients (APIs) exhibit inadequate aqueous solubility, hence constraining the attainable concentration-informed solutions. In numerous instances, a viable solution includes the application of solubility enhancement techniques, including surfactants and co-solvents such as glycerol, polyethylene glycol (PEG), and ethanol [55]. Nonetheless, the application of these technologies necessitates safety considerations due to their substantial impact on pediatric health. Exposure to solvents and solubility-enhancing compounds commonly results in irritation, intestinal tissue damage, hyperosmolality, and toxicity at the local administration site. The dangers are significant when these drugs are incorporated into parenteral formulations instead of oral formulations [56]. Acetone and ethanol were the solvents employed in a prior study conducted by Abdelhakim HE, who utilized coaxial electrospinning as a taste-masking technology for pediatric drug delivery [57].

C. Antioxidants

In pediatric formulations, antioxidants are frequently included to augment the stability and shelf life of the substance by inhibiting the oxidation of active components in formulations [58]. Nevertheless, the safety and effectiveness of these treatments in children need careful evaluation, considering pediatric patients' distinct physiological features. The criticality of the safety profile of antioxidants included in pediatric formulations cannot be underlined. Specific antioxidants deemed safe for adults may not be appropriate for children because of metabolism and organ function variations [59]. For example, exceedingly high levels of some antioxidants can result in toxicity in children. Regulatory organizations such as the Food and Drug Administration, FDA, and European Medicines Agency EMA have precise recommendations for using excipients, including antioxidants, in formulations intended for children [60].

D. Sweeteners

While considering some of their effects, sweeteners such as sucrose, fructose, sorbitol, xylitol, and aspartame should be used with caution. Avoid formulations containing a high concentration of sucrose since it reduces the pH of dental plaque, leading to the dissolution of tooth enamel and the promotion of dental caries [61]. Likewise, excessive consumption of fructose might result in laxative effects in children. Both sorbitol and xylitol can induce osmotic diarrhea,

whereas xylitol provides protective effects against tooth caries [62]. Pediatric patients with lactose intolerance may exhibit heightened sensitivity to lactose. Given the different levels of lactose sensitivity, even a small quantity (less than 3g) can cause the symptoms indicated in those who are lactose intolerant [26].

In earlier work, 5% sucralose was utilized in the formulation of carbamazepine orodispersible 3D-printed mini-tablets for pediatric application. This sweetener inhibited bitterness signals throughout testing and demonstrated an effective taste-masking strategy for formulating child-appropriate CBZ ODMTs [63].

E. Filler (diluent)

Alternatively referred to as bulking agents or diluents, fillers are employed in pediatric formulations to help increase the volume and optimize the precise dosage of active pharmaceutical ingredients (APIs) [64]. Nevertheless, the safety and effectiveness of these treatments in pediatric patients need detailed evaluation, considering children's distinct physiology. Specifically, lactose, a frequently used filler, can lead to gastrointestinal problems in children who are unable to tolerate lactose. Moreover, specific fillers can interact with other excipients or active pharmaceutical ingredients (APIs), which may result in negative consequences [65].

Suksawat T et al. employed D-mannitol as a filler to enhance the compressibility of powders while investigating the formulation of orodispersible dosage forms containing Rhinacanthin, which is extensively utilized in traditional medicine and demonstrates antifungal, anticancer, antiviral, antibacterial, and antiplatelet aggregation properties, devoted to Pediatric Patients [66].

F. Surfactants

In pediatric formulations, Surfactants represent a primary component of liquid and semisolid medicinal formulations. Surfactants are commonly employed as solubilizers, improving the solubility and stability of drugs with low water solubility and guaranteeing the efficacy and ease of administration of the medicine. Nevertheless, considering children's distinctive physiological features, their application in pediatric patients necessitates careful consideration [67]. Furthermore, surfactants can facilitate the development of liquid pharmaceuticals, which children more readily ingest than pills or capsules. Many surfactants considered harmless for adults may provide hazards to children. For instance, polysorbate Hypersensitivity responses and other harmful effects in children have been linked to commonly used surfactants such as polysorbate 20 and polysorbate 80. Propylene glycol, Applied as a solubilizer, has the potential to induce hyperosmolality and lactic acidosis in newborns [68].

Betamethasone 0.05% oral solution is authorized for use in newborns and children for different immunological and inflammatory conditions. Organor is the pharmaceutical company that commercializes the originator medicine Celestene®, whereas Arrow, Biogaran, EG, and Zentiva distribute generic versions. The maintenance therapy involves administering propylene glycol at a dosage of 19 mg.kg−1 (Celestene®) to 21 mg.kg−1 daily, which does not adhere to the acceptable daily intake (ADI) for newborns but is appropriate for infants older than 1 month [69].

G. Taste masking agents/flavoring agents.

Considerable importance is placed on the acceptable taste of a medicinal dosage form when developing a formulation for administration to a child. Children may object to the bitterness or metallic tastes of unmasked formulations. A disagreeable taste sensation poses the potential for patient non-compliance or even termination of treatment. A thorough description and confirmation of flavorant selection are necessary due to the potentially harmful effects that certain flavors may have on pediatric populations [70].

It is essential to acknowledge the safety issues, which encompass the potential for allergies and sensitization. Artificial sweeteners are widely used to conceal taste since they are cheaply available, well-known, and do not affect API release. Sweeteners cannot hide bitterness; thus, they must be used in large amounts or combinations. Chemical interactions like complexation (cyclodextrins) can enhance flavor. Coating the API for physical shielding is the most effective way, but it may affect bioavailability, is expensive, and requires specific methods and equipment, making it more technologically challenging. Among various flavors, peppermint oil is noted for its acute toxicity in children [71].

In prior research, Pereira M et al. introduced novel sugar-free oral vehicle hydrogels aimed at enhancing the safety and enjoyment of oral solid dosage forms for pediatric patients. The majority of volunteers selected strawberry (27.4%) as their preferred flavor, followed by vanilla (22.3%) and caramel (12.7%). The least favored were grape (11.5%), banana (10.8%), mint (10.2%), and orange (5.1%) [72].

H. Coloring agents or dye

Coloring compounds play distinct functions in the pharmaceutical, cosmetics, and food sectors. Consumer attraction, product identification, and protection of light-sensitive items are among the roles of coloring agents. Colorants commonly employed in pharmaceutical oral formulations are categorized as azo dyes (such as tartrazine), triphenylmethane dyes, xanthene dyes (such as erythrosine), and quinoline dyes (such as quinoline yellow). The number of coloring agents that are universally recognized as appropriate from a regulatory standpoint is restricted due to the association of several compounds with hypersensitivity and other adverse reactions among the pediatric population [73].

FD&C Green No. 3 (Fast Green FCF) was utilized as a coloring agent in the formulation of Pullulan-based Orally Disintegrating Films containing Amlodipine Besylate, as conducted by Pezik E et al. [74].

Physiological consideration

The route of oral administration is widely utilized in pediatrics. Several physiological parameters are seen in Figure 5, including gastric pH and emptying time, intestinal transit time, and intestinal volume, which influence oral administration absorption. These factors can vary depending on sex, race, food effects, and illnesses [75]. Children and adults have different physiological features. Physiological differences affect absorption, transport, metabolism, and excretion, which regulate

drug availability in the bloodstream at its action site.

Oral medication absorption requires saliva. Saliva's fluid environment helps drugs release, degrade, and absorb. Saliva composition and flow alter during life. The average electrolyte content increases while saliva flow decreases after 5–6 years. Children had significantly lower buccal mucosal salivary secretion (0.22–0.82 mL/min) than adults (0.33–1.42). Saliva hydration and ingesting unpleasant drugs are linked. The "saliva washout effect" occurs when high-flow salivary patients swallow drugs rapidly. This activity may cause unequal saliva distribution and impaired mucosal tissue absorption, resulting in a wide range of systemic bioavailability [76].

GIT pH varies by tissue location and patient age. It affects drug solubility and diffusion, favoring the unionized form. Illness, medicine, food, and saliva also affect oral mucosa pH. Increased saliva production usually raises pH. Intestinal cytochrome p450 activity increases with age, and newborns have an intra-gastric pH of over 4. The average pH of the oral mucosa is 6.78 ± 0.04 and 6.64 ± 0.44 in healthy adults and pediatric patients [77].

The oral absorption of drugs in children might be affected by factors such as gastric pH. The gastric pH of newborns is initially higher (pH 6–7) than that of adults during the first 30 days of life. However, it gradually decreases during the next 20–30 months to pH 1–2 as the secretion of gastric acid increases [78]. Adsorption of weak acid medications (such as amoxicillin, cephalexin, and furosemide) will be reduced, while it will be enhanced for weak base medications (such as morphine and metoprolol). This influences the degree of absorption [79]. Additionally, the gastric emptying time in children is extended, potentially leading to delayed drug absorption and, therefore, impacting the absorption rate. The rate and degree of absorption are influenced by developmental changes accompanying the aging process in children. Pharmacological variations in children persist as medications progress through the gastrointestinal tract [80]. Children exhibit diminished expression of enterocytic CYP3A4, pancreatic enzymes, and intestinal drug transporters in the duodenum. Bioavailability is influenced by several aspects, which are contingent upon the specific properties of the therapeutic agent [81].

In the first two weeks of life, newborns without stomach acid have achlorhydria. This can significantly affect drug release and absorption. Additionally, these neonates have slow, irregular, and unexpected stomach emptying [82]. Due to stomach contents exposure, prolonged gastric emptying can degrade medicine. Pancreatic enzyme activity decreases early in development and increases later. This affects the bioavailability of enzyme-sensitive drugs [83]. Due to decreased bile acid and lipase secretion, neonates may have lower lipid-soluble drug absorption. Fetuses have 94% body water, full-term infants 78%, and adults 60%. The distribution volume of hydrophilic drugs is bigger, and lipophilic drugs are smaller due to this discrepancy. Infants have lower plasma albumin levels and altered protein binding characteristics, increasing

competition for endogenous molecule binding [84].

Essential characteristics include blood flow through tissues, drug passage through tissues, and drug binding to tissues that affect medication distribution. These parameters alter in children [85]. Drug metabolism decreases due to liver size and blood circulation issues. The liver's main drug metabolism enzyme is cytochrome P-450. Pediatric drug metabolism is slower than in older children and adults because of underdevelopment in the newborn metabolic pathway. Drug elimination through the kidneys depends on glomerular filtration, tubular secretion, and tubular reabsorption. These systems are not fully established in the first year of life, yet they impact renal drug clearance efficiency. In addition to differing from adults, many physiological markers vary over the pediatric age range [86].

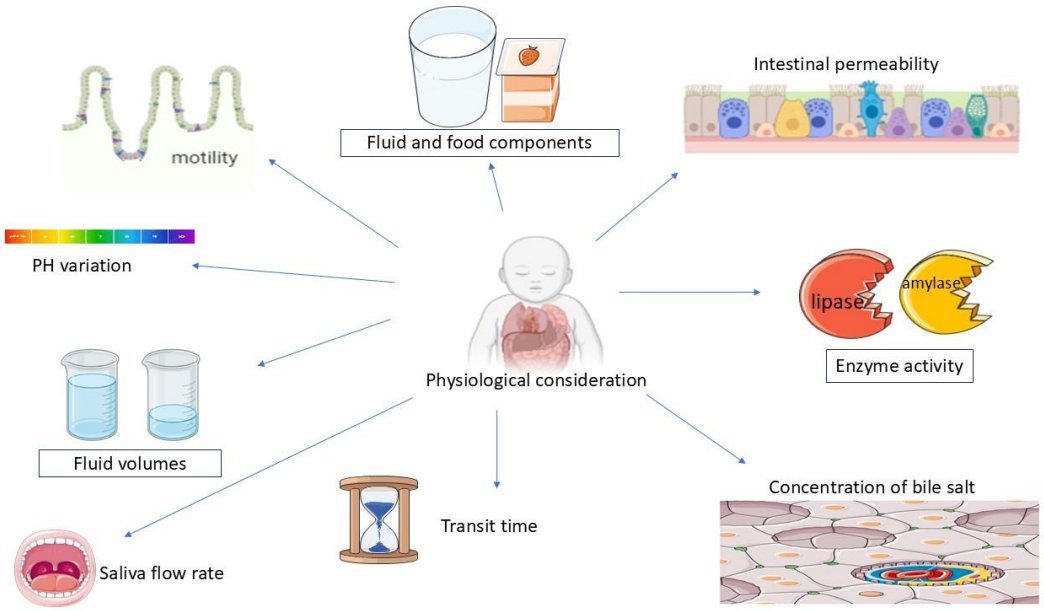

Figure 5: Physiological consideration in pediatric formulation

To enhance palatability and promote compliance, (soft) foods and beverages are often utilized to facilitate medicine administration to the pediatric population. Significant variations were noted in the variety of food and beverages, particularly across different types of vehicles and even among vehicles of the same subtype. Expected variations are likely to impact the characteristics of the drug, including its solubility and dissolution, particularly in the instance of a drug with low solubility [87].

Regulatory consideration

This focuses on investigating the variations in regulatory expectations, requirements for developing pediatric formulations, and important patient-centric aspects to consider while creating new pediatric formulations. The patient-centric drug product design process refers to identifying the complete requirements of individuals or the target patient population and using these requirements to develop pharmaceutical drug products that offer the optimal overall benefit

within the intended treatment period for that specific patient population [88].

Regulatory authorities promote the early preparation of a pediatric formulation plan to accelerate the development of pediatric programs. The timely development of pediatric formulations is further complicated by perceived regulatory obstacles to establishing unique dosage forms and regulatory concerns associated with the incorporation of new excipients. Public access to a comprehensive database of approved excipients might accelerate the creation of formulations containing non-novel excipients [89].

Regional variations exist in the regulatory prerequisites for the execution and finalization of acceptability evaluations and if the evaluation should be performed before using a specific formulation in pediatric clinical trials. Ethical considerations may arise when conducting an acceptability assessment as independent research instead of integrating it into a pediatric clinical trial [90].

Usually, the first studies of a pediatric formulation are carried out in adults to establish that it has sufficient bioavailability. Clinical trials are carried out in children after confirming the formulation's safety and effectiveness in adults [91]. Due to the significant variation among age groups of pediatric patients and their susceptibility, careful and sufficient planning is necessary while conducting pediatric clinical trials [92]. Failure to initiate a sufficient clinical examination can lead to many medical problems and negative consequences in pediatric patients. Moreover, creating an appropriate therapy outcome measuring instrument for pediatric patients of various ages is necessary while constructing the clinical trial proposal. The study methodologies and environment should integrate ethical and regulatory norms alongside the child's cognitive, physical, and emotional growth. Undertaking clinical trials in pediatric patients can sometimes provide challenges because of the limited number of children sharing the same medical condition [93].

Types of pediatric oral dosage forms

Various oral medications are designed for children that can be taken by mouth. These include solid forms like tablets, capsules, orodispersible formulations, powder for reconstitution, and chewable tablets. There are also liquid forms, such as solutions, suspensions, elixirs, and syrups. The pharmaceutical industry continues to choose solid dosage forms as the preferred method of formulation due to their benefits of extended stability, manufacturing adaptability (including the capacity for film coating and controlling the release of active medicinal ingredients), and overall cost-effectiveness [94, 95].

The rationale for solid formulations

Their application may be restricted in pediatric patients, owing to the incapacity of very young children to ingest solid dosage forms whole, in addition to the absence of evidence elucidating how geometric characteristics such as size and shape must be considered to make their design suitable for children. Usual dosage forms for adults are not universally suitable for children of varying ages, necessitating pharmaceutical compounding and pharmacological modifications [96]. It is widely recognized that patients, carers, and healthcare professionals frequently need to modify existing dosage forms for the convenience of administration, to achieve the correct pediatric dosage or both. The risks associated with the physical alteration of dosage forms, in terms of both safety and efficacy, are well acknowledged; thus, this practice should be

replaced by the development and approval of carefully created pediatric formulations [97]. Recent solid formulations encompass multiparticulate, oro-dispersible, and chewable variants. These eliminate the necessity of ingesting as big units whole and may offer a customizable and personalized method of drug delivery, particularly applicable in pediatrics. The key advantages of liquid medications are their ease of swallowing and dose flexibility, which have historically resulted in their preference over solid formulations for children. Liquid formulations, in contrast to solid dosage forms, are famously more complex and costly to develop and typically possess a more restricted shelf-life [98].

Solid dosage forms provide additional significant benefits associated with the favorable characteristics outlined in Table 1. From a production standpoint, these are related to stability, utilization of excipients, palatability, and functionality. Numerous drugs exhibit inadequate stability in aqueous solutions, necessitating the inclusion of excipients such as preservatives, stabilizers, suspending agents, and solubility enhancers. This requirement is further complicated by the limited evidence regarding their safety and toxicity in children of varying ages [99]. The creation of acceptable formulations presents a significant problem, as numerous drugs possess an undesirable taste, which is a crucial formulation characteristic influencing total patient approval [100].

Monolithic dosage forms provide enhanced taste-masking techniques, including encapsulation and polymer coatings; However, the creation of chewable and oro-dispersible formulations may face similar taste-masking difficulties as liquids. A significant advantage of solid dosage forms is the potential for developing functionalized formulations (such as modified, prolonged, and delayed-release systems), which presents greater technical challenges with liquids. This not only enables focused drug delivery but also serves patients by decreasing dosage frequency and minimizing lifestyle difficulties (e.g., the necessity to take drugs at nursery or school) [101].

An additional significant benefit for patients and carers is the provision of simple, safe, and convenient dose administration through solid formulations. Measuring small quantities can be challenging and inaccurate for both age limits of the population while administering greater doses to older children would be unsuitable [102]. There exists restricted control to guarantee total dosage consumption, especially for very young children who might expel the drug. Liquid formulation necessitates the use of means of administration (e.g., spoons, cups, or oral syringes) which have previously been associated with pharmaceutical administration problems [103]. The precision of dosage may be affected by the utilization of unsuitable measuring instruments (e.g., teaspoons) and insufficient knowledge about health among carers. In contrast, solid formulations provide precise and complete dose delivery, enabled by individual, uniform dosage units or packaging (e.g., sachets or capsules for multiple particulates), which are simple to give [104].

The formulation of suitable products is a global health problem, necessitating consideration of the specific needs in resource-constrained environments [105]. The World Health Organisation (WHO) has advised promoting the creation of formulations appropriate for developing countries, including flexible solid dosage forms that can be delivered in several ways (e.g., dispersed or ingested whole) [106].

An example is orodispersible tablets or those that can be utilized to formulate oral liquids appropriate for younger children, such as dispersible and soluble tablets. An essential basis for this reasoning is cost; oral liquid medications are typically more costly than

solid formulations, whereas the production of oro-dispersible tablets is achievable in environments equipped with standard tableting facilities [107]. However, careful packaging for reducing moisture absorption, and the requirement for particular excipients may impose some cost restrictions [108].

Recent innovations in pediatric dosage forms

Recent innovations in pediatric dosage forms have offered various new formulations aimed at enhancing drug delivery and patient compliance in children. Presented here are some examples:

1. Orodispersible Tablets (ODTs): These are fast-dissolving tablets that dissolve orally without the necessity of water, rendering them suitable for young children who may have trouble swallowing conventional tablets. An orodispersible tablet containing cannabidiol, a phytocannabinoid derived from Cannabis sativa, was developed by Vlad R. A. et. al for the treatment of Lennox-Gastaut and Dravet syndromes [109].
2. Oral Soluble Films are thin, flexible films that dissolve on the tongue or within the oral cavity, offering a practical and palatable delivery system for pediatric drugs. Wang, B. et al. produced Oro dispersible films containing 30 mg of racecadotril for pediatric use, aimed at enhancing compliance among pediatric patients and avoiding the danger of choking [110].
3. 3D Printing Technology: This technology facilitates the customization of dosage forms, permitting accurate dosing and the integration of numerous pharmaceuticals inside a single dose. It also enables the creation of age-appropriate formulas. A prior study conducted by et al. developed a 3D-printed spikelets formulation (Spinklets are small, solid oral dose forms intended as an alternative to conventional tablets or capsules, particularly for pediatric patients who may have difficulties in swallowing pills) of celecoxib, a nonsteroidal anti-inflammatory drug, utilizing hot melt extrusion to overcome the constraints of conventional production techniques [111].
4. Medicated Dosing Straws: These straws provide medication concurrently with the child's beverage, providing precise dosing and enhancing patient adherence. Previous investigations conducted by Purandare; S. et al. focused on the fabrication of pellets using extrusion-spheronization for the delivery of Famotidine via specialized straws for pediatric use [112].
5. Buccal drug Delivery: This technique entails positioning the drug between the gum and cheek, facilitating direct absorption into the bloodstream. It serves as an acceptable choice for children unable to ingest oral drugs. Buccal foams incorporating omeprazole have been created by et al as promising drug delivery systems [113].

Techniques to enhance solubility in pediatric formulation

The selection of the ideal drug delivery technology for pediatrics necessitates an efficient, systematic approach that considers the drug's physical and chemical properties alongside the specific requirements of the target patient demographic [114]. Table 2 and Figure 6 elucidate techniques for improving solubility in pediatric formulations.

Table 2: Techniques to enhance solubility in the pediatric formulation

Techniques	Brief Description	Examples from the previous study	Excipient used in the study
Salt formation	Is a simple and effective way to increase the water solubility of acidic or basic active pharmaceutical ingredients (APIs) and develop dosage forms for different age groups, such as oral and parenteral liquids. It also controls drug solubility for various purposes [115].	Methotrexate.	Polyethylene glycol, glycerol, sucrose, orange flavors, ethyl parahydroxybenzoate, methyl parahydroxybenzoate sodium salt [116].
Prodrug	Prodrugs are morphologically inert or less potent parent drugs that biotransform in the body to release the active pharmacological molecule. This approach could improve pharmaceutical solubility, stability, and pharmacokinetics[117].	Valganciclovir liquid formulation [118].	_____
Cosolvents	Cosolvents reduce the polarity of many solvents to match nonpolar solutes, improving the solubility of nonpolar medicinal molecules. Methanol, ethanol, glycerol, propylene glycol, dimethylacetamide, and polyethylene glycol 300 are common cosolvents. Cosolvent approaches improve medication solubility and dissolving rates, but they are dangerous, especially at high doses. Dilution can also produce medication precipitation due to the exponential link between cosolvent ratio and solute solubility [119, 120].	Praziquantel oral solution	Polyethylene glycol 400 (PEG 400), propylene glycol (PPG), N-methyl-2-pyrrolidone (NMP), sodium dihydrogen phosphate, sodium hydrogen phosphate, methylparaben sodium salt, mint flavor, strawberry flavor, and sucralose [121].
surfactants	Pharmaceuticals can be made more soluble by adding surfactants. Due to their amphiphilic nature, surfactants are employed to break down water-insoluble drugs into micelles, thereby increasing their surface area[122].	Tadalafil nanoemulsion mists	Cremophor, Poloxamer-407,tween-80, and propylene glycol [123].
Lipid-based drug delivery system	Due to their biocompatibility, biodegradability, and nontoxicity, they are suitable for pediatric formulations. Nanoparticles' small particle sizes and large surface areas make them economically attractive because they boost low-water-soluble drug solubility and dissolution. Drug pharmacokinetics can be altered to improve efficacy and safety. [124].	Propranolol Hydrochloride liposomes	Dextrose 5%, and NaCl 0.9%

Nanosuspension formulation	A nanosuspension (NS) is a colloidal particle having solid drug particles under 1 µm. Recent nanopharmaceutical attention has focused on these formulations. Wet milling, dry milling, high-pressure homogenization, and co-grinding can produce nanosuspension (NSs), as can anti-solvent precipitation, liquid emulsion, and sono-precipitation [125, 126].	Mefenamic Acid	Hydroxypropyl methylcellulose K4M, sodium dodecyl sulfate, Tween 80, acetone [127].
Cyclodextrin complexation	Cyclodextrins (CDs) are defined by their hydrophilic outer surface and hydrophobic interior cavity. They are recognized for their capacity to create inclusion complexes with many lipophilic drugs, which enhances their solubility and chemical or physical stability [128].	propranolol hydrochloride	Sucrose, anhydrous citric acid, sodium citrate dihydrate, raspberry flavor, monohydrate citric acid [129].
Solid dispersion	Spray drying, solvent evaporation, and hot melt extrusion can make solid dispersions. Under certain conditions, grinding the inert polymer with the API produces this dispersion. Reduced particle size, amorphous API, porosity, and wettability are achieved [130].	Indomethacin	Microcrystalline cellulose (MCC), lactose monohydrate, magnesium stearate, food colorants, and ethanol [131].

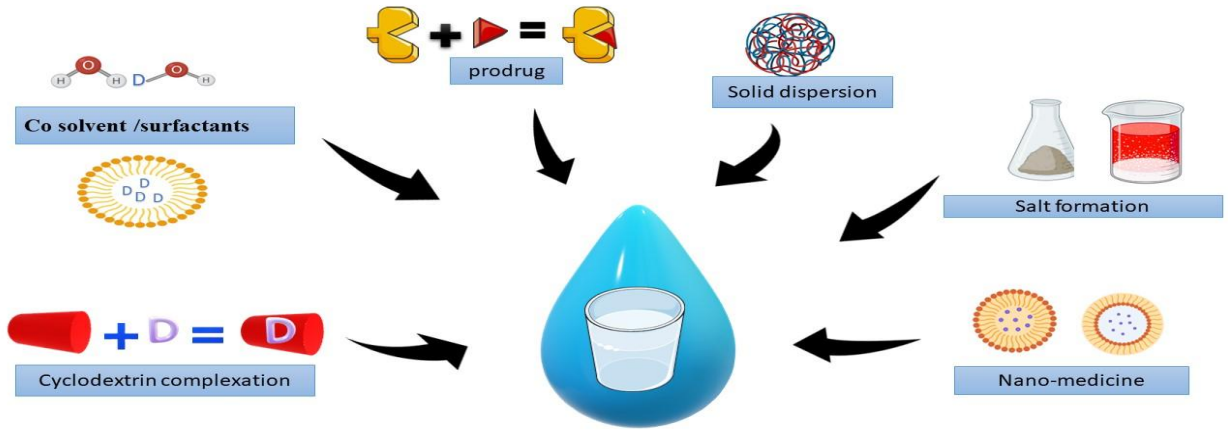

Figure 6: Strategies to enhance solubility in pediatric formulation

Preclinical and Clinical Trials Products for Pediatric Use

Table 3 illustrates some examples of pediatric products that have undergone preclinical and clinical trials:

Table 3: Examples of preclinical and clinical pediatric products

Product	Indication	Notes
Pfizer-BioNTech	COVID-19 Vaccine	Animal studies were performed to evaluate the safety, immunological response, and possible adverse effects of the vaccination. Complete trials involving children aged 5 to 11 were performed to evaluate the vaccine's safety and efficacy [132].
Kymriah (tisagenlecleucel)	Paediatric Leukaemia	a Phase II clinical trial demonstrated the efficacy of Kymriah in treating relapsed/refractory B-cell acute lymphoblastic leukemia in pediatric patients [133].
Acetaminophen (Tylenol)	Analgesic	a multitude of studies validate its safe application in pediatric pain management, with dosage adjustments contingent upon age and weight [134].
Flovent (fluticasone propionate)	Asthma	Investigations were performed on pediatric patients with asthma to assess the safety and effectiveness of Flovent in managing asthma symptoms [135].
Strattera (atomoxetine)	Attention deficit hyperactivity disorder (ADHD)	animal studies with Comprehensive Phase III trials established Strattera's effectiveness in managing ADHD in children and adolescents [136].
Zolgensma	Spinal Muscular Atrophy (SMA) [137]	Clinical trials demonstrated that Zolgensma was highly efficacious in treating SMA in newborns and children, resulting in FDA approval [138].
Norditropin (somatropin)	Growth Hormone Deficiency	Investigations in animals to assess the pharmacodynamics and safety profile of recombinant human growth hormone [139].

Conclusion

The advancement of pediatric formulations continues to be a crucial field of pharmaceutical research and development; yet, there is a notable deficiency in evidence-based understanding of their appropriateness and acceptability within the population. Despite substantial advancements, several obstacles remain, such as the requirement for dosage forms suitable for different age groups, enhanced taste quality, and safer administration methods. The EMA pediatric guideline mandates that the acceptability of pediatric medicinal products by end-users be evaluated as a fundamental component of pharmaceutical development research. Evaluating both the children's capacity and desire to accept these formulations, while also taking into account the requirements and preferences of carers, is essential. More recent developments, such as the transition to oral solid formulations and novel drug delivery technologies, have shown potential in solving some of these problems. By using these strategies, we can ensure that each child has universal access to safe, effective, and appropriately formulated drugs according to their physiological and developmental requirements.

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