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EXPLORING PEDIATRIC ACCEPTANCE OF MINI-TABLETS: A COMPREHENSIVE REVIEW OF KEY STUDIES AND FUTURE PERSPECTIVES

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Abstract:
This comprehensive review synthesizes key insights from a series of studies that examining acceptance and swallowability of mini tablets in pediatric populations. The summarized research systematically explores the acceptability, safety and swallowability of mini-tablets across diverse pediatric age groups. Noteworthy findings include high acceptability and swallowability of filmcoated mini tablets, positive outcomes in various pediatric populations, and the well-tolerated nature of mini tablets in children aged 6–23 months. Despite acknowledging limitations such as recruitment challenges, potential biases, and ethical constraints, the review emphasizes the significance of optimizing formulations and exploring alternatives for mini-tablets in pediatric pharmacotherapy. Future research recommendations include prioritizing multi-center studies, addressing potential biases, and delving into real-world scenarios to enhance the acceptance and utilization of mini tablets in pediatric medication administration.

Keywords: Pediatric medication, mini-tablets, acceptance, swallowability, film-coated, formulation optimization, real-world scenarios, pharmacotherapy, pediatric populations.

Introduction:

In the ever-evolving landscape of pharmaceutical formulations, mini-tablets have emerged as a groundbreaking solution, representing a paradigm shift in drug delivery [1]. These novel multiple unit solid dosage forms, characterized by a size equal to or smaller than 4.0 mm in diameter, embody a compact and precise approach to medication administration [2]. Their diminutive size, depicted in Figure 1, sets them apart from conventional tablets and opens avenues for addressing longstanding pharmaceutical challenges [1].

Fig. 1: Size of a typical mini tablet (left) compared with conventional tablets.

Over the last twenty years, considerable efforts have been dedicated to developing formulations suitable for children, aiming to achieve optimal dosing of medications while prioritizing safety in the pediatric population [3–6]. Children often face difficulties ingesting standard sized solid dosage formulations and may find many oral medications unpleasant to taste [3, 4]. Additionally, the pharmacokinetic profile of drugs may be influenced by body weight and age, emphasizing the need for flexible dosing in pediatric demographic [3].

Although syrups are commonly utilized in pediatric medicine, they come with several limitations, including drug instability, subpar taste, unpredictable release of active ingredients, inconsistent dosing, and a lack of understanding regarding safe additives suitable for pediatric patients [7,8]. Acknowledging these obstacles, the European Medicines Agency (EMA) and the World Health Organization (WHO) have suggested transitioning towards compact solid dosage forms, like mini-tablets. This approach could present benefits such as reduced expenses, simplicity in administration, and applicability across various dosage ranges. [6,9,10].

The concept of mini-tablets extends beyond their physical dimensions; it encapsulates a transformative potential for advancing drug delivery precision, particularly in contexts where conventional formulations face limitations. Mini tablets, with their small and manageable size, emerge as a promising solution to bridge this gap [11-13]. Offering the stability and uniformity associated with traditional tablets, mini tablets are tailored to cater to the specific need of pediatric patients [14]. They not only enhance swallowability but also introduce dose flexibility, enable fixed-dose combinations, and outperform liquids and particulates in terms of accuracy, stability, and safety [15]. This introduction of mini tablets as a versatile solid oral dosage form aligns with the contemporary trend of tailoring formulations to meet the unique requirements of diverse patient populations, notably pediatric and geriatric groups with varying characteristics [12][14]. Recent clinical studies have showcased the acceptance of mini-tablets among children, marking a significant stride in pharmaceutical innovation [16]. However, challenges persist, particularly in addressing potential aversions [16]. While the potential applications of mini-tablets span a range of drug types, there is a crucial need for further research to navigate limitations in high drug loading [17, 18]. The ultimate goal is to develop patient friendly mini tablet formulations and dosing devices which finds practical use, especially in targeted medical contexts [17, 18].

As we embark on a comprehensive exploration of acceptance studies focused on pediatric mini tablets, this review aims to dissect the wealth of information available, critically assess the contributions of key studies, acknowledge existing challenges, and chart a course for future research. In doing so, we navigate through the intricate landscape of mini-tablets, recognizing their transformative potential in shaping the future of pharmaceutical formulations.

Methodology:

This review systematically assessed acceptance studies on pediatric mini-tablets, employing rigorous inclusion criteria. Studies within a specified timeframe, focusing on pediatric populations, were considered, encompassing diverse designs and assessment parameters. The search strategy involved reputable databases and relevant keywords. Data extraction covered study characteristics, mini-tablet details, and key findings. Quality assessment ensured robustness. Synthesizing methodologies and outcomes revealed a nuanced landscape of pediatric mini-tablet acceptance, paving the way for a comprehensive understanding.

Pediatric Accepatance of the Mini tablets: Research Insights and Advances (2013–2023)

Klingmann's Study (2013–2022): Advancements in Pediatric Medication Acceptability

Klingmann's research, spanning from 2013 to 2022, has significantly contributed to understanding and improving the acceptability of pediatric medications. In 2013, a prospective, open, randomized crossover study conducted to evaluating the acceptability of 2 mm uncoated mini tablets as another drug administration method for patients of aged 6 months 5 years compared to syrup [19]. The study, involving 306 pediatric patients, revealed superior suitability of uncoated mini tablets over syrup, with a 14.8% difference in proportions (95% CI 10.2-19.4; $P < .0001$). The ability to swallow

uncoated mini tablets was also higher by 12.3% compared to syrup (95% CI 5.4-19.3; P = .0008). Coated and uncoated mini-tablets were well-tolerated, and no adverse reactions were reported. The authors suggest that mini tablets are a valued alternative to syrup, emphasizing their higher acceptability in pediatric populations aged 6 months-5 years [19]. They recommend regulatory bodies to consider these findings for guideline updates and future drug approvals.

In a separate pilot study, Klingmann et al. (2013) explored the acceptance and swallowability of uncoated 2 mm mini tablets in children aged 0.5-6 years [19]. Contrary to expectations, the study found that children preferred mini-tablets over syrup, with acceptance rates exceeding expectations across different age groups. Even infants as young as 6 to 12 months have shown the ability to swallow mini tablets, challenging the presumption that liquid formulations would be preferable. The study suggests that uncoated mini tablets could be a promising substitute to liquid formulations, potentially expanding their use in pediatric drug therapy to an earlier age than previously anticipated.

Building on this foundation, Klingmann et al. (2015) delved into the suitability of 2 mm uncoated mini tablets for neonates in a randomized crossover study [20]. The study involved 151 neonates of aged 2-28 days. The primary objective was met, as all neonates accepted both the uncoated mini tablets and the syrup (100%; 95% CI 97.6% - 100%). The swallowability of uncoated mini-tablets was not worse than syrup and, in fact, surpassed it (with a difference in proportions of 10.0%; 95% CI 1.37%-19.34%; P = .0315). Both formulations were well-tolerated, with no serious adverse events reported, including no incidents of inhalation or coughing in any neonate [20].

The study reported that uncoated mini tablets provide a valuable alternative to syrup for term neonates, suggesting the potential for a single formulation across different age groups. These findings align with recommendations from the World Health Organization and support the shift towards small sized solid drug formulations for children of all ages groups [20]. While valuable, Klingmann et al. (2015) acknowledged certain limitations in their study, including a focus on term neonates, a short-term assessment, a single-center design, and a lack of diverse comparisons. To address these limitations, future research should explore the long-term implications of using mini-tablets, include a more diverse neonatal population, consider multi-center settings, and assess caregiver perspectives. This would provide all-inclusive understanding of the use of mini tablets in neonatal drug administration.

Klingmann et al. (2018) conducted a study to evaluate how well children aged 6 months to 5 years could accept and swallow multiple minitablets as a single dose compared to taking an equivalent dose of syrup [16]. In this randomized, 3-way, single administration cross-over study involving 372 children, the researchers concluded that the administration of at least 25 minitablets was well tolerated and superior to the equivalent dose of syrup in terms of both acceptability and swallowability in children aged 6-23 months. For children's of aged 2-5 years, noninferiority of acceptability was demonstrated for 400 minitablets, and these children accepted minitablets better than the equivalent dose of syrup. The results indicate that minitablets offer a viable and secure substitute for liquid formulations, potentially reshaping the approach to pediatric medication by favoring compact solid drug forms. [16].

The study conducted by Klingmann et al. (2018) is subject to certain limitations. Primarily, its design exclusively enrolled children capable of swallowing and who were compliant and receptive to the study procedures. This introduces a potential bias in the outcomes. Additionally, the focus on drug-free minitablets as placebos may not fully represent the acceptability of commercial minitablets containing active pharmaceutical ingredients, as taste considerations can vary. The study also relied on the subjective assessment of acceptability by caregivers, which might be influenced by individual perceptions.

Recently in 2022 a randomized cross-over study led by Wargenau M, Klingmann V and colleagues, the acceptability and swallowability of multiple coated placebo mini-tablets were examined in comparison to glucose syrup across 50 children in five age groups (1 to <6 years) [21]. The research indicated favorable acceptance rates (80%–100% for mini-tablets, 90%–100% for syrup) and ease of swallowing (30%–70% for mini-tablets, 20%–80% for syrup) across all age brackets, without significant clinical distinctions. These findings imply that employing multiple coated mini-tablets might offer a feasible and suitable substitute to liquid forms, mitigating worries regarding precise

dosing, drug stability, storage requirements, and taste concealment [21]. Safety concerns were not identified, although the study had limitations, including its single-center nature and the lack of investigation into repeated mini-tablet use in real-world conditions. Future research could involve multicenter studies in diverse settings, assess long-term use, and explore the impact of active pharmaceutical ingredients on mini-tablet palatability for a more comprehensive understanding of their utility in pediatric drug administration.

Throughout this decade-long research journey, Klingmann's studies collectively showcase a consistent emphasis on understanding and improving pediatric medication acceptability. The evolution from exploring specific formulations to broader comparisons and considerations highlights the commitment to advancing the field. The studies not only contribute valuable insights into formulation preferences across different age groups but also advocate for the development of innovative and acceptable pediatric medications.

Research by Hida and Colleagues (2022-2023)

The study conducted by Hida et al. (2023) investigates the pharmacokinetics of acetylsalicylic acid (ASA) administered through mini-tablets compared to a powder formulation in healthy adult males. This open-label crossover study with six participants reveals no significant differences in key pharmacokinetic parameters, including Cmax and AUC0–12, between the mini-tablets and powder [22]. Despite these findings suggesting equivalent drug effects for mini-tablets formulated to improve medication adherence in pediatric population, the study has limitations. It involved healthy adult males, potentially limiting the applicability of results to the intended pediatric population [22]. Children's distinct physiological factors influencing drug metabolism were not directly addressed, emphasizing the need for future research utilizing physiologically based pharmacokinetic methodologies for a more targeted understanding of drug distribution and efficacy. Additionally, the study did not explore real-life clinical experiences or adherence patterns in the pediatric population, necessitating investigations considering practical clinical scenarios.

Miyazaki et al. (2022) conducted a study to evaluate the suitability of mini-tablets, fine granules, and liquid forms for children aged 2–8 years [23]. In this study, which was conducted at a single center, involving three periods of crossover, and employing randomization, a total of sixty-five participants from various age categories were recruited. The main focus of the trial was to evaluate the acceptability among healthcare professionals according to predetermined criteria [23]. Although the majority of participants accepted all formulations, mini-tablets showed reduced swallowability in comparison to fine granules and liquid forms. Nonetheless, both fine granules and liquid formulations were well accepted and easily swallowed. The study's conclusion suggests that Japanese children accepted mini-tablets, albeit with lower swallowability, possibly due to a tendency to chew on mini-tablets. The research contributes valuable insights into the acceptability of various formulations in the pediatric population, emphasizing the importance of formulation characteristics in medication adherence.

The exploratory study conducted by Mitsui et al. (2022) mainly focused on assessing the swallowability of minitablets, comparing them with liquid formulations and fine granules in children of aged 6–23 months [17]. In a randomized crossover design with 40 participants, the study found that children of aged 6–23 months were able to take mini tablets without adverse events. Notably, 80% of children aged 6–11 months successfully swallowed all four minitablets without chewing, suggesting potential ease of administration compared to dispersed fine granules or liquid formulations [17]. Caregivers found minitablets easy to use, and many expressed the intention to use them in the future. While the study acknowledged limitations, such as the small sample size and the need for further modifications to the evaluation method based on caregiver experiences, the positive outcomes contribute valuable insights into the potential viability of minitablets as an easy-to-take formulation for children in Japan.

In summary, Hida and colleagues' works provide valuable foundational insights into pediatric drug delivery. The equivalence of drug effects between mini-tablets and powder is a significant finding, but the studies highlight the necessity for more targeted investigations in children and consideration

of practical clinical scenarios. Future research endeavors should focus on overcoming the identified limitations, incorporating physiologically based pharmacokinetic models, and addressing the specific challenges faced by pediatric patients to ensure the development of effective and acceptable formulations for this unique population.

Research by Münch and Colleagues (2021-2023)

In their dedicated pursuit of enhancing pediatric drug formulations, Münch et al. conducted significant studies in 2021 and 2023, specifically focusing on the swallowability, acceptability, and palatability of different tablet formulations.

The objective of the 2021 study was to determine whether oblong tablets were non-inferior to glucose syrup for children between the ages of 1 and 5 years [18]. Utilizing an open, , cross-over, randomized design the research demonstrated that not only were oblong tablets non-inferior, but they also exhibited superiority in terms of swallowability over syrup, indicating their potential as a safe alternative for drug administration in young children. Involving 280 children and utilizing a two way cross over design, the study found noninferiority in the acceptability of oblong tablets compared to syrup across all age groups (84.4% vs. 80.1%) and superiority in swallowability (74.5% vs. 53.2%). Palatability assessments indicated fewer unpleasant reactions after taking oblong tablets or mini-tablets (less than 10%) compared to syrup (up to 40%) [18].

In 2023, Münch et al. investigated the suitability of film-coated mini-tablets for pediatric use, focusing on acceptability, swallowability, palatability, and safety. Their initial study, employing an open-label, single-dose, cross-over design, evaluated drug-free film-coated mini-tablets in children aged 1 month to 6 years. The results revealed high acceptability rates, particularly in swallowability (at least 87%), across different tablet sizes and age groups. This suggests that 2.0 mm and 2.5 mm film-coated mini-tablets are suitable for young children. Although recruitment proved challenging in the 1–<6-months group, the findings still indicated these mini-tablets as favorable formulations [24].

In the subsequent 2023 study, researchers conducted an open-label, randomized, parallel-group investigation. This study centered on evaluating the effectiveness of film-coated mini-tablets, each with a diameter of 3 mm, in children aged ≥2 to <7 years. The findings revealed high rates of acceptability, swallowability, and palatability for a single administration of either 16 or 32 film-coated placebo mini-tablets, all surpassing 80%. Notably, there were no significant disparities observed between different groups or age brackets. These results affirm the practicality of administering mini-tablets with soft food or water to children aged ≥2 to <7 years [25].

While these studies provide valuable insights into pediatric drug formulations, challenges remain, particularly in administering film-coated mini-tablets to very young children (1–<6 months). Halted recruitment in this age group emphasized potential difficulties, urging further optimization of formulations and administration methods. Strategies such as adjusting tablet size, coating properties, or considering alternative administration routes are essential to enhance safety and acceptability for infants. Collaborative efforts between researchers, pediatricians, and caregivers remain pivotal for developing user-friendly mini-tablet formulations for the youngest pediatric

In conclusion, all studies collectively contribute valuable insights into the realm of pediatric drug formulations. The results imply that oblong tablets and film-coated mini-tablets stand as promising alternatives to traditional liquid formulations, boasting high acceptability rates and providing a convenient and well-tolerated option for drug administration in young children. Münch's extensive body of work underscores the viability of these tablet forms in addressing the challenges of pediatric medication administration, paving the way for safer and more acceptable methods in pediatric drug therapy.

Batchelor's study (2021): Comparison of Episenta® Minitablets and Epilim® Tablets

In their 2021 study, Batchelor et al. sought to comprehensively compare Episenta® minitablets with Epilim® monolithic tablets regarding adherence, healthcare resource usage, and cost implications in treating pediatric epilepsy in England. They employed a retrospective analysis of data from both Primary Care (Clinical Practice Research Datalink) and Secondary Care (Hospital Episode Statistics)

in the UK, focusing on patients diagnosed with epilepsy who received a new prescription for either minitablets or monolithic tablets of sodium valproate. The cohort involved 793 patients, and the analysis yielded noteworthy findings [26].

The investigation revealed that measures of medication adherence did not show significant differences between the two formulations, suggesting that patients generally adhered similarly to both minitablets and monolithic tablets. However, a distinctive pattern emerged concerning healthcare resource utilization. The pediatric population using the tablet formulation showed a greater annualized incidence rate of epilepsy related primary healthcare contacts compared to those treated with minitablets. This observation suggests that minitablet formulations might contribute to a reduction in the frequency of healthcare interactions related to epilepsy in children [26].

A particularly notable outcome was the effective therapy achieved at a lower dose in the mini tablet cohort (595 mg) compared to the tablet cohort (945 mg) within the 0-17 age group. This implies that minitablets, specifically Episenta® minitablets, may offer enhanced therapeutic outcomes in pediatric epilepsy treatment, potentially leading to optimized health outcomes and reduced the cost of healthcare resources.

Although the study yields favorable results concerning minitablet formulations, it underscores the necessity for further research to produce aligned data for future comparative analyses. Furthermore, the call for further research underscores the complexity of understanding why minitablets resulted in better outcomes in the pediatric population. The interpretation of the findings is acknowledged to be limited by the substantial difference in sizes of samples between the two groups, highlighting the importance of conducting additional research to validate and build upon these initial observations in the realm of pediatric epilepsy treatment.

Hecken et al. (2020): Orodispersible minitablet (ODMT) containing enalapril

In 2020, Hecken and colleagues undertook a notable investigation centered on crafting an orodispersible minitablet (ODMT) suitable for various age groups, containing 1 mg of the angiotensin-converting enzyme inhibitor enalapril. This formulation aimed to address the challenge of medication administration in children who may encounter difficulties swallowing conventional tablets or capsules. As a member of the EU-funded LENA consortium, the research sought to aid in the clinical assessment of the novel ODMT formulation by conducting a relative bioavailability study involving healthy adults [27].

In a randomized 3-way crossover study, 24 healthy participants were given a 10-mg dose of enalapril through different methods: either as two 5-mg tablets of the reference product (RP) Renitec swallowed with water, ten 1-mg orally disintegrating mini tablets (ODMT) swallowed with water, or ten 1-mg ODMT dispersed on the tongue. The findings demonstrated that the relative bioavailability of the ODMT formulation swallowed with water was comparable to that of the RP, meeting established bioequivalence criteria. Even when the ODMT was dispersed on the tongue, there was a slightly higher maximum concentration (Cmax) of enalapril observed compared to the RP, but this did not significantly affect its bioavailability [27].

Despite the valuable insights provided by Hecken et al.'s study, several limitations warrant consideration. The study's relatively small sample size of 24 healthy subjects may limit the generalizability of findings to a broader population, especially pediatric patients. The focus on healthy adults may not perfectly extrapolate to the target pediatric population, and further investigations involving pediatric subjects are essential for a more accurate assessment. The study's short duration and the absence of a comprehensive evaluation of long-term safety and tolerability aspects may restrict a thorough understanding of the ODMT formulation's performance over extended periods, particularly in pediatric patients who may require prolonged treatment.

In conclusion, while acknowledging these limitations, Hecken et al.'s study is a crucial step in establishing the bioequivalence of the ODMT formulation and its potential for use in pediatric patients. Future research with larger sample sizes, diverse patient groups, and extended follow-up periods could provide a more comprehensive understanding of the ODMT formulation's suitability and safety in clinical practice.

In Vitro Swallowability Studies by Lavoisier et al. (2022) and Avila-Sierra et al. (2023)

In 2022, Lavoisier et al. introduced the innovative Pediatric Soft Robotic Tongue (PSRT) to conduct in vitro studies on the swallowability of mini-tablets. Modeled after the anatomy of a 2 year old child, the PSRT explored crucial factors influencing swallowability, encompassing carrier types, administration methods, mini tablets size, and volume fraction [28]. The findings emphasized that semisolid foods like apple puree and yogurt were more suitable carriers for mini tablets swallowing compared to thin liquids. Intriguingly, reducing mini-tablets size did not significantly enhance swallowability within the studied range [28]. The study recommended spreading mini-tablets on a teaspoon of carrier for improved swallowability. However, limitations include the study's in vitro nature and a focused exploration of carrier types and sensory aspects. Future research suggestions include diversifying populations, incorporating sensory evaluations, and considering patient-reported outcomes for a more comprehensive understanding of oral medication acceptability.

In 2023, Alejandro Avila-Sierra and colleagues explored the enhancement of in vitro swallowability for pediatric oral solid dosage forms, specifically mini-tablets and pellets, using binary mixtures [29]. Utilizing the Pediatric Soft Robotic Tongue, the researchers investigated multiple factors influencing swallowability, such as bolus volume, feeding method, particle size, carrier type, and particle volume fraction. The study showcased that incorporating pellets into mini-tablets in a binary mixture significantly improved swallowability, presenting potential applications for flexible formulations in pediatric combination products [29]. Similar to the previous study, limitations encompass the in vitro nature of the research and the need for further exploration in clinical settings. Subsequent research endeavors could entail broadening the scope of the investigation to encompass intricate scenarios, including combination products featuring multiple drug substances. Additionally, evaluating the repercussions of deviations in batch mean values on content uniformity could be a focal point of interest.

In their in vitro studies, Lavoisier et al. (2022) and Avila-Sierra et al. (2023) investigated swallowability factors for pediatric mini-tablets. Lavoisier's study underscored the suitability of semisolid foods as carriers, while Avila-Sierra's work demonstrated enhanced swallowability using binary mixtures, particularly with pellets. Although both studies acknowledge the limitations of their in vitro focus, they lay a crucial foundation for developing pediatric medications with improved swallowability, emphasizing the necessity for further clinical exploration and diverse considerations.

Key Findings from Acceptance Studies:

Pediatric drug formulations present unique challenges in terms of palatability, swallowability, and overall acceptability. Below table provides a comprehensive overview of recent studies that delve into various aspects of pediatric medication formulations. The studies cover a range of topics, including the acceptability of mini-tablets, comparisons with traditional formulations, pharmacokinetics, in vitro assessments, and real-world applications.

Table: Key findings from acceptance studies

Study	Focus	Methodology	Key Findings	Limitations	Conclusions/Recommendations
Münch et al. (2023)	Pediatric acceptability of film coated mini-tablets	Open-label, cross-over design (two studies)	High acceptability rates, pleasant palatability; coughing in 1–<6 months group	Controlled hospital setting, single administration focus	Valuable insights into suitability; Optimize for very young children; Explore alternative routes
Klingmann et al. (2023)	Acceptability of coated mini tablets vs. glucose syrup	Randomized cross-over study	Good acceptability and swallowability for both; No safety concerns	Single-center trial, single administration focus	Coated mini-tablets as a viable alternative; Explore in real-world settings
Hida et al. (2023)	Pharmacokinetics of ASA in mini-tablets vs. powder	Open-label crossover study	Equivalent pharmacokinetic parameters between mini-tablets and powder	Limited to healthy adult males	Mini-tablets exhibit equivalent drug effects; Need for pediatric-focused research
Alejandro Avila-Sierra et al. (2023)	In vitro swallowability improvement for	In vitro study using Paediatric Soft	Pellets in binary mixtures enhance swallowability	Limited to in vitro; Explore clinical settings	Potential applications for flexible formulations; Further research needed

	pediatric solid oral dosage forms	Robotic Tongue			
Miyazaki et al. (2022)	Acceptability of mini tablets, liquid and fine granules, formulations	Prospective crossover trial	Mini tablets exhibit lower swallowability; Fine granules and liquid good acceptability	Small sample size, focus on acceptability	Formulation characteristics impact medication adherence; Importance of formulation
Mitsui et al. (2022)	Mini tablets Swallowability vs. fine granules and liquid	Randomized crossover design	Children aged 6–23 months successfully swallow minitablets; Positive caregiver feedback	Small sample size, need for evaluation method modification	Positive outcomes suggest potential ease of administration; Further modifications needed
Lavoisier et al. (2022)	In vitro investigation of mini-tablet swallowability	In vitro study with Pediatric Soft Robotic Tongue	Semi-solid foods enhance swallowability; Reduction in size doesn't significantly improve	In vitro study, limited exploration of carrier types	More suitable carriers identified; Future research should diversify populations
Münch et al. (2021)	Acceptability of oblong tablets vs. glucose syrup	Randomized, single-dose crossover study	Non-inferiority of oblong tablets; Superior swallowability	Single-dose design, specific age group inclusion	Oblong tablets as a promising alternative; Considerations for pediatric drug formulations
Batchelor et al. (2021)	Adherence and healthcare resource use in Episenta® minitablets vs. Epilim® tablets	Retrospective analysis of UK healthcare data	Minitablets lead to better outcomes and reduced healthcare costs	Large difference in sample size between groups	Additional research needed for matched data and understanding minitablet outcomes
Hecken et al. (2020)	Orodispersible minitablet (ODMT) containing enalapril	Open-label, randomized crossover study	ODMT bioavailability comparable to reference product	Small sample size, focus on healthy adults	ODMT formulation suitable for clinical use; Further investigations needed
Klingmann et al. (2018)	Acceptability of multiple minitablets vs. syrup	Randomized, 3-way crossover study	Minitablets well-tolerated and superior to syrup	Subjective assessment by caregivers	Minitablets as feasible and safe alternatives; Explore with active pharmaceutical ingredients
Klingmann et al. (2015)	Suitability of 2 mm uncoated mini-tablets for neonates	Randomized crossover study	Uncoated mini-tablets well-accepted, higher swallowability than syrup	Focus on term neonates, short-term assessment	Potential single formulation across different age groups; Future research diversity needed
Klingmann et al. (2013)	Acceptability of 2 mm solid dosage forms in children	Prospective, open, randomized crossover study	Uncoated mini-tablets superior in acceptability and swallowability	Ethical constraints, focus on compliant children	Minitablets as a valuable alternative across different age groups; Regulatory considerations

This structured summary aims to distill essential information from each study, offering insights into the innovative approaches, challenges, and recommendations for improving pediatric drug formulations. This compilation is valuable for understanding recent advancements and the ongoing discourse in pediatric pharmaceutical development.

Conclusion:

The cross-study analysis reveals substantial progress in the field of pediatric medication formulations, with particular attention to challenges surrounding acceptability, swallowability, and safety, especially for the youngest age groups. Younger populations present distinct challenges, necessitating tailored formulations to address age-specific considerations for successful pediatric drug delivery. The significance of formulation characteristics, including size, coating, and taste-masking, is underscored, and fine-tuning these aspects is vital for both acceptability and swallowability across diverse age groups.

Safety concerns and ethical considerations, particularly in studies involving very young children, highlight the need for a delicate balance between ensuring safety and maintaining acceptable formulations. Advocacy for regulatory revisions is prominent, reflecting the necessity to accommodate innovative pediatric formulations, emphasizing the crucial role of updated guidelines and approval processes.

Acknowledging the diversity in drug substances, studies underscore the need for generalizing findings to a broad spectrum of medications. Tailoring formulations based on specific drug characteristics is essential for comprehensive pediatric drug delivery strategies. Caregiver experiences play a pivotal role in determining the success of pediatric formulations, and acknowledging and incorporating caregiver feedback are crucial for real-world applicability and patient satisfaction.

The importance of in vivo validation is highlighted, especially in studies relying on in vitro methodologies. Real-world scenarios and patient-reported outcomes become significant in ensuring the practicality and effectiveness of pediatric formulations. Insights into healthcare resource utilization provide economic considerations for specific pediatric formulations, contributing to the broader evaluation of formulation success.

Future research priorities include optimizing formulations for the youngest age groups, considering factors such as size, taste, and alternative administration methods. Real-world scenario investigations are essential to validate findings beyond controlled settings. Broader representation of pediatric populations, encompassing diversity in ethnicity, cultural backgrounds, and medical conditions, is crucial for enhancing the general applicability of pediatric formulations.

Continued advocacy for regulatory revisions and updated guidelines is crucial to encourage the development of innovative pediatric formulations, aligning with the overarching goal of promoting patient-centric approaches in pediatric drug delivery. Exploring the long-term implications of pediatric formulations, including adherence, safety, and efficacy, is essential for guiding sustained clinical use and ensuring positive patient outcomes.

Collaboration between the pharmaceutical industry and regulatory bodies is essential to navigate challenges and streamline the development and approval processes for pediatric formulations. This collaborative effort can expedite the translation of research findings into practical solutions. Future research should adopt patient-centric approaches, incorporating patient and caregiver preferences, experiences, and feedback to ensure the success of pediatric formulations in real-world settings, aligning with broader goals of improving medication adherence and overall healthcare outcomes for pediatric populations. In conclusion, the evolving landscape of pediatric medication formulations emphasizes ongoing efforts to address challenges and enhance the success of drug delivery in diverse pediatric populations, providing a roadmap for future research with a focus on collaboration, regulatory support, and patient-centric approaches.