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Original Article

Paediatric oral dosage forms: Why do caregivers need drug modifications and how?

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ABSTRACT

Background and Aims: A major obstacle to developing appropriate medications is the lack of understanding of what is acceptable for paediatric patients and the types of alterations that can be made to the dosage form. This study aimed to identify problems encountered when administering oral dosage forms to paediatric patients and solutions identified by patients' caregivers.

Methods: A questionnaire was developed by the research team based on relevant literature and their experiences. The first part involves questions to determine the demographic characteristics of the paediatric patient and their caregivers. The second section includes 11 statements about the problems experienced by caregivers regarding the child's medication use. The last part consists of 4 closed-ended questions and one open-ended question to evaluate the solutions offered by the patient's caregivers.

Results: A total of 419 caregivers participated in the study. In particular, it has been revealed that children experience problems regarding the taste, smell, and size of medicines. When the caregivers' solutions are evaluated, it was observed that the most common method is convincing or forcing the child to take, followed by dosage form alterations such as breaking, crushing, and dividing the form.

Conclusion: This is the first study to evaluate problems encountered when administering oral dosage forms to paediatric patients in Türkiye. The results show that the absence of age-appropriate medicines forces caregivers to alter their dosage forms. This study also highlights the necessity of considering user preferences in the dosage form design, which is an essential parameter of the target product quality profile that ensures patient compliance.

Keywords: Acceptability, Age-appropriate, Alteration, Paediatrics, Dosage forms

INTRODUCTION

The active pharmaceutical ingredient (API) is a primary consideration for determining dosage, clinical effects, and adverse drug responses in pharmacology and clinical paediatrics. However, formulation is crucial as it determines whether the dose can be given to the paediatric patient (Liu, Ghaffur, Bains, & Hamdy, 2016; Liu et al., 2015). Pharmaceutical drug product design should consider patients' needs and preferences to simplify drug administration and resolve medicine-related problems (Drumond, van Riet-Nales, Karapinar-Çarkit, & Stegemann, 2017). Drug product design that is patient-centric can be characterised as "the process of identifying the comprehensive needs of individuals or the target patient population and utilising the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target population over the intended duration of treatment" (Stegemann, Ternik, Onder, Khan, & van Riet-Nales, 2016; Walsh, Ranmal, Ernest, & Liu, 2018).

The incidence of medication errors is notably higher in children than in adults. A study in Korea that analysed data from 1989 to 2012 found that medication errors occurred three times more frequently in children than in adults (Woo, Kim, Chung, & Park, 2015). Similarly, Stratton et al. (2004) reported a higher rate of medication errors in paediatric patients (67%) than in adult patients (56%) (Stratton, Blegen, Pepper, & Vaughn, 2004). Doherty and McDonnel (2012) highlighted that 43.3% of errors in paediatric patients were due to prescribing mistakes, while 34.5% were due to practise errors (Doherty & Mc Donnell, 2012). The FDA studies conducted between 1993 and 1998 identified the most common errors as inappropriate dos-

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ing (41%), incorrect drug administration (16%), and incorrect drug delivery (16%) (Phillips et al., 2001). Sears et al. (2013) found that the most frequent errors in paediatric patients were incorrect timing (45.2%) and incorrect dosing (22%) (Sears, O'Brien-Pallas, Stevens, & Murphy, 2013). Özkan et al. (2013) revealed that nurses in Türkiye most commonly made timing (10.6%) and dosing (10.3%) errors when administering medications to children (Özkan, Kocaman, & Ozturk, 2013). Adams et al. (2013) investigated the medication administration practises of families and caregivers in Tanzania and concluded that the taste and formulation of medicines significantly influenced children's adherence to treatment regimens (Adams et al., 2013). Additionally, Venables et al. (2015) conducted a focus group study with healthcare professionals in the UK and identified that the taste and oral sensations of dosage forms were key factors affecting children's compliance with oral medication (Venables, Batchelor, Stirling, & Marriott, 2016).

While the pharmacists' roles in paediatric drug usage have been evaluated, several studies have addressed this issue. Pirhan and Özçelikay (2005) focused on evaluating pharmacists' roles in paediatric drug usage (Pirhan, 2005). Nahata and Taketomo emphasised the importance of having clinical pharmacists in paediatric wards to increase patient safety (Nahata & Taketomo, 2017). The American Academy of Paediatrics (AAP) emphasises the role of multidisciplinary teams—including doctors, nurses, pharmacists, laboratory staff, and information specialists—in reducing medication errors in children. Stucky (2003) highlighted the critical role of clinical pharmacists, physicians, and nurses, especially in intensive care and oncology services, to minimise paediatric medication errors (Stucky, 2003). The Joint Commission (JCI), in its 2008 report "Prevention of Medication Errors in Paediatric Patients," suggested integrating pharmacy personnel into paediatric services and assigning pharmacists and technicians with paediatric expertise to neonatal/paediatric intensive care units and paediatric oncology services (D'Errico et al., 2021). Sanghera et al. (2007) reported from a different perspective that the error rate in paediatric patients was four times higher than in adults. Clinical pharmacists made 2,449 recommendations for paediatric patients, of which 99.2% were approved by physicians.

Due to the scarcity of research focused on the appropriate formulations for paediatric patient group, the drug product needs were initially not well understood (van Riet-Nales, de Jager, Schobben, Egberts, & Rademaker, 2011; van Riet-Nales, Schobben, Egberts, & Rademaker, 2010). Therefore, pharmaceutical scientists may face considerable difficulties in developing formulations suitable for paediatric use (Nunn & Williams, 2005; Stegemann et al., 2016). As an integral component of developing these medications, the pharmaceutical industry must demonstrate that novel paediatric formulations are acceptable to target age groups while considering user needs (Kozarewicz, 2014). This prerequisite is essential for ensuring the best possible treatment compliance and the therapy's effectiveness and safety (Ranmal, Cram, Tuleu, 2016). When attempting to find an acceptable solution, two questions arise: "Which dosage form should be chosen for each target age group?" and "How should it be formulated after the dosage form is determined?" (Liu et al., 2016; Liu et al., 2015)

Given the significant impact of formulation preferences, medication palatability, and home administration practises on paediatric medication adherence, understanding parent/caregiver behaviours and involving them in initiatives to improve administration options and promote responsible use are crucial (Adams et al., 2013). Any alterations to the dosage form not authorised by the label can potentially compromise effectiveness or, in extreme cases, endanger the patient because the responsibility for patient care often lies with the drug administrator rather than the pharmaceutical manufacturer (Schiele, Quinzler, Klimm, Pruszydlo, & Haefeli, 2013). Concerns about high off-label prescription rates and inappropriate modifications to drug products are widespread globally (van Riet-Nales et al., 2010). Regulatory support and frameworks play a crucial role in overcoming these challenges, transforming paediatric formulation development into a vital aspect of drug development. Both the European Medicines Agency (EMA) and the FDA mandate detailed formulation development strategies in Paediatric Investigation Plans (PIPs) and Paediatric Study Plans (PSPs), respectively (Ranmal et al., 2016). According to the EMA, an age-appropriate paediatric medication is one whose pharmaceutical design makes it suitable for use in the target age group(s), encompassing factors such as composition, dosage form, dosing frequency, and packaging (EMA, 2013). Ensuring patient acceptance of formulations defined as "the overall ability and willingness of the patient and its caregiver to use and administer the medicine as intended is highly prioritised (EMA, 2013; Kozarewicz, 2014)." The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Product Development Guidelines (Q8 (R2)) emphasise that pharmaceutical products should be designed to meet patient needs and intended performance standards ((ICH), 2009). Therefore, alongside technical challenges in pharmaceutical development and manufacturing, considering patient needs is crucial in defining the Quality Target Product Profile (QTPP) and selecting suitable dosage forms (Walsh et al., 2018).

A significant barrier to developing appropriate medications is the limited understanding of what constitutes acceptability for paediatric patients, how to evaluate a new product's acceptability, and how caregivers modify dosage forms to enhance acceptability. The lack of research on challenges in administering oral pharmaceuticals to paediatric patients and caregivers' solutions to these problems, particularly in Türkiye, motivates this study. In this regard, this study aimed to reveal problems encountered when administering oral pharmaceutical dosage forms to paediatric patients, especially concerning the taste and shape of the dosage form as acceptability criteria and solu-

tions found by patients' caregivers to overcome problems based on the shape and taste of medicines.

MATERIALS AND METHODS

According to the study's aim, a Turkish questionnaire was administered to caregivers of paediatric patients and comprised three parts. The first part collected demographic data about the patients and caregivers. The second section included 11 statements assessing caregivers' challenges with child medication use. To determine the common problems encountered by paediatric patients, firstly, relevant literature (ICH, 2019; Schiele et al., 2013; Stegemann et al., 2016; Venables et al., 2016; Zajicek et al., 2013) was evaluated by all research team members. Accordingly, a statement tool was created, which included 15 statements. After evaluating these statements by the research team, which also considered their pharmacy experiences, 11 were selected as appropriate. A pilot study was then conducted with eight individuals to test the face validity of the statements. Because of the pilot study, it was observed that the questionnaire had face validity.

To evaluate the frequencies of the selected problems, statements were graded with a 4-point Likert-type scale (Never "1", Always "4"). The last part of the questionnaire includes four closed-ended questions and one open-ended question to evaluate the solutions offered by the patient's caregivers.

Sample size and data collection

The study population comprised male and female individuals aged between 18 and 65 who applied to community pharmacies for paediatric patients in Van and Istanbul city centres. The minimum sample size was calculated using the Cochran sample size formula at a 95% confidence level with a margin of error of 0.10 equal to 88. To increase the reliability of the results obtained, we attempted to reach the maximum possible number of individuals. After obtaining informed consent, the researchers applied the questionnaires face-to-face and online via Google Forms. Two researchers administered the survey face-to-face to the caregivers of patients eligible for the study sample in pharmacies where they were interned during the research period. To increase the sample size, individuals who participated in the face-to-face survey were asked to share the online survey link with appropriate individuals. In addition, all researchers shared the survey link with individuals who met the study criteria and asked them to share it.

The study was conducted between 04.03.2020 and 15.04.2020 with the ethical approval of the Van Governorship Provincial Health Directorate (73040253-044-E.438 and the Van-Bitlis-Hakkari Chamber of Pharmacists with number 2019/1626 and the World Medical Association (WMA) Declaration of Helsinki Ethical Principles in Medical Research on Human Volunteers.

Data analysis

The data obtained from the questionnaire were subjected to descriptive statistical analysis, including frequencies, percentages, and histograms, using the IBM SPSS 22.0 (IBM Electronics, USA) package programme.

RESULTS

419 caregivers of patients participated in the questionnaire. A total of 314 participants (74.9%) were female, and 105 (25.1%) were male. Most participants were in the 25-50 age range (81.1%). Among the participants, 140 were primary school graduates, 153 were high school graduates, 111 had a university degree, and 15 had postgraduate degrees. When the information about the children to whom the caregivers participating in the study administered the medication was evaluated, it was determined that 57% of the children were girls and 43% were boys.

Only 9 caregivers of the patients stated that the child had an eating/chewing disorder, and 49 of them indicated that the child had chronic disease. Chronic ailments reported by caregivers include asthma, allergic rhinitis, allergies, and diabetes.

The percentage of caregivers' responses to the statements prepared for the problems experienced by children regarding medication use are presented in Table 1.

In light of the information presented in Table 1, when the sum of the "often" and "always" responses given to the statements was considered, it was revealed that children experienced problems, especially regarding the taste, smell, and size of the medicine.

When the patient's caregivers were asked which form of solid medicine the child had the most difficulty swallowing, 40.6% of the caregivers answered that it was in rectangular form. The bar diagram of the answers is shown in Figure 1.

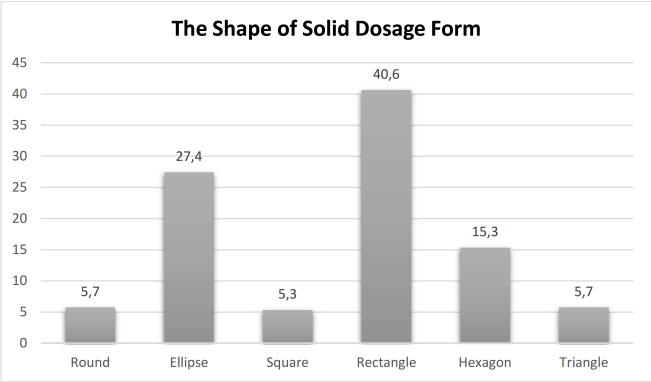

Figure 1. Percentages of the answers given by the caregivers of the patient to the question of which form of solid medicine the child had the most difficulty swallowing.

Table 1. Percentage of responses from caregivers of patients to statements about problems experienced by children regarding medication use

Statements	Response Percentages (n=419)			
	1 (Never)	2 (Rarely)	3 (Often)	4 (Always)
Does not want to swallow/drink, does not like the taste of the medicine	9.8%	32.7%	31.3%	26.3%
Does not want to swallow/drink because he/she does not like the smell of the medicine	20.5%	28.2%	26.5%	24.8%
Does not want to swallow/drink because he/she does not like the colour of the medicine	48.4%	18.6%	16.5%	16.5%
The dimensions of the medicine make it difficult to swallow	13.6%	30.5%	33.9%	22.0%
Difficulty swallowing due to the form of the medicine	18.4%	39.4%	26.5%	15.8%
Medicine is very intense and is difficult to consume	21.7%	38.7%	23.2%	16.5%
It is difficult to drink because the medicine is too	22.2%	37.5%	22.2%	18.1%
The medicine makes the child become nauseous	31.7%	28.4%	19.6%	20.3%
The medicine stuck to the child's throat	53.7%	30.1%	11.2%	5.0%
The medicine is caught in the child's throat	56.1%	30.1%	10.5%	3.3%
Coughing while taking the medicine	53.0%	32.0%	9.3%	5.7%

The caregivers of the patients were also asked which flavour syrups the child took more easily, and the answers are presented in Figure 2.

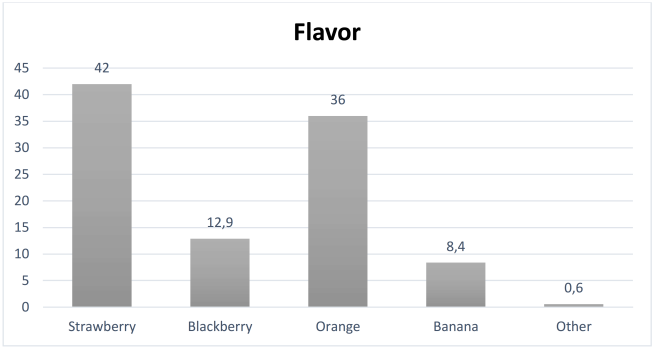

Figure 2. Percentages of the answers given by the caregivers of the patients to the question of which flavor syrup the child took more easily

Another critical finding obtained in the study was the solution suggestions offered by the patients' caregivers so that the patients could take the medicine when it was difficult to swallow/take. The recommendations and information about the number of respondents giving similar responses are presented in Table 2.

In Table 2, it can be seen that the most common method used by caregivers, other than convincing or forcing them to take medicine, is trying to give it by breaking it, crushing it into powder, or dividing it into two. When asked who the caregivers consult regarding these solution suggestions, it was revealed that they consult physicians and pharmacists the most. This was followed by other healthcare professionals, caregivers, friends, and the other groups, and a bar diagram for the results is presented in Figure 3.

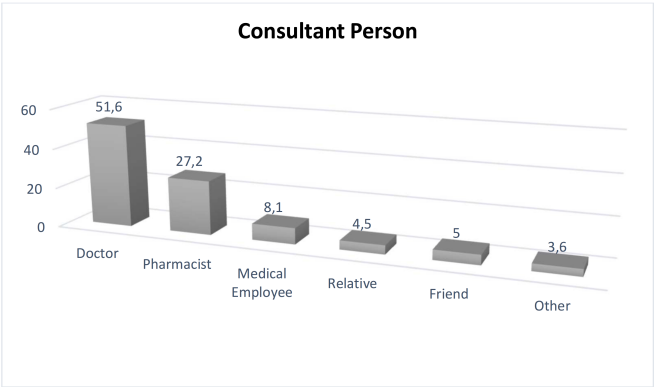

Figure 3. The graph of the people whom the caregivers refer to for solution suggestions

Finally, the caregivers of the patients were asked what they did when they could not find a solution. Responding to this question, of the patients' caregivers, 255 stated that they had consulted a doctor, 118 stated that they had consulted a phar-

Table 2. Solution suggestions offered by the patient caregivers.

Suggestions	Number of responses
I try to encourage them to take medicine by playing games with them, distracting their attention.	27
I try to persuade people by talking (saying that if they take medicine, they will get better, or I will take them to the park, I will give them candy, or I will buy them their favourite toys).	68
I make them take medicine with the help of an apparatus (dropper, injector, etc.)	26
I try to make them take medicine with plenty of water.	30
After taking the medicine, I try to give them water immediately.	6
I give medicine by dissolving it in water.	21
I give medicine by adding it to a drink she or he likes.	27
I give medicine by adding it to a food she or he likes.	26
I try to give medicine little by little.	1
I try to give medicine by breaking it up, crushing it into powder, or dividing it into half.	43
I give medicine by force (such as covering their noses and pouring medicine into their mouths)	60

macist, and 46 said that they had stopped giving the medicine. The bar diagram of these responses is shown in Figure 4.

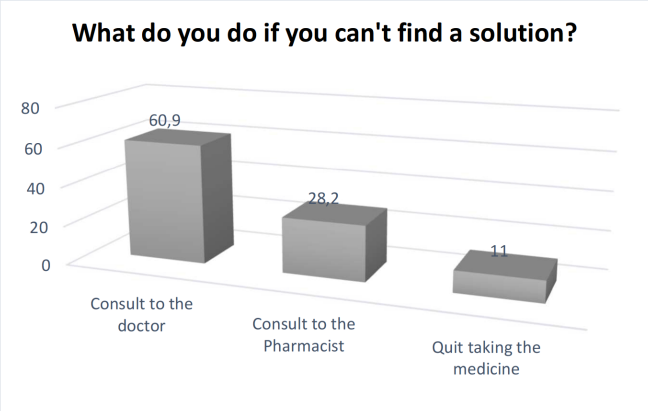

Figure 4. Percentage of the answers given by the caregivers of the patients to the question of what they did if they could not find a solution

DISCUSSION

The design of patient-oriented drug formulations has become one of the main topics that researchers are interested in and working on with technological developments in recent years. However, drug formulation designs targeting paediatric and geriatric populations are particularly challenging because of variations in design parameters. One of the obstacles hindering the development of age-appropriate paediatric medications is the lack of understanding of the dosage forms that are acceptable for the paediatric population. Additionally, there is a shortage of studies on patient populations that reveal their preferences and behaviours.

The oral route is the most commonly used of all administration methods because it is the easiest and most convenient (Kim & De Jesus, 2023). The overall acceptability of an oral paediatric medication is influenced by the choice of oral dose form and formulation features, such as tablet size or oral suspension palatability (van Riet-Nales et al., 2013; van Riet-Nales et al., 2014). Nevertheless, this route of administration poses the greatest challenge in designing age-appropriate formulations for paediatric populations. Since API is typically not dispersed evenly throughout the tablet, the EMA does not recommend solid oral dosage forms that are split or crushed to obtain the target dose unless the method has been validated (Shah et al., 2010; Zajicek et al., 2013; Zhao, Zidan, Tawakkul, Sayeed, & Khan, 2010). However, the absence of age-appropriate formulation force caregivers and medical professionals to alter dosage forms. These alterations include breaking, crushing, or dissolving the pills, taking the contents out of the capsules, and mixing them with meals. These changes may compromise the active ingredient's purity and affect the drug's stability and/or absorption (Juárez-Hernández & Carleton, 2022).

Within the scope of this study, the patients' caregivers evaluated the difficulties children experienced in the oral administration of solid and liquid dosage forms. The most frequently mentioned problems by caregivers of the patients were "She/he does not want to take medicine because she/he does not like the taste of the it.", "The medicine is difficult to swallow because of its large size." and "She/he does not want to take medicine because she/he does not like the smell of the it." These three problems have been among the factors that negatively affect compliance with medication in the literature (Bergene, Nordeng, Rø, & Steinsbekk, 2019; Marconati, Raut, Burbidge, Engmann, & Ramaioli, 2018; Schiele et al., 2013). Venables et al. (2015) evaluated children's compliance with medicine treatment at the point of the dosage form, and it was stated that one of the most critical factors reducing compliance was the taste of the form (Venables et al., 2016). Similarly, Adams et al. (2013) revealed that the type of dosage form, especially its taste, affects adherence to medication in children, and in concordance with study findings, sweet-tasting medicines are pre-

ferred by paediatric patients (Adams et al., 2013). Breitkreutz and Boos (2007) stated that the taste and size of the medicine are essential factors in the difficulties experienced by paediatrics and geriatrics group in oral medicine use (Breitkreutz & Boos, 2007). In addition, Klingmann (2017) revealed that small solid dosage forms are preferred by the paediatric group (Klingmann, 2017). Hence, the findings are in parallel with literature that is independent of socioeconomic and geographic conditions. The respondents emphasised the struggle they face when giving ellipse and rectangular shapes of solid medicines, which are mainly used in antibiotic-type medications used for many conditions.

Because liquid oral dosage forms are easier to swallow and have adjustable doses, they are frequently used when giving medications to children (EMA, 2013). However, issues with poor flavour and unfavourable ingredients could make them less suitable (Nunn & Williams, 2005; Walsh et al., 2014). Oral solid dosage forms, including tablets and capsules, are considered to be better than liquids in terms of logistics, production costs, stability, and the capacity to cover undesirable tastes (Nunn & Williams, 2005). Studies conducted in the past few decades have demonstrated that newborns and early children can swallow tiny pills measuring 2-4 mm and may even favour solid formulations over liquid formulations (Drumond et al., 2017; Klingmann, 2017; Wargenau, Reidemeister, Klingmann, & Klingmann, 2022). However, in clinical settings, solid monolithic formulations are rarely found at suitable doses and sizes for common paediatric diseases (Lajoinie, Henin, Kassai, & Terry, 2014). Children have been observed to find it challenging to swallow typically sized solid monolithic formulations, although studies suggest that this skill can be improved with guidance (Patel, Jacobsen, Jhaveri, & Bradford, 2015).

It has been observed that children mostly prefer strawberry fruit. Taste masking is essential in the design of pharmaceutical dosage forms. Most active ingredients are tasteless or can be bitter, and some may even be extremely salty. With the taste masking process, the unpleasant taste of the medicine can be reduced or eliminated physiologically (Coupland & Hayes, 2014). After drug dissolution in saliva, it remains in the oral cavity until swallowing. If the active substance has an unpleasant taste, this may adversely affect patient compliance. The results obtained in this study guide the choice of sweetener and indicate that strawberry and orange flavours are favourable among others (Figure 2).

Considering the solutions caregivers have found for the difficulties encountered while administering oral medication to their children, the study findings revealed that the most common method used by caregivers, aside from convincing or forcing their children to drink the medication, is to modify the dosage form. This involves breaking the slurry into a powder or dividing it into two parts. This practise is observed both in Türkiye and in the UK (Alessandrini et al., 2021). Schiele et al. (2013) also emphasised that dosage modifications, if not allowed in the patient leaflet, will diminish the effectiveness of the medicine and, in some occasions, can cause harm to the patient (Schiele et al., 2013). Zajiscek et al. (2013) emphasised the negative effect of dosage form alterations and called attention to the differences between the adult and paediatric age groups regarding bioequivalence and responsiveness of clinical data (Zajicek et al., 2013). In summary, crushing or breaking of dosage forms seems to facilitate drug intake; but it may cause insufficient dosage, adverse effects on bioavailability, and antagonistic effects (Akram & Mullen, 2012).

It has been revealed that caregivers of patients mostly consult physicians for the solutions they benefit from. In fact, 52% of caregivers of patients consult physicians, and 27% consult pharmacists about their solution suggestions. Fewer people consulted with caregivers, friends, or other healthcare professionals. 61% of the patient's caregivers who could not find any solution stated that they consulted a doctor and 28% consulted a pharmacist.

Ultimately, our findings align with the current literature and highlight the significant influence of taste and shape on patient preferences, even when the medicine is intended for therapeutic use. Furthermore, the results of this study illuminate the challenges caregivers face in administering medication and addressing acceptance issues without appropriate guidance.

This study has two main limitations. The first concerns were the data collection process, which was affected by the onset of COVID-19 and the resulting restrictions, which led to a lower than expected rate of face-to-face surveys and forced a switch to online surveys. Despite this, the sample size remained adequate, so the analysis results were not compromised. The second limitation is that only the syrup and tablet forms of oral dosage were evaluated. Future studies will segment the survey by age group and include other oral dosage forms, such as lozenges and chewable tablets.

CONCLUSION

This study aimed to enhance the treatment of paediatric patients by identifying the challenges faced by caregivers when orally administering medications. This is the first detailed evaluation of these issues in Türkiye, highlighting the importance of considering user preferences in dosage form design, which is a key aspect of the Quality Target Product Profile (QTPP) that is crucial for patient adherence. Notably, caregivers tend to prefer consulting physicians over pharmacists for formulation development, indicating the need for attention during formulation development and patient counselling.

The findings contribute significantly to the literature and provide preliminary data for future research. Pharmacists should have a thorough understanding of paediatric medications and to offer comprehensive counselling to caregivers. Furthermore,

incorporating children's preferences regarding oral dosage forms during the formulation research phase is vital for creating more child-friendly medications. This patient-centered approach recognizes that children have unique physiological characteristics and are not simply smaller adults. Therefore, paediatric formulations must meet regulatory safety and efficacy standards while allowing for dosage adjustments across various age groups.

Ethics Committee Approval: The study was conducted with the permission decisions of the Van Governorship Provincial Health Directorate numbered 73040253-044-E.438 and the Van-Bitlis-Hakkari Chamber of Pharmacists with number 2019/1626 and the World Medical Association (WMA) Declaration of Helsinki Ethical Principles in Medical Research on Human Volunteers.

Informed Consent: Informed consent was obtained from the participants

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: Ö.A.D., M.A.; Data Acquisition: F.İ., G.T.; Data Analysis/Interpretation: M.A., Ö.A.D.; Drafting Manuscript: Ö.A.D., M.A.; Critical Revision of Manuscript: Ö.A.D., M.A.; Final Approval and Accountability : Ö.A.D., M.A., F.İ., G.N.T.

Conflict of Interest: The authors have no conflict of interest to declare.

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