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Palatability studies of oral formulations: an overview about drug acceptance in pediatrics

Estudos de palatabilidade de medicamentos: análise sensorial e aceitabilidade de formulações pediátricas

Marina dos Santos Garruti de Medeiros[I,*]

Deborah dos Santos Garruti[II]

ABSTRACT

Introduction: Children often reject non-palatable medications. Pediatric formulations contain sweeteners and flavorings to mask the unpleasant taste and avoid problems in administration and adherence. Taste assessment is an essential part of the development of oral liquid medicines. **Objective:** This paper aims to contextualize assessment and influence of palatability on the acceptance of pediatric medicines. **Method:** Narrative review of the literature through the electronic databases PubMed and Google Scholar. Articles related to the development of formulations, use of electronic tongue, and abstracts without access to the complete work were not considered. **Results:** Flavor is considered one of the main determinants for medications' adhesion in pediatrics. Access to palatable and safe pediatric formulations can have a substantial effect on infant morbidity. Adults and children appreciate flavors in different ways, so sensory testing with children is the most reliable method regarding formulations for this population. Studies of sensory perception and acceptance of medications already used by children may be ethically feasible, given the concerns about research with children. **Conclusions:** Sensory analyzes should be carried out whenever there is a new formulation to be introduced on the market, addressed to different age brackets and cultural contexts, in order to assess the product's acceptability.

KEYWORDS: Pharmaceutical Preparations; Medication Adherence; Children; Sensory Analysis; Taste Acceptability

RESUMO

Introdução: Crianças geralmente rejeitam medicamentos não palatáveis. Formulações pediátricas contêm edulcorantes e flavorizantes para mascarar o sabor desagradável e evitar problemas na administração e adesão. A avaliação do sabor é parte essencial do desenvolvimento de medicamentos líquidos orais. **Objetivo:** Este trabalho visa contextualizar a palatabilidade, sua avaliação e influência na aceitação de medicamentos pediátricos. **Método:** Revisão narrativa da literatura através das bases eletrônicas PubMed e Google Acadêmico. Excluíram-se artigos relacionados ao desenvolvimento de formulações, uso de língua eletrônica e resumos sem acesso ao trabalho completo. **Resultados:** O sabor é considerado um dos principais determinantes para a adesão em pediatria. O acesso a formulações pediátricas palatáveis e seguras pode ter um efeito substancial sobre a morbidade infantil. Adultos e crianças apreciam gostos de formas diferentes, então testes sensoriais em crianças são o método mais confiável para a avaliação do sabor de formulações para esse público. Estudos da percepção sensorial e aceitação de medicamentos já utilizados pelas crianças podem ser eticamente viáveis, dadas as preocupações acerca de pesquisas com crianças. **Conclusões:** Análises sensoriais devem ser realizadas sempre que se deseje introduzir no mercado uma nova formulação, destinada a diferentes faixas etárias e contextos culturais, a fim de avaliar a aceitabilidade do produto.

PALAVRAS-CHAVE: Preparações Farmacêuticas; Adesão à Medicação; Criança; Análise Sensorial; Aceitabilidade do Sabor

[I] Universidade Federal do Ceará (UFC), Fortaleza, CE, Brasil

[II] Empresa Brasileira de Pesquisa Agropecuária (Embrapa), Fortaleza, CE, Brasil

* **E-mail:** garruti.marina@gmail.com

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INTRODUCTION

According to the World Health Organization, ideal medicines for children should be appropriate for the child's age, physiological conditions and body weight. They should also be available in flexible oral dosage forms, i.e. forms that can be ingested easily as a whole, dissolved in liquid or mixed with food[1] to meet the clinical needs and capabilities or preferences of different age groups between childhood and adolescence[2,3]. They should also be readily produced using minimal amounts of non-toxic excipients, in a final stable, commercially viable, low-cost and taste-pleasant formulation. Moreover, they must cause minimal impact on the child's lifestyle and have scientific data that support their preparation and determination of expiration date, as well as chemical, physical and microbiological stability information[4].

The administration of a pediatric medicine is optimized when the formulation does not require time to prepare the dose and is easy to swallow, as most liquid preparations[4,5]. When available, liquid formulations are almost always chosen for children[6]. With the use of suitable measuring devices, such as syringes for oral administration, for example, it is possible to adjust different doses for administration in children of different ages and weights with flexibility and accuracy in measuring the dose from a single formulation[2,7].

The term "palatability" refers to the quality of what is palatable, that is, pleasing to the sense of taste [7,8]. Bitter substances cause certain innate rejection reflexes in humans[9]. A few hours after birth, babies already notice the taste differences[6]. The taste buds and olfactory receptors are already well developed in childhood[10], with a natural tendency in children to prefer sweet and reject bitter food. Children generally refuse anything that does not taste or smell good, and it can be extremely difficult and exhausting to administer medicines to children, especially in cases of chronic diseases, when they need daily long-term medication. This explains in part why parents often use sugar or honey to mask the taste of medicines to make them more appealing[10].

Many drugs have an intrinsic unpleasant taste[11]. Palatable drug products are those in which the aversive sensory attributes have been minimized, masked or eliminated in the formulation[12]. The bitter taste of the active principle is more difficult to mask because it leaves an aftertaste (a taste that remains on the palate after the ingestion of the medicine)[13]. A flavoring agent is a natural or artificial substance that is added to the formulation to give or enhance its taste and aroma, while the sweetener imparts a sweet taste to the preparation[14]. The use of sweeteners and flavorings is of paramount importance to improve palatability, since they usually help conceal the unpleasant taste of a product. Oftentimes the chemical properties and taste of a drug determine the choice of the flavoring additive in a way that it is effective in masking the flavor without adversely affecting the drug's stability or bioavailability[15].

Sensory Evaluation is defined as "A scientific discipline used to evoke, measure, analyze, and interpret those responses to products such as food, cosmetics and medicines that are perceived by the senses of sight, smell, touch, taste, and hearing[16]. Principles of experimental planning and statistical analysis are applied to prepare the (sensory) samples and to analyze the results of the use of senses in product evaluations[17].

This paper aims to contextualize the importance of palatability and the conduction of sensory analysis of medicine formulations design to pediatric population, in terms of the acceptance, ease of administration and compliance with the treatments.

METHOD

We carried out a literature survey in the form of a narrative review, which is appropriate to describe and discuss the development or the state of the art of a certain subject, from a theoretical or contextual perspective, without, however, having the systematization that allows the reproduction of the method. It consists of the search of studies in the published literature and critical analysis of the studies found[18].

The studies were searched on PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.com/) electronic databases, without time delimitation. They were restricted to the English, Spanish, French and Portuguese languages.

Searches were made from October 2016 to April 2017, using the following keywords: Sensory analysis or Taste assessment or Palatability or Taste acceptability and Pediatric formulations or Children or Drug, in English and in Portuguese.

At first, the texts were selected according to their titles and abstracts. Only papers dealing with the palatability of drug formulations were read in full. We excluded the papers related exclusively to the development of formulations, papers reporting the use of electronic language and papers to which we did not have access to the full text. Special attention was paid to publications dealing with pediatric medicines and Brazilian studies.

RESULTS AND DISCUSSION

We found 91 publications, of which 48 were included in this paper, in English, Portuguese and French languages. Seven of these publications were made in Brazil. Because of the lack of time delimitation, we could find studies from 1984 to 2017, so we could understand the discussion of this problem over the past three decades.

We grouped the publications based on the analysis of the findings, according to the topics they addressed predominantly. A single paper could address more than one topic. Thus, we obtained four categories covering the relationship of palatability in medicine selection and compliance, sensory analysis of medicines, how the industry relates to this practice and how it is

performed with children. The categories correspond to the following subsections.

Selection, compliance and palatability of medicines

When there are similar alternatives in terms of efficacy and safety, other factors may come into play to determine the best medicine in a given context. Some of these factors are the inclusion of the drug into therapeutic forms, cost and factors that influence the ease of administration, acceptance and compliance with the treatment, such as the length of the treatment, the number of daily doses required and the sensory attributes of the formulation, both for children and adults[19,20,21,22,23,24].

Children's compliance is influenced by several factors, such as adverse events and toxicity, dosage schedule, length and frequency of treatment, individual, emotional and cognitive characteristics, family stability, caregivers' motivation, detailed verbal and written instructions, social support, cost of medicines, quality of the health system and the disease itself[25,26]. However, an acceptable flavor is especially critical in pediatric patients[7,27]. In order for children to comply with a treatment regimen, in addition to the caregivers' commitment, it is important that the taste of the medication be acceptable, thus reducing the struggle they face at the time of administration[13,28,29].

Lin et al.[25] carried out a study in which Canadian physicians who treat children and adolescents (aged zero to 18 years) with the Human Immunodeficiency Virus (HIV) answered a questionnaire about the palatability of the medicines they prescribed. They referred to the active ingredient and not to the brandname. All the physicians reported that children hated liquid ritonavir. Despite this, there was a greater tendency to prescribe liquid ritonavir as first-line treatment compared to other liquid formulations. Nelfinavir and amprenavir liquids were also classified as not pleasant to children. The use of liquid ritonavir generated the need to change treatment due to its low palatability in more than 50% of the cases. In this study, physicians' knowledge and perceptions of patients' preferences and the low palatability of certain medicines rarely prevented them from prescribing them for children although palatability is one of the factors that most influence children's compliance with drug treatments, causing better results and less family stress[23,25].

In another investigation, Gee et al.[13] brought together medical and pharmacy students, medical interns and pediatricians to evaluate the sensory characteristics of 24 antimicrobial formulations. At the occasion, the taste of the antibiotics and the effects that it can have on the compliance with the treatments were discussed. After a month, an interview was made with the participants about how these activities affected their prescribing and counseling habits, and 42% of the respondents reported that their habits had changed. Among the changes reported were: consideration of flavor and texture of the formulation at the time of prescribing, not prescribing medicines of recognized bad taste and prescription of crushed tablets instead of liquid formulations with unpleasant taste. Although prescription of crushed tablets is inadvisable when there is a suitable alternative, this attitude demonstrates that the physicians considered the importance of palatability for treatment success. Nevertheless, many respondents reported that their prescribing habits had not changed as there were no other equivalent options for some medicines like clindamycin and metronidazole.

One of the most important factors to consider in the selection of medicines for children is how easily the doses can be swallowed and retained. Medicines with bad taste associated with high volume doses lead to refusal and even vomiting at the time of administration[20]. Palatability seems to be a preponderant factor in the preference for certain medicines, either in the use of antibiotics in community-based services with basic healthcare[19,24], in the treatment of acute attacks of asthma[20,21] or in chronic diseases like nephropathies[22].

In the study by Wollner et al.[30], the two factors that most increased compliance were the lower number of daily doses and the acceptance of the taste. The taste of a pediatric formulation is considered by several authors to be one of the main determinants of pediatric compliance[13,21,31,32,33,34,35,36,37,38,39,40]. Studies have shown that strategies used to improve patient compliance such as information leaflets, self-monitoring calendars and telephone reminders do not have as much influence on compliance with treatments in children as the taste of the formulation[13,41]. Particular attention should be paid to cases in which the drugs are not available in formulations suitable for children and it is then necessary to change the pharmaceutical form or concentration of the drug in adult formulation, which, in addition to dosage and stability problems, might hinder palatability[4,41].

Resistance to bitter or bad taste liquid formulations may encourage parents to alternatively try medicines in other pharmaceutical forms, like tablets, which are often crushed and mixed with food[6]. Although it may mask the taste of the drug, mixing medicines with food, fruit juice or yogurt may have negative effects on bioavailability, either because of drug-food interaction or inaccurate dosage[42].

The literature reports difficulties in administering medications to children due to taste. McCrindle et al.[43] reported that one of the first available formulations of bile acid sequestrant resins for treating hypercholesterolemia was in the form of a powder to be mixed with a liquid chosen by the patient. The palatability of this preparation was not good, so both adult and pediatric patients had problems following the dosing regimen, leading to failure in complying with the treatment. Later, tablets of these drugs were developed to overcome these problems. However, the tablets were relatively large and pediatric patients with difficulties in swallowing those tablets continued to have problems complying with the treatment.

Lucas-Bouwman et al.[44], studying the treatment of acute asthma in children with prednisolone in two formulations (oral solution or crushed tablets), found that the oral solution was better tolerated. Vomiting was observed in 23% of the patients who took the tablets, but in none of the patients who took the solution, probably because the solution had excipients such as sweeteners

and flavorings that help mask the taste of the drug. Prior to the availability of oral corticosteroid solutions, physicians fall back on crushed tablets, which were often not tolerated by children. This left them with only one alternative: drug parenteral administration for treatment of severe acute asthma[45]. Gries et al.[45] in an evaluation children treatments with mild to moderate exacerbation of asthma with a single dose of dexamethasone acetate intramuscularly or with five days with oral prednisone (suspension or tablets, according to patient's choice) reported that many parents preferred intramuscular administration because of the struggle they faced to administer the oral drug for five days, although children often dislike injections.

Acknowledge the importance of palatability at the time of prescribing is part of patient-centered care and may improve compliance and the clinical outcome[27]. According to Gee and Hagemann[13], it is important that healthcare professionals are aware of issues related to compliance with medicinal therapy in pediatric patients, in which palatability plays a key role.

Sensory Analysis of medicines

The palatability of medicines is the subject of many papers published in scientific journals around the world, discussed below.

In 1984, when few studies in this area had been published, Sjövall et al.[35] made an investigation comparing two methods of assessing the taste preference of three formulations of bacampicillin in pediatric patients. They noticed that the hedonic scale was the most appropriate method. Uhari, Eskelinen and Jokisalo[39] investigated the acceptance of pediatric patients regarding pairs of pharmacologically identical phenoxymethylpenicillin and erythromycin formulations that differed only in taste and manufacturer. The brands were not mentioned. The time required for administration was used as the criterion for the acceptance evaluation. They observed that one of the formulations of phenoxymethylpenicillin tended to be more accepted, but with no significant difference between them, and that one of the formulations of erythromycin was significantly more accepted than the other.

Evaluations of sensory attributes of corticosteroid medicines have been published with different populations of participants. Gerson et al.[46] evaluated three nasal corticosteroids in adults. Several sensory attributes related to the type of formulations in question were evaluated, like smell, taste, moisture, irritation and comfort. This showed that triamcinolone was preferred over beclomethasone and fluticasone in the smell and taste attributes. The study of Meltzer et al.[23], done by researchers from a pharmaceutical company, analyzed the preference of adult patients between nasal sprays of fluticasone propionate and the most recent, fluticasone furoate, produced by the manufacturer. The study investigated sensory attributes like smell, taste, aftertaste, irritation, among others, in addition to the overall preference between the two drugs. The newer drug was preferred.

Studies comparing generic drugs with reference drugs have also been published. Since the tests required for a generic drug to be registered and released on the market do not include sensory aspects, the palatability of a generic drug may be quite different from that of the original drug. This can dramatically affect compliance with the treatment[27,47,48]. Samulak, El-Chaar and Rubin[49] compared the taste of oral pediatric formulations of reference antibiotics with their generic version in adult volunteers. For two of the formulations, original drug were significantly rated as having better taste than the other products. However, for three other medicines, at least one generic version did not have any significant difference in taste relative to its reference product.

A similar study was carried out by El-Chaar et al.[50], with children aged 3 to 14 years treated with antibiotics. The study concluded that the reference presentations are not necessarily better accepted than their generic equivalents. Despite the taste preference for the reference presentation of trimethoprim-sulfamethoxazole, children did not discriminate the other medicines in relation to preference between the reference presentations and their generic ones. In Japan, Ishizaka et al.[48] compared taste, granularity and dose uniformity of 11 generic formulations of clarithromycin with the reference product. They found considerable variations in granularity between various pairs of products. In France, in 2009, Cohen et al.[47] observed children using liquid antibiotic formulations, both generic and reference, at home, and assessed acceptance and palatability, among other aspects of the treatment, through the children's parents. Differences in palatability were found between generic and reference formulations of amoxicillin + clavulanate, but not in amoxicillin formulations alone. The authors believe that this difference is due to the intrinsic bad taste of clavulanate, which makes the taste of the medicine difficult to improve[47]. Therefore, if the generic medicine is more palatable, its choice becomes even more advantageous. If compliance is significantly higher with the reference drug than with generic formulations, the prescription of more expensive reference products may be warranted. However, if compliance is similar, the least expensive product should be used[49,51].

In 2013, a systematic review of the literature was published[52]. It evaluated the tools used in studies of palatability and ease of swallowing in clinical trials with oral pediatric formulations during the years 2008 to 2013, in which 27 papers were included in the final analysis. The authors highlighted the multiple approaches that are used to evaluate palatability in pediatric populations. They concluded that the palatability of formulations is often evaluated in clinical trials of pediatric formulations using visual scales, without a standard statistical methodology to analyze the results. However, these scales have been widely accepted by the scientific community. An example of a visual scale is the child-appropriate hedonic scale, in which the taster expresses his or her acceptance of the product following previously established categories that vary gradually, described by a series of drawings of facial expressions ordered in a sequence that ranges from a smile (indicating the approval of the product) to a sad face (which indicates the disapproval of the product). Another example is the visual analog scale, which consists of a continuous line, anchored at the ends by terms that correspond

to the intensity of some attribute, low on the left and high on the right end. In this scale, the judge marks his or her perception at any point on the line.

Despite the reported importance of palatability for therapeutic compliance, in this study, limited evidence on the correlation between them was identified in pediatric patients[52].

In 2017, a further literature review was published[51]. It was oriented at the acceptability of pediatric medicines in various pharmaceutical forms, including tablets, dispersible and chewable tablets, mini-tablets, capsules, mini-capsules, oral liquids, lozenges, among others. Nineteen publications were specifically focused on evaluating the palatability of oral formulations for children. This study highlights that more information is needed regarding the influence of sensory attributes besides taste (shape, size and volume) on the palatability of dosage forms different from oral liquids (like mini-tablets and lozenges)[51].

In Brazil, few studies have been found in the literature reporting sensory analysis of pharmaceutical products, mostlyassociated with the development of new formulations. Fregonezi-Nery et al.[53] evaluated three formulations of albendazole subjected to different storage conditions with 24 trained judges and found differences between control and storage samples, concluding that sensory analysis is an important tool in the quality control of pharmaceutical products. In the study of Leite[54], four mouthwash formulations were made with microemulsions containing extract and essential oil of *Baccharis dracunculifolia*. In addition to physicochemical analyses, these formulations were submitted to sensory analysis by preference test. One of them was preferred over the others. Batista and Siqueira[55] evaluated the efficacy of flavoring and sweetener combinations in masking the bitter taste of ranitidine in 20 volunteer users. It has been found that, in formulations with sucrose, the flavoring that showed the best results was raspberry, but fructose in association with saccharin is more effective at masking the bitter taste of ranitidine, regardless of the flavoring used. In 2011, Gonçalves, Srebernich and Souza[56] developed and evaluated a dermocosmetic formulation (topical use) based on propolis extract for stability and sensory characteristics. In that study, they concluded that the association of propolis extract and tocopheryl acetate seemed promising, due to the sensory preference and to the good stability.

In 2012, Isaac et al.[57] presented a critical review on the sensory analysis of cosmetics, as well as results of sensory tests obtained by the research group. They considered that the sensory analysis is a useful tool to obtain products that are not only safe and effective, but acceptable to consumers.

In the development of a nanoencapsulated praziquantel formulation, Fonseca et al.[58] performed sensory analysis with a trained panel at two moments: immediately after reconstitution and 10 minutes after the reconstitution. Sensory evaluation did not detect the bitter taste of the drug immediately after reconstitution due to the encapsulation and the high content of sweeteners. However, the bitter taste was perceived 10 minutes after dispersion of the freeze-dried solid into water, which indicates fast release of the drug. The authors considered the possibility of prolonging the release time to avoid the appearance of a bitter taste in the mouth after exposure to the medicine.

In 2016, Medeiros et al.[59] analyzed the acceptance of extemporaneous formulations of captopril and furosemide, sweetened and flavored in three flavors in children with heart diseases who were taking these drugs. The evaluation was done through two approaches: the responses given by the caregivers and the researchers' direct observation of the children's reactions, using a hedonic scale. Suspensions in neutral and strawberry flavors were considered accepted for both drugs. The results obtained from the two approaches were compared using Pearson's linear coefficient, which showed a moderate correlation between the two methods for captopril formulations, but showed no correlation in the results of furosemide formulations. The neutral flavor results showed that addition of flavorings did not influence the acceptance of the suspensions. It could therefore be avoided and represent a safety advantage for babies and newborns. The evaluation made by the caregiver through the hedonic scale was considered the most discriminative method of acceptance in young children.

Pharmaceutical Industry and Sensory Analysis

The development of palatable pediatric formulations is a considerable challenge that pharmaceutical industry is still facing so that adequate preparations are available for all age groups and accessible to the entire population[3]. Pharmaceutical companies invest time and resources in adopting various flavor masking techniques to develop palatable products[60]. To achieve this objective, evaluating formulations flavor in the process of developing a new oral formulation is essential[34]. However, sensory analysis of drugs at early stages of their development is very complex, since new molecules cannot be tested by humans because of the lack of adequate toxicological data.

Information on product taste may come from various methods, like electronic language, cell- or animal-based models and human panel assays[37,60]. With the progress of the pharmaceutical and food industries in flavor modifying techniques, the importance of sensory evaluation is steadily increasing[31]. It is important to evaluate and classify products taste in a scientifically reliable manner[35]. Certain *in vitro* and *in vivo* techniques for predicting taste, such as electronic language technology and animal models, are making some progress, however, they should be efficient and inexpensive. In 2007, Anand et al.[60] described the current status of *in vitro* and *in vivo* methods to measure the sensory characteristics of pharmaceutical products. The authors stated that sensory analysis in humans was the most widely used technique for evaluating the taste of medicines or formulations under development. Nevertheless, their use is limited because of individuals subjectivity, potential toxicity of new drugs and ethical issues related to the recruitment of tasters, especially children, making it a particularly difficult task when working with pharmaceuticals[60]. Nonetheless, consumer testing is routinely performed with children,

results of these studies howeve, usually remain in the property of the companies that sponsor them[61].

According to Anand et al.[60], the emerging *in vitro* approaches could result in a decrease in reliance on human panel assays. However, in a later article, published in 2008[31], the same authors provided an overview of sensory evaluation trials in human volunteers. They commented that, despite the new *in vitro* approaches, sensory evaluation trials are and will continue to be the standard, preferable and most reliable approach to evaluate taste, since these new *in vitro* approaches are still dependent on human trials for validation purposes. *In vitro* approaches have emerged as ancillary methods, but they cannot replace assays with tasters' panels[31].

In an article published in 2013[62], reviewing an electronic language technology and its applications in food, beverages and pharmaceuticals, the researchers considered that the evaluation of all tastes and sensations perceived by humans is only possible with the combination of different techniques. Furthermore, humans have other perceptions such as smell, texture, visual appearance and factors based on cultural knowledge, such as preference, experience and memories not captured by *in vitro* techniques[62].

The European Medicines Agency (EMEA) establishes guidelines for the conduction of clinical research and development plans in order to register medicines for the pediatric age group. These guidelines emphasize the importance of overcoming the challenges related to medicine palatability[63,64]. For the plan preparation , drug registration applicant shall provide an overview of the studies carried out or planned measures, including studies on palatability and formulation taste improvement[27]. As we have seen so far, these studies are particularly relevant and an intrinsic and essential part of the development and quality control of oral drugs targeted at populations with special needs (pediatrics, geriatrics, patients suffering from mental disorders and people with swallowing disorders)[7,31,37]. In addition to the benefits for patients, children in this case, bad taste masking provides commercial gains to laboratories, due to greater commercial success and greater demand for products, protection of patents for new formulations of masked taste and also, in some cases, extended marketing exclusivity rights[52].

Sensory Analysis of medicines with children

Results of sensory evaluations of pediatric formulations in healthy adult volunteers are not always valid for other populations, particularly children[35]. Adults and children present differences in pharmacokinetics and pharmacodynamics of medicinal products[65], but there is another important difference that is often overlooked: children prefer significantly higher concentrations of sweeteners when compared with adults[6,66]. Furthermore, some children are more sensitive to bitter taste than adults, making the bad taste of some drugs more of a problem for them[6]. Pharmaceutical companies try to announce that the taste of their medicines is more acceptable to pediatric patients than their competitors, even when evidence of such claims is based on studies with a small number of adult tasters and do not include children[32,39]. Thus, since an adult and a child can evaluate tastes very differently, acceptability of pediatric formulations should be evaluated by children[7,10,19,32,39]. Sensory tests in children are considered as the most reliable method for predicting how taste will be accepted, since children are the target population of most masked taste formulations. *In vitro* methods cannot yet discriminate or take into account differences in preferences between adults and children[31,34,37].

Matsui et al.[34] evaluated palatability of four antibiotic suspensions for children and adults (mentioning the brands) and compared results. Although there were similarities in responses regarding taste of three antibiotics and in selection of the best flavored antibiotic (azithromycin), there was a significant difference in proportion of children and adults who chose each of the antibiotics as having the worst taste. Children tended not to like clarithromycin and adults tended not to like erythromycin-sulfisoxazole. In view of this, authors conclude that palatability assessment of medicinal products intended for pediatric use should be done with children[34].

In addition to divergences between adults and children, preferences may also differ between age subgroups in pediatric population as well as between different geographic and cultural regions[35,67]. Newborns and younger children tend to prefer tastes and flavors that are familiar to them[66]. Ethnic and cultural diversity must be taken into account when determining the taste that is suitable to a specific country or community. What is accepted as palatable is affected by customs and food flavors typical of each country[40]. In addition, the medicines taste perception is likely to differ between healthy and sick children[64].

However, there are ethical questions regarding the conduction of drug studies with healthy children. Even if the drug is known to have a good safety profile and if we try to prevent children from swallowing the drug when they taste it, research with children is always a sensitive and delicate matter. Some argue that healthy children are also vulnerable, just like children with some special disease or condition, since they are not old and competent enough to consent in a free and autonomous manner[64]. It would be extremely helpful if palatability studies with adults could be validated in a way that could be transferred to the pediatric population, which would simultaneously make them acceptable to regulators and ethics committees. One way to achieve this assessment could be to identify adults with particular childlike taste preferences. Methods for the identification of tasters with special sensory capabilities are a commonly used approach in the food and cosmetic industry[64].

Evaluation of sensory perception and acceptance of medicines already used by children with health conditions that require their prescription are found in the literature, like in El-Chaar et al.[50], Cohen et al.[47] and Martinez et al.[67], who evaluated newborns' acceptance of two formulations with vitamin D3. Similarly to this study, in 2011, Lava et al.[68] compared the acceptance of two vitamin D3 formulations administered to babies, where the mothers rated their babies' facial reactions, in a method

analogous to that used by Medeiros et al.[59]. Once treatments target population and studied population of these studies coincide, problems concerning ethical issues can be overcome.

CONCLUSIONS

The development of new drug formulations for children should always consider palatability in order to avoid future problems in their administration and treatment compliance. Formulations of the same drug from different manufacturers with different compositions may have differences in acceptability due to palatability. On the other hand, the same formulation in different cultural contexts can be perceived distinctly. Ideally, therefore, sensory analysis should be carried out whenever a new formulation of a drug is introduced on the market for different age groups, populations and cultural contexts, so that we can assess product acceptability . Since an adult and a child can appreciate t tastes very differently, in theory, pediatric medicine acceptability should be evaluated by children.

Ensuring access to palatable, safe and appropriate pediatric formulations for pediatric population can have a substantial effect on infant morbidity as it contributes to correct and rational use of pediatric medicines.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.