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DEVELOPMENT AND SENSORY ANALYSIS OF ORAL VEHICLE TO CARRY DRUGS FOR PEDIATRIC USE

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ABSTRACT

The shortage of pharmaceutical formulations appropriate for different age subgroups that compose of the pediatric population, requires health professionals to prepare extemporaneous formulations. The present study deals with the development of a low-cost vehicle to be used in transformation of solid dosage form into liquid form for use on children, the study of the product's stability and the acceptability by healthy children. We formulated preparations with different suspending agents, and evaluated in terms of manufacturing facility, flavor, compatibility with actives and rheological behavior. The vehicle without actives was investigated by acceptance testing with the hedonic scale, involving 61 healthy children, between the ages of four and twelve years. The vehicle with the mint, cherry and strawberry flavors was widely accepted by children. Has pseudo-plastic behavior, density close to 1.00, sweet flavor, low cost, few components, absence of unsuitable substances to the health of children, physical, chemical and microbiological stability and acceptability. The vehicle was successfully employed for the preparation of oral liquid dosage forms containing furosemide, hydrochlorothiazide and valganciclovir with stability above 3 months.

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INTRODUCTION

The absence of suitable formulations, i.e. drugs in pharmaceutical forms, concentrations and doses suitable for use among children, is a particular aspect in the lack of pediatric drugs. Although adults may use solid oral dosage forms such as tablets or capsules, which are acceptable to most patients, children and infants find it difficult or impossible to swallow solid dosage forms, which are the forms most often put on the market [1,2]. The population of pediatric patients includes neonates, infants, toddlers, children and teenagers, and those individuals with very different developmental characteristics and therapeutic needs that affect their use of medicines [3]. In particular, pediatric clinical practice requires a wide range of dosages and concentrations that allow administration of the correct dose according to the patient's age, as well as acceptable dosage forms for the different age subgroups. The most feasible solution would be a single flexible dosage form that would fit all these variations, at present the development of multiple preparations of the same drug is usually not commercially viable [4].

This reality, which is seen in many regions of the world, has resulted in dissemination of the practice of adaptation of adult dosage forms for use among children, especially in the cases of newborns and infants [5]. The preparations thus obtained are considered to be extemporaneous formulations, and they result from reformulation of oral, injectable or topical medications [6-9]. Such preparations have limited storage life, given that the conditions for the drug's stability have been changed. These formulations are considered to be off-label, since changes have been made to the pharmaceutical form of products registered in the country [8]. Although their use is accepted, it is not considered ideal, since it is frequently not based on clinical studies of pharmacokinetics and bioequivalence and also lacks stability studies [5]. Added to this, there are the risks of technical limitations and inadequate conditions for handling medicines, which is common in situations with scarce economic resources [9-13].

The extemporaneous formulations, presented as liquids or as suspensions ready for use, have in common lower physical, chemical and microbiological stability than the solid dosage forms from which they originated. Chemical instability is characteristic of these drugs and can be minimized through strategies such as pH control, use of antioxidants and non-aqueous vehicles. Microbiological instability is inherent to the presence of water in the preparation, which promotes microorganism proliferation, but can be controlled through using preservatives. Finally, physical instability is characterized by sedimentation of insoluble or low-solubility drugs, caused by difficulty in achieving re-dispersion or crystal growth, and this can be reduced through using vehicles with pseudo-plastic rheological behavior and through better control over the product storage conditions. Despite these limitations, extemporaneous preparations can effectively fulfill their functions, even with their short expiration dates [4, 14, 15]. One problem with using extemporaneous formulations is the unpleasant taste of re-suspended active agents, which usually taste bitter. Palatability, which includes the attributes of appearance, flavor, aroma and texture, is an extremely important factor in drug products. Pleasant-tasting drugs, especially for treating chronic conditions, are associated with greater willingness among children to take the medication, and thus better adherence to treatment [16, 17]. Therefore, sensory analysis is an essential part of the development and quality control of oral formulations adapted to the needs of the pediatric population, since children and adults differ with regard to their preferences for flavors [18, 19].

To simplify the process of preparing oral extemporaneous formulations and make them safer, it is convenient to obtain a vehicle that is suitable for the drug and for the target population. Some vehicles of this nature are commercially available in different countries. Such vehicles may be flavored in order to mask unpleasant tastes and adapt them to patients' preferences [20]. They should not contain excipients that may put the child's health at risk, with due regard to their age and medical condition [21, 22]. Vehicles are formulations that have the function of adding volume to pharmaceutical preparations by diluting them to an appropriate concentration, thereby providing greater ease of administration or serving as a base in situations in which the drug is incorporated in solid form after conversion into powder or granules [20]. Suitable vehicles for pediatric use are marketed in the United States and imported from other countries. However, importation leads to bureaucratic difficulties and also increases the product cost, such that it becomes impractical in situations of scarce economic resources [15, 23].

This study aims to develop a low-cost vehicle for use in processing solid forms into liquid forms for use among children. It also includes assessment of the product's stability and its acceptability among healthy children.

MATERIALS AND METHODS

PROPOSED FORMULATION

Firstly, information was found in the literature regarding ingredients that are safe to use for children and which might be useful for the composition of the vehicle [24, 25, 26, 34]. From this, preparations with different suspending agents (carmellose, xanthan gum, methylcellulose, hypromellose) were formulated separately and in combinations, in varying proportions, and these were evaluated in terms of ease of preparation, flavor, compatibility with active agents and rheological behavior [34].

After choosing the suspending agent and all the components required for the quality of the vehicle (preservative, sweetener, chelating, humectant) the liquid formulation was prepared by dissolving preservatives in warm water, along with edetate and sucralose, while the suspending agent was dispersed in the humectant agent separately. The aqueous solution was then quickly poured into the dispersion of the suspending agent, while stirring vigorously to homogenize the mixture [27].

The concentrated formulation was prepared by dissolving the preservatives in the humectant agent, followed by dispersion of all the components in the same solvent, without water. The final product was then diluted at the time of use, at a ratio of 50 ml of concentrated formulation to 950 ml of water, under mechanical agitation to obtain a liquid formulation with the same final composition as before employed.

Through replacing the liquid humectant agent with a solid aqueous soluble diluent, a solid formulation could be obtained, such that 50 g could be dissolved in 950 ml of water, thus resulting in a vehicle ready for use.

The aqueous liquid vehicle and the reconstituted solid vehicle were evaluated for physical stability (pH, density and rheology) and microbiological stability (counting viable microorganisms). The concentrated preparation was evaluated after dilution, resulting in liquid vehicle. In solid form, the ability to acquire the same quality of liquid product at different times after storage was evaluated. The pH was measured using glass electrode, calibrated with buffer pH 4.0 and 7.0. The density was measured in a glass picnometer and analytical electronic balance. The rheological behavior was measured in viscosimeter (Haake Visco Tester 6L), with spindle L1, over a velocity range from 0.3 to 200 rpm [25].

The liquid vehicle was subjected to flavoring with different flavors, in order to determine the minimum amount of each flavoring that would result in a mixture with pleasant and noticeable flavor. Assays were conducted among healthy adult volunteers, who received 5 ml of the vehicle with decreasing amounts of each flavoring, interspersed with sips of water to cleanse the mouth between the tests. After determining the minimum amount of each flavoring, the three flavors that provided the most pleasing results were selected for subsequent tests.

SENSORY ANALYSIS

The acceptability of the vehicle without active agents among healthy children was investigated through overall acceptance tests on a hedonic scale [28]. These tests were conducted on 61 healthy children of both genders, between the ages of four and twelve, who were attending an educational institution in a northeastern Brazilian city. For all participants, parental consent was obtained through the requirement to sign an informed consent statement (Research Ethics Committee of the Federal University of Ceará, under protocol no. 41/12).

The samples used were the liquid vehicle flavored with mint, strawberry and cherry flavors, which were presented at room temperature in balanced order and blind coded [29]. After the test had been explained, each child received about 5 ml of the first sample on a disposable spoon. Immediately after tasting the sample, the child was asked to indicate the figure on the scale that best represented how much he/she liked the taste, according to his/her own judgment [28]. Then, after the child had taken a sip of water to cleanse the mouth, he/she was asked to do the same with the subsequent samples. The responses were then recorded by the researcher. A gender-specific facial-verbal hedonic scale depicting seven degrees of satisfaction was used, ranging from 1, "hate it", to 7, "love it" (Figure 1) [30]. The drawings of facial expressions were specially made for this study, in an attempt to improve the model previously used by other authors [21, 32].

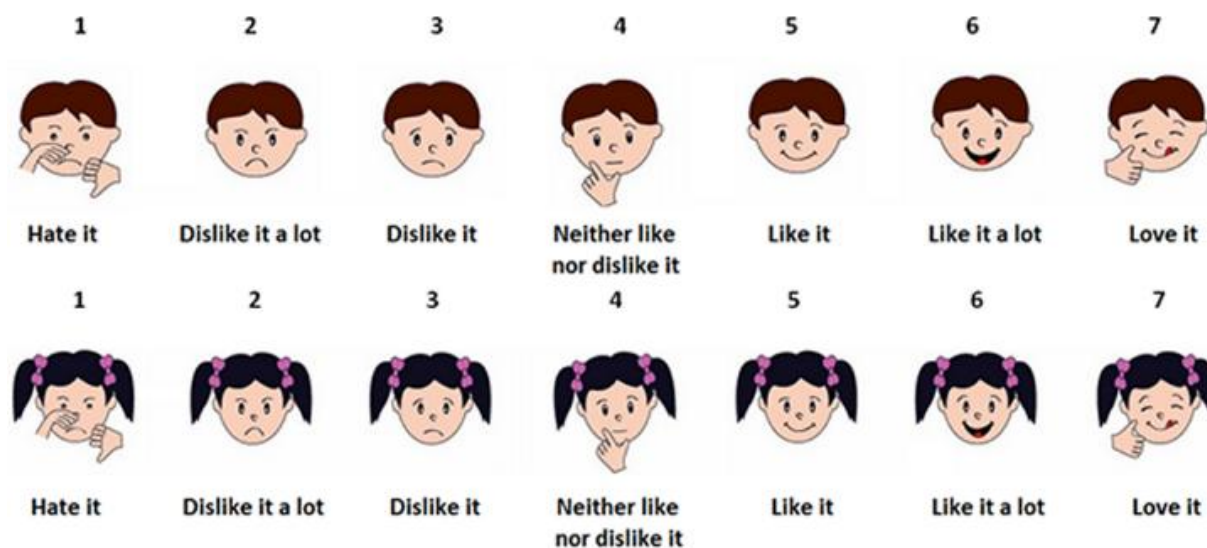


Figure 1 - Gender-specific facial-verbal hedonic scales [30, 31, 32].

The acceptance test results were evaluated using Analysis of variance (ANOVA) and Tukey's test in order to compare the mean acceptance, both at the significance level of 0.05, with the SAS® (Statistical Analytical System software) [32, 33]. The results were presented as frequency histograms and subjected to principal component analysis (PCA). Formulations were considered to be accepted if their calculated acceptability index (AI) reached 70%, such that $AI (\%) = \text{mean hedonic value given to the sample} \times 100 / \text{maximum value given to the sample}$ [11]. The results were analyzed according to the participants' age group (4-6, 7-9 or 10-12 years) and gender.

PHARMACEUTICAL COMPOUNDING

Tablets containing furosemide (40 mg), hydrochlorothiazide (25 mg) or valganciclovir (450 mg) were grinding with mortar and pestle or in rotor mill (fritish pulverisette 14) at 18,000 rpm through mesh 0.5 mm. Calculated amount of powder was weighted and suspended in liquid vehicle or mixed with solid vehicle. When in the solid form, this was mixed with water until the volume. The liquid dosage forms obtained (furosemide 4 mg/mL, hydrochlorothiazide 4 mg/mL or valganciclovir 50 mg/mL) were observed in drug concentration, density, viscosity, pH, sedimentation and chemical stability.

RESULTS AND DISCUSSION

From data in the literature and considering the characteristics of the excipients and the purpose of the vehicle, the components glycerol, xanthan gum, sucralose, methyl and propylparabens, and disodium edetate were selected such that they would result, when formulated, in a pseudo-plastic liquid with the following characteristics: density of around 1.01, unbuffered pH of between 5 and 7, sweet flavor, colorless and slightly opalescent. The solid form for reconstitution was a fine white powder dispersible in water. The components used in the solid form are: mannitol, xanthan gum, sucralose, methyl and propylparabens, and disodium edetate. The vehicle developed was denominated Gute.

For at least six months at 30 °C and 75% relative humidity (RH), the liquid vehicle maintained its physical characteristics, with a small reduction of viscosity, while preserving the pH and density. The effects of pH and the presence of electrolytes were almost imperceptible and were not considered significant to the vehicle quality, especially during agitation, as shown in Figure 2. The viscosity and pH of the normal vehicle, with added citric acid, ascorbic acid and sodium citrate, measured at 30 rpm velocity, with spindle L1, were 169 cP and 6.33, 123 cP and 3.35, 134 cP and 3.92 and 148 cP and 6.98, respectively. Microbiological stability was shown over the same time period and ambient conditions, with a microbial load below the limits required by the pharmacopoeias, and absence of pathogens. The solid vehicle stored for at least six months at 30 °C and 75% RH retained the ability to be reconstituted in water, thus resulting in a liquid form of quality comparable to the liquid product, and it could be stored for at least six months after reconstitution.

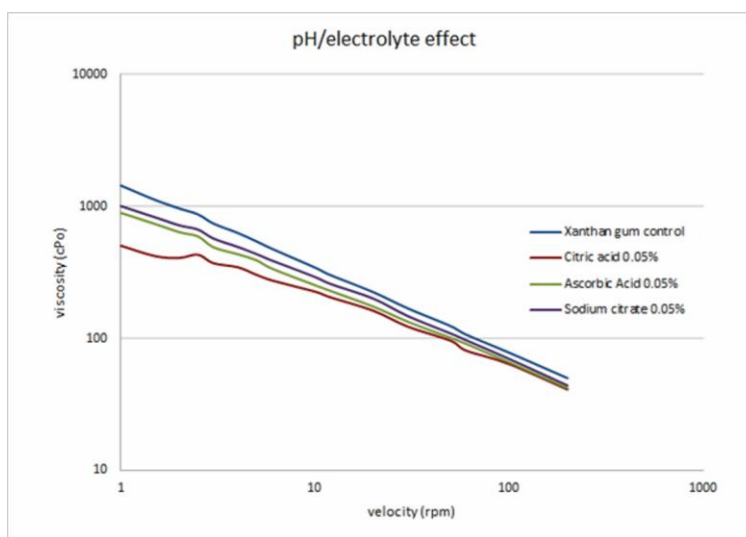


Figure 2 – Effect of electrolytes and pH on the rheological behavior of the vehicle containing xanthan gum.

In flavorization assessment, performed only with the vehicle, the volumes of flavoring, supplied by Novo Aroma, employed and considered necessary for clear perception of the flavor in 100 ml of the vehicle were: 0.58 ml of cherry, 0.66 ml of chocolate, 0.16 ml of peppermint/spearmint, 0.52 ml of pineapple, 0.46 ml of orange, 0.46 ml of strawberry, 0.50 ml of raspberry and 0.50 ml of lemon, each one used individually. Among these, cherry, mint and strawberry had the most pleasant taste.

Sensory analysis

The acceptance testing among healthy children involved 27 boys (44.3%), and 34 girls (55.7%), with mean and median ages of 7.9 and 8.0 years respectively (standard deviation 2.3 and mode 9.0).

ANOVA showed a significant difference between at least two samples, with $p = 0.0295$. The effect of the tasters presented $p = 0.1019$, thus showing that the response did not change significantly among the children. There was no significant difference in acceptance between the age groups ($p = 0.8299$) or between the genders ($p = 0.5326$).

The three flavors tested were accepted by the children, with mean hedonic scores of between 5 and 6, corresponding to the categories "Like it" and "Like it a lot", respectively (mint: 5.85; strawberry: 5.42; cherry: 5.11). Tukey's average test showed a critical difference of 0.6524 between the samples, and therefore only the mint and cherry flavors presented a statistically significant difference in acceptability. The frequency histogram of the acceptance test (Figure 3) shows the distribution of the scores attributed by the children to the samples. The regions of the hedonic scale correspond to the rejection region (from "Hate it" to "Dislike it"), indifference region ("Neither like nor dislike it") and acceptance region (from "Like it" to "Love it"). For the mint flavor, 86.9% of the responses were in the acceptance region and only 4.9% in the rejection region. For the strawberry flavor, 78.7% of the responses were in the acceptance region and for the cherry flavor, 70.5%, while 14.7% and 18.0%, respectively were in the rejection region. Regarding the scores obtained in individual categories for the mint and cherry flavors, the values obtained for the category "Love it" were 42.6% and 23.0% respectively, while for the category "hate it", the scores were 1.6 % and 6.6%, respectively.

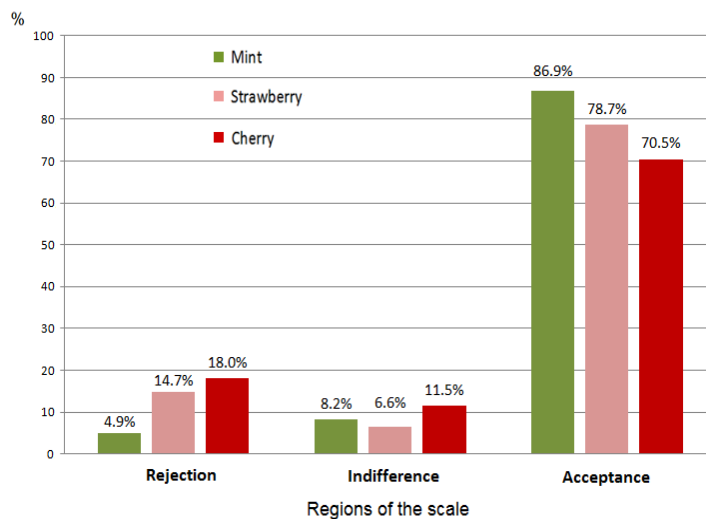


Figure 3 – Frequency distributions of children's hedonic values according to the regions of the scale.

The acceptability index of the samples was 83.57% for mint, 77.43% for strawberry and 73.00% for cherry. Therefore, these three flavors were well accepted by children: mint was the most accepted flavor and cherry the least accepted.

The principal component analysis (Figure 4) shows the individual preferences of each child. In this graph, each point is associated with one or more child, broken down by letters corresponding to gender and age. Each child is located close to the samples to which they gave higher hedonic values. The closer that a point is in the sample (mint, strawberry or cherry), the greater its acceptance was among those children. Thus, there is a concentration of children located in the upper right quadrant of the graph, showing that more children accepted the mint flavor better, while the upper left quadrant shows the children who accepted the cherry flavor better. Children in the center of the graph did not discriminate between the samples, thus indicating that they neither liked nor disliked all the flavors. It can also be seen that children of all ages and both genders were well distributed in each quadrant of the graph.

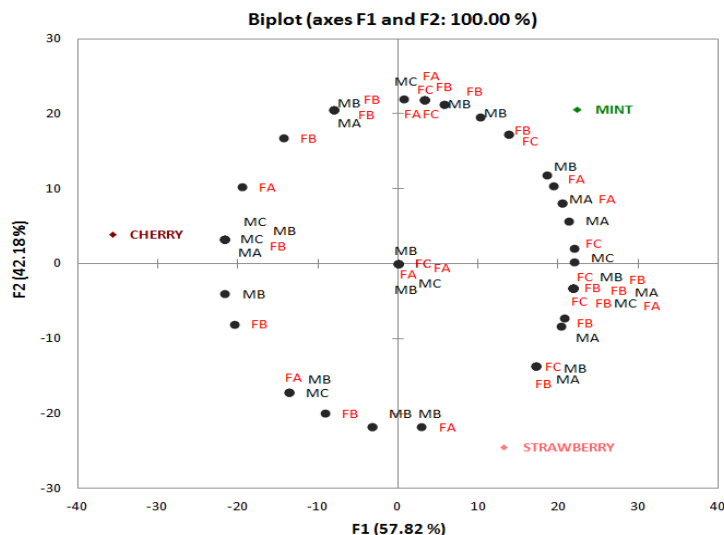


Figure 4 - Principal component analysis representing the children's acceptance of the vehicle in the mint, strawberry and cherry flavors.

F = Female (in red); M = Male (in black); A = 4 to 6 years old; B = 7 to 9 years old; C = 10 to 12 years old.

Pharmaceutical Compounding

Liquid preparations obtained with furosemide at a concentration of 4 mg/ml as a solution in alkaline pH and as suspension at acid pH presented chemically and physically stable for a period of 90 days when in Gute [43]. The flavor of the liquid preparations was improved by the use of flavoring, suspension as being more palatable than as solution because the drug is dissolved and thus give the most intense taste to the product. Furthermore, the pH near 10 also causes a change in the perception of taste of the product.

Liquid preparation containing valganciclovir at a concentration of 50 mg/ml presented as suspension obtained from the milling of the coated tablets were chemically and physically stable for a period of 160 days when in Gute [38]. There was no need to add flavoring.

Liquid preparations containing hydrochlorothiazide in a concentration of 4 mg/ml presented as suspension obtained by grinding the tablets and dispersion of the drug in the vehicle Gute were chemically and physically stable for a period of 30 days [44].

DISCUSSION

In planning for a vehicle to incorporate drugs for use among children, the challenges include achieving a stable, palatable and safe preparation with a cost that does not make the product inaccessible to those who need it. The vehicle developed in this study has these characteristics and is appropriate for incorporating active ingredients with pKa in the range 3-10, such as captopril, hydrochlorothiazide and furosemide. These drugs are frequently used in cardiology and have no suitable pharmaceutical form for use among children, in several countries [12]. For drugs with other physicochemical characteristics, the pH can be adjusted by means of alkalization or acidification, or even through a buffering agent. If antioxidants need to be used, ascorbic acid, sodium ascorbate may be added, while emphasizing that variations in pH and the presence of electrolytes produce changes in viscosity.

In choosing excipients with an improved safety profile that can be used at low concentrations to achieve the objectives, we decided to use xanthan gum, because this is compatible with various drugs, has a large range of pH stability and is produced from low-cost biotechnological resources. Sucralose, which was chosen as the sweetener, has a sweetening power 300 to 600 times greater than sucrose, and therefore is used at low concentrations [34]. The flavorings used in the present study were artificial products intended for food and pharmaceutical use; their compositions may vary between manufacturers, which can lead to different results in terms of acceptability. Furthermore, these are aldehydes and esters, and show reactivity to other organic substances. Thus, they may interact with other drugs and excipients in pharmaceutical formulations [35]. Another critical point is that the flavors are alcoholic solutions and the lowest possible amounts of them should be used, as was done in this study.

The Gute vehicle, which was presented in liquid form, was stable for at least six months, which was the length of the evaluation. This length of time is quite a suitable period for use in incorporating drugs for pediatric patients. The vehicle in solid form stored for more than six months at 30°C and 75% RH, reconstituted with water, when tested in liquid form, resulted in the same physical quality of the original reconstitution.

In the sensory analysis, no criteria was used for selecting the participants, apart from age, in order to reduce the population and situational variety that products can achieve in terms of children's personal preferences and their familiarity with drugs. Children who had any chronic disorder or who were ill at the time were also not excluded. This can be considered to be a limitation of the study, given that some diseases may hinder sensory evaluation, such as problems in the upper respiratory tract [28, 36 37]. However, the study intended to simulate drug use in daily practice, when colds and respiratory allergies often occur. Other limitations of the study were that the participants were not asked to refrain from eating or drinking before the tests and no intervals were used between samples, which would have enabled better cleansing of the taste [38].

The facial-verbal hedonic scale with seven points was an appropriate method for children over the age of four years, as already shown in the literature [9, 31]. This is corroborated by the fact that age had no effect on acceptability between the children, i.e. the responses did not differ statistically between the groups of tasters aged 4-6 years, 7-9 years and 10-12 years. ANOVA also showed that the responses did not vary significantly between the children, which mean that the groups were internally homogeneous in relation to acceptance of flavors.

The children accepted the three flavors well, with acceptability indexes of greater than 70%. The mean hedonic values showed statistical differentiation between the mint and cherry flavors, such that the cherry flavor was less accepted. The mint flavoring used in the test did not show the refreshing sensation that is characteristic of this flavor, but had a sweet taste, which is generally preferred by children [39, 40], and this may have contributed to the greater acceptance.

The principal component analysis graph relating to Gute vehicle acceptance shows that the mint flavor was better accepted than the cherry flavor, thus confirming the ANOVA results. The distribution of age and gender groups also corroborates the ANOVA result, which did not show any significant difference in acceptance between the groups. Few children (only six of them) attributed the same hedonic value to the three samples proved: these children did not consider that the flavors were different from each other regarding their acceptability.

In the case of the Gute vehicle, it is also possible that the use of flavorings may not be necessary, depending on the flavor characteristics of the active agent. This would be ideal because, although the use of flavorings in products for pediatric use increases the acceptability of these drugs, their use has been questioned by clinicians, given the possibility of adverse reactions, as occur with other excipients such as dyes and sweeteners. Other technologies have been developed for masking the taste of active agents that present low palatability, such as microencapsulation techniques, but unfortunately, this does not apply to extemporaneous formulations [41].

The Gute vehicle also achieved a desirable cost, calculated from the price of each component, the 250 ml glass bottle, label, taxes and an multiplier factor (5) to address not quantified data as how personnel, equipment depreciation, energy and income.

It has few components and low concentrations of each of them, and therefore the cost is very low, about US\$ 1.00/100 ml, thus allowing them to be available even in situations with scarce economic resources. It was demonstrated physical and chemical stability of the liquid preparations obtained with furosemide, hydrochlorothiazide and valganciclovir for up to 60 days, for which the methods and results are presented in the respective manuscripts [42, 43, 44].

CONCLUSION

The Gute vehicle, which was developed and presented in liquid form ready for use and in concentrated liquid and solid forms for reconstitution, has characteristics that make it suitable for use in carrying drugs for oral administration to pediatric patients. These features include: few components; absence of prohibited substances that are harmful to children's health; acceptability; physical and microbiological stability; and low cost. The vehicles flavored with mint, cherry and strawberry showed wide acceptance among children between 4 and 12 old years. Of these, mint was the best accepted flavor and cherry the least accepted. Flavoring of the vehicle must be done carefully in preparations containing drugs for pediatric use, particularly in those for children under two years of age, and should be avoided when possible. A vehicle such as Gute would help in the work of the person responsible for administering medicines to children in hospitals or at home, and would also reduce occurrences of errors in medication preparation and increase acceptance and treatment compliance among children. Recommend future research in the use of Gute as a carrier vehicle of drugs in pediatrics.

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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