



## Methods of administering oral formulations and child acceptability



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### ABSTRACT

**Introduction:** Children may be unable or unwilling to swallow medicines. In order to avoid or accommodate any such problems, parents may decide to administer medicines other than intended. The aim of this study was to investigate how parents administered four oral placebo formulations to infants and preschool children and how the applied methods correlated with child acceptability.

**Methods:** Parents were asked to administer a 4 mm mini-tablet, powder, suspension and syrup to their child twice on one day and to report the child characteristics and administration details in a participant diary.

**Results:** A 151 children were included. The tablet, syrup and suspension were mostly given on their own, whereas the powder was commonly given with food or drink. Generally, the higher the child acceptability (VAS-score) of the first administration of a specific formulation, the less frequently its method of administration was changed. A change in the method of administration of the same formulation involving (a larger quantity of) food or drink generally resulted in a higher VAS-score.

**Conclusions:** The joint administration of medicines with food or drink is an effective strategy to ensure swallowing. This study supports earlier findings that 4 mm mini-tablets are a suitable dosage form from infant age.

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### 1. Introduction

In young children, the correct use of medicines poses specific challenges to parents, caregivers and health care professionals that are usually not encountered in adults (Matsui, 2007; Breikreutz and Boos, 2007; Polaha et al., 2008; Bain-Brickley et al., 2011; Terry and Sinclair, 2012). For example, the medicine may not be commercially available in the required strength (a 2 mg tablet needs breaking or splitting to administer a 1 mg dose), the medicine may not be available in a dosage form that the child is able to take (babies cannot swallow large tablets), or the medicine may not be available in a dosage form that the child is willing to

take (bad taste; adequate taste, but child does not like it; recalcitrance) (Balakrishnan et al., 2007; Balakrishnan et al., 2006; van Riet-Nales et al., 2011; Walsh et al., 2014).

Clear instructions on how to overcome any administration challenges are hardly available (Ernest et al., 2012). As a consequence, parents, caregivers and health care professionals may handle medicines in ways that they consider best in a particular situation, such as breaking, crumbling or crushing tablets, mixing medicines with food or drink, or even refraining from administering them (Ernest et al., 2012; Richey et al., 2013; Milani et al., 2010). All these strategies may reduce clinical efficacy and/or increase the risk of adverse drug reactions when the dosing accuracy, chemical stability, physical stability and/or bio-availability of a formulation is affected (Choonara and Conroy, 2002; Cuzzolin et al., 2006; Bellis et al., 2013).

In a previous study amongst infants and preschool children in the domiciliary setting, we showed that the child and parent acceptability were related to the type of an oral formulation, e.g., tablet or syrup, and that there is no reason to question the

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acceptability of 4-mm tablets in children from one year old (van Riet-Nales et al., 2013). In this study, we investigated how parents administer different types of oral formulations to infants and preschool children at home, and whether the applied methods correlate with child acceptability.

## 2. Materials and methods

### 2.1. Study design and setting

The analysis is based on data collected for a randomized cross-over trial (RCT) that investigated the child and parent acceptability of four oral placebo formulations in infants and preschool children in the Netherlands and that has been described in detail elsewhere (van Riet-Nales et al., 2013). The current analysis had already been planned in the RCT protocol (ISRCTN63138435). In brief, 151 children were recruited through six preschool preventive health care clinics in the Netherlands. Children were eligible for inclusion if they were 1–4 years old and excluded if they suffered from a condition that might negatively affect swallowability. They were also excluded if they were (potentially) hypersensitive to any of the excipients in the formulations.

Parents were instructed verbally and in writing to offer the formulations to their child at home in the same way as they would administer a prescribed medicine, but without any mental or physical pressure. Each formulation had to be administered twice on the same day and in a randomized order for the type of formulation i.e., at eight occasions. Parents did not receive any additional instruction on how to administer the formulations to their child other than that the suspension had to be shaken prior to use. This implies that tablet chewing was neither recommended nor forbidden. The placebo character of the formulations was known to the parents and, when appropriate, explained to the child.

Acknowledging that participant adherence to the study protocol and the correct recording of data cannot be fully controlled in a domiciliary setting, particular attention was paid to assuring that parents well understood the aim of the study; why it was so important to behave similarly as if they needed to administer a prescribed medicine with the only instruction “twice daily”; and how the diary had to be filled in.

The four tested formulations (Fig. 1) were aimed at a neutral taste by choosing a composition that was simple, applying



Fig. 1. Oral placebo formulations in this study (4-mm tablet, powder, suspension, syrup).

excipients that are commonly used in (pharmacy compounded) paediatric medicines and by omitting the use of flavouring substances and/or taste maskers:

- White to off-white, round, biconvex, uncoated tablet (also referred to as mini-tablet), diameter 4 mm, height 3.05/2.50 mm (top/edge), weight 43.0 mg. Composition: lactose monohydrate 34.69 mg; maydis amyllum 6.46 mg; maydis amyllum pregelificatum 1.42 mg; magnesium stearate 0.43 mg. The tablets were packed in a PVC/Al blister.
- White, freely flowing powder (granules), 250 mg per single dose. The composition of the powder is proportionally identical to the tablet with exception of the lack of magnesium stearate i.e., lactose monohydrate 203.7 mg; maydis amyllum 38.0 mg; maydis amyllum pregelificatum 8.3 mg. The powder was packed in a white sachet.
- White, opaque suspension; 2.5 ml per single dose. Composition: methylparahydroxybenzoate 46.0 mg; aluminium magnesium silicate 484.4 mg; carboxymethylcellulose 484.5 mg; citric acid 36.3 mg; sucrose 12.74 g; purified water 37.95 g; microcrystalline cellulosis 2.50 g; purified water ad 50 ml. The suspension was packed in a 50-ml brown glass container with white, syringe adapter that could be connected to a 3-ml oral syringe.
- Clear, colourless syrup (solution); 2.5 ml per single dose. Composition: methylparahydroxybenzoate 63.1 mg; propylparahydroxybenzoate 10.0 mg; citric acid monohydrate 37.5 mg; saccharose 8.28 g; purified water ad 50 ml. The container closure system and dosing device were identical to those used for the suspension.

In order to avoid that parents would accidentally mix up the suspension and syrup upon administration and/or data recording, a red sticker was put on the cap of the suspension and a blue sticker on the cap of the syrup. In the participant diary, the colour of the sticker was repeated where appropriate. Also, parents were asked to confirm that they had used “the bottle with the correct colour of the sticker” when starting the data recording of the suspension and syrup.

### 2.2. Data collection

After each of the eight administrations, parents were asked to provide information in a participant diary on: (1) whether the formulation was offered to the child (yes, no) and, if not, why not; (2) by whom the formulation was offered to the child (father, mother, other); (3) whether the tablets were broken, crumbled or crushed prior to administration; (4) whether the oral liquids (suspension and syrup) were administered with the co-dispensed oral syringe or otherwise; (5) whether the formulations were given with food or drink and, if so, which type and quantity; (6) child acceptability according to the parents' observation as measured on a 0–10 cm Visual Analogue Scale (VAS-score); (7) child acceptability as measured by the result of each intake (fully swallowed, partly swallowed; not swallowed); (8) other aspects of the administration (optional).

The majority of the information could be provided by ticking box outcomes that were based on the results of an earlier questionnaire study in the Netherlands on the problems encountered by parents when administering medicines to children (van Riet-Nales et al., 2010). Where appropriate, parents were given the possibility to provide an open answer. Other questions in the participant diary related to child and family characteristics and child and parent formulation preferences.

### 2.3. Data analysis

The method of administration was classified as “directly” when a formulation was given on its own, as “co-administered” when a formulation was given with a small quantity of food or drink (one bite/sip), and as “mixed” when a formulation was given with a larger quantity of food or drink (several bites/sips). For the purpose of testing associations involving these three methods of administration, we have taken the ordinal character of this variable into account by labelling its three levels as 1, 2 and 3.

The association between the method of administration and the type of formulation, which is naturally expected to exist, was checked first. Then the following associations were investigated separately for each type of formulation: (1) association between the method of administration and the VAS-score; (2) association between the method of administration and the result of the intake; (3) association between the first VAS-score (the score at the first administration) and the change in the method of administration (from the first to the second administration); (4) association between the change in the method of administration (from the first to the second administration) and the change in VAS-scores.

The analysis took account of the small effect that was observed for the order in which the four formulations were administered to a child (van Riet-Nales et al., 2013). The testing of associations was based on a permutation version of Spearman’s test for independence. In this test the null distribution is approximated by randomly permuting the data separately within the 24 groups pertaining to the different orders of administration of the four formulations.

The data were analysed by Excel 2007 (Microsoft Corporation, Redmond, Washington), SPSS version 17.0 (IBM) and R (version 2.13, R development team). Spearman’s test was conducted with the R package coin (Hothorn et al., 2006).

### 3. Results

A hundred and fifty-one children were included, 72 (48%) of which were boys and 79 (52%) girls. Fifty-five (36%) children were 12–23 months old; 32 (21%) 24–35 months, and 64 (42%) 36–51 months old. For the first/second administration, the tablet was offered to the child on all occasions, the powder on all but two/five

occasions; the suspension on all but one/five occasions and the syrup on all but four/five occasions. One thousand and six (84.8%) of all administrations were carried out by the mother, 173 (14.6%) by the father, and 7 (0.6%) by another caregiver.

The main reason ( $n = 17$ , 77%) for not offering a formulation to a child was either that the parent considered that the child would refuse it anyway or that the child actually said so to his/her parent. On 14 (4.6%) occasions the tablet was broken, crumbled or crushed prior to administration, in one occasion at the first administration only (age child 16 months), in three occasions at the second administration only (age children 19, 31, 45 months) and in five occasions at both administrations (age children 12, 20, 33, 31, 48 months). On 58 (20%) occasions the suspension was emptied into a spoon prior to administration and so was the syrup on 57 (19%) occasions.

The tablet, suspension and syrup were given mainly directly (tablet  $n = 249$ , 82%; suspension  $n = 266$ , 90%; syrup  $n = 271$ , 92%). However, the powder was mainly given with food or drink (co-administered:  $n = 119$ , 40%; mixed  $n = 71$ , 24%). On two occasions (first and second administration of the powder for the same child) the method of administration was unknown.

As expected, the method of administration depends significantly on the type of formulation ( $p$ -value  $< 0.001$  from a chi-square test). An illustration of this dependence for children of different ages is provided in Fig. 2 (children of 48–51 months are presented as 3 years). The foodstuffs most commonly used for co-administration or mixing were vanilla pudding, quark, yoghurt, porridge and fruit sauce.

An evaluation of the acceptability of the formulations (overall child and parent VAS-score, result of the intake) has already been published elsewhere (van Riet-Nales et al., 2013). For formulations fully swallowed, an illustration of the association between the method of administration and the (child) VAS-score is given in Fig. 3 for each type of formulation. The differences suggested by Fig. 3 appear to be significant for the tablet and suspension even when ignoring the result of the intake i.e. when, considering all administrations ( $p$ -values  $< 0.001$  and  $0.0146$ ), but not for the powder ( $p = 0.701$ ) nor the syrup ( $p = 0.495$ ).

Considering all occasions where a particular formulation was given to a child (tablet  $n = 302$ ; powder  $n = 295$ ; suspension  $n = 296$ , syrup  $n = 293$ ), a VAS-score of 8–10 was obtained for the tablet on

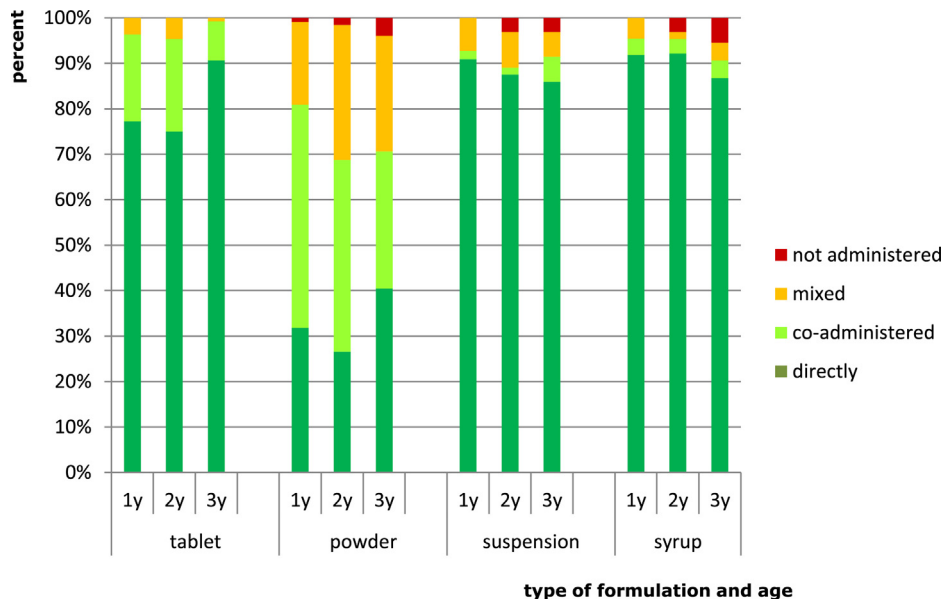
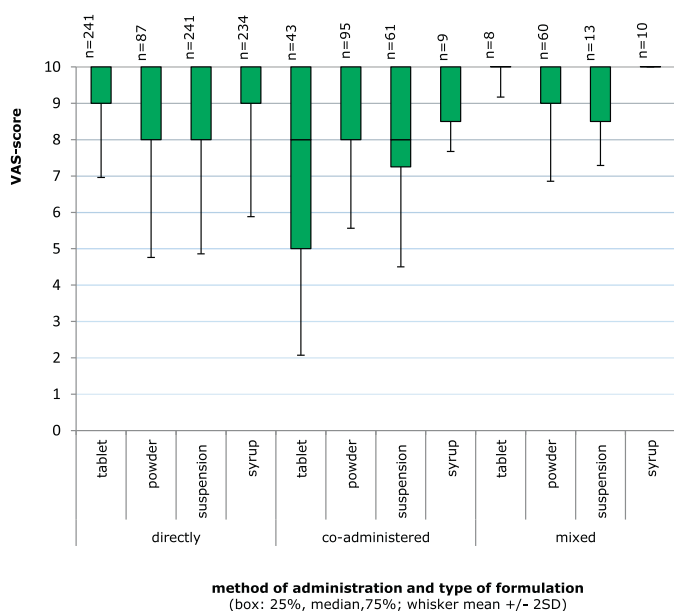


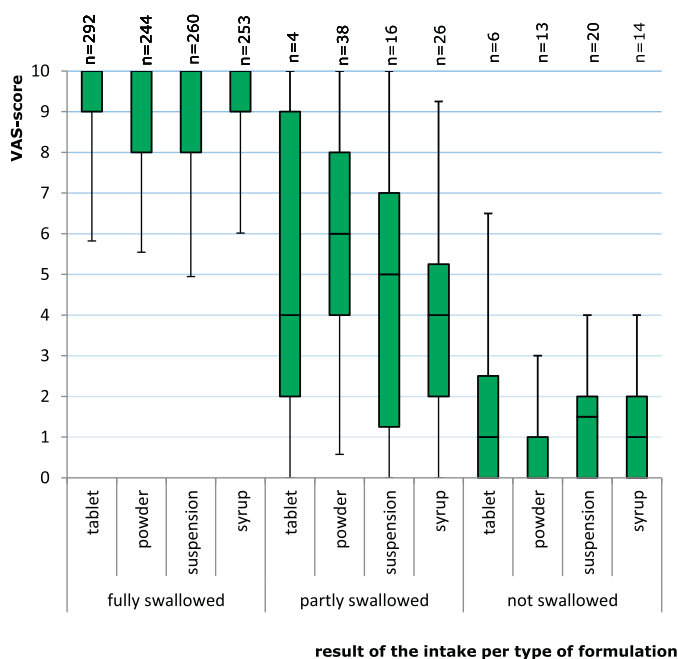
Fig. 2. Illustration type of formulation and method of administration for children of different ages ( $n = 1206$  administrations).



**Fig. 3.** Illustration association method of administration and child VAS-score (formulations fully swallowed only).

222 (74%) occasions when given directly, on 29 (10%) when co-administered and on 8 (3%) when mixed; for the suspension, on 196 (66%) occasions when given directly, on 5 (2%) when co-administered, on 12 (4%) when mixed; for the syrup, on 201 (69%) occasions when given directly, on 9 (3%) when co-administered and on 10 (3%) when mixed. For the powder, a VAS score of 8–10 was almost as often achieved when given directly ( $n = 74$ , 25%) as when co-administered ( $n = 78$ , 26%) or mixed ( $n = 59$ , 20%).

As expected and illustrated in Fig. 4, the VAS-score is in good agreement with the result of the intake. However, it is clear that good acceptability did not guarantee full swallowing on all occasions, e.g., because parents stated that the formulation got spoiled during the intake or that it dropped out of the child's mouth. Similarly, bad acceptability did not always imply lack of



**Fig. 4.** Illustration agreement result of the intake and child VAS-score.

swallowing, as parents indicated that the child only showed its disgust afterwards.

When given directly, the tablet was fully swallowed on 241 occasions (equalling 97% of all direct tablet administrations), the powder on 87 (85%), the suspension on 241 (91%) and the syrup on 234 (86%). When co-administered, the tablet was fully swallowed on 43 (95%) occasions and the powder on 95 (80%). Finally when mixed, the tablet was fully swallowed on 8 occasions (100%) and the powder on 60 (84%). Considering the youngest children only (12–23 months), the tablet was given directly and fully swallowed by 82 (75%) of these children.

Considering only occasions on which the formulations were given directly and fully swallowed, good acceptability (i.e., a VAS-score 8–10) was obtained for the tablet on 221 occasions (73%), for the powder on 70 (24%), for the suspension on 195 (66%), and for the syrup on 199 (68%). The association between the method of administration and the result of the intake was found to be significant for the suspension ( $p < 0.001$ ), but not for the tablet ( $p = 0.271$ ), the powder ( $p = 0.383$ ) and the syrup ( $p = 0.105$ ). There was good evidence that the higher the VAS-score of the first administration of a formulation to a child is, the less frequently the method of administration of this formulation is changed from the first to the second administration (tablet  $p = 0.001$ , powder  $p = 0.367$ , suspension  $p = 0.031$ , syrup  $p = 0.046$ ). For example, when the VAS-score in the first administration was 8–10, the method of administration was not changed in most cases (tablet 94%, powder 82%, suspension 98%, syrup 96%).

A change in the method from the first to the second administration is denoted as “more complex” when it involved a larger quantity of food or drink (going from “directly” to “co-administered”, from “directly” to “mixed” or from “co-administered” to “mixed”). Conversely, it is denoted as “less complex” when it involved a smaller quantity of food or drink (going from “mixed” to “co-administered”, from “mixed” to “directly” or from “co-administered” to “directly”). Except for the suspension, strong evidence was found for an association between changes in the method of administration and changes in the VAS-score. The results indicated that a change into a more complex method of administration overall resulted in higher VAS-scores (tablet  $p = 0.005$ , powder  $p < 0.001$ , suspension  $p = 0.168$ , syrup  $p = 0.001$ ).

In Fig. 5, the changes in the method of administration and the resulting changes in VAS-scores are illustrated in three groups that are indicative of the acceptability of the first administration. The groups were based on the results displayed in Fig. 3 i.e. bad acceptability VAS-score 0–2; moderate acceptability VAS-score 3–7 and good acceptability VAS-score 8–10. As expected, the method of administration changed more frequently into a more complex method when the VAS-score of the first administration was low (VAS score 0–2;  $n = 11/45$ ; 24%) than when it was higher (VAS score 3–10;  $n = 33/552$ ; 6%).

#### 4. Discussion

This study showed that oral placebo formulations in the form of a 4 mm tablet, a suspension and a syrup were mostly administered to infants and preschool children on their own and that the placebo powder was mostly given with food or drink. As the joint administration of the formulations with food or drink was neither recommended on the product label nor in the participant information, from a regulatory perspective this implies that the formulations had to be given on their own. Thus the result of this study indicate that the tablet, suspension and syrup were given as intended, and the powder was not.

As expected, the method of administration was clearly associated with the type of formulation. For the tablet and suspension, the method also appears to be associated with child

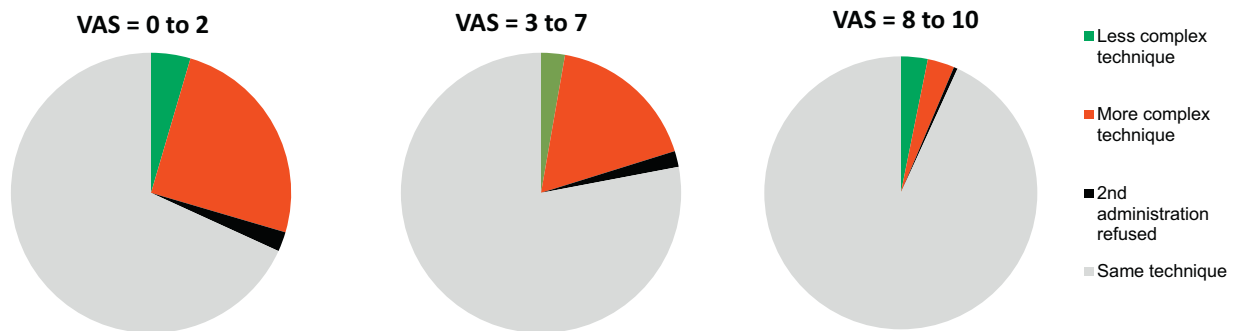


Fig. 5. Association child VAS-score first administration of a formulation and changes in method of administration from first to second administration.

acceptability as measured on a 0–10 cm Visual Analogue scale i.e., the VAS-score, and for the suspension with the result of the intake. Parents were more likely to administer a formulation with (a larger quantity of) food or drink when the VAS-score of the earlier administration of the same formulation was low than when it was high(er). Changes in the method from the first to the second administration of the same formulation generally resulted in higher VAS-scores.

The limited availability and age-appropriateness of medicines for children has resulted in a globally emerging effort towards an improvement of paediatric medicines (van Riet-Nales et al., 2011; Ranmal and Tuleu, 2013; Choonara, 2008). As suggested by Kozarewicz (2014), this requires the collection of pre-marketing data on the acceptability of medicines by children. However, a suitable methodology for collecting and making sense of such data is yet to be developed. Therefore, the selection of the test methods and the proposals for data assessment are currently left to researchers (Ranmal and Tuleu, 2013; Kozarewicz, 2014).

According to Ranmal and Tuleu (2013), researchers should, amongst other things, consider the variability in child acceptability in typical and atypical populations, acknowledge that acceptability testing based on small samples may lead to inconsistent and limited findings, and realise that parents may be more likely to participate in a study when they feel positive about the formulation being investigated. Kozarewicz (2014) and Ranmal and Tuleu (2013) remarks were considered in the patient recruitment and design of our RCT.

In order to mimic the administration of paediatric medicines by parents to the best extent, the study was conducted in the domiciliary setting and tablet chewing was neither recommended nor forbidden. The latter approach is consistent with current regulatory provisions indicating that “immediate release tablets are normally intended to be swallowed intact, but unless otherwise indicated in the SmPC and PIL, they may also be chewed” (European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PRAC), 2013).

Generally, parents and caregivers will have less experience in administering medicines to children than nurses working on paediatric wards. However, Akram and Mullen (2012) indicated that parents often advised staff as to whether their child’s medication needed to be co-administered or mixed with food or drink or otherwise modified in order to enable swallowing. Also Alsulami et al. (2012) indicated that the most frequent type of deviations from hospital policy on the administration of medicines to children was that the formulation was given by the parents without the nurse being present. Thus the findings of our study will also be of relevance to children who are hospitalized.

The variability in child characteristics was addressed by focusing on generally healthy domiciliary children who did not have any difficulties swallowing food or drink. In addition, the

variability in parents’ attitudes to study participation was acknowledged by two means. First, recruitment was conducted through national preventive health care clinics in view of the high response to invitation of the overall population of parents (Rijksinstituut voor Volksgezondheid en Milieu, 2011). Second, the likelihood that parents were more willing to participate in a study when they were positive to a certain formulation was avoided by studying four types of oral placebo formulations and allowing parents not to administer a particular formulation if they rather did not like to do so.

Following discussions with Dutch health care professionals and taking data from the palatability and pain literature into account, we measured child acceptability by two instruments, namely the child VAS-score and the result of the intake. For the VAS-scale, the commonly applied facial expressions below the line indicating “like” and “dislike” were replaced with words relating as to whether the child considered the intake unpleasant or not at all. This is because we consider there is no need that children actually “like” taking medication.

The increasing global focus on better medicines for children has also resulted in an increased focus on small i.e. mini-tablets. Whereas our study related to 4 mm tablets, other authors tend to study smaller sizes, e.g., 3-mm by Thomson et al. (2009) 2-Klingmann et al. (2013). Such smaller tablet sizes entail an increased need to swallow several mini-tablets to arrive at the recommended dose as the maximum amount of active substance per mini-tablet is limited. However, at the same time this would allow better dosing flexibility. In any case it should be acknowledged that a larger number of mini-tablets may make the administration more “powder like”. Or alternatively more “suspension like” when applying a novel approach by which the addition of some water to several mini-tablets results in a semi-solid mass. In both cases, child acceptability may change in comparison to the administration of a single mini-tablet. Recently, Kluk et al. (2015) have studied the swallowability of five to ten 2-mm and 3-mm tablets that were administered on a spoon with fruit gel to children aged two to three years old in an institutional setting. The results showed that children could swallow these numbers of mini-tablets safely (Kluk et al., 2015). Nevertheless, the acceptability of several mini-tablets of different sizes, in children of different ages and in different settings remains subject to further investigations.

Current studies on medication adherence focus mainly on the ability of parents to calculate and measure the recommended dose, on the eventual relationship between health literacy and deviations from the written user instruction, and on the effectiveness of verbal, written or pictogram interventions designed to encourage adequate administration practices (Anderson et al., 2013; Bertsche et al., 2010; Lokker et al., 2009). Studies on the associations that were investigated in this study are more scarce. Akram and Mullen (2015) investigated the prevalence and

nature of, and the reasons for, mixing medicines with soft foods by nurses working in a national health service, and (Richey et al. (2013) studied which dosage forms and drugs were routinely modified in paediatric clinical practice. Both studies were conducted in the United Kingdom amongst nurses, in relation to any type of prescribed medicine and to a wide variety of children. These studies as well as our study share the conclusion that medicines may be given with food or drink or otherwise be modified to guarantee adequate child acceptability and/or medication intake.

Akram and Mullen (2012) indicated that nurses rather added the medications to the foodstuff instead of adding the foodstuff to the medicines. This aspect was not investigated in our study as we considered that it is the quantity of the food or drink that is being used that is most important. First, it is likely that the contact time and/or area will be smaller when a formulation is given with a small quantity of food or drink (one bite/sip) than when it is mixed with a larger quantity (several bites/sips). If so, this may reduce the risk for and/or impact of any chemical or physical interactions on the bioavailability and stability of the formulation, and therewith on its clinical efficacy and risk for adverse drug reactions. Second, children may not be willing to swallow larger quantities of medicated food or drink fully. Depending on the criticality of the disease and the type of medicine, this may put the child at an immediate risk. Third, verbal reports from Dutch health care professionals stated that feeding problems may be due to negative experiences involving medicated food. Consequently, they argued that it is important that medicines be given only with a small quantity of food or drink, and that the remaining quantity of the non-medicated food or drink should be given immediately after. However, this opinion was not confirmed by evidence in the public domain (Lifschitz, 2001).

This study has several strengths. It is, to the best of our knowledge, the first study comparing the method of administration and child acceptability of different types of oral formulations in infants and preschool children in the domiciliary setting. This setting was selected because oral formulations are frequently taken by children who are not and also have not been hospitalized, whereas hospitalized children may need to take oral formulations at home for long periods of time after discharge. The choice for the domiciliary setting also implied that the study outcomes take account of any impact on the method of administration and child acceptability caused by child–parent relations, child–sibling relations, parents' understanding of the user instruction and the absence of a supervising health care professional (Thomson et al., 2009; Klingmann et al., 2013).

This study has some weaknesses also. First, the participant diary included tick-box outcomes that were supplemented with the possibility to provide an open answer. Although unlikely because of the detailed verbal instructions to data in the participant diary, it cannot be excluded that the pre-printed administration possibilities might have influenced the method actually applied by the parents. Second, the sample size was based on the primary aim of the former RCT rather than this analysis itself. Third, the taste of the two oral solid formulations was identical as they were manufactured from essentially the same blend. However, the taste of the two oral liquid formulations differed due to the intrinsic nature of their dosage form. Although the taste of all four formulations was aimed at neutral, it cannot be excluded that any differences in child acceptability or the method of administration were due to taste aspects rather than the type of dosage form itself. Fourth, the current analysis did not consider the 22 occasions where the syrup, suspension and powder were not offered to the child for anticipated child refusal i.e., when the child acceptability was expected to be bad. This weakness must be considered when disputing the suitability of small tablets as an

alternative dosage form to a powder, suspension or syrup for the reason that they were broken, crumbled or crushed in 14 occasions.

In addition, the results of this study should be considered realizing that the study was limited to four types of oral formulations with defined characteristics and to Dutch parents and children living in a small region of the Netherlands ("Rivierland"). Finally, this study showed that parents may empty the dose from the oral syringe onto a household spoon prior to administration. We consider that this handling can be accepted without any further justification as the risk for additional loss of dose is negligible.

The method of administration was associated with the type of formulation. However, it was only associated with the VAS-score and the result of the intake in the case of the suspension. Overall, this suggests that it is mainly the type of formulation that made parents decide to administer a formulation with food or drink. However, when parents observed that the VAS-score of the first administration was low, they frequently chose to administer the formulation with (a larger quantity of) food or drink. This approach turned out to be effective i.e., to improve child acceptability.

Considering clinical practice and the fact that pharmaceutical companies are generally reluctant to conduct compatibility studies between a formulation and a specific type of food or drink, regulators are considering precautionary warnings in the user instruction stating that the formulations should not be taken with food or drink unless compatibility had been demonstrated. Although these warnings are intended to protect the health of the child by avoiding any impact of food or drink on the stability and bio-availability of the formulation, they may in fact put the child at risk if the warning withholds the child from taking its medicine. Since our study points towards the latter possibility, it is recommended that regulators carefully consider the risk for reduced adherence rates when implementing warnings. This may be especially relevant for powders, which are commonly given with food or drink. Actually, we consider that it is not at all in the interest of children to implement warnings that are solely based on the absence of data supporting adequate compatibility, and certainly not when an interaction is not to be expected on scientific grounds.

The optional remarks written by the parents on the participant diary indicate that the type of dosing device may have had an effect on child acceptability. Some parents stated that their child "wanted more" of the suspension or syrup because the child knew it would be allowed to play with the empty syringe when both doses were taken, whereas other parents indicated that they emptied the oral suspension or syrup into a spoon because the child was afraid of the syringe. Thus, the design and child acceptability of syringes for oral use should be further investigated.

## 5. Conclusions

The 4-mm tablet, suspension and syrup were largely administered without any food or drink and without breaking, crumbling or crushing tablets. This shows that parents who master the Dutch language are generally handling these types of formulations in a manner that is consistent with the regulatory perception that users may only handle medicines in a manner that is recommended in the authorised product/user information (package label, patient information leaflet, Summary of Product Characteristics)

The powder was commonly given with food or drink, yet this handling was not recommended on the package label and also not in the participant information. This underpins the need for better instructions in the user information on the method of administering this dosage form.

Formulations that were administered with food or drink were generally so for good reason i.e., to improve child acceptability.

Consequently, any warnings in the user formation on the mixing of medicines with food or drink must be carefully balanced against the risk of reduced child acceptability and reduced adherence rates, especially when there is no clear evidence of a medicine–food interaction that is likely to result in a clinically relevant effect.

Our results indicate that the overall acceptability of a small i.e. mini-tablet) versus a powder, suspension or syrup formulation is unlikely to alter due to crumbling, crushing or giving the tablet with food or drink. Therefore, this study further support our earlier conclusion that there is no reason to dispute the acceptability of small tablets in young children (van Riet-Nales et al., 2013).

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## References

- Akram, G., Mullen, A.B., 2012. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. *Int. J. Pharm. Pract.* 20 (3), 191–198.
- Akram, G., Mullen, A.B., 2015. Mixing medication into foodstuffs: Identifying the issues for paediatric nurses. *Int. J. Nurs. Pract.* 21 (2), 125–131.
- Alsulami, Z., Conroy, S., Choonara, I., 2012. Double checking the administration of medicines: what is the evidence? A systematic review. *Arch. Dis. Child.* 97 (9), 833–837.
- Anderson, C., Rolfe, P., Brennan-Hunter, A., 2013. Administration of over-the-counter medication to children at home—a survey of parents from community health centers. *J. Community Health Nurs.* 30 (3), 143–154.
- Bain-Brickley, D., Butler, L.M., Kennedy, G.E., Rutherford, G.W., 2011. Interventions to improve adherence to antiretroviral therapy in children with HIV infection. *Cochrane database Syst. Rev.* 12, Cd009513.
- Balakrishnan, K., Grieve, J., Tordoff, J., Norris, P., Reith, D., 2006. Pediatric licensing status and the availability of suitable formulations for new medical entities approved in the United States between 1998 and 2002. *J. Clin. Pharmacol.* 46 (9), 1038–1043.
- Balakrishnan, K., Tordoff, J., Norris, P., Reith, D., 2007. Establishing a baseline for the monitoring of medicines availability for children in the UK: 1998–2002. *Br. J. Clin. Pharmacol.* 63 (1), 85–91.
- Bellis, J.R., Kirkham, J.J., Thiesen, S., Conroy, E.J., Bracken, L.E., Mannix, H.L., et al., 2013. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. *BMC Med.* 11 238.
- Bertsche, T., Bertsche, A., Krieg, E.M., Kunz, N., Bergmann, K., Hanke, G., et al., 2010. Prospective pilot intervention study to prevent medication errors in drugs administered to children by mouth or gastric tube: a programme for nurses, physicians and parents. *Qual. Saf. Health Care* 19 (5), e26.
- Breitkreutz, J., Boos, J., 2007. Paediatric and geriatric drug delivery. *Expert Opin. Drug Deliv.* 4 (1), 37–45.
- Choonara, I., Conroy, S., 2002. Unlicensed and off-label drug use in children: implications for safety. *Drug Saf.* 25 (1), 1–5.
- Choonara, I., 2008. WHO wants safer medicines for children. *Arch. Dis. Child.* 93 (6), 456–457.
- Cuzzolin, L., Atzei, A., Fanos, V., 2006. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Exp. Opin. Drug Saf.* 5 (5), 703–718.
- Ernest, T.B., Craig, J., Nunn, A., Salunke, S., Tuleu, C., Breitkreutz, J., et al., 2012. Preparation of medicines for children—a hierarchy of classification. *Int. J. Pharm.* 435 (2), 124–130.
- European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) and Paediatric Committee (PRAC). Guideline on the pharmaceutical development of medicines for paediatric use. EMA/CHMP/QWP/805880/2012 Rev. 2, 1 August 2013.
- Hothorn, T., Hornik, K., van de Wiel, M.A., Zeileis, A., 2006. A lego system for conditional inference. *Am. Stat.* 60 (3), 257–263.
- Klingmann, V., Spomer, N., Lerch, C., Stoltenberg, I., Fromke, C., Bosse, H.M., et al., 2013. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. *J. Pediatr.* 163 (6), 1728–1732.
- Kluk, A., Sznitowska, M., Brandt, A., Sznurkowska, K., Plata-Nazar, K., Mysliwiec, M., et al., 2015. Can preschool-aged children swallow several minitablets at a time? Results from a clinical pilot study. *Int. J. Pharm.* 485 (1–2), 1–6.
- Kozarewicz, P., 2014. Regulatory perspectives on acceptability testing of dosage forms in children. *Int. J. Pharm.* 469 (2), 245–248.
- Lifschitz, C.H., 2001. Feeding problems in infants and children. *Curr. Treat. Options Gastroenterol.* 4 (5), 451–457.
- Lokker, N., Sanders, L., Perrin, E.M., Kumar, D., Finkle, J., Franco, V., et al., 2009. Parental misinterpretations of over-the counter pediatric cough and cold medication labels. *Pediatrics* 123 (6), 1464–1471.
- Matsui, D., 2007. Current issues in pediatric medication adherence. *Paediatr. Drugs* 9 (5), 283–288.
- Milani, G., Ragazzi, M., Simonetti, G.D., Ramelli, G.P., Rizzi, M., Bianchetti, M.G., et al., 2010. Superior palatability of crushed lercanidipine compared with amlodipine among children. *Br. J. Clin. Pharmacol.* 69 (2), 204–206.
- Polaha, J., Dalton 3rd, W.T., Lancaster, B.M., 2008. Parental report of medication acceptance among youth: implications for everyday practice. *South Med. J.* 101 (11), 1106–1112.
- Ranmal, S., Tuleu, C., 2013. Demonstrating evidence of acceptability: the catch-22 of pediatric formulation development. *Clin. Pharmacol. Ther.* 94 (5), 582–584.
- Richey, R.H., Shah, U.U., Peak, M., Craig, J.V., Ford, J.L., Barker, C.E., et al., 2013. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. *BMC Pediatr.* 13, 81.
- Rijksinstituut voor Volksgezondheid en milieu. Zorgbalans. Available at 2011. Accessed 1 March 2012.
- Terry, D., Sinclair, A., 2012. Prescribing for children at the interfaces of care. *Arch. Dis. Child. Ed. Pract. Ed.* 97 (4), 152–156.
- Thomson, S.A., Tuleu, C., Wong, I.C., Keady, S., Pitt, K.G., Sutcliffe, A.G., 2009. Minitablets, new modality to deliver medicines to preschool-aged children. *Pediatrics* 123 (2), e235–8.
- Walsh, J., Cram, A., Woertz, K., Breitkreutz, J., Winzenburg, G., Turner, R., et al., 2014. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. *Adv. Drug Deliv. Rev.* 73, 14–33.
- van Riet-Nales, D.A., Bouwman, N., Schobben, A.F.A.M., Egberts, T.C.G., Rademaker, C.M.A., 2010. Drug administration related problems in outpatient children: more than formulation aspects (abstract 1295). *Pediatr. Res.* 641.1.
- van Riet-Nales, D.A., de Jager, K.E., Schobben, A.F., Egberts, T.C., Rademaker, C.M., 2011. The availability and age-appropriateness of medicines authorized for children in The Netherlands. *Br. J. Clin. Pharmacol.* 72 (3), 465–473.
- van Riet-Nales, D.A., de Neef, B.J., Schobben, A.F., Ferreira, J.A., Egberts, T.C., Rademaker, C.M., 2013. Acceptability of different oral formulations in infants and preschool children. *Arch. Dis. Child.* 98 (9), 725–731.