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Mini-tablets as an alternative galenic formulation for neonates

A single-centre, randomised, open, two-way, cross-over study investigating the acceptability and swallowability of two different oral placebo formulations in neonates

Dissertation

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“Childhood is entitled to special care and assistance.”

UN, Declaration of the Rights of the Child, 1959

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Acceptability of Uncoated Mini-Tablets in Neonates - A Randomized Controlled Trial

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Zusammenfassung

In der Pädiatrie ist der Mangel an evidenzbasierten Empfehlungen zu galenischen Darreichungsformen noch immer sehr hoch. Unpassende Darreichungsformen können zur ungenauen Dosierung führen. Dieses Problem ist besonders groß bei Neugeborenen, der verwundbarsten Altersgruppe. So müssen beispielsweise Medikamente auf Neugeborenen-Intensivstationen in bis zu 90% der Fälle off-label eingesetzt werden.

Aktuell werden orale Medikamente meist in Form von flüssigen Lösungen oder Sirup verabreicht, sehr oft als selbst hergestellte Lösungen aus festen Darreichungsformen. Die Gefahr ungenauer Dosierung ist dabei sehr hoch. Des Weiteren werden zum Teil schädliche Inhalts- und Füllstoffe verwendet. Die Notwendigkeit, adäquate altersgerechte galenische Darreichungsformen auch für die jüngsten Patienten bereitzustellen, liegt klar auf der Hand. In den letzten Jahren wurden von der European Medicines Agency (EMA) und der Weltgesundheitsorganisation (WHO) viele Ansätze entwickelt, klinisch-pharmazeutische Studien an Kindern attraktiver zu machen und somit den evidenzbasierten Einsatz von Medikamenten auch im Feld der Pädiatrie zu erhöhen. Trotzdem gibt es noch immer einen hohen Forschungsbedarf, insbesondere im Bereich der Neonatologie.

Unsere Studiengruppe hat in der Vergangenheit bereits zwei klinische Studien an insgesamt 355 Kindern im Alter von 0,5 bis 6 Jahren durchgeführt. Die damit gewonnen Daten zeigen, dass sowohl die Akzeptanz als auch die Schluckbarkeit von Minitabletten in diesen Altersgruppen höher sind als die von Sirup.

Da es bisher noch keine Daten zu diesen Parametern bei Neugeborenen gab, hat unsere Studiengruppe eine klinische Studie mit 151 Neugeborenen durchgeführt.

Es konnte nicht nur gezeigt werden, dass Neugeborene die Minitabletten akzeptieren (100%, 95% KI: 97,6%-100%), sondern auch, dass die Schluckbarkeit von ihnen signifikant größer ist als von Sirup (Δ10%; 95% CI 1.37%-19.34%; p=0.0315).

Schlussfolgerung: Minitabletten können sicher von Neugeborenen geschluckt werden, was sie zu einer ernstzunehmenden Alternative zu anderen galenischen Darreichungsformen wie Sirup macht.

Abstract

In the field of paediatrics the lack of evidence-based knowledge about treatment options for children is still remarkably high, which may result in administration of inaccurate dosages and inappropriate formulations of drugs in young patients. This problem occurs even more in neonates, the most vulnerable age group. As a result, an off-label drug use of up to 90% in Neonatal Intensive Care Units (NICUs) has been estimated.

Currently, oral medication is given to neonates in the form of liquid solutions or syrup. This has a high potential of inaccurate dosing and therefore may result in over- or underdosing. In addition sometimes harmful ingredients and bulking agents are used to create the syrups. Obviously, there is a need to investigate appropriate, age-adapted galenic formulations even for the youngest.

In the last years there have been many approaches by the European Medicines Agency (EMA) and World Health Organization (WHO) to undertake clinical pharmaceutical trials involving children more attractive and therefore to increase the evidence-based knowledge of paediatric medication. Nevertheless, there is still a huge need for clinical studies especially in the neonatal period.

Our study group of the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* of the *Universitätsklinikum Düsseldorf* has already performed 2 trials with 355 children aged 0.5 to 6 years, providing data that the acceptability as well as the swallowability of mini tablets is higher in these age groups compared to, for example, syrup.

Based on a lack of data investigating acceptability and swallowability of mini tablets in neonates, the trial team, including the writer of this thesis, has performed a study involving 151 neonates with the aim to close the gap in factual knowledge about this age group.

The trial could not only show that neonates accept the mini-tablets (100%, 95% CI: 97,6%-100,0%) but also that the swallowability is significantly higher in mini-tablets than in syrup (Δ10%; 95% CI 1.37%-19.34%; p=0.0315).

In conclusion, it can be said that neonates are able to swallow mini-tablets safely, which makes them a considerable alternative to other galenic formulations like syrup.

List of Abbreviations

ADR(s)	adverse drug reaction(s)
AMG	Arzneimittelgesetz
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BPCA	Best Pharmaceuticals for Children Act
CI	confidence interval
EC	European Commission
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice
GFR	glomerular filtration rate
ICH	International Conference of Harmonisation
NDDI	Newborn Drug Development Initiative
NICHD	National Institute of Child Health and Human Development
NICU(s)	Neonatal Intensive Care Unit(s)
p	probability value
PD	pharmacodynamics
PDCO	Paediatric committee
PIP(s)	Paediatric Investigation Plan(s)
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
SAE(s)	serious adverse event(s)
SAS	Statistical Analysis System (software)
WHO	World Health Organization

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1. Introduction

1.1 Background

Children are a very complex and heterogeneous subgroup of humankind: Their bodies, contingent on growth, maturation and development, experience enormous physical changes within a comparably short period of time. Consequently this population itself can be subdivided into several age groups, all having their own particularities. Within the paediatric population neonates obviously constitute the most vulnerable of those subgroups.

Regarding healthcare the continuous change of the child's physiology challenges paediatricians and the pharmaceutical industry. Among others, pharmacokinetic (PK) and pharmacodynamic (PD) processes differ a lot between the age groups due to the maturity of e.g. hepatic and renal function (1,2). As a consequence, pharmaceutical substances are metabolized differently in different age groups and furthermore the dissimilarities between child and adult metabolism seem to be immense (1,2). While PK and PD of most active ingredients are well known and based on scientific evidence in adults, they are predominantly unknown in young children as studies investigating this field are rare (3). The dosages of medication that young children receive are therefore commonly calculated from data gained from studies involving older children or adults (2,4,5). In addition, there is a lack of appropriate galenic formulations for children, which exacerbates the difficulty of adequate treatment (6). Thus, off-label and unlicensed use of medication is still a common practice in paediatrics as most pharmaceuticals are not licensed for use on children due to the lack of trials involving them (1,3,4,7). This problem is intensified in neonates: in a Neonatal Intensive Care Unit (NICU) up to 90% of the administered medication is used off-label or unlicensed (8,9).

In the past years there have been many regulatory initiatives to improve the medical treatment of children by increasing the appeal to conduct clinical trials involving them. Despite achieving initial success in increasing the number of studies involving older children, the proportion of off-label and unlicensed use as well as the lack of appropriate formulations is still alarmingly high in toddlers and neonates (7,9,10). In general, it can be said that the adequacy of paediatric drugs regarding their authorisation status, dose capability and dosage form

increases with age (11). Clearly, there is a huge need to eliminate these grievances with the aim that even the most vulnerable members of our society are offered age-appropriated optimized treatment.

1.2 Neonates' pharmacological specificities

Children are not small adults as the childish physiology differs from the adult body enormously, especially in neonates. As a result of maturity and growth their physiology is contingent on continuous change. Therefore, it is necessary to stratify between different age groups within the paediatric population, e.g. the EMA divides children into 6 different age groups (12):

- Preterm new-born infants
- Term new-born infants: 1 – 28 days
- Infants and toddlers: 1 month – 2 years
- Children (pre-school): 2 – 5 years
- Children (school): 6-11 years
- Adolescents: 12 – 16 or 18 years.

The immense dissimilarities between the physiology of neonates, children and adults also have influence on PD und PK of drugs.

In their article "*Drug policy in Europe – Research and funding in neonates: Current challenges, future perspectives, new opportunities"* published in 2011 Jacqz-Aigrain et al. provide a useful summary of neonatal pharmacological specificities (8):

They emphasize that all pharmacokinetic phases of many drugs differ between neonates, children and adults. Firstly, oral absorption may already be modified by dissimilarities in gastroenterological physiology and further the neonates' intragastric pH is comparatively high, because the basal acid output as well as the total volume of gastric secretions are lower than in older children and adults. The higher pH increases the bioavailability of acid labile compounds in comparison to older children. Moreover the body compositions of neonates and adults regarding proportions of extracellular and body water as well as of fat differ, which has an influence on the distribution of drugs. This dissimilarity in distribution is reinforced by the fact that protein binding in neonates is lower than in adults and older children, whereby the free fraction of drugs is increased

in neonates. Besides, metabolism, which is particularly influenced by age, also differs between the age groups as the activities of drug-metabolising enzymes (e.g. cytochrome P450 oxidases) are generally lower in neonates and furthermore even vary inter-individually. In addition, the neonatal kidneys are still in their maturing process: the renal tubes experience prolongation and maturation, blood flow is increased and shifted to the more superficial nephrons and the filtration efficiency is improved in the first months of life. As a consequence the glomerular filtration rate (GFR) is much lower in neonates and still matures postpartum. The GFR reaches an adult rate 6-12 months after birth.

Those differences demonstrate how inaccurate dosage calculations for neonatal medication can be when calculated according to the data of older children or adults and emphasize the importance of further paediatric research.

1.3 Paediatric research

1.3.1 Challenges of paediatric research

It is not a coincidence that studies involving children are very rare. Indeed, there are several different aspects provoking this situation as clinical research in children holds its unique challenges (4).

First of all, pharmaceutical companies do not have any great interest in the development of new paediatric medications on account of the low financial profit compared to research in adult treatments: Usually children have to take a lower amount of drugs for a shorter period of time, which limits the expected financial gain. This conflicts with the high development costs (13,14). Moreover, the number of eligible study participants is often limited**,** which provides its own practical problems, like inadequately powered trials and inability to indicate small or moderate but clinically relevant treatment effects, for instance (4). This problem is augmented by the heterogeneity of the paediatric population and the associated necessity to stratify according to age group (13). Furthermore recruitment of participants is difficult in paediatric research due to the finite number of children with specific diseases, strict inclusion and exclusion criteria and fear or reluctance of parents to let their child participate (15).

Ethical considerations, even more emphasized in paediatric research than in research with adults (16), are another important cause of the complication of involving children in clinical research (13,17). To ensure the safety of the young participants and to facilitate paediatric investigations at all, these considerations were laid down in different regulations and guidelines.

1.3.2 Legislative: Initiatives to increase paediatric research

Because of the comparatively poor state of evidence-based, licensed paediatric health care, several international initiatives have been founded to increase paediatric research and therefore advance the situation by**,** for example, the development of new age-adapted formulations to administer drugs to children.

In the USA the Food and Drug Administration (FDA) introduced the first paediatric labelling requirement in 1979, which was the beginning of the American regulatory framework on paediatrics (18). The FDA's "Best Pharmaceuticals for Children Act" (BPCA) of 2001 led to growing paediatric research and thus an increased number of drug studies involving children by the promulgation of new FDA regulations enclosing financial incentives for the pharmaceutical industry and legal obligations (19). The goal was to evaluate new and older paediatric medicines and indeed, as a consequence, there were more than 500 changes in the labelling of drugs (7). But there was still a lack of clinical trials involving neonates, therefore the Newborn Drug Development Initiative (NDDI) was founded and held its first workshop in 2004. It is a collaboration between the FDA and the National Institute of Child Health and Human Development (NICHD) with neonatologists and experts of industry, clinical trial design, pathophysiology, and pharmacology and is regarded as an opportunity to bring together experts from different fields of research and clinical medicine to "guide and inform the design of clinical trials for drugs in newborns under the BPCA" (20). In 2007 the BPCA was re-authorised through the "FDA Amendment Act" (FDAAA). Despite this positive trend in creating frameworks for paediatric research, neonates still stayed "pharmaceutical orphans" as off-label use remained a problematic issue in this age group. Therefore, the "FDA Safety and Innovation Act" (FDASIA) was approved in 2012 to advance neonatal drug studies (21). In 2013 "The Pediatric Research Equity Act" (PREA)

became law in order to oblige pharmaceutical companies to conduct studies on safety and effectiveness of medicines used in children (22).

In Europe first steps to form a legal framework for the development of medicines for the paediatric population and for paediatric research in general were undertaken later than in the United States. After the EMA had noticed the need for legal guidance, the European Commission (EC) held a round table for experts in 1997, which expressed the aim to introduce new legal regulations and to develop a system of incentives (23). In 2000 the EC supported an international discussion on clinical trials in children, where an International Conference of Harmonisation (ICH) guideline could be agreed. In 2002 the EC published a consultation paper on “Better medicines for children – proposed regulatory actions in paediatric medicinal products” (23). As no significant improvements in the situation could be seen, the European Commission introduced the “Paediatric Regulation n. 1901” in 2006 (24), which came into force in January 2007. This Regulation had the aim to increase the available scientific evidence and therefore reduce the need for off-label use in children by forcing pharmaceutical companies to study medicines in children, to report experimental research results and last but not least to develop age-adapted formulations. Moreover, it was aimed to prevent children from non-essential clinical trials and to improve the quality of research including improved consideration of the ethical standards in paediatric medicinal production. Paediatric Investigation Plans (PIPs) are the central instrument of this regulation and controlled by the Paediatric Committee (PDCO). The PDCO is the replacement of the Expert Group on Paediatrics, which was created to advice the EMA (23).

The most recent attempt by the EMA is a new guideline, which came into force in February 2014 and should influence the galenic development of medicines for paediatric utilisation. Its goal is to enable the development of age-appropriate medication for children and to facilitate this without any unnecessary clinical trials, on the one hand, as well as without delays in the authorization process on the other hand (25).

1.4 Off-label use and drug manipulation in neonates

1.4.1 Character and incidence

Medical treatment of neonates is still contingent on a lack of systematic clinical research and the adjunctive deficiency of sufficient prescribing data as well as of adequate formulations, although the necessity of clinical trials in this vulnerable population has been recognised as a priority by the WHO (World Health Organisation) and the EMA (26–28) and the occurrence of adverse events after inadequate study of drugs prior to their widespread use is well known and documented by alarming historical examples (9,29,30). The lack of suitable formulations and routes of administration is one of the main causes (26,31) why off-label and unlicensed drug use in neonates is an international problem and a common paediatric practice in in- and outpatient treatment, especially in NICUs (26,32–38) .

Off-label use implies that a drug has marketing authorisation but is used outside the terms of this authorisation (39). In literature different authors use the term “off-label” inconsistently and additionally different types of off-label use exist. According to Turner et al. 6 possible types of off-label medication can be defined:

- Administration of a different *dose* than recommended,
- administration in a different *frequency* than recommended,
- use for an *indication* that is not described in the license,
- use in a patient outside the licensed *age range*,
- administration via a not described *route*,
- administration although a *contra-indication* was described (40,41).

Unlicensed or unauthorised medicine means that a medication does not have a marketing authorisation for medical use in a specific country (42).

In 2014 Cuzzolin et al. published a review summarizing the current worldwide state of off-label and unlicensed drug use in the neonatal population (9). They found out that most neonates in European NICUs (up to 100%) receive off-label or unlicensed used drugs, whereas the proportion of these prescriptions varies between 34 and 87%. They further stated “in fact, if we compare articles published before […] and after the new legislation […], no significant differences

either in the number of off-label prescriptions or in the percentage of neonates receiving an off-label prescription have been observed […].”

It is necessary to point out drug manipulation when talking about paediatric off-label use of medication. The lack of available age-appropriate formulations challenges paediatricians (43–45), as many drugs dispensed to their young patients use dosage forms that were developed for adults (46) and further the required doses can alter up to 100-fold during childhood (12). Thus just a small fraction of the commercially-available dosage form may be required (47). As a consequence, drugs are manipulated to obtain the required dose for administration (48).

In 2013 Richey et al. published the results of an observational study with postal survey investigating manipulations of drugs in paediatric wards in the UK (48). They found out that 46 to 62% of drug manipulations involve tablets, which are split, broken or cut to administer just a segment, crushed to give a proportion of the powder or dispersed in liquid to give a proportion of the liquid. Oral liquid pharmaceutics are diluted and only a proportion of the new formulation is given, “to make the measurement of a small dose volume easier”. In addition they discovered that drug manipulations appear in all paediatric in-patient environments but occur more regularly in specialist areas like neonatal and paediatric intensive care areas. They furthermore revealed that most of the specialists performing the manipulations are concerned that the achieved dose is not precise.

1.4.2 Risks of off-label use and drug manipulation

It is important to emphasise that off-label and unlicensed drug use is not necessarily contra-indicated. On the contrary, it is often required as long as there is no other treatment option available and the expected benefit of the chosen treatment is higher than its risk (7,9). However, this scientifically undocumented use could expose the neonate to high risk due to absence of adequate information about safety.

The WHO defines an Adverse Drug Reaction (ADR) as “any response to a drug which is noxious and unintended and that occurs *at doses used in man for prophylaxis, diagnosis or therapy*” (49). Whether there is a correlation between off-label or unlicensed drug use and the occurrence of ADRs is still uncertain

(39) but there is an educated guess that off-label used medications increase the risk of ADRs. In their systematic review and meta-analysis Impicciatore et al. described predisposing determinants of ADRs in children, whereas polypharmacy seemed to be the main reason, but off-label use of drugs and age-related differences in physiological function also turned out to be predisposing to ADR occurrence (50). In general, the risk of potential ADRs is higher in neonates, especially in NICUs, than in any other age group (51).

Drug manipulations provoke under- or overdosing of medication, thus toxic or sub therapeutic concentrations, as they are imprecise and have unknown effects on the stability and bioavailability of the drug (43,52). Hence, they could increase the rate of medication errors, whereas dose calculation errors are the most frequent in neonatal and paediatric practice (53). In addition, errors with potential for harm seem to hit the youngest, most vulnerable patients of a NICU most commonly (51).

1.5 Paediatric galenic formulations

Obviously, there is an immense need to enhance the medical treatment of neonates by the development and usage of adequate galenic formulations, which, on the one hand, allow precise dosage and on the other hand have an age-appropriate size and texture to enable a reliable, safe application.

In 2008 Krause and Breitkreutz published ‘Improving Drug Delivery in Paediatric Medicine’, an overview of the stage of paediatric drug development at that time (54). They emphasize: “A major challenge in drug development is paediatric drug delivery; however, the problems associated with drug administration in this population are manifold. Because of the highly heterogeneous nature of the patient group, ranging from new-borns to adolescents, there is a need to use suitable excipients and dosage forms for different age groups and suitable delivery devices for certain formulations. So far, there is a lack of suitable and safe drug formulations for children, especially for the very young and seriously ill“.

The predominant route to administer drugs to small children is oral application (25,55). In 2006 the EMA published the ‘Reflection Paper: Formulations of choice for the Paediatric population’ (12). In this paper the EMA provides a table of preferred dosage forms per age group (see Table 1), which is based on

evidence from prescriptions for different dosage forms in relation to age, anecdotal reports of very young children being trained to manage oral solid dosage forms for chronic illness (e.g. leukaemia or HIV) and a questionnaire to 40 experts.

Route: Peroral	Preterm Neo-nates	Term Neo-nates (0-28 d)	Infants and toddlers (1m-2y)	Pre-school children (2-5y)	School children (6-11y)	Adolescents (> 12y)
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent dosage forms	2	4	5	5	4	4
Powders/ multiparticu-lates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Oro-dispersable dosage forms	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Table 1 **Matrix: Route of administration / oral dosage form vs. age**

Early ages: The code implicates mainly the *applicability* of the route and the dosage form:
1 not applicable
2 applicable with problems
3 probably applicable, but not preferred
4 good applicability
5 best and preferred applicability

Higher ages: All dosage forms are principally applicable but with increasing age the *preference* gets more important:
1 not accepted
2 accepted under reserve
3 acceptable
4 preferred acceptability
5 dosage form of choice

Obviously, it was the EMA's opinion that tablets are not applicable to thus not accepted by children younger than 2 years.

On the contrary to the EMA, in 2008 the WHO recommended giving children of all age groups their orally applied medication in the form of flexible solid dosage forms as it emphasized "there was general acceptance of the benefits of solid dosage forms over liquid dosage forms for stability, dosing and administration

issues” (56,57).

Still, the EMA stayed with its statement: In 2011 it published the ‘Draft: Guideline on pharmaceutical development of medicines for paediatric use’ (58) in which it repeated its opinion stating “oral liquid dosage forms are normally considered acceptable for children from full term birth” and “young children may be able to accept small tablets, but not large tablets. Unless otherwise justified by appropriate studies or clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameter, width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets (i.e. tablets from 5 to 10 mm) for children below the age of 6 years; large tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15 mm) for children below the age of 18 years.” After the publication of this draft many comments on improvement were made during the consensus process also containing information on research results of our own study group (see 1.5.1.2 “previous research by the study group”). As a result, the EMA published a second version of the abovementioned draft in 2013, in which it does not give any recommendation for the suitability of solid oral dosage forms in different age groups anymore and furthermore evaluates the mini-tablet approach more positively (see 1.5.1. “The mini-tablet approach”) (59). In the final version of the guideline, which was published in August 2013 and came into effect in January 2014, the content of the chapter regarding solid oral dosage forms including mini-tablets wasn’t changed anymore (25). This shift might also be due to the previous research of the trial team of the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* which had shown that it is save for young children to swallow mini-tablets or rather that they are capable to do so (see 1.5.1.2 “previous research by the study group”).

Notwithstanding, regarding oral medication syrup or liquid solutions are still the current ‘standard’ in paediatric practice, especially in neonates and toddlers. This is due to the lack of knowledge about the young patients’ ability to swallow solid particles and furthermore commercially available tablets often contain active agents in dosages that are too high for small children. Although it is common paediatric practice to administer e.g. vitamin D and in some countries also vitamin K tablets to newborns**,** no data proving that they are able to accept those tablets can be found in literature.

However, liquid oral medication is an inaccurate method to apply drugs to small children. There is a risk of imprecise dosing (56) and thus reaching toxic or sub therapeutic concentrations, as small runlets could flow out of the child's mouth, drops could remain on the spoon and furthermore the production of solutions, for example by dissolving tablets in liquid does not guarantee a homogeneous distribution of the drug. In addition, about 52% of oral liquid paediatric medicines contain at least one potentially harmful excipient and for the main proportion of these drugs there is no alternative with or without less harmful excipients available (11). Regarding the neonatal population many of the excipients contained in commercially available medication have never been tested in this age group (60). One of the major drawbacks of liquid preparations is their short shelf life and the associated requirement of stabilizing agents (56); commonly their effects in children have not been tested either. Another disadvantage of liquid formulations that should not be underestimated is the usually unpleasant taste. Palatability plays an important role in paediatric medication (23), as the young patients are intellectually not able to understand the clinical importance of a treatment yet. Therefore, the more inconvenient a treatment is the more complicated it is to apply to children. Consequently, the taste of a drug can have a remarkable influence on the application and therefore on the accuracy of dosage as the palatability is one of the main acceptance criteria.

In the above-mentioned final guideline (25), the EMA not only defines 'acceptability' as "the overall ability and willingness of the patient to use and its care giver to administer the medicine as intended" but also lists parameters that have an influence on the acceptability. Furthermore, the EMA stresses that it should be a fundamental part of pharmaceutical and clinical trials and development to evaluate the patient's acceptability of paediatric dosage forms. It continues that the acceptability "should preferably be studied in children themselves as part of a clinical study involving the proposed medicinal product."

1.5.1 The Mini-tablet approach

Solid oral dosage forms have many convincing advantages over liquid formulations, as they are safer regarding excipients, easy to handle, consistent in uniformity and drug administration and allow precise dosing. In addition, they

are superior to liquids concerning drug stability, storage conditions (61) and production costs, which is also of particular interest regarding the health care of young patients in developing countries. Nevertheless, commercially available ‘standard sized’ tablets are not the perfect dosage form for small children in general and neonates in particular, as their size may cause swallowing and hence compliance problems. Furthermore, the contained dose might be too high for the small patients and therefore manipulation of the tablets is usually required, which increases the risk of dosing errors (52).

Based on these deficiencies, there have been many ambitions to develop tinier solid dosage forms that also are appropriate for the youngest, e.g. mini-tablets. Clinical experience with mini-tablets has already been gained from drugs with textures that are difficult to press into tablet form (e.g. Omeprazole): mini-tablets containing these drugs are filled into capsules or sachets to allow adequate dosing.

There is no set definition of mini-tablets available neither in pharmacopoeias (Ph.Eur. (62), USP (63), JP (64)) nor from regulatory authorities. The only definition can be found in literature by Lennartz et al. describing mini-tablets as small solid dosage forms with a diameter of maximum 3.0 mm (65). However, mini-tablets have the size of just a fraction of ‘standard sized’ tablets, thus it is much easier to swallow them in comparison to ‘standard sized’ tablets. Because of their small size mini-tablets are mostly considered as “multi-particulate formulations”, therefore they usually are administered with different types of devices, like dosing spoons. To enable the use of the mini-tablet technology in the paediatric population it is necessary to precisely apply the exact number of mini-tablets according to age and weight, thus different mechanical and electronic mini-tablet delivery systems have been developed or are under construction to allow a flexible choice of the required amount (66–68).

Mini-tablets exist in two different forms: uncoated and coated. Just like in ‘standard sized’ tablets these different types allow reliable and suitable administration depending on the contained active agent.

Uncoated mini-tablets dissolve in the mouth cavity within a few seconds as soon as they have contact with saliva, thus the risk of choking on them is very low. Therefore, they are now rated as being a suitable and safe dosage form to administer medicine to small children and neonates. On a less positive note, the

fast disintegration and drug dissolution could decrease the compliance when administering drug molecules with an unpleasant taste.

Coated mini-tablets do not disintegrate in the mouth cavity and therefore entail the possibility of taste masking (69). Moreover, an adequate coating could protect the oral mucosa from excipients or active agents that are potentially irritating**,** avoid early gastric digestion of agents that need to be set free in the intestine and furthermore enable sustained-release characteristics when using polymer coating.

1.5.1.1 Previous research

A few trials comparing paediatric formulations involving mini-tablets have already been performed prior to the study of this thesis, including two studies that have been conducted by our study group of the *Heinrich-Heine-Universität Düsseldorf*.

The first to investigate the capability of children to swallow mini-tablets were Thomson et al. (69), who published the results of their open, prospective, uncontrolled, single-dose trial enrolling 100 children aged 2 to 6 years in 2009. The children, divided into 4 subgroups according to age (2-3 y, 3-4 y, 4-5y, 5-6 y), were administered one 3 mm diameter drug-free uncoated mini-tablet each, whereas the result of the swallowing act was not actively controlled. The swallowability of the mini-tablets varied a lot between the different age groups: only 46% of the 2 year-olds were able to swallow the mini-tablets, whereas an outcome of up to 86% could be seen in the oldest children. Thomson et al. concluded that the use of 3 mm mini-tablets would be safe in children aged 4-6 years.

In 2011 Van de Vijver et al. (70) published the results of their prospective randomized study in 16 children with cystic fibrosis. These participants, aged 6 to 30 months, were administered 4 different doses of pancrelipase using 1 to 4 enteric-coated 2 mm diameter mini-tablets over 5 days. Whereas the primary objective of this trial was the effect of pancrelipase, the secondary parameter was the palatability of the mini-tablets, which was scored “fair to good by the parents in each of the treatment groups”. In contrast to Thomson et al. they involved children younger than 2 years and the results allowed the assumption

that children aged younger than 4 years are able to swallow smaller mini-tablets.

Those two studies gave first indications that, in contrast to the EMA recommendations at that time (58), even small children were able to safely swallow oral solid formulations. However, no probability value p was calculated for either of the studies to show that the rather small sample sizes are statistically powered and furthermore they did not provide any information about the suitability of mini-tablets in comparison to other oral dosage forms like the gold standard syrup. Therefore, our study group conducted two studies, investigating the swallowability and acceptability of 2 mm diameter drug-free uncoated and coated mini-tablets in comparison to 3 ml glucose syrup in 366 children in total, aged 6 months to 5 years inclusively. The results were published by Spomer et al. in 2012 (71) and Klingmann et al. in 2013 (72) and revealed that the acceptability as well as the swallowability was higher for the mini-tablets compared to the syrup in children of all age groups. The studies are described in "1.5.1.2 Previous research by the study group" in more detail.

In 2013 Van Riet-Nales et al. (73) published a study using small tablets of a diameter of 4 mm. In this trial, they used data of 148 children aged 1 – 4 years who got 4 different oral placebo formulations following a randomised crossover design. The formulations were the abovementioned small tablet, a powder, a suspension and syrup, which were administered by the children's parents at home using 2 formulations per day. At the end, the parents had to report the children's acceptability using a VAS score and also name the preferred formulation of their child and themselves. They found out that children accept all of the formulations, whereas the tablets were the best-accepted formulation.

1.5.1.2 Previous research of the study group

As mentioned above, before conducting the trial for this thesis the study group had already performed two previous paediatric studies at the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* of the *Universitätsklinikum Düsseldorf*.

In 2010 (published 2012) Spomer et al. conducted a pilot study in an open, randomised, two-way crossover design (71), with 60 out-patient as well as in-patient patients aged 6 months to 5 years inclusive and divided into 6 age

groups of 10 participants each (0.5 to <1 y, 1 to <2 y, 2 to <3 y, 3 to <4 y, 4 to <5 y and 5 to <6 y) to compare the acceptability and swallowability of uncoated, drug-free, 2 mm diameter mini-tablets to 3 ml glucose syrup. They closely observed the deglutition process and assessed the result of swallowing by oral inspection. The outcome was assessed using the following 5 evaluation criteria:

1.) Swallowed (mini-tablet) / everything was swallowed (glucose syrup)
- Mini-tablet: Which implies that no chewing took place during deglutition and no residuals of the solid were found during oral inspection.
- Glucose syrup: Which means that no liquid was left in the mouth and no drops left the mouth.
- Interpreted as accepted and swallowed.

2.) Chewed (mini-tablet) / Small runlet flowed out of the mouth (glucose syrup)
- Mini-tablet: Which implies that chewing was observed before deglutition or that a part of the solid, broken into a minimum of two pieces, was found during oral inspection.
- Glucose syrup: which means that the child did not swallow completely.
- Interpreted as accepted but not swallowed.

3.) Spat out
- Mini-tablet: Which means that no deglutition took place and that the solid is no longer in the child's mouth.
- Glucose syrup: Which means that no deglutition took place because the child disgorged the glucose syrup directly.
- Interpreted as not accepted and not swallowed.

4.) Choked on
- Mini-tablet: Which means that the solid was swallowed the wrong way or that a cough was caused.
- Glucose syrup: Which means that the solid was swallowed the wrong way or that a cough was caused.
- Interpreted as not accepted and not swallowed.

5.) Refused to take
- Mini-tablet: Which implies that the child did not allow the investigator to place the solid in the mouth.
- Glucose syrup: Which implies that the child did not allow the investigator to place the pipette or teaspoon in the mouth or that the child did not close the mouth correctly and that all glucose syrup was leaking out of the mouth because no deglutition took place.
- Interpreted as not accepted and not swallowed.

The number of participants was applicable providing sufficient data to calculate the sample size of the following confirmatory study and, moreover, the

measurement method proved to be appropriate to distinguish between the effects of the two different oral formulations. The pilot study gave first indices that the acceptability of the mini-tablet (= the aggregate of “swallowed” and “chewed”) was superior to the glucose syrup in most of the investigated age groups.

After the success of this exploratory study Klingmann et al. and thus the same study group performed a confirmatory study in 2011 (published 2013) (72) to verify the results and to further investigate whether coated or uncoated mini-tablets differ from syrup in acceptability and swallowability of toddlers and preschool children. It was designed as a single-centre, randomised, open, three-way crossover study and included 306 paediatric in- and outpatients, divided into 6 age groups, equal to the age groups of the pilot study, with 51 participants in each. This time every child received 3 oral placebo formulations: One uncoated mini-tablet, one coated mini-tablet (2 mm diameter each) and 3 ml of glucose syrup consecutively, whereas they were randomized to 1 of 6 possible sequences. The deglutition was assessed using the same evaluation criteria as the previous pilot study. As a main result this study could demonstrate that the acceptability of uncoated mini-tablets was superior to syrup in the overall patient population and further even the swallowability was higher for mini-tablets compared to syrup. Besides, all age groups tolerated all 3 formulations: none of the children inhaled or coughed neither because of the syrup nor the uncoated mini-tablet and only 2 children, both of the youngest age group, coughed because of the coated mini-tablet, without clinical relevance in both cases. Hence, the trial team concluded that “mini-tablets are a valuable alternative to syrup for children 6 months to 6 years of age and are more acceptable compared to liquid formulation.”

The results of the study group’s trials achieved international success: In 2011 the EMA “Draft: Guideline on Pharmaceutical Development of Medicines for Paediatric Use” (58) recommended the use of oral liquid dosage forms for small children as they were “normally considered acceptable for children from full term birth”. Furthermore it was stated, “young children may be able to accept small tablets, but not large tablets. Unless otherwise justified by appropriate studies or clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameter, width or length whichever is the longest) will not be considered acceptable for

children below the age of 2 years, medium sized tablets (i.e. tablets from 5 to 10 mm) for children below the age of 6 years; large tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15mm) for children below the age of 18 years."

After the consensus process for this draft guideline had resulted in various comments for improvement, including the above-mentioned studies of our trial team, a second version of the draft guideline was published for comments in early 2013 (58). In contrast to the previous version there is no age-related recommendation for the suitability of solid oral dosage forms anymore and further the mini-tablet approach was assessed more approvingly. This new content of the chapter on solid oral dosage forms stayed unchanged in the final version of the guideline, which was published in August 2013 after a second consensus process and came into effect in February 2014 (25).

1.5.1.3 Objectives of this thesis

Although these studies provided data showing that children aged 6 months and older are capable of accepting and swallowing solid oral medication in form of mini-tablets, there still remained a gap in information about the acceptability and swallowability of mini-tablets of children younger than 6 months, including neonates. The proportion of off-label medication and manipulation of drugs is high in children and highest in newborns, thus there is a great necessity to establish suitable formulations for them. Furthermore, in the study groups' prior study children aged 6 months to 1 year were better capable to swallow the mini-tablets than older children aged 2-4 years (72). Therefore, the question remained open how even younger children are able to swallow the mini-tablets. So far, there have been no data available on the acceptability and swallowability of oral galenic forms in neonates.

Thus, this study's purpose was to expand the knowledge on acceptability and swallowability of mini-tablets as an oral dosage form to the population of neonates and therefore to investigate whether mini-tablets differ from syrup regarding those parameters.

Specifically, our objectives were:

Primary Objective
To prove that the acceptability of the uncoated mini-tablet is not inferior to the suitability of the syrup in neonates between 2 and 28 days of age.

Secondary Objectives
To identify the percentage of neonates capable of swallowing (swallowability) a solid oral formulation.

To investigate the differences in the deglutition of two different oral placebo formulations.

To investigate the differences in the acceptability of the uncoated mini-tablet versus the syrup.

To prove that neonates are able to swallow a solid formulation as well as a liquid.

To analyse the compliance of neonates requested to swallow a mini-tablet or glucose-syrup.

To identify any possible problem, that could occur during deglutition.

To identify the percentage of children who inhaled or coughed during ingestion of any of the two oral placebo formulations.

To investigate the safety of the two oral placebo formulations.

To investigate the percentage of preterm neonates capable of swallowing (swallowability) a solid oral formulation.

To prove that preterm neonates are able to swallow a solid formulation as well as a liquid.

To analyse the compliance of preterm neonates requested to swallow a mini-tablet or glucose-syrup.

2. Material and Methods

2.1 Material

To investigate and prove the study objectives two different oral drug-free formulations were used: Uncoated mini-tablets with a diameter of 2 mm (see Figure 1) and a mass of approximately 7 mg as well as 0,5 ml 15% glucose syrup, as these amounts could contain a similar portion of a drug.

The uncoated mini-tablets were produced by Next Pharma, Waltrop, Germany under Good Manufacturing Practices and consist of the following ingredients:

Microcrystalline cellulose (Avicel PH-105; FMC BioPolymer, Philadelphia, Pennsylvania, USA), 61.577% 5.1454 mg/unit *α-lactose monohydrate* (FlowLac 199; Meggle, Wasserburg, Germany), 31.145% 2.6025 mg/unit *Anhydrous colloidal silica* (Aerosil 200; Evonik, Essen, Germany), 0.939% 0.0785 mg/unit *Magnesium stearate* (Barlocher, Unterschleissheim, Germany), 0.235% 0.0196 mg/unit

The 15% glucose syrup was newly manufactured by the investigators of the study group at the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* of the *Universitätsklinikum Düsseldorf* prior to administration. Concentrated glucose syrup from Caesar & Loretz, Hilden, Germany was used for this.

We did not use coated mini-tablets in the study of this thesis, as two participants of the previous one, both belonging to the youngest age group, had coughed when swallowing the coated mini-tablet (72), even though there has not been any clinical relevance in either case. To provide a high safety standard for the even younger participants in this trial as our study group has been the very first to include neonates into a trial investigating mini-tablets, it was decided to only use the uncoated version of the mini-tablets. The uncoated mini-tablets and their dimension can be seen in Figure 1.

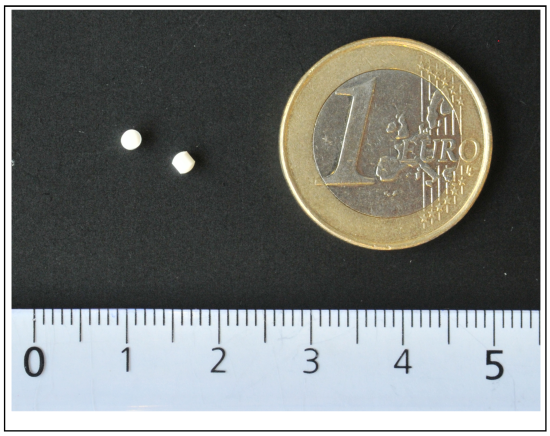

Fig. 1 : **Dimension of mini-tablets in comparison to a 1€ coin**

2.2 Methods

2.2.1 Study Design

The trial was designed as a single-centre, randomised, open two-way crossover study. The order of application of the two oral placebo-formulations each participant received was randomized using *SAS, Version 9.1* (74) to avoid a bias in the effects of the two formulations caused by the sequence.

There was no need for controls or blindfolding as neither of the investigated formulations contained any active ingredient and furthermore each participant swallowed both formulations. Also, this two-way crossover design enabled an intra-individual comparison of the swallowing results. Furthermore, for a parallel design many more children would have been required to be exposed to the study risk and stress in order to achieve statistically relevant results. A double-blinded dummy technique was not feasible as the two formulations had different appearances and contained only placebo anyway. Therefore, it was designed in an open design without blindfolding.

As described in the publication of this trial, “the study was conducted according to the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Guideline on Good Clinical Practice* with a risk-adapted level of monitoring, adequate insurance coverage, received a favourable opinion from the *Ethics Committee of the Medical Faculty of the Heinrich-Heine-University, Dusseldorf, Germany* (No. 3863) and was registered in the *German Clinical Trial Registry* (No. DRKS00005609). As the study medication did not contain any active

ingredient the trial did not fall under the German Drug Law and was thus not subject to review and approval from the German competent authority, the Federal Institute for Drugs and Medical Devices" (75).

2.2.2 Study population

The trial was conducted with neonates of both genders, aged between the 2nd and 28th day of life in the *Frauenklinik* and the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* of the *Universitätsklinikum Düsseldorf*. Neonates with the following exclusion criteria (see 3.2.2.2 Exclusion criteria) were barred from taking part in the study.

The average proportion of neonates capable of swallowing either syrup or the uncoated mini-tablet was estimated to be similar to the average proportion of toddlers and young infants (84.5%) and in any case not lower than 10 percentage points (i.e. ≥ 74.5%), which was calculated based on data of prior studies (71,72). In the prior confirmatory study (72) a correlation of 0.336 was calculated for children swallowing either syrup or the uncoated mini-tablet. On the basis of the sample size formula approach (76,77) in a non-inferiority approach and considering a crossover design, the calculated correlation of study groups in the prior study, a one-sided α of 0.05, and a power of 0.9, a sample size of 151 children was calculated.

The parents of 362 neonates were informed thoroughly about the trial, its background and its risks and benefits. The information was given both orally by the investigators and in writing in form of a detailed patient information sheet (see attachment 8.6). After that, the parents were given a suitable period of time to consider the given information, ask questions and think over whether their new-born should participate or not. Both parents of each participant were required to give written informed consent (see attachment 7.7) in order that their child could take part in the trial. Due to the age of the young participants they were obviously not able to give their own assent as well. Afterwards, the inclusion and exclusion criteria were double-checked by reviewing the patient files, a physical examination including an oral inspection and asking the parents precisely about their child's medical history.

In 163 of the 362 cases inclusion criteria were not fulfilled. Most of the time the mother and child were discharged before the consent could be given. In some cases the parents were afraid that the neonate could choke on the mini-tablets or feared that the child could be stressed through the investigation. All parents of the remaining 199 neonates opted for their child to take part in the study and signed the informed consent. Although all of those neonates fulfilled the inclusion criteria, not all of them could be included: 48 were discharged before the trial could be performed. As it was part of the ethical vote (see attachment 7.5) that all the participants were in-patients during the trial-activities, the 48 discharged neonates were not allowed to participate. Consequently, 151 neonates were included in this study and the data of all of them were used for the statistical evaluation. An overview of the recruiting process can be seen in Figure 2.

As pointed out previously, the participants were 2 to 28 days old, thus in the first month of their life. The average age was 4.07 days, the median 4 days.

Eleven of them were preterm neonates (= born <37 weeks of gestational age) with a gestational age of between 33+1 to 36+6 weeks, whereas the average gestational age was 35+6 weeks, the median 36+1 weeks. The average age of the preterm neonates was 6.9 days, the median 4 days.

To protect severely sick patients from potential harm through a non-effective treatment, this trial was only performed on healthy neonates, as it was necessary to firstly demonstrate that neonates are able to swallow mini-tablets in general. Moreover, performing the study on healthy newborns allowed the inclusion of a comparatively large number of patients within a short period of time:

The recruitment of participants and the implementation of study activities were executed within 4 months from November 2013 up to and including February 2014.

Participants' recruitment

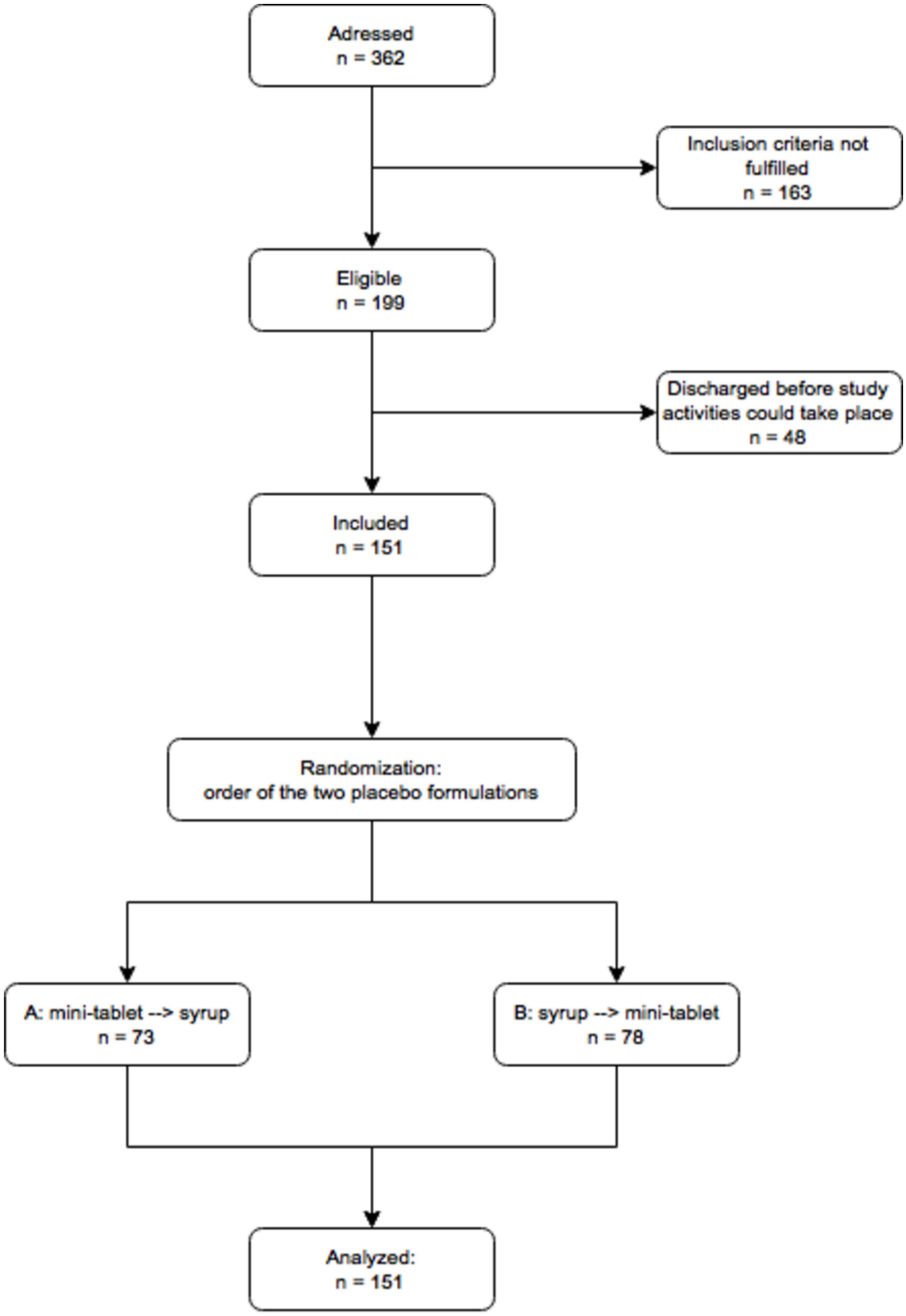

Fig. 2: **Flowchart of participants' recruitment**

2.2.2.1 Inclusion criteria

Age:
Children aged from 2 to 28 days.

Sex:
Male or female.

Recruitment:
Recruiting took place in the *Frauenklinik* and the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* of the *Universitätsklinikum Düsseldorf* (inpatients).

Health:
Neonates were healthy and not suffering from any illness. Based on medical history, physical examination and all other appropriate diagnostic procedures they were able to swallow the two formulations.

Compliance:
Participants' parents understood and were willing, able and likely to comply with examination procedures and restrictions.

Consent:
Participants' parents were capable of understanding the examination procedures, participant obligations as well as risks and benefits of participation in this study and both gave written informed consent.

2.2.2.2 Exclusion criteria

Any impairment of swallowing either solids or glucose-syrup as a consequence of
- chronic illness (e.g. chronic lung disease),
- acute illness (e.g. sepsis, respiratory distress, gastroenteritis, respiratory tract infection) and/or
- oral deformation.

Intolerance:
- occurrence of lactose-intolerance in family history.

Pre- and Concomitant Medication
- Any drug that causes nausea, fatigue or palsy.

Intervention:
- No conducting of the trial-activities shortly after surgical intervention until child was allowed to drink.

2.2.3 Administration and medical assessment

Every participant received one uncoated placebo mini-tablet as well as 0.5 ml of the glucose syrup in a randomized order. “Randomization Type A” corresponded to administration of the mini-tablet first and of the glucose syrup afterwards; consequently “Randomization Type B” corresponded to administration of the glucose syrup first and of the mini-tablet afterwards.

After the administration of the first oral formulation the investigator directly proceeded with the administration of the second one. Altogether, the study examination took about 10 - 15 minutes per participant and was conducted as follows for Randomization Type A:

First of all the investigator inspected the neonate’s mouth with the help of a penlight and a tongue depressor to see if there were e.g. any oral deformations or other reasons the study couldn’t be conducted with the child. The mini-tablet was placed in the child’s cheek pouch by the investigator. Afterwards, the child was given a drink to trigger the deglutition process; therefore the parents were allowed to choose between mother’s milk, milk, water, tea or maltodextrin. Thereupon, the investigator inspected the child’s mouth cavity thoroughly with the help of a penlight and a tongue depressor to detect possible residuals of the mini-tablet. This assessment of the deglutition process had proven to be suitable in the previous studies, therefore it was used in this study as well.

Before administering the next formulation, the mouth cavity was inspected again. Next, 0.5 ml of the glucose syrup were administered using a pipette; this time without the child being given another liquid to drink afterwards as the syrup itself was a trigger of the paediatric deglutition. After that the investigator inspected the neonate’s mouth cavity once again to assess if there were any runlets left.

For Randomization Type B the procedure was performed starting with the glucose syrup.

The test results of the intervention were classified in 4 evaluation criteria:

1. Everything swallowed
   - Mini-tablet: which means that no residuals of the solid were found during oral inspection.
   - Glucose syrup: which means that no liquid was left in the mouth and no drops left the mouth.
   - Interpreted as accepted and swallowed.

2. Partially swallowed
   - Mini-tablet: Which means that the child did not swallow directly or that residuals of the solid were found during oral inspection.
   - Glucose syrup: which means that the child did not swallow completely because a small runlet was flowing out of the mouth or a leftover was found in the pipette.
   - Interpreted as accepted but not swallowed.

3. Inhaled / Coughed / Choked on
   - Mini-tablet: Which means that the solid was inhaled or that cough was caused.
   - Glucose syrup: which means that the syrup was inhaled or that a cough was caused.
   - Interpreted as not accepted and not swallowed.

4. Termination of the examination by the parents
   - Mini-tablet: Which implies that the parents did not allow the investigator to place the solid in the child's mouth for any reason after having signed the informed consent.
   - Glucose syrup: which implies that the parents did not allow the investigator to place the pipette in the child's mouth for some reason after having signed the informed consent.
   - Interpreted as not accepted and not swallowed.

According to the very young participants' age of only a few days the evaluation criteria had to be modified in comparison to the previous studies (see "1.4.1.2 Previous research by the trial team"), for instance the category "chewed" of the mini-tablet assessment was changed to "partially swallowed" and "refused to take" to "termination of the examination by the parents".

The availability of a qualified neonatologist during the study activities was ensured at all times to guarantee competent treatment in case of possible medical problems such as severe adverse events caused by the deglutition.

2.2.4 Statistical Evaluation

The primary objective was assessed utilizing the REML-based test for non-inferiority for paired binary data (76,77). The one-sided α was set at 0.05.

The secondary objectives were assessed using descriptive statistics with number of observations, arithmetic means, minimum, Q1, media, Q3, maximum. Furthermore, they were also analysed by the above-mentioned REML-based test (77) and additionally the McNemar-test (78), a subsequent two-sided testing, was performed when significant.

2.2.5 Collaboration

A strong collaboration between different university departments was vital for this investigational trial to ensure state-of-the-art pharmaceutical development, a proper design within the national legal framework and furthermore to execute the trial rapidly. Therefore, as in the two previous studies, the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* of the *Universitätsklinikum Düsseldorf* and the *Institut für Pharmazeutische Technologie und Biopharmazie* of the *Heinrich-Heine-Universität Düsseldorf* were supported by the University Hospital's clinical coordination centre, the *Koordinierungszentrum für Klinische Studien (KKS)*, once again to enable the investigation to take place in a short period of time. For the first time, the collaboration with the *Frauenklinik* of the *Universitätsklinikum Düsseldorf* was also necessary as the recruiting of the main part of the study's participants took place in the neonatal ward of its obstetric department.
The *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie*, the *Institut für Pharmazeutische Technologie und Biopharmazie* and the *KKS* agreed on the study objectives, endpoints, design, evaluation criteria and study procedures as presented in the study protocol (attachment 7.4) and as approved by the *Ethikkommission* of the University (attachment 7.5). Prof. Dr. Jörg Breitkreutz of the *Institut für Pharmazeutische Technologie und Biopharmazie* provided the liability insurance for the study participants. The Principal Investigator with responsibility for study organisation and all medical aspects was Dr. med. Hans Martin Bosse*, Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie*. Responsible for preparation, coordination

and execution of the trial were Dr. med. Viviane Klingmann, *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie*, and the author of this thesis, GCP-certified investigators. The KKS ensured GCP compliance by providing regular monitoring and Trial Master File support. Furthermore it provided the paper-based Case Report Form and the database. Dr. Andreas Möltner of the *Kompetenzzentrum für Prüfungen in der Medizin, Medizinische Fakultät der Universität Heidelberg* provided sample size calculation, randomization list and the statistical evaluation. Dr. med. Viviane Klingmann, Prof. Dr. Jörg Breitkreutz, Dr. med. Hans Martin Bosse and the author of this thesis prepared the first draft of the publication and were supported by Prof. Dr. med. Thomas Meissner, *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie*. All parties involved contributed to data interpretation, reviewed the draft and approved the final version of the publication.
To specifically point out the obligations of the writer, she substantially contributed to the study design and evaluation criteria as well as to preparing the first draft of the publication. Furthermore, she was responsible for addressing the parents of potential participants, conducting the pre-investigational discussions and informed consent, conduction of the investigation and the collection and entering of the data to the database.

2.2.6 Legal framework

To perform this study the national legal framework had to be fulfilled:
The clinical trial had to follow the ethical standards of the Declaration of Helsinki (79) as well as the quality standard of ICH-GCP regarding planning, performance, evaluation and reporting. However, as the galenic formulations used in this study were only placebo-containing, this clinical trial did not fall under the German *Arzneimittelgesetz* (AMG) (80). Only clinical trials containing a medicinal product fall under the legal obligations of the AGM, which is defined in *§4.23.1*. Placebo medication as used in our trial is not an active medicinal product according to the definition given in the AGM therefore it did not need Clinical Trial Authorisation by the *Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM). Nevertheless, according to the German physicians' law the study needed a favourable opinion from the university hospital's independent ethic commission (attachment 8.5) as well as a positive benefit-risk

ratio with minimal risk and minimal stress for the children involved. According to the Declaration of Helsinki (79) §17 medical research in vulnerable populations is justified “if the research is responsive to the health needs and priorities of this population […] and if there is a responsible likelihood that this population […] stands to benefit from the results of the research”. The strain caused by of this study was considered minimal. It took place in a child friendly setting as the children could stay in the arms of their parents, no invasive investigations were needed, the risk of coughing or choking was expected minimal and further there was a qualified neonatologist available immediately throughout the whole investigation. Although the individual child did not benefit from the participation in this clinical trial there was still a group benefit given for the corresponding population. This group benefit is legally accepted.

3. Results

3.1 Overview

124 of the 151 participating neonates swallowed the mini-tablets completely, whereas the remaining 27 neonates were able to swallow them partially at least.

109 participants swallowed all of the syrup; 42 swallowed it partially.

Not any of the neonates inhaled, coughed or choked on any of the two formulations.

The examination was never terminated by any of the parents, neither during investigating the deglutition of the mini-tablets nor of the glucose syrup.

An overview of the abovementioned results can be seen in table 1.

	Everything swallowed	Partially swallowed	Inhaled/ coughed/ choked on	Termination of the examination by the parents
mini-tablet	124	27	0	0
syrup	109	42	0	0

Table 2: **Overview of the results: Distribution within the 4 categories**

To assess the suitability of the uncoated mini-tablets for neonates our study group focused on measuring acceptability including swallowability as it was defined and standardised in the study groups previous studies (71,72) as this standardised assessment methodology has proven to be reliable.

3.2 Acceptability

As an aggregate of the two categories “everything swallowed” and “partially swallowed” the acceptability, which is the primary objective of this study, was 100% for both of the oral placebo formulations (95% CI: 97,6%-100,0% each). No non-inferiority test was performed for the acceptability. The acceptability of the mini-tablets was not inferior to the acceptability of the syrup. The results can be seen in figure 3.

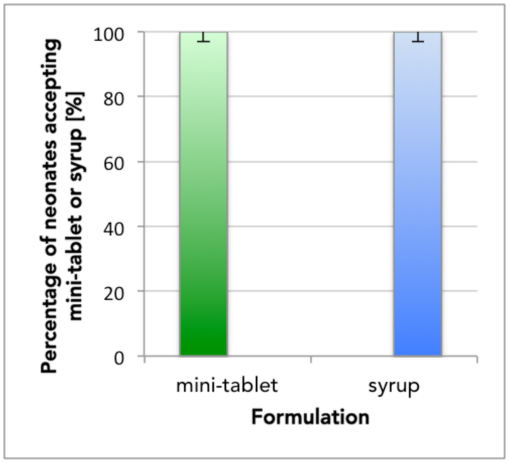

Fig. 3: **Acceptability**

3.3 Swallowability

The swallowability, which just corresponds to the category 'everything swallowed' and does not include the category 'partially swallowed', was high for both oral placebo formulations: the swallowability of mini-tablets was 82.2% (95% CI: 75.1%-87.9%) and that of the syrup a bit lower with 72.2% (95% CI: 64.3%-79.1%). The swallowability of the mini-tablets was not inferior to the one of the syrup ($p<0.0001$). An additional two-sided test was performed which proved that the swallowability of the mini-tablets even was significantly higher than the swallowability of the syrup (Δ10%; 95% CI 1.37%-19.34%; $p=0.0315$). The results of the swallowability can be seen in Figure 4.

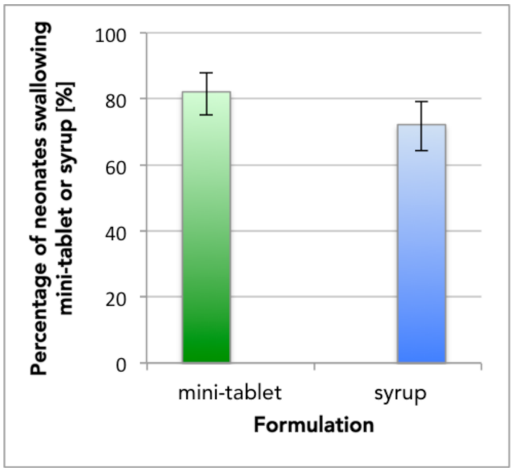

Fig. 4: **Swallowability**

3.4 Acceptability in the subset "preterm neonates"

In the subset of the 11 preterm neonates the acceptability as a sum of the

categories “everything swallowed” and “partially swallowed” was also 100% for both placebo formulations (95% CI: 71,5%-100,0% each). The swallowability was 82% for the mini-tablet (95% CI: 48.2%-97.7%) compared to 73% (95% CI: 39.0%-94.0%) for the syrup. An overview of these results can be seen in table 3. No additional statistical analysis was performed for this subset.

	Everything swallowed	Partially swallowed	Inhaled/ coughed/ choked on	Termination of the examination by the parents
mini-tablet	9	2	0	0
syrup	8	3	0	0

Table 3: **Agglutination results of preterm neonates**

3.5 Serious adverse events

Neither in the deglutition of the mini-tablets nor in the deglutition of the glucose syrup was any serious adverse event seen in any of the 151 neonates. None of the participants inhaled the formulations or coughed during the investigation.

4. Discussion

As off-label and unlicensed medication use is still unsatisfactorily high in children, especially in infants and neonates, there is an undeniable need to establish new appropriate dosage forms and conduct trials to entrench suitable clinical guidelines for the medical treatment of the various paediatric age groups.

Thus, the EMA demands adequate trials or clinical evidence to improve the medical care of the paediatric population and particularly calls for the enhancement of oral formulations that ensure acceptability and dosing flexibility as well as accuracy (26).

Although it is common paediatric practice to administer e.g. vitamin D and in some countries vitamin K tablets to newborns, no data proving that they are able to accept those tablets could be found in literature.

Concerning this, the study group including the writer of this thesis is the first to provide statistical evidence that healthy neonates and further even healthy preterm neonates are able to swallow and accept one single uncoated mini-tablet with a diameter of 2 mm. Compared to syrup the acceptance is 100% for both formulations, whereas the neonates are capable of swallowing mini-tablets significantly better than syrup. As a consequence, the research team concludes that uncoated mini-tablets are a therapeutic alternative to liquid medication for neonates. This therefore underlines or further broadens the results of the two previous studies, which proved similar outcomes in acceptability and swallowability of mini-tablets in infants and preschool children aged 0.5 to 6 years (71,72).

Unlike Thomson et al. (69), who included children from the age of 2 years upwards and concluded that swallowing mini-tablets is safe for children from the age of at least 4 years, our trial could show that also younger children even neonates are capable of swallowing mini-tablets safely. As Thomson et al. used mini-tablets with a diameter of 3 mm and we used 2 mm diameter mini-tablets it can be inferred that it is not recommendable to use mini-tablets that have a larger diameter than 2 mm in neonates and toddlers. A further important difference from the trial of Thomson et al. is that they did not control the

swallowing result of the participants actively, whereas this was done in the trial for this thesis with the aim to gain more precise results.

The study by Van de Vijver et al. (70) included participants who were younger than 1 year for the first time as they were aged from 6 months up to 30 months. They also used smaller mini-tablets with a diameter of 2 mm and were able to give indications that even children younger than 4 years are able to swallow solid oral medication. But in comparison to the trial for this thesis Van de Vijver et al. just had a small sample size of 16 patients, which is too small to form a set definition. Moreover, it remained uncertain if mini-tablets are a suitable oral dosage form for neonates. It must be emphasized that the trial by Van de Vijver et al. had the palatability of the mini-tablets only as a secondary outcome, whereas the main endpoint of the research was the effect of pancrelipase as they used mini-tablets containing an active agent. This is another main difference to the trial of this thesis just utilising placebo formulations.

However, Thomson et al. as well as Van de Vijver et al. were able to show that small children have the ability to swallow solid oral medication. Nevertheless, none of them compared the acceptability and swallowability of mini-tablets to liquid formulations e.g. syrup, the ‘gold standard’ at that time, and therefore it was not possible to give an evidence-based assertion if mini-tablets could be taken **s**eriously as an alternative to liquid medication.

In the publications of Spomer et al. (71) and Klingmann et al. (75) the study group of the *Klinik für Allgemeine Pädiatrie, Neonatologie und Kinderkardiologie* was the first to compare the mini-tablets to the ‘gold standard’ syrup and could prove that mini-tablets are not only better accepted of but also easier to swallow for young children aged from 6 months to 6 years.

To round off its findings, the study group including the writer of this thesis have hereby supplemented the neonatal population (75) and finally closed the ‘gap’ knowledge about the acceptability and swallowability of mini-tablets in neonates. From the results it emerges that mini-tablets are definitely a serious alternative dosage form to syrup and liquid solutions, as the swallowability of the solid formulation is significantly higher than the swallowability of the liquid formulation.

To assess the “suitability” of oral formulations for children, the swallowability seems to be the superior discriminator as the acceptability hinges on this aspect in this study as well as in the two previous studies. This should be considered in the design of future studies investigating the suitability of appropriate medical formulations for children of all age groups.

Limitations

However, limitations and weaknesses of this study need to be pointed out.

First of all, the participants received just one uncoated, rapidly dissolving mini-tablet, a fact which neither allows any conclusion about the suitability of coated mini-tablets in neonates nor about the amount of mini-tablets that can be administered to one neonate. It remains uncertain how many mini-tablets one neonate can swallow consecutively or even at a time, although this could be necessary to reach the required doses of the active agents (maximum of active agents each mini-tablet can contain: 2 to 3 mg), assuming that mini-tablets will be a licensed dosage form for neonates in future. Thus, further trials investigating the capability of neonates to swallow coated as well as several mini-tablets have to be conducted.

Moreover, all the participants of this trial were healthy and appropriately developed according to age. This cannot be presumed for the potential future patients who are dependent on medication. Thus, this study does not provide a clear statement about the suitability of the mini-tablets for ill neonates.

The sample size of preterm neonates admittedly was too low to form an evidence-based statement about the capability of this specific age group to accept mini-tablets. Nevertheless, our findings allow the assumption that even these preterm neonates from a gestational age of 33+1 weeks are able to swallow mini-tablets safely. Further studies with a bigger sample size are necessary to prove this.

Furthermore, the neonates received the oral placebo formulations from medical staff, either from one of two paediatricians or from the author of this thesis as a medical student, in an inpatient setting. Therefore, this study does not provide any data about neonates receiving the mini-tablets by lay people, who will indeed be the main persons to administer mini-tablets to children in the domestic setting. Consequently, further studies need to involve lay people,

preferably the children's own parents, as the ones dispensing the formulation to the participants to create realistic outpatient conditions.

Moreover, this trial most notably focused on the suitability of uncoated mini-tablets as a galenic formulation for neonates and as a consequence does not provide any data on bioavailability of active agents. In future, many more studies investigating the bioavailability of miscellaneous agents have to be carried out.

Also, the study was designed in an open, non-blinded scheme, which means a higher risk for investigator and patient bias.

On top of this, the sample size of this clinical trial is too small to state reliable assertions about the factual risk of SAE.

Further and prospective research

Since this trial was conducted more research has been carried out during the last few years. As mentioned previously there is a necessity to investigate whether children are able to swallow more than one mini-tablet at a time to enable dose escalation of active agents in future.

In 2015 Kluk et al. (81) published the results of their clinical trial investigating the ability of children to swallow more than one mini-tablet at a time. 60 children aged 2 to 3 years, divided in 2 subgroups (24 - 36 months and 36 - 48 months), were enrolled in this single-centre, open crossover study. The participants had to swallow 5 or 10 coated, drug-free mini-tablets with a diameter of 2 mm or 3 mm, which were mixed in a fruity jelly on a spoon (day 1: 5 x 2 mm, day 2: 10 x 2 mm, day 3: 5 x 3 mm, day 4: 10 x 3 mm). 75% of the 2-year-olds and 93% of the 3-year-old**s** were capable of swallowing the mini-tablets with or without chewing, whereas 57% of all participants were able to swallow them without chewing. Furthermore "neither the number nor the diameter of the administered mini-tablets have significantly influenced the ability to swallow units."

As mini-tablets have a very limited maximum of active agents **(**they can contain 2-3 mg per mini-tablet), it presumably will be compulsory to administer more than 10 mini-tablets to one child. Therefore, the study of Kluk et al., despite proving that children are able to swallow more than one mini-tablet at the same time, is not convincing enough regarding the amount of mini-tablets in one

deglutination process. Also, because of the sample size of just 60 participants and the narrowly chosen patients' collective of just 2 and 3 year olds participants, many questions remained open.
Therefore, in February 2018 our own study group published the results of its fourth study assessing the acceptability and swallowability of multiple drug-free mini-tablets in comparison to syrup in a randomised, three-way, single administration cross-over study (82). 376 children aged between 6 months and 5 years were divided into two age groups. The children in age group 1 (6 – 23 months) had to swallow 25 mini-tablets at a time, 100 mini-tablets at a time and 5 ml glucose syrup. The children in age group 2 (2 – 5 years) had to swallow 100 mini-tablets at a time, 400 mini-tablets at a time and 10 ml glucose syrup. It could be shown that the administration of at least 25 mini-tablets is safe and well tolerated by children aged from 6 months; furthermore, the administration was even superior to the equivalent dose of glucose syrup. Children aged above 1 year accepted even up to 400 mini-tablets at a time better than the equivalent dose of glucose syrup. It was concluded "mini-tablets open the perspective for introducing small-sized solid drug formulations for all children, thus further shifting the paradigm from liquid towards small sized solid drug formulations."

But not only mini-tablets can be considered as an innovative solution for paediatric drug administration in future. In fact, progress is also being made regarding orally disintegrating films, which are a field of upcoming interest. These films are a solid dosage form prior to administration but dissolve when placed in the mouth (orodispersible films) or on mucosal tissue (mucoadhaesive buccal films). In comparison to mini-tablets the low risk of choking on these films is presumably even decreased and one single film can contain a higher drug dosage of an active agent than one single mini-tablet with up to 62,5mg per dose (23).

Obviously, pharmaceutical and clinical research in solutions for paediatric drug administration is a very interesting and complex field. Due to different initiatives and laws some progress has been made during recent years but still much

remains to investigate before these ideas and approaches become securely established in paediatric practice.

5. Conclusion

In line with the two previous study group's trials, the methodology of this investigational study proved to be appropriate to distinguish between the effects of the two galenic formulations, 2 mm diameter uncoated placebo mini-tablet and 0.5 ml glucose syrup; this time for the age group of neonates.

The acceptability was 100 % for the uncoated mini-tablet as well as for syrup. The swallowability of the uncoated mini-tablet was significantly superior to the swallowability of syrup. Although the sample size of the subset of preterm neonates was comparatively small, it allows the assumption that preterm neonates are able to swallow uncoated mini-tablets safely.

The trial provides reliable data for the utilisation of mini-tablets in neonates and consequently expands the results of previous studies by finally including the most vulnerable age group. It closes the gap in knowledge regarding the capability of neonates to swallow solid oral formulations in form of a 2 mm diameter uncoated mini-tablet. It provides a sound basis for further development and investigation of solid oral medication in children, which is necessary to guarantee age-adapted medical treatment for all age groups and to reduce off-label use, drug manipulation and the associated risk of serious ADRs.

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7. Attachment
7.1 Figures and tables

Figure 1:

Fig. 1 : **Dimension of mini-tablets in comparison to a 1€ coin**

Figure 2:

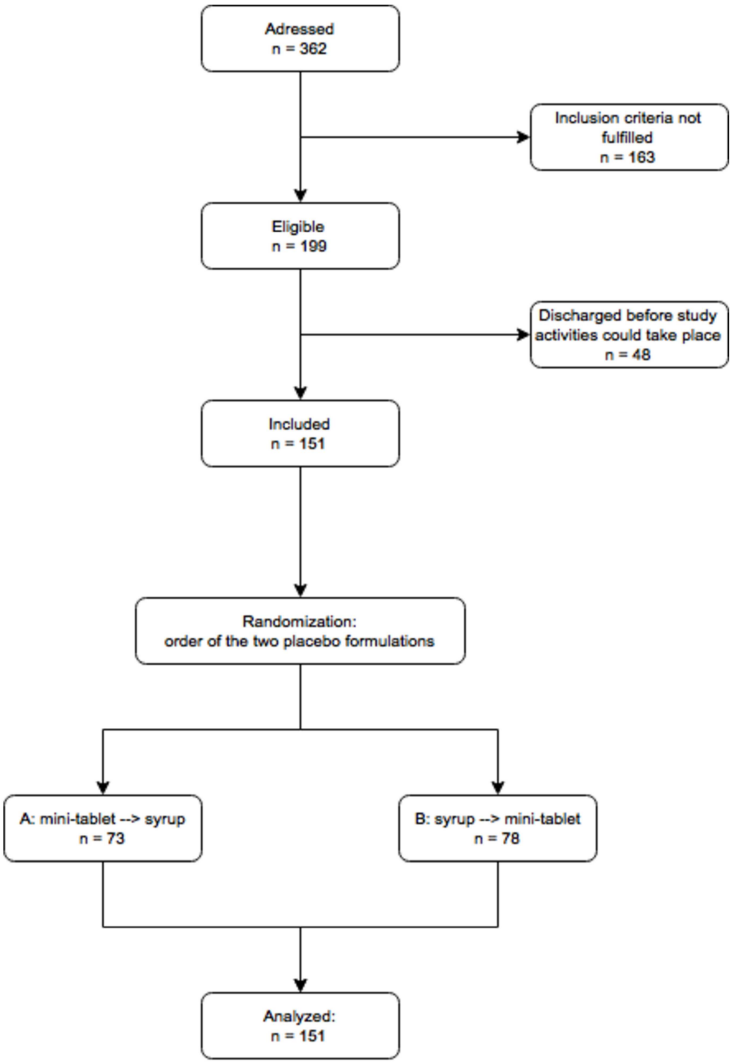

Fig. 2: **Flowchart of participants' recruitment**

Figure 3 + 4:

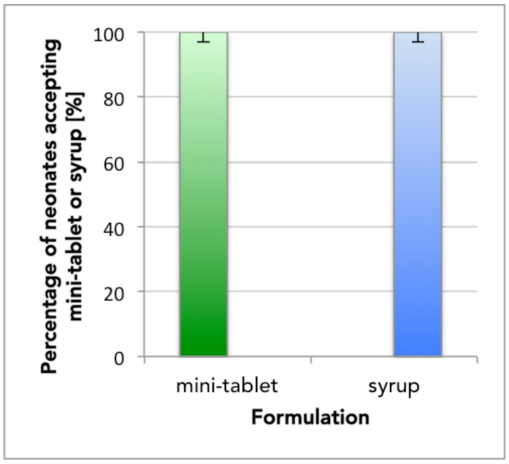

Fig. 3: **Acceptability**

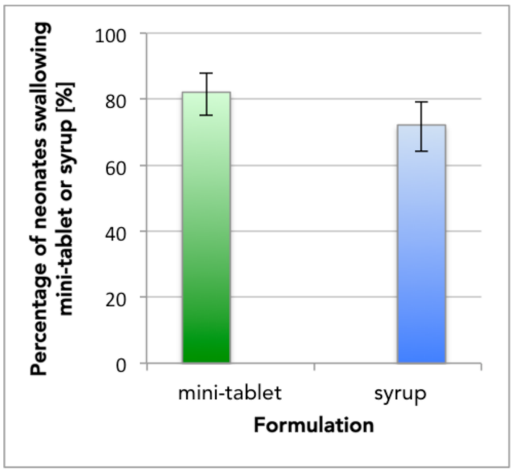

Fig. 4: **Swallowability**

Table 1:

Route: Peroral	Preterm Neo-nates	Term Neo-nates (0-28 d)	Infants and toddlers (1m-2y)	Pre-school children (2-5y)	School children (6-11y)	Adolescents (> 12y)
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent dosage forms	2	4	5	5	4	4
Powders/ multiparticu-lates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Oro-dispersable dosage forms	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Table 1 **Matrix: Route of administration / oral dosage form vs. age**

Early ages: The code implicates mainly the *applicability* of the route and the dosage form:
1 not applicable
2 applicable with problems
3 probably applicable, but not preferred
4 good applicability
5 best and preferred applicability

Higher ages: All dosage forms are principally applicable but with increasing age the *preference* gets more important:
1 not accepted
2 accepted under reserve
3 acceptable
4 preferred acceptability
5 dosage form of choice

Table 2:

	Everything swallowed	Partially swallowed	Inhaled/ coughed/ choked on	Termination of the examination by the parents
mini-tablet	124	27	0	0
syrup	109	42	0	0

Table. 2: **Overview of the results: Distribution within the 4 categories**

Table 3:

	Everything swallowed	Partially swallowed	Inhaled/ coughed/ choked on	Termination of the examination by the parents
mini-tablet	9	2	0	0
syrup	8	3	0	0

Table 3: **Agglutination results of preterm neonates**

7.2. Publication

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Acceptability of Uncoated Mini-Tablets in Neonates—A Randomized Controlled Trial

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Objective To evaluate the suitability of drug-free solid dosage forms (2 mm mini-tablets) as an alternative administration modality in neonates in comparison with syrup.

Study design A total of 151 neonates (inpatients; aged 2-28 days; median 4 days) were recruited. An open, randomized, prospective cross-over study was conducted to compare the acceptability and swallowability of 2 mm uncoated mini-tablets compared with .5 mL syrup.

Results All neonates (N = 151) accepted the uncoated mini-tablet as well as the syrup (both formulations 100%; 95% CI 97.6%-100.0%; primary objective). The level of swallowability of uncoated mini-tablets was not inferior ($P < .0001$), in fact even higher (difference in proportions 10.0%; 95% CI 1.37%-19.34%; $P = .0315$) compared with syrup. Both pharmaceutical formulations were well tolerated, and in none of the 151 neonates, serious adverse events occurred; particularly none of the neonates inhaled or coughed in either of the formulations.

Conclusions The administration of uncoated mini-tablets proved to be a valuable alternative to syrup for term neonates. Our data on neonates close the age gap of prior findings in toddlers and infants: uncoated mini-tablets offer the potential of a single formulation for all age groups. These findings further shift the paradigm from liquid toward small-sized solid drug formulations for children of all age groups, as the World Health Organization proposes. *(J Pediatr 2015;167:893-6)*.

Trial registration German Clinical Trials Register (Deutsches Register Klinischer Studien [DRKS; germanctr.de]): DRKS00005609.

Worldwide more than 50% of all medicines administered to children are off-label, with comparable numbers in The European Union,[1] the US, Australia, and many more countries.[2,3] Even higher rates are reported in term neonates and in the premature—up to 90% of prescribed medication, particularly in pediatric intensive care units.[1] This global situation of the treatment of children is unacceptable and has been addressed by the World Health Organization by its resolution WHA60.20 Better Medicines for Children in 2007[2] and its Make Medicines Child Size campaign.[3]

Moreover, even authorized pediatric medicines may not always be age appropriate with respect to dosing, suitability of dosage forms, and safety of excipients, especially in very young children and neonates.[4] The main concern with oral formulations in general is that especially very young children could be unable to swallow solid formulations. Because of the paucity of detailed knowledge regarding the development, maturation, and pediatric physiology of the deglutition act, the risk of inhalation and aspiration in this age group is hard to predict. To date, there is limited valid scientific data on most suitable, age appropriate pediatric dosage forms to ensure full dose ingestion for oral administration of medicines to very young children,[5] although it is not questioned that special attention should be paid to innovations that improve drug delivery in these age groups.[4]

Administering drugs to neonates is an even greater problem for caregivers than administering them to infants because of a low, variable, and rapidly changing body weight, low dosages, and differences in pharmacokinetic and pharmacodynamic properties that are aggravated by the fact that the latter both are frequently not well determined in neonates. Still, there are no studies so far on neonates determining the advantages of different pharmaceutical forms.

So far, liquid formulations are the most frequently used pharmaceutical forms, especially for the very young children, as solid formulations are widely considered not to be suitable, at least for very young children.[6] However, the use of syrup has major disadvantages, such as chemical, physical, or microbial instability, taste issues, lack of controlled release properties, limited number of safe excipients, and unreliable dosing.[7] Little is known about the safety of excipients in children, and accepted daily and cumulative intakes of excipients have not been established. Dosing in the very young children is unreliable because of the potential incomplete swallowing; in addition, small doses pose greater risks of dosage variations and errors.[7,8]

SAE Serious adverse event

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Our 2 previous studies[9,10] conducted with, in total, 366 children between 6 months and 6 years of age suggested superior suitability of uncoated and coated mini-tablets compared with glucose syrup for drug administration to very young children including toddlers. In this study, we assess the potential use of uncoated, rapidly dissolving mini-tablets in neonates regarding their suitability and swallowability compared with the current standard, the syrup.

Methods

The trial was performed as a single-center, randomized, open cross-over study. Participants sequentially received 2 oral drug-free formulations, an uncoated mini-tablet and syrup randomized to the order of application. The study was conducted according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 Guideline on Good Clinical Practice[11] with a risk-adapted level of monitoring and adequate insurance coverage. The study received a favorable opinion from the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University, Dusseldorf, Germany (3863) and was registered voluntarily in the German Clinical Trials Register (Deutsches Register Klinischer Studien [DRKS; www.germanctr.de] DRKS00005609). As the study medication did not contain any active ingredient, the trial did not fall under the German Drug Law and was, thus, not subject to review and approval from the German competent authority, the Federal Institute for Drugs and Medical Devices.

The study was performed in neonates at the Department of Obstetrics and Gynecology of the University Hospital and at the Department of General Pediatrics, Neonatology and Pediatric Cardiology, University of Dusseldorf, Germany. Exclusion criteria were obtained from the current medical records of participants and were double-checked with the medical staff. Neonates with swallowing impairment for any reason, illness, lactose intolerance in family history, potentially impairing pre- and concomitant medication, as well as neonates who recently had surgery or who reportedly had vomited were excluded from the trial.

A total of 362 neonates between 2 and 28 days of age were eligible for the study, and their patents were approached. Parents were invited to an informed consent session where they received detailed oral and written information in the form of a patient information sheet. After adequate time to read and consider the information, ask questions, and make a decision on study participation, both parents were required to give written informed consent and were asked detailed information about the child's medical history. The medical examination, patient files, and an oral inspection ensured that all inclusion and exclusion criteria were fulfilled. 151 neonates were included in the study and their data subject to statistical analysis (**Figure 1**; available at www.jpeds.com). The neonates were between 2 and 28 days old with an average age of 4.07 days (median 4 days).

Eleven neonates were born pre-term (<37 weeks of gestational age) with a gestational age of 33+1 to 36+6 weeks with an average of 35+6 weeks and a median of 36+1 weeks.

The participants' randomization to the sequence of administration of the 2 formulations was generated with SAS v 9.1 (SAS Institute, Cary, North Carolina) by the study statistician.

Uncoated, drug-free, and rapidly dissolving mini-tablets with a diameter of 2 mm and a mass of approximately 7 mg (**Figure 2**) were produced under good manufacturing practices by NextPharma, Waltrop Germany. The biconvex mini-tablets were composed of microcrystalline cellulose, α-lactose monohydrate, anhydrous colloidal silica, and magnesium stearate. The 15% glucose syrup was freshly produced from concentrated glucose syrup from Caesar and Loretz (Hilden, Germany) at University Children's Hospital Düsseldorf, Germany prior to administration.

Both formulations, syrup and uncoated mini-tablets, were administered in the respective order according to randomization. For the event of a possible medical problem as severe adverse event during deglutition the availability of an experienced pediatrician was ensured.

The investigator placed the mini-tablet in the child's cheek pouch and the child was offered a drink of the parent's choice (breast milk, milk, tea, water, or maltodextrine) to facilitate swallowing. Accordingly, one-half a milliliter of the glucose syrup was administered with a pipette into the slightly opened mouth. The glucose syrup needed to be swallowed without additional liquid. Each deglutition process was thoroughly observed. After each deglutition, the participant's mouth was inspected by the investigator using a flashlight to assess residuals of the mini-tablets or leftover of the syrup. Assessment criteria were "everything swallowed," "partially swallowed," "choked on" (including inhalation or cough), and "termination of the examination by the parents" (**Figure 3**; available at www.jpeds.com).

As soon as the administration and assessment procedures with the first formulation procedures were completed the

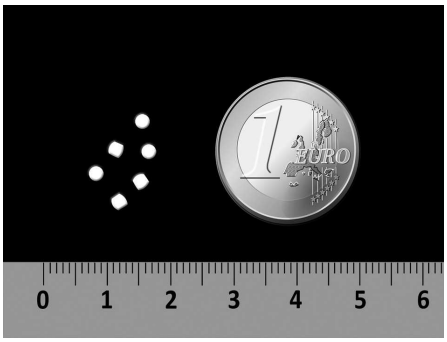

Figure 2. Dimensions of 6 uncoated mini-tablets (*left*) in relation to a 1 Euro coin (*right*).

second formulation was administered. The 2 formulations were administered within a maximum of 10 minutes.

Objectives

In earlier studies,[9,10] we demonstrated that the parameters "acceptability" and "swallowability" are valid parameters to assess the most adequate oral formulation for infants. "Acceptability" was chosen as primary endpoint, "swallowability" as secondary endpoint. The primary objective of this trial was to prove that in neonates the acceptability of the uncoated mini-tablet is not inferior to the acceptability of the syrup. The primary outcome measure of acceptability was defined as an aggregate of the 2 first evaluation criteria (everything swallowed and partially swallowed; **Figure 3**).

The secondary objectives relating to swallowability (as defined as the first evaluation criterion everything swallowed only; **Figure 3**) included the neonates' percentage of swallowability, as well as potential differences in the swallowability of the 2 oral placebo formulations. Further secondary objectives were the percentage of children who inhaled or coughed during ingestion of any of the formulations and percentage of approached parents willing to participate in this study.

Statistical Analyses

The primary objective was investigated using the restricted or residual maximum likelihood-based test for noninferiority for paired binary data.[12,13] Sample size calculation was based on the sample size formula approach[12,13] in a noninferiority design considering a cross over design. Based on the results of prior studies of our research group,[9,10] the average proportion of neonates able to swallow either the control vehicle "syrup" or the intervention vehicle "uncoated 2 mm mini-tablet" was estimated to be comparable with that of toddlers and young infants (approximately 85%) with a correlation of .336 for children swallowing either syrup or uncoated mini-tablet, respectively. To detect an effect of at least 10% with a power of .9, a sample size of 151 was calculated. The 1-sided α was set at .05.

The evaluations of the secondary objectives were performed in the form of descriptive statistics with number of observations, arithmetic mean, minimum, median, and maximum. In addition, they were also analyzed by the residual maximum likelihood-based test, and, when significant, a subsequent 2-sided testing (McNemar-test) was performed. For acceptability and swallowability, Clopper–Pearson confidence limits were computed.

Results

Patients were enrolled between November 5, 2013, and February 27, 2014. The trial was registered voluntarily on December 18, 2013. Although patients were enrolled prior to registration, no analyses occurred prior to trial registration.

Acceptability (Primary Objective)

The acceptability as an aggregate of the 2 categories everything swallowed and partially swallowed was 100% for both oral placebo formulations (95% CI 97.6%-100.0% for both groups). No noninferiority test was performed.

Swallowability (Secondary Objective)

Swallowability was high for mini-tablets (82.2%; 95% CI 75.1%-87.9%) as well as for syrup (72.2%; 95% CI 64.3%-79.1%) with a swallowability of mini-tablets noninferior to syrup ($P < .0001$). Subsequently, in a 2-sided test swallowability of mini-tablets proved to be even higher than syrup (Δ10.0%; 95% CI 1.37%-19.34%; $P = .0315$; **Table**).

In the pre-term neonates (N = 11) with a mean gestational age of 35+6 weeks and a mean age of 7 days the acceptability as an aggregate of everything swallowed and partially swallowed was 100% for both oral placebo formulations. No statistical analysis was performed for the subgroup.

Serious Adverse Events

No serious adverse events (SAEs) were seen in any of the neonates (N = 151) including the preterm neonates (N = 11) in any of the 2 oral placebo formulations. Specifically, no neonate inhaled the formulation or coughed during ingestion of any of the formulations.

Table. Assessment of the total population and the subgroup of preterm neonates

Evaluation criteria	Mini-tablets, N (%)	Syrup, N (%)	Noninferiority test	Two sided test
Total population				
Everything swallowed	124 (82.1)	109 (72.2)	$P < .0001$	$P = .0315$
Partially swallowed	27 (17.9)	42 (27.8)		
Choked on	0 (0)	0 (0)		
Termination	0 (0)	0 (0)		
Total	151 (100)	151 (100)		
Subgroup: preterm neonates				
Everything swallowed	9 (81.8)	8 (72.7)	ND	ND
Partially swallowed	2 (18.2)	3 (27.3)		
Choked on	0 (0)	0 (0)		
Termination	0 (0)	0 (0)		
Total	11 (100)	11 (100)		

ND, not determined.
In total, 151 neonates were investigated. Swallowability (criterion 1) was significantly higher for mini-tablets compared with syrup. The proportion of the 11 preterm neonates swallowing the mini-tablet completely is similar to the total population.

Discussion

Off-label and off-license medication is unacceptably high in very young children and most frequent in oral medication. This in part is due to lack of adequate and well-tested oral formulations. The European Medicines Agency, thus, calls for appropriate studies or clinical evidence of such oral formulations ensuring acceptability, dosing flexibility, and particularly in neonates and preterm newborns.[1] Although vitamin K and vitamin D are regularly administered to neonates orally and generally are perceived as safe, no data are available on the safety of the deglutition process of neonates regarding solid oral formulations as such.

We are the first to provide sound statistical evidence that term neonates accept 1 uncoated single mini-tablet just as well as syrup; both pharmaceutical forms were accepted by 100%. Neonates are even able to swallow a mini-tablet significantly better than syrup; the deglutition process of neonates seems to allow for swallowing such particles without any problem. These data are in line with prior findings of our study group: infants and toddlers accept mini-tablets well, and they swallow mini-tablets even better than syrup.[9,10] Of note: no SAEs were seen in any of the 151 neonates when swallowing the uncoated mini-tablet, although our numbers are too small to allow for a definitive conclusion on SAE.

In line with prior studies,[9,10] the acceptability of mini-tablets is higher than the swallowability with the acceptability reaching a ceiling effect in our study. Thus, we propose swallowability being the superior discriminator to assess the suitability of oral pharmaceutical forms in children in future studies. In contrast, acceptability may be the more valid parameter to assess the practicability for caretakers.

In the subgroup of 11 preterm neonates, acceptability was also high for both formulations—both formulations were accepted by 100%, just as in the whole study population. These are descriptive data with no post-hoc statistical analysis of this subgroup. Further studies are needed to confirm this finding.

In this study, we administered only a single uncoated mini-tablet. Thus, it remains unclear whether our findings apply to acceptability or swallowability of coated mini-tablets as well. The problem uncoated mini-tablets pose is that when they contain unpalatable substances, they may not be accepted or swallowed equally well. Furthermore, the case numbers in our study are too small to reliably estimate the true risk of SAE.

For some active pharmaceutical ingredients 1 mini-tablet (each enclosing a maximum 2-3 mg of active ingredient) may suffice (ie, enalapril maleate). However, for many drugs more than 1 mini-tablet will be necessary, even in neonates. For other substances, fixed dosages in 1 mini-tablet may even exceed the required dosage of neonates, thus, potentially requiring a liquid formulation.

We do not provide data on bioavailability of active ingredients; this study is focused exclusively on the suitability of uncoated mini-tablets as pharmaceutical form. Furthermore, we do not provide data on lay persons dealing with either pharmaceutical forms, but these are the ones to administer the majority of mini-tablets in future. This needs to be addressed in future studies.

Our results show that 1 mini-tablet may be safely administered even in neonates and that they actually swallow mini-tablets better than syrup. Our data close the age gap in current data referring to neonates and open the perspective for introducing such a small-sized solid drug formulations as a single formulation for all children including the very young, thus, further shifting the paradigm from liquid towards such small-sized solid drug formulations for children, as the World Health Organization proposes. ■

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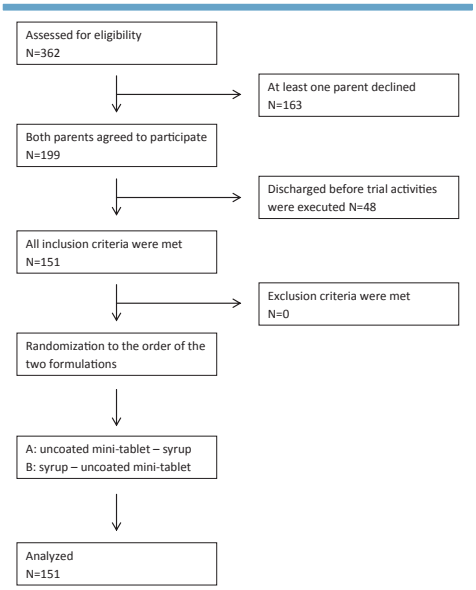

Figure 1. CONSORT flow diagram.

Criteria	Mini-tablets	Syrup
1	**Everything swallowed** no residuals found during oral inspection interpreted as accepted and swallowed	**Everything swallowed** no liquid left in the mouth and no drops left the mouth interpreted as accepted and swallowed
2	**Partially Swallowed** no direct swallowing or residuals found during oral inspection interpreted as accepted but not swallowed	**Partially Swallowed** no complete swallowing due to a small runlet flowing out of the mouth or a leftover in the pipette interpreted as accepted but not swallowed
3	**Choked on** the solid was inhaled or a cough was caused interpreted as not accepted and not swallowed	**Choked on** the syrup was inhaled or a cough was caused interpreted as not suitable and not swallowed
4	**Termination of the examination by the parents** the parents didn't allow the investigator to place the solid in the child´s mouth for any reason after having signed the informed consent interpreted as not accepted and not swallowed	**Termination of the examination by the parents** the parents didn't allow the investigator to place the pipette in the child´s mouth for any reason after having signed the informed consent interpreted as not suitable and not swallowed

primary outcome parameter: **acceptability**

secondary outcome parameter: **swallowability**

Figure 3. Evaluation criteria for the outcome of mini-tablets or syrup administration.

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