Universidade de Lisboa

Faculdade de Farmácia

Design of innovative formulations baby size for individualized therapy

Sara Maria Castelo Domingues

Monografia orientada pela Professora Doutora Joana Marques Marto, Professora Auxiliar da Faculdade de Farmácia da Universidade de Lisboa e coorientada pela Drª Ana Filipa Cosme Silva, Farmacêutica Assistente no Hospital Santa Maria

Mestrado Integrado em Ciências Farmacêuticas

2021

Universidade de Lisboa

Faculdade de Farmácia

Design of innovative formulations baby size for individualized therapy

Sara Maria Castelo Domingues

Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

Monografia orientada pela Professora Doutora Joana Marques Marto, Professora Auxiliar da Faculdade de Farmácia da Universidade de Lisboa e coorientada pela Drª Ana Filipa Cosme Silva, Farmacêutica Assistente no Hospital Santa Maria

2021

Resumo

Os recém-nascidos são uma das populações com menos medicamentos aprovados. A sua fisiologia e farmacodinâmica tão específicas, dificulta o estudo e previsão da forma como os fármacos vão atuar no seu organismo. Além disso, por serem tão diferentes dos adultos, é necessário ter em atenção muito mais pormenores aquando do desenvolvimento de uma formulação para esta população. Os carateres organolépticos, a osmolaridade e os próprios excipientes utilizados devem ser cuidadosamente estudados para que não constituam um risco para os recém-nascidos e ao mesmo tempo apresentem compatibilidade com as suas caraterísticas fisiológicas e farmacológicas.

Nos últimos anos, tem havido um esforço coletivo para que o desenvolvimento e aprovação de novas formas farmacêuticas, especificamente desenhadas e pensadas para esta população, tenha uma maior aposta por parte da indústria farmacêutica. Ainda assim, ainda são poucos os casos em que estes incentivos levaram a uma aprovação real de medicamentos apropriados para os recém-nascidos.

Apesar de algumas formas farmacêuticas como as suspensões, soluções e supositórios serem ainda a grande maioria das apresentações disponíveis para esta faixa etária, tem-se vindo a estudar a sua adequação a esta. As suas desvantagens fazem com que, por vezes, sejam desaconselhadas, mas ainda assim, na prática clínica, ainda se vê um amplo uso destas, por falta de formulações apropriadas para os recém-nascidos.

A manipulação, muitas vezes utilizada para cobrir a falta de especialidades farmacêuticas, é também uma área que deve ser estudada e atualizada. É necessário reunir as evidências disponíveis para que globalmente haja a maior uniformidade possível e, assim, permitir o tratamento igual a todas as crianças.

Novas formas farmacêuticas em neonatologia, como mini comprimidos, filmes e comprimidos orodispersíveis, geles, entre outros, podem ser algumas hipóteses viáveis para administração de fármacos a recém-nascidos pela sua dose precisa, baixo custo, fácil transporte e por não necessitarem de ser deglutidos.

Palavras-chave: Recém-nascido, formulação, inovação, orodispersíveis.

Abstract

Newborns are one of the populations for which fewer medications have been approved. Their physiology and pharmacodynamics are specific, which complicates the study and prediction of how drugs will act in their body. Moreover, because newborns are so different from adults, more details need to be considered when developing formulations aimed at this population. The organoleptic characters, osmolarity and the excipients used should be carefully studied so that they do not pose a risk to newborns and, simultaneously, they must be compatible with their physiological and pharmacological characteristics.

In recent years, there has been a collective effort to develop and approve new pharmaceutical forms for the newborn population, with an increasing investment by the pharmaceutical industry. Still, there are only a few cases where these incentives have led to a real approval of age-appropriate medical products.

Traditional pharmaceutical forms available to newborns, are mainly represented by suspensions, solutions and suppositories, which are still widely used in the clinical practice. These forms, however, have several disadvantages which would discourage their use if appropriate formulations for newborns were available.

Compounding, often used to cover the lack of approved medicines, is a pharmaceutical area that should be studied, updated and considered when developing medication for newborns. It is necessary to gather the available evidence so that, overall, there is the greatest possible uniformity and, thus, allow equal treatment to all children. Additionally, new pharmaceutical forms, such as mini tablets, orodispersible films and wafers, gels, among others, may be viable hypotheses to deliver medicines to neonates for its precise dose, low cost, easy transportation and for overcoming the need of swallowing.

Keywords: Newborns, formulation, innovative, orodispersible

Agradecimentos

Esta monografia, cúmulo de 5 anos de trabalho, alegrias, desesperos, aprendizagens e crescimento, não teria sido possível sem a ajuda e incentivo de várias pessoas. A todas elas, deixo o meu muito obrigada.

À Professora Joana por este ano e meio em que me permitiu abordar temas tão interessantes. Pela ajuda constante, pelos desafios que me levaram a pensar fora da caixa, pela confiança para realizar este trabalho. Um agradecimento também à Drª Filipa Cosme por toda a ajuda e por trazer sempre a vida real e a prática clínica àquilo que fui abordando.

À equipa do Hospital de Santa Cruz, em especial à Drª Liliana e à Drª Alexandra, agradeço profundamente tudo o que me ensinaram no estágio, pela confiança no meu trabalho, por me desafiarem a seguir os meus sonhos e pela disponibilidade em todos os momentos. O vosso profissionalismo deu-me uma nova paixão pela profissão farmacêutica. Um obrigada também à Ana e toda a equipa da Farmácia Mem Martins pelos ensinamentos e por toda a ajuda durante o meu estágio.

Aos meus amigos, cada um à sua maneira, por todo o apoio ao longo dos anos. Sem vocês não teria sido possível.

Ao David, por toda a ajuda, confiança, força e companhia ao longo destes anos. Por todos os almoços, passeios, lanches, filmes e afins, por ter sido porto de abrigo quando as coisas correram menos bem, e por celebrar comigo cada vitória. Venha a próxima etapa, sempre juntos.

Ao João, pela paciência, em especial para rever toda a monografia, pelas conversas e pela amizade incondicional.

A todo o grupo de jovens, por terem acompanhado o meu percurso ao longo dos anos, pela força, pela amizade sem igual, pela família que somos.

Aos meus amigos da AMSC, Marta, Guilherme, à Cristina e à Professora Dora, pela amizade há mais de 10 anos, alguns há 20, por acreditarem sempre em mim e por toda a força que deram ao longo dos anos. Sei que vos tenho para o resto da vida.

Às meninas do Rainha: Ana, Joana, Joaninha, Dani, por me fazerem rir, pela preocupação constante, pelas memórias e por todas as conversas tontas. Ao Tiago, pela amizade, por todo o apoio e carinho ao longo dos anos.

Às minhas amigas da FFUL. À Mariana e à Patrícia pela amizade desde o início, mesmo com a distância geográfica. À Cláudia, por me ter dado a conhecer o mundo da

farmácia e por ter sido farol ao longo dos 5 anos na FFUL. Sem a tua ajuda e amizade não estaria aqui hoje.

À Alexandra e à Sara pela companhia ao longo dos anos, por me fazerem rir tanto e por acreditarem sempre em mim. Desejo-vos a maior sorte. Sei que serão excelentes farmacêuticas em qualquer área que escolham.

E, por fim, à Tatiana, que me salvou várias vezes ao longo do MICF. Pela proximidade, pela ajuda em tudo, pelos passeios, pelas aventuras e por estar sempre comigo ao longo destes 5 anos. Pela amizade em todas as horas e por me manter sempre com os pés bem assentes na terra. Sucesso não te vai faltar.

E o agradecimento mais importante: aos meus pais, por me terem proporcionado uma educação de excelência durante estes 21 anos. Pelo carinho, preocupação, confiança, força e por me terem sempre dado a liberdade de fazer tudo o que sonhei fazer. Aos meus irmãos, pelo apoio ainda que discreto, pelo ânimo e por acreditarem sempre em mim. Aos meus avós e restante família que sempre me apoiaram nas decisões que tomei.

Estou profundamente grata por todos os que me rodeiam. Um obrigada nunca será suficiente.

Abbreviations

API – Active Pharmaceutical Ingredient

CHMP – Committee for Medicinal Products for Human Use

CYP450 – Cytochrome P450

DPI – Dry Powder Inhaler

EMA – European Medicines Agency

EU – European Union

ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IM – Intramuscular

IV – Intravenous

MDI – Metered Dose Inhaler

NEC – Necrotizing Enterocolitis

ODTs – Orally Disintegrating Tablets

PDCO – Pediatric Committee

PIP – Pediatric Investigation Plan

PUMA – Pediatric-use marketing authorization

SC – Subcutaneous

SmPC – Summary of Product Characteristics

Table of contents

1 Introduction 6

2 Objectives 7

2.1 General 7

2.2 Secondary 7

3 Neonatal Population 8

3.1 Pharmacokinetics 8

3.1.1 Absorption 9

3.1.2 Distribution 9

3.1.3 Metabolism 10

3.1.4 Excretion 11

3.2 Pharmacodynamics 11

3.3 Characteristics of neonatal age-appropriate formulations 12

3.4 Pediatric Drug Development Regulation 15

3.5 Drug Delivery 16

3.5.1 Oral Delivery 17

3.5.2 Parenteral Delivery 18

3.5.3 Rectal Delivery 18

3.5.4 Dermal and Transdermal Delivery 19

4 Oral Dosage Forms 20

4.1 Solid and Semi Solid Dosage Forms 20

4.2 Liquid Dosage Forms 26

5 How to Overcome Inadequate Dosage Forms 29

5.1 Compounding 29

5.2 Challenges in Compounding Formulas 31

6 Alternative dosage forms for newborns 34

7 Conclusion 37

Bibliography 38

Annex 49

A1. Vehicle composition 49

A2. Compounding Formula: Tacrolimus 0.5 ng/mL Oral Suspension..... 50

Figure Index

Figure 1 - Decision pathway for providing oral doses to children 14

Figure 2 – Orodispersible biconvex mini tablets with 2 mm diameter 24

Figure 3 – Solid Dosage Forms 25

Figure 4 - Orodispersible films with 6 cm^2 35

Figure 5 – Nipple Shield delivery system. 36

Table Index

Table 1 - Pediatric age groups 8

Table 2 - Excipients in neonates 13

Table 3 - Route/Dosage Form vs. Age. 21

Table 4 - Dosage forms manipulation 29

Table 5 – Galenic Preparation: 40% Dextrose Gel 30

Table 6 - Frequency of compounding formulas 32

Table 7 - Frequency of initial dosage form to compound suspensions 33

1 Introduction

The last two decades have been crucial concerning the development and study of medical products for neonates (1). It is often said that "neonates are not small children" as well as "children are not small adults" thus pediatric drug development is extremely challenging (2,3).

The pharmacokinetics, pharmacodynamics, capability of swallowing, taste and overall toxicity concerning medicines in newborns are very different from those of adults and older children (2). They often have different responses to the Active Pharmaceutical Ingredient (API) as well as to the excipients used. In pediatric pharmacotherapy, drug formulations should be adapted to children's needs regarding their age, physiologic condition, weight, neuropsychomotor development and treatment requirements. Suitable pediatric medicines are the key to safe and accurate dose administration, increase of medication adherence, reduction of the risk of errors and the improvement of therapeutic outcomes in this population. Unfortunately, only a small fraction of the marketed drugs is, in fact, age-appropriate which results in many adult drugs being used off-label in children, leading to considerable health and environmental risks (4).

In order to guarantee an adequate treatment to all children, different routes of administration, dosage forms and doses are required (4). Dose, volume and drug manipulation in neonatology calls for tailored formulations, leading to a predictable and safe exposure to the API and excipients (5).

Recently, the European Medicines Agency (EMA) acknowledged that neonates are still a neglected population regarding the development of medicines (6). Nevertheless, the lack of guidelines on development of neonatal formulations is still a problem. In 2018, a revision of the ICH E11 Guideline on Clinical Investigation of Medical Products in the Paediatric Population mentioned neonates in the age classification of pediatric groups, but this subject was approached in a very general and brief way. Considering the complex needs of this population, this guideline is quite deficient, and shows the limited guidance available to safely develop age-appropriate dosage forms (7).

Further progress must be made by stimulating the interaction between industry, regulatory agencies, caregivers and academia to achieve age-appropriate formulations (5).

2 Objectives

2.1 General

The main goal of this monograph is to gather the most recent and novel innovation regarding age-appropriate formulations and dosage forms, the challenges, and the new approaches in the pharmaceutical field to overcome the need for formulations for a more personalized treatment in neonatology.

2.2 Secondary

1. Review general information about the newborn population and the various routes of administration available for newborns.
2. Review the dosage forms available for neonates and their suitability for enteral feeding administration.
3. Assess the challenges in compounding and evaluation of pediatric hospitals compounding formulas.
4. Review new approaches to oral delivery in neonates and innovative systems to safely deliver medicines in this population.

3 Neonatal Population

The pediatric population is, by far, the most heterogeneous one, and different regulatory authorities around the world consider different age ranges for this population. According to the EMA, the pediatric population can be subdivided in 5 different age groups (Table 1) (2).

Neonates are the pediatric subgroup with ages ranging from birth to 27 days and include term, post-term, and preterm babies. However, even between term newborns, there are several differences, for example, regarding pharmacotherapy and pharmacology, due to their rapid development and variability in some pharmacokinetic and pharmacodynamics characteristics (7).

Table 1 - Pediatric age groups (2)

Pediatric subgroup	Common name	Age
Preterm newborn infants	Prematures	< 37 weeks
Term newborn infants	Newborns or neonates	0 - 27 days
Infants and toddlers	Infants	1 - 23 months
Children	Children	2 - 11 years
Adolescents	Adolescents	12 - 16 or 18 years

3.1 Pharmacokinetics

A safe treatment is dependent on how the drug is metabolized, cleared and how it interacts with its target (8). In the newborn population, physiological differences such as size and maturation are two important factors that affect absorption, distribution, metabolism and excretion (1,9). These factors differ greatly from those of older children and adults (8). Organ function and physiological processes are immature in newborns, making them more predisposed to disparate responses when compared with adults (10).

The knowledge of the pharmacokinetics of the neonates allows the understanding of the dose, dose frequency and bioavailability, making possible to determine the most adequate dosage form and dose for this population (2).

3.1.1 Absorption

The effectiveness of a drug depends on its absorption from the administration site into the systemic circulation, except in the intravenous administration. Gastrointestinal track and skin development changes can affect the bioavailability. Oral-administered drugs undergo the gastrointestinal barrier before they enter the circulatory system and are absorbed by a passive diffusion through lipophilic membranes (2,9).

The biggest changes of the pH and transit time occur during the newborn period. During the early hours after birth, the gastric pH is neutral (pH 6 to 8), on account of the amniotic fluid still present in the stomach. Around the second day of life it starts to fall, due to the secretion of hydrochloric acid, reaching values of 1-3 within 6 months (2,9). The high gastric pH influences the bioavailability of the drugs according to their nature, thus weak bases have higher bioavailability, while weak acids have a diminished bioavailability (3).

Gastric emptying also affects drug absorption: slow emptying delays the small intestinal reaching, where most of drugs will be absorbed. In neonates, this process is prolonged, reducing and delaying the absorption. Gut motility matures in the first months of life and splanchnic blood flow, enzymes, microflora and transporters change. Thus, the rate of absorption is slower in newborns when compared with older children and adults (2,9).

Some drugs require biliary and pancreatic exocrine function for adequate absorption. In newborns, both these functions are immature, with levels of most enzymes reduced, as well as reduced bile formation, bile acid synthesis and metabolism, bile acid pool size and bile acid intestinal absorption. These deficiencies may result in a decreased bioavailability of the drugs that need to undergo this type of processes (10).

Intestinal surface area and intestinal transit time are also lower in newborns compared to adults, also leading to decreased bioavailability of drugs (10).

3.1.2 Distribution

The body composition, active transport mechanisms, plasma protein concentrations, permeability of cell membranes, blood flow and protein binding depend on the age of the

child. The drug distribution will occur according to its physiochemical properties, ionization, solubility (aqueous and lipid) and molecular size (11).

Newborns have a higher water compartment and lower fat content in comparison to adults. These compartments tend to adult values in the first years of life and their changes influence the distribution of water-soluble drugs as well as lipophilic ones (9). This means that hydrophilic drugs will have higher volumes of distributions, unlike lipophilic drugs, which will have a diminished volume of distribution (3).

On the other hand, plasma protein binding is reduced in newborns, thus the free fraction of the administrated drug is higher, increasing the reaching, and penetration of several tissues, and extending the volume of distribution. This relates the amount of a drug in the blood to the concentration measured in a body fluid. Therefore, the administered dose may need to be adjusted to avoid toxicity (3). The binding of drugs to plasma proteins is reduced in children up to 2 years due to a lower concentration of proteins (albumin, globulins, alpha 1-acid glycoprotein and lipoproteins) in children compared to adults (59 g/L and 72 g/L, respectively), as well as their reduced ability to bind to the drugs, leading to higher fractions of free drug in the blood (3,12).

3.1.3 Metabolism

Metabolic processes, Phase I and Phase II reactions, are both immature at birth, leading to reduced clearance and higher half-life for drugs that undergo important metabolism.

Often, drug metabolism transforms lipophilic compounds into hydrophilic polar ones, easing the renal or bile elimination of the drug. The liver is the major organ responsible for metabolic drug reactions. The activity of hepatic enzymes is diminished in newborns, which prolongs the elimination of drugs. However, between the age of 1 and 2 years, the enzyme activity approach the adult activity. Most of the phase I reactions are mediated by the CYP450 enzymes.

Due to these immature mechanisms, the risk of drug toxicity in newborns and infants is substantial, leading to necessary dose adjustments to this population (3,9)

3.1.4 Excretion

Systemic clearance allows a measure of the efficacy of elimination. In newborns, hepatic and renal elimination processes are generally underdeveloped and still not totally efficient (10).

Renal excretion is dependent on three processes: glomerular filtration, tubular secretion and reabsorption. In neonates, this excretion is reduced with the glomerular filtration reaching adult values at around 3 to 5 months of life. Tubular secretion matures by 15 months after birth, while tubular reabsorption reaches adult levels by the second year of life (3). Renal tubes, where passive reabsorption, active secretion, and reabsorption occur, are anatomically and functionally immature at birth. Limited tubular size and maturity, reduced urine concentration ability, poor blood flow and lower urinary pH all contribute to a reduced renal tubule function in neonates (10). Consequently, drugs with high renal excretion may require dose adjustments due to their prolonged half-lives and inefficient elimination (3).

3.2 Pharmacodynamics

Pharmacodynamics relates the drug concentration at the receptor and the pharmacological response. Contrasting with the knowledge about the pharmacokinetics in the newborn, the receptor's development is not well known, and how maturation affects drug-receptor interaction and response is also poorly understood. The assessment of pharmacodynamics in newborns must consider the efficacy and safety of a drug, taking into account the age differences (3,13).

Commonly, it is assumed that the systemic drug exposure in children is comparable to what is observed in adults, and that the desired or adverse drug effects are similar in both age groups. However, in some cases, this is incorrect and can lead to toxicity or lack of effect. This knowledge gap impacts the pediatric drug development since the understanding of the pharmacokinetics and pharmacodynamics is crucial to attain a secure and well-known drug effect in this population (14).

3.3 Characteristics of neonatal age-appropriate formulations

Neonates are a very particular age group thus the formulation characteristics must be carefully addressed to obtain safe and suitable dosage forms (15). Pediatric drug administration can be extremely challenging, as children are more sensible to flavors, can have swallowing difficulties and poor pharmaceutical adherence. Thus, it is imperative that pediatric dosage forms are formulated to best suit the child's size, age, physiologic condition and treatment requirements (16).

Parents and caregivers are often concerned about the newborn's ability to swallow. It is widely known newborns and infants are not able to swallow conventional solid dosage forms, such as pills or capsules. However, small solid dosage forms have been tested in this population, and positive results regarding mini tablets and multiparticulate systems such as powders, beads and granules, have been observed (2,7).

As for palatability, it is more common to consider the volume and texture rather than the taste. The taste buds in newborns are fully developed, however, their analytical skills are not totally developed making it difficult to recognize tastes as adults do. Newborns can taste sweet, sour, bitter, and savory flavors but are not able to fully assimilate the taste. When formulating, unusual flavors and taste mixtures must be avoided to increase acceptability (2,17,18).

Numerous studies relate oral liquid formulations with high osmolality that may negatively affect the gastrointestinal transit in the neonate population leading to intolerance and later contributing to the development of necrotizing enterocolitis (NEC) (2,7,19). Osmolality is the number of osmoles of solute per kilogram of solvent and it is expressed as mOsm/kg. NEC is a disease that occurs once in every 1000 live births and has a notable morbidity and mortality rate. It can be related to the immature development of the immune system, gut motility and intestinal epithelial barrier of the newborn population, especially premature babies, born weighing less than 1500 grams (20).

Recent systematic reviews concluded that there is no consistent evidence that osmolality of 300 to 500 mOsm/Kg are harmful to newborns. Hence, some authors, following the American Academy of Pediatrics, recommend that enteric products should not have an osmolalilty higher than 450 mOsm/Kg, and that hyperosmolal formulations and excipients should be avoided (2,21).

Another important factor to consider when developing medicines for neonatology is

the choice of excipients. The excipients used in neonatal formulations demand functional requirements and should be justified along with a risk-based evaluation. The CHMP for Human Use guideline affirms that "*excipients to be used in formulations for the paediatric population should be selected with special care and possible sensitivities of the different age groups should be taken into consideration*". Table 2 summarizes the best-known excipients that can be harmful for neonates.

Table 2 - Excipients in neonates

Potentially harmful excipient	Excipient function	Negative effects in newborns	Threshold (daily dose)	References
Ethanol	Solvent, permeation enhancer, antimicrobial preservative	Effects on nervous system	12.5 mg/100 mL (75 mg/kg)	(22)
Propylene glycol	Solvent, antimicrobial preservative	Respiratory, cardiovascular, central, and hepatic adverse effects	No safe dose recommendation	(23)
Peanut oil	Solvent	Hypersensitivity	-	(17)
Benzalkonium chloride	Surfactant, antimicrobial preservative, antiseptic	Bronchospasm	-	(17)
Benzyl alcohol	Solubilising agent, preservative	Metabolic acidosis, seizures, gasping, neonatal toxic syndrome	-	(17)
Parabens	Preservative	Hyperbilirubinemia and oestrogenic effects	No safe dose recommendation	(24)
Sulphites	Antioxidant	Wheezing, dyspnea and non-immunologic anaphylactic reactions	-	(17)
Lactose	Sweetener	Gastrointestinal symptoms in intolerant neonates	Not recommended in intolerant neonates due to a lack of established safety data	(25)
Sorbitol	Sweetener	Gastrointestinal symptoms in intolerant neonates	Not recommended due to a lack of established safety data	(25)
Sucrose	Sweetener	Cariogenic	Not recommended due to a lack of established safety data	(26)
Aspartame	Sweetener	Headache and seizures in subjects with phenylketonuria	Not recommended due to a lack of established safety data	(27)
Saccharin	Sweetener	Cancer and dermatological reactions	Not recommended due to a lack of established safety data	(28)

The lack of safety data about excipients or available data that does not apply to neonates, require a justification on their use including non-clinical safety data that support their safe use (7).

The lack of suitable formulations for neonates has been forcing the medical community to resort to adult medicines to cover the children's needs. Off-label drugs are medicines administered in indications, dosage, age, or route of administration that are not contemplated in the authorization granted by the country's regulatory agency. Approval of medicines labelled for pediatric use are delayed when compared with adults. Additionally, even approved pediatric drugs may not be appropriate to administration in newborns, leading to off-label and unlicensed use of adult medicines (29,30).

As previously described, drug therapy in newborns is extremely challenging, because pharmacodynamics, pharmacokinetics and overall toxicity of various drugs are usually unknown in this population. The lack of information on the safety and efficacy of medicines escalate the risk of bad clinical outcomes, medical errors and adverse drug reaction when off-label medicines are prescribed to neonates (29,30). Figure 1 sums up the options to administer oral medicines to children (31).

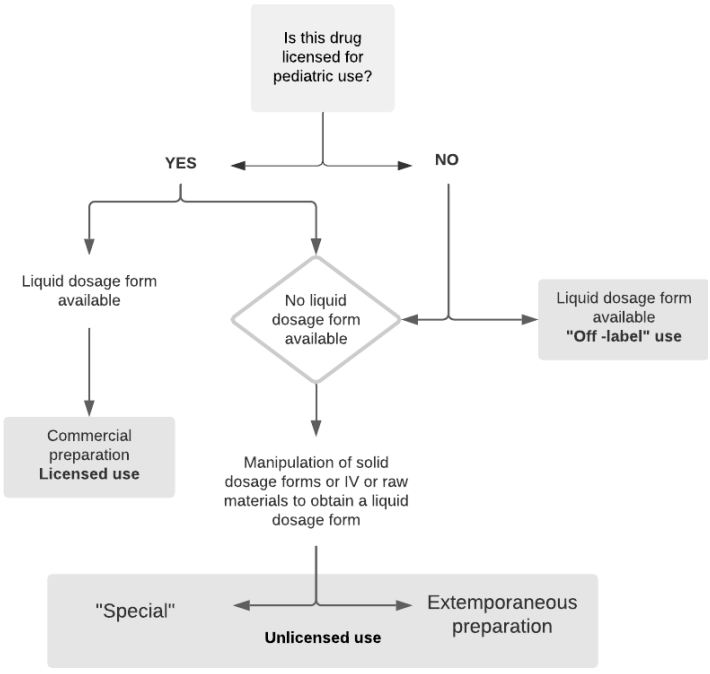


Figure 1 - Decision pathway for providing oral doses to children (adapted from (31)).

3.4 Pediatric Drug Development Regulation

Pediatric drug development has political, legal, economic, and clinical dimensions and implications. In 2000, with the adoption of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E11) guideline, the first joint pediatric regulative action was taken. The main goal was to facilitate and encourage pediatric drug development internationally and provide an overview of problems in this area, to approach safe, moral and economical studies of medicines. The ICH (E11) guideline became indispensable in the planning of clinical analysis around the globe (32,33)

The key objectives of the Regulation are to facilitate the development and accessibility of medicines for children for the improvement of their health, to ensure the ethnical research of these medicines as well as their appropriate authorisation, and to improve the information available on the use of medicines in the pediatric population (34,35).

The EMA's guideline on Pharmaceutical Development of Medicines for Pediatric Use of 2014 tackles dosage form, route of administration, dosing frequency, excipients safety, modified release and adaption of formulation regarding the specific needs of children (35). The 2016 addendum to the ICH (E11) guideline for public consultation was designed to clarify topics pertinent to the pediatric population. The pediatric formulations should include age-appropriate dosage forms, instructions for use for caregivers, acceptability, ease of preparation and acceptability, choice and number of excipients used (36).

The ICH (E11) guideline enforced the conduction of clinical studies in children, according to an agreed Pediatric Investigation Plan (PIP). The PIP is a research and development plan which describes the measures to be taken to obtain safety, efficacy, and quality of a medicine in the pediatric population. This includes pre-clinical, clinical and quality studies, timings in which the trials will be performed and the results obtained (37). The PIP aims at ensuring the development of medicinal products to be used in children and it is submitted early in the development stages (32). They are scientifically assessed and agreed by the Pediatric Committee (PDCO), that may grant waivers if the development of a medicine in children is not needed nor appropriate. The PDCO may also grant deferrals when it is appropriate to perform studies in adults prior to the pediatric

studies or whenever the studies in the pediatric population will take longer than in adults (34). The EU Commission estimates that the elaboration of a single PIP costs around 20 million euros. More than 1000 PIPs have already been issued, assembling about 20 billion euros to allow pediatric approved drugs (33).

However, since not only new drugs should be evaluated for pediatric use, the Pediatric Regulation created a unique European concept of Pediatric-use marketing authorization (PUMA). This process establishes incentives for off-patent medicines that are already approved. The application for PUMA foresees the submission of a PIP containing data to the use of the drug in children (38). If, after the evaluation of the submitted plan, the feedback is positive, a financial incentive is warranted. That includes 8 years of data protection, along with 2 additional years of marketing exclusivity (39). In 2017, almost 270 new drugs were approved for pediatric use (37).

The health authorities have shown a high commitment to increase the available medicines for children. The legislation related to the pediatric population has a complex framework leading, hence industries have been modifying different needs and obligations to receive incentives (34). Studies have shown that the Pediatric Regulation in 2007 had a positive impact in the drug development for the pediatric population: more medicines are available for children in the EU and more information is available to clinicians on pediatric use in the Summary of Product Characteristics (SuPC) of authorised medicines (34,40).

3.5 Drug Delivery

Neonates require particular care when choosing the appropriate route to safely deliver drugs. Absorption is one of the most important pharmacokinetic parameters to consider when discussing the most adequate dosage form and route of administration. For some dosage forms, their absorption differences are documented and well-known, but the rapid developmental changes that occur after birth add complicated variables to consider in most cases. Differences between some delivery routes will be discussed next.

3.5.1 Oral Delivery

Oral delivery is the preferred and appropriate route to administrate medicines to pediatric patients since it is not invasive and has a low risk of inducing pain. Generally, all age groups accept an oral formulation as long as it suits their needs and physiological differences, allowing a high compliance towards the treatment. In younger children, like neonates and infants, liquid formulations are preferred due to their inability to swallow solid dosage forms. Most oral processes are present from birth (biting, lip, rooting, mouth opening and others) but even oral syrups are not always totally swallowed by newborns and infants (41–43).

However, when the newborn is seriously ill, not even the oral route may be available and, instead, the drug administration may resort to enteral tubes where liquids are usually the preferred dosage forms, ideally suspensions and solutions. Emulsions can also be delivered via enteral tube, such as enteral nutrition and milk although their compatibility with drugs may lead to changes in the pharmacokinetics. The use of enteral tubes requires special considerations, like the flush volume needed to ensure the entire dose is correctly delivered, the viscosity of the formulation, particle size, adsorption and the possible interaction between the drug and the formula/breast milk (7,16,44). Tube blocking is a great concern in newborns with nasogastric tubes as they have a narrow bore (French size 6 has an internal diameter of 1300 μm). Most recommendations on drug administration through enteral feeding tube are only focused on adults, leading to a lack of guidelines for pediatric use (45). Ineffective drug administration via enteral feeding tube may lead to serious adverse consequences and errors such as inappropriate dosage forms, wrong administration techniques and crushing non-crushable drugs can lead to reduced drug therapy, tube obstruction or increased adverse effects (44,46).

In cases where the medicine is administered with breast milk or formula, without enteral feeding tubes, palatability issues should be considered to avoid a reduced milk intake by the neonate due to the unpleasant taste of the drug. Incompatibilities should also be studied to avoid bioavailability changes. Besides, it is important to assure the entire dose is administered, i.e., that the neonate drinks the entire volume of milk in which the drug was mixed in (41,42,47).

As discussed before, physiological, pharmacokinetic and pharmacodynamic differences must be considered regarding oral delivery. Absorption, gastric emptying, gastric pH, reflux mechanisms, transit time and other may affect the drug therapy and are

not yet fully understood in neonates. Nevertheless, even with some withdraws, the oral route is still the preferred route to deliver medicines to young children (7).

3.5.2 Parenteral Delivery

In seriously ill children, intravenous administration is the preferred route of administration. Blood volume conditions the amount that can be administered; in full term neonates the average blood volume is 250 mL, which allows IV fluid infusions rates of about 10-20 mL/h in this population (42).

Subcutaneous and intramuscular parental routes are also used, although the muscular mass in neonates is diminished, conditioning the use of IM injections. The IM route of delivery is highly challenging because muscle mass, muscular vascularization and blood flow are variable in the first few weeks of life. Nevertheless, when this route is used, the injection site is, usually, the anterolateral thigh (15,42).

The subcutaneous route is commonly used in children, for example, to administer vaccines, anticoagulants and insulin. Subcutaneous injections in children are limited to a very small volume, lower than 1 mL. Volume overload should be avoided during IV administration. Overall, often parenteral routes result in pain for the neonate and therefore, when available and appropriate, other dosage forms and routes of administration should be used (5,42).

One of the biggest problems regarding parental delivery in small children is the accurate measurement in preference of serial dilutions than can lead to errors and therefore have negative consequences (48,49). As explained before, it is also crucial that the drug solution has a proper osmolality, similar to the one on the serum, to avoid pain, tissue irritation or, in more severe cases, trauma or necrosis of the injection site (42,48,49).

3.5.3 Rectal Delivery

Rectal administration is one available route of administration in the pediatric population and can be used for local and systemic effects. In neonates, the rectal length is about 4 cm and, by age 1, is at 6 cm. The shorter rectal length and the reduced thickness of the rectum wall leads to erratic absorption. Bioavailability is also affected by the drug placement in the rectum. If the placement is in the proximal rectum, it can undergo first-

pass metabolism, which can easily happen in neonates since the rectum size is reduced, leading to decreased bioavailability for some drugs. If, on the other hand, the drug is placed in the distal rectum, it will be absorbed by the rectal veins and will avoid the portal blood system (15,42).

Moreover, appropriate dosing is difficult to obtain due to this high variability in absorption and clearance, as well as poor absorption. Intrinsic characteristics and the type of formulation can also affect absorption (e.g., lipophilic suppositories will have a diminished absorption time in warmer rectums) (42,50).

3.5.4 Dermal and Transdermal Delivery

Newborns have an almost intact stratum corneum but the way it transports, and stores water is different from that observed in adults. The extent of transdermal drug absorption is directly related to the skin hydration and surface area and inversely related to the thickness of the stratum corneum. Additionally, the ratio (surface area)/ (body weight) and skin hydration in newborns is much higher when compared with an adult, leading to a lower volume of distribution per area of skin and therefore to a higher exposure and absorption. Theoretically, this enhanced absorption could be useful to delivery drugs but the risk of overexposure and unintentional systemic delivery is concerning to the health professionals (42,48,51).

Topical agents used in newborns, such as antimicrobial agents, moisturizers or treatment for rashes, should contain excipients considered safe for newborns, even if their action is only topical, due to their skin characteristics, as it can lead to some systemic exposure (15,48). Considering these skin permeation variations, the transdermal route is rarely used in pediatrics, especially in newborns (15,48,52).

4 Oral Dosage Forms

The standard oral product administration in neonates are the liquid dosage forms. Even though they are the most common in this population, they often contain harmful excipients that may cause toxicity in neonates, since their maturation and organ development are not as complete as in adults. Usually, excipients in solid dosage forms are safer when compared with the ones in liquid forms (7). There is no consensus regarding what are the most appropriate dosage forms for the different age groups, within the pediatric population. However, EMA does have a matrix with different dosage forms and their adequacy to the different pediatric group ages (Table 3).

As mentioned previously, severely ill neonates may need enteral tubes to deliver medicine. Many factors should be taken into consideration when deciding which formulation is appropriate for administering drugs via an enteral feeding tube. Liquid formulations are not always preferred over a tablet, since excipients used in liquid formulations may be harmful and lead to unwanted side effects. Soluble tablets, effervescent tablets, dispersible tablets, orodispersible tablets, conventional tablets and hard gelatin capsules are the most accepted solid dosage forms that, after manipulation, may be administered via enteral feeding tube. Concerning liquid formulations, the most adequate are solutions. Suspensions can also be used but the lack of accuracy of dosing should be taken into account (45).

4.1 Solid and Semi Solid Dosage Forms

Oral solid dosage forms comprise from powders to tablets and are supposed to be swallowed or applied on the mouth such as orally dissolving tablets, chewable tablets or orodispersible tablets.

The World Health Organization has actively promoted the use of flexible solid oral dosage forms to overcome the challenges of appropriate medicines for children. Flexible solid oral dosage forms do not need to be swallowed whole (i.e., dispersible tablets, orodispersible tablets, effervescent tablets, and sprinkled capsules). Although they are flexible in administration, they may not be in dose and therefore need to be manipulated before they are suitable for administration in a neonate (7,53).

Table 3 - Route/Dosage Form *vs.* Age (adapted from (2)).

Route	Dosage form	Preterm newborns	Term newborns	Infants and toddlers	Children (2-5 years)	Children (6-11 years)	Adolescents
Oral	Solution/Drops	2	4	5	5	4	4
	Suspension/Emulsion	2	3	4	5	4	4
	Effervescent dosage form	2	4	5	5	4	4
	Powders/Multiparticulate	1	2	2	4	4	5
	Conventional tablets	1	1	1	3	4	5
	Capsules	1	1	1	2	4	5
	Orodispersible dosage form	1	2	3	4	5	5
	Chewable tablet	1	1	1	3	5	5
Nasal	Solution	3	4	4	4	4	4
	Semisolid dosage form	2	3	3	4	4	4
Rectal	Suppositories	4	5	5	4	3	2
	Enema	5	4	4	3	3	2
	Rectal capsule	2	3	4	4	4	3
Topical/ Transdermal	Ointment/Cream/Gel	4	4	4	5	5	5
	Liquid dosage form	4	4	4	5	4	4
	Transdermal patch	1	2	2	4	4	5
Parenteral	IV solution	5	4	4	4	4	3
	IM	3	3	3	4	4	3
	SC	4	4	4	4	4	3
	Pump system	5	4	4	4	4	3
Pulmonary	Nebuliser	2	3	4	5	4	3
	MDI/Spacer	1	3	4	5	4	4
	DPI	1	1	3	4	5	5
Ocular	Eye drops	3	4	4	4	5	5
	Semisolid dosage form	2	3	4	4	4	4

1 - not applicable/not accepted; 2 - applicable with problems/accepted under reserve; 3 - probably applicable, but not preferred/acceptable; 4 - good applicability/preferred acceptability; 5 - best and preferred applicability/dosage form of choice

Hard capsules and tablets

The age at which young children, such as neonates, can safely swallow tablets and capsules, is of great concern, and it is the primary limitation when considering the use of these dosage forms in pediatrics. One of the advantages of these dosage forms is the opportunity to develop modified-release formulations, which allows a reduction of dosing frequency, therefore improving acceptability. Stability, accuracy of dosing and flexibility

of portability are other advantages when compared with liquid formulations (2,15).

Both capsules and tablets present the limitation of the swallowing ability, but some hard capsules may be opened and sprinkled or mixed with food or even taken as such, since usually they contain powder or multiparticulate formulations. As for tablets for older children, it is possible to accurately divide a tablet in two, four or even eight equal pieces and administer them after dispersion in milk (7). An example of this is the development of fixed-dose combination of zidovudine and lamivudine tablets in fast-disintegrated subunits (54).

Tablets may be suitable for delivering the drug via enteral feeding tube. Most tablets will easily disperse in a small volume of water or, if needed, they may be crushed and then suspended. Either way, the possibility of reduced drug delivery should be taken in account, as well as the obstruction of the tube and the variability in the crushing process. Particle size and gel formation should be accessed before administering the suspension through the feeding tube to avoid clogging in the tube (55).

As mentioned above, hard capsules can be opened, and the content mixed with water. However, if the capsule contains granules, these may not be small enough to pass through the tube and, if they contain powder, the size of the particles and possibility of gel formation should be studied before administering the suspension to avoid the obstruction of the feeding tube (45).

Dispersible and soluble tablets

The biggest advantage of dispersible tablets is the dose flexibility. These tablets are meant to be dispersed or dissolved (in the case of soluble tablets) in water or other liquids, before being administered. The convenience of these formulations is that they disintegrate or dissolve within a few seconds. Furthermore, they require a minimum volume of water to be dispersed or dissolved that should be indicated by the manufacturer (15). Nevertheless, in neonates it is strongly recommended that the volume to be administered is less than 0.5 ml (56), as EMA established 5 ml as the maximum volume in this population (2).

Soluble tablets are suitable for enteral feeding tube administration since the API will be totally dissolved in the solvent. Dispersible tablets, on the other hand, are not always suitable for this type of administration as the resultant particles may be too large for

administration through a fine-bore tube (45).

Effervescent dosage forms

Effervescent tablets, granules or powders need to be dissolved in water before being administered and require a rather large volume of water, which, as discussed for dispersible and soluble tablets, may be problematic for newborns. In addition, the solution should not be ingested before effervescence has subsided, to avoid the high ingestion of hydrogen carbonate. Furthermore, this dosage forms are sensitive to humidity and moisture during manufacture, packing, transportation, and storage. Finally, the high sodium content is also concerning in neonates, along with the contraindication for hypernatraemic patients since they require sodium restrictions. In summary, although effervescent dosage forms are suitable for enteral feeding tube administration, they are not the best when the aim is to deliver drugs to neonates (7,15,45).

Orodispersible dosage forms

Orodispersible dosage forms overcome the need for swallowing, being quite interesting for administration to neonates. However, there are no previous studies on the use of orodispersible formulations in this population. Orodispersible tablets are prepared by compression and contain a super-disintegrant, such as mannitol. They are quite flexible dosage forms and are especially suited for highly water-soluble APIs. Figure 2 illustrates orodispersible biconvex mini tablets (54).

Oral lyophilisates are tablets prepared by freeze-drying of aqueous liquids, creating pores within the tablet. Alginate or gelatin are often used excipients that facilitate the formation of the porous. These dosage forms incorporate limited amounts of water-soluble APIs and are very sensitive to humidity, requiring a vapour-tight package (54).

Flat films, also called wafers, are water-soluble polymers impregnated with the API, which will be dissolved or dispersed in it. They have different release profiles, depending on the type of polymer and on the different thickness (15).

Just like with dispersible tablets, orodispersible dosage forms may not always be suitable for administration via enteral feeding tube since the particles may be too large to

pass through a fine-bore tube (45).

Figure 2 – Orodispersible biconvex mini tablets with 2 mm diameter. Data adapted with permission from (52).

Powders and multiparticulate formulations

Both powders and multiparticulate formulations can be provided in sachets or hard capsules. This allows them to be mixed with food or beverages, sprinkled on food, or directly ingested.

Multiparticulate formulations include granules, pellets, and mini tablets. Pellets are small particles, with a size ranging from 0.5 to 2 mm, prepared by extrusion or spheronization. Mini tablets, on the other hand, are obtained by compression and have a diameter lower than 4 mm (15). Some articles preconized a diameter of 2 mm as acceptable for neonates (57). Thabet *et al*. (52), for example, performed a clinical trial with newborns to evaluate the acceptability of uncoated mini tablets with a 2 mm diameter. About 82% of the newborns fully swallowed the mini tablet, while all of them partially swallowed it.

Some authors assert that mini tablets are preferred over oral suspensions or oral powders. These preparations present several advantages, such as great flexibility and the opportunity of taste masking, as well as being suitable for controlled drug release. Higher doses may need a counting device to obtain the precise amount needed for the patient. In multiparticulate dosage forms, texture is relevant and therefore hardness, roughness, fracturability and cohesiveness are important attributes (56,58). Figure 3 illustrates powders and granules of different sizes.

(a)

(b)

Figure 3 – Solid Dosage Forms. (a) Powders and granules of different sizes. Original data. (b) Mini tablets and tablets of different sizes. From left to right to right: 2 mm mini tablet, 4 mm mini tablet, 5 mm tablet, 6 mm tablet, 13 mm tablet. Data adapted with permission from (53).

Gels

Gel-based preparations are semi solid dosage forms that can be categorized into two groups based on the external liquid phase's polarity. Hydrogels have water as the external phase, while oil is the external liquid phase of oleogels. Gelling agents are used to form aggregates and linkages between aggregates, resulting in the formation of three-dimensional networks, characteristic of this kind of formulation. In hydrogels, this three-dimensional network immobilizes the aqueous phase (59).

Gels ensure a better patient compliance due to their specific properties, especially as a mucoadhesive formulation. Hydrogels present high biocompatibility and mucoadhesive

properties but also have disadvantages, such as not being an adequate vehicle for hydrophobic drugs. These drugs are soluble in oleogels, which do not require preservatives due to the absence of water (59,60).

Despite seeming that gels could be used to deliver drugs via enteral feeding tube, this will only be possible after studying the gel viscosity and overall rheological properties, to assure the tube will not be obstructed with the gel (61).

4.2 Liquid Dosage Forms

Liquid formulations include suspensions, solutions, emulsions and syrups and are the most used dosage form in pediatric patients, especially newborns, since they are not able to swallow conventional oral dosage forms such as tablets and capsules. Oral liquid formulations may be supplied as multidose or as single-dose preparations.

The dose volume affects the acceptability of liquid formulations. For children under 5 years of age, the preconized volume is <5 mL since higher volumes may be inconvenient for the child and the caregiver (2,48). For neonates, the volume may need to be as low as 0.1 mL (7). Additionally, liquid controlled release formulations deficiency leads to the need of administering several doses throughout the day to cover the patient's needs (62,63).

Oral Drops (Suspension, Solution and Emulsion)

Oral drops allow the delivery of small volumes or low doses and are of very convenient use in pediatrics, particularly in neonates. Oral liquid drops require the use of measuring devices, such as syringes or graduated pipettes (48). However, this dosage form has high potential for dosing errors and therefore, the drug potency and side effects must be evaluated on a risk-based approach (15)

Oral Solutions

Oral solutions are clear liquid preparations for oral use and are, presumably, the most used liquid pharmaceutical product. In solutions, one or more APIs are completely dissolved in the solvent, meaning it is homogenous. The evenly distribution of particles

throughout the solution ensures that a certain volume of solution always contains the same amount of API. Thus, solutions do not require being shaken before administration. Some solutions may be viscous due to the high concentration of sugar, which is added to help with palatability, and inhibits the growth of microorganisms. However, sugar but is not recommended especially if in high concentrations and in medicines to be used in long term treatment regimes. Other excipients are used in oral solutions and their inclusion determines the suitability of the solution for administration via enteral feeding tube (45,63,64).

Oral Suspensions

Oral suspensions look similar to solutions, but in the former, the API is not dissolved, instead it is suspended in the solvent. Thus, the particle distribution is not even throughout the suspension. Thereby, a phenomenon of instability called sedimentation, where the particles suspended tend to accumulate in the bottom of the recipient, occurs due to external forces, such as gravity. This can be reversed by shaking the suspension, leading to the re-suspension of the particles. Several excipients are used to achieve the maximum stability of the suspension, such as suspending agents (cellulose derivatives, acacia, and xanthan gum) or bulking agents (cellulose, microcrystalline cellulose and calcium carbonate) (63,65).

In summary, the particles in suspensions should always be re-suspended before being measured to administration. To be administered via enteral tube, it must be a non-granular suspension, and according to the viscosity and osmolarity, it may require previous dilution. Granular suspensions require previous assessing to know if they are suitable to be administered via enteral feeding tube (45,63,65).

Oral Emulsion

Oral emulsions are liquid dispersed formulations for oral use that contain one or more active ingredients. They are composed of small globules dispersed throughout a vehicle in which they are immiscible with each other. Emulsions are oil-in-water or water-in-oil dispersions, where each or both phases may contain dissolved or suspended APIs (63,66,67).

Like suspensions, emulsions can show evidence of flocculation but are quickly re-

dispersed after shaking. Phase separation or coalescence demonstrates physical instability and will not be reversed by simple shaking. The use of surfactants is important to assure physical stability through the phases and on drug release. They also take part in the drug uptake from the emulsion (63,66,68).

Emulsions are compatible with enteral tube administration, since the enteric nutrition preparation may be an emulsion itself (68).

Powders and Granules for Oral Preparations

Powders for oral preparations are multidose dosage forms consisting of solid, dry particles of varying degrees of fineness. They may have one or more APIs, and may present color and flavor, provided by excipients. Other excipients might be present, such as compounds to facilitate dispersion or dissolution and to prevent caking, as well as preservatives. After suspension or dissolution in the prescribed liquid, these powders become oral solutions, suspensions or drops (63).

Granules for oral preparations are multidose dosage forms consisting of solid, dry aggregates of powder particles, resistant to handling. Just as powders for oral preparations, they may contain different excipients to improve the quality of the final product. They become oral solutions, suspensions or drops after dissolution or suspension in the prescribed liquid (63).

5 How to Overcome Inadequate Dosage Forms

5.1 Compounding

As said before, newborns require suitable age-appropriate dosage forms and flexible dose strength. Pharmacotherapy in young children needs to be tailored to their specific therapeutic outcomes to improve their acceptability and avoid medication errors. The lack of commercially available age-appropriate dosage forms in the required dose strength makes safe and accurate administration of medicines to children challenging. Besides, when the neonate is using a feeding tube, tablets and capsules are not able to be taken. To overcome these difficulties, commercially available dosage forms must be manipulated to extract a portion of the whole dosage form, in order to achieve the desired dosage dose strength or to improve acceptability (41,69).

Drug compounding includes a variety of actions that can be executed by pharmacists. Table 4 summarizes the possible physical alterations the initial dosage form may undergo, depending on the type of dosage form (41).

Table 4 - Dosage forms manipulation (41).

Dosage Form	Manipulation for dose accuracy
Tablet	• Split/cut and a segment is given • Crushed and a proportion of the powder is given • Dispersed in liquid and a portion of the liquid is given
Capsule	• Opened, dispersed in a liquid and a portion of the liquid is given • Opened and a portion of the powder/granules is given
Powder	• Opened, dispersed in a liquid and a portion of the liquid is given • Opened and a portion of the powder/granules is given
Oral liquid	• Diluted and a portion is given
Suppository	• Split/cut and a segment is given
Transdermal patch	• Patch cut and a portion is applied • Portion of patch uncovered and applied
Intravenous injection	• Reconstituted solution, further diluted to allow a smaller dose to be measured • Volume of fluid removed from IV container and drug the is added • Drug added to the infusion bag, portion with smaller dose removed and infused

Although these procedures are commonly used in pharmacies, they are rarely supported by the manufacturer through the Summary of Product Characteristics (SmPC) or other guidelines. This increases the risk of adverse reactions since manipulation can affect bioavailability, dose accuracy and integrity of the dosage form. Subtherapeutic or toxic doses may be used in vulnerable patients such as newborns leading to medication errors that can be prejudicial (69).

Liquid formulations are usually the final product after manipulation, especially in young children. Moreover, in neonates with a feeding tube, solid dosage forms always need to be manipulated to obtain liquid formulations that can be administered through the tube, and liquid dosage forms may sometimes need to be diluted to obtain the desired dose strength or to adjust the viscosity and avoid the obstruction of the tube. In newborns, osmolality must be taken into account. Boluses with high-osmolality medicines can delay gastric emptying and lead to reflux (45).

Recently, in Australia and New Zealand, a compounding of 40% Dextrose gel was proposed to treat neonatal hypoglycemia. The sublingual administration of the gel showed evidence of more effectively raise blood glucose levels than breastfeeding alone. Sublingual absorption allows rapid access of the API to the bloodstream. Besides that, the use of glucose gel has no negative impact with the breastfeeding rates after hospital discharge when compared with other types of treatment. The preparation consists of a glucose 50% solution, thickened into a gel, using carboxymethylcellulose, glycerol, parabens, and water. The simple and unexpensive formulation can be prepared by hospital pharmacies and, therefore, provide a safe and effective treatment to this population (70,71). Table 5 resumes the excipients and quantities proposed to prepare the 40% dextrose gel.

Table 5 – Compounding: 40% Dextrose Gel

Excipients	Quantity
Glucose 50% solution	80 mL
Glycerol	4 g
Carboxymethylcellulose	2 g
Propylparaben	0.02 g
Methylparaben	0.16 g
Water for injections	14 mL

5.2 Challenges in Compounding Formulas

Pharmacy compounding is the preparation of customized medicines for patients with unique medical needs and for whom there are no commercially available products. This kind of drug preparation is appropriate in a small scale by pharmacists that prepare the formulation based on an individual prescription. However, compounded drugs may present risks to the patients since the regulatory oversight of pharmacy compounding is significantly less rigorous than the regulatory agencies' approved drugs. The compounded products are not evaluated for safety and efficacy, and they usually do not have prescribing information with instructions for their safe use. Despite all that, the risk-benefit ratio is favourable for compounded medicines comparing to the patient not having access to suitable dosage forms (72,73). A compounding pharmacist can ensure that the patient receives a personalized medication. When deciding on the best delivery vehicle, pH, chemical compatibility and drug stability must be taken to account (74).

As discussed before, usually oral liquid formulations are considered the preferred dosage form for newborns. However, extemporaneously prepared oral suspensions require special caution due to the variation between doses (75). They can be prepared by the dilution of a pre-existing liquid formulation, and they can also be prepared from raw materials such as powders. Crushing conventional tablets and suspending them in water or other vehicles, presents a high risk of errors when dispensing extemporaneous preparations since it is difficult to control the preparation (31).

Patients with enteral feeding tube often receive their medication through such tube which requires a variety of skills to assure a correct and safe drug administration. Choosing and preparing the suitable dosage form to administer drugs via enteral feeding tube can be difficult. Nasoenteric tubes may clog with crushed dosage forms and only liquid formulations should be used in this situation. On the other hand, nasogastric and orogastric tubes are larger and do not clog so easily (76). Once again, liquid preparations are the preferred dosage forms when considering enteral feeding tube drug delivery since they are less likely to obstruct the tube. Some authors defend suspensions and solutions are preferred over syrups since these can cause clumping when exposed to the enteral nutrition (77). However, suspensions also have to be studied before administration regarding their osmolality and may require dilution prior to administration to help decrease the tonicity. Still regarding suspensions, it is important to consider that if the suspended particles are too large, the tube may be clogged and therefore when crushing

tablets is required, they must be crushed to a fine powder and suspended in a suitable vehicle (77,78). Many problems can occur when crushing solids prior to administration. Changes in absorption patterns, blood concentration and, consequently, dose-related toxicity may be present when tablets are crushed (61,79).

Even though suspensions may have the disadvantages and problems described before, they are, by far, the most prepared formulation in the pharmacies. After consulting five pediatric hospitals' websites which have publicly available Compounding Formulas, it was possible to observe the most commonly prepared formulations as well as the starting dosage form. Table 5 shows the frequency of the dosage forms prepared per hospital.

Table 6 - Frequency of compounding formulas in pediatric hospitals

Pediatric Hospital/Health Center	Suspensions	Solutions	Syrups	Others (Ointments, eye drops, etc.)
IWK (80)	n=46 (88.5%)	n=4 (7.7%)	n=0 (0.0%)	n=2 (3.8%)
NATIONWIDE CHILDREN'S (81)	n=86 (74.1%)	n=11 (9.5%)	n=3 (2.6%)	n=16 (13.8%)
SICK KIDS (82)	n=53 (91.4%)	n=3 (5.2%)	n=1 (1.7%)	n=1 (1.7%)
CHEO (83)	n=27 (90.0%)	n=0 (0.0%)	n=1 (3.3%)	n=2 (6.7%)
MICHIGAN (84)	n=87 (83.7%)	n=12 (11.5%)	n=5 (4.8%)	n=0 (0.0%)

Suspensions are, clearly, the most common compounding dosage forms. Between 68% and 87% of the proposed suspensions used several commercially available oral bases as the suspending vehicles. However, after consulting vehicles composition (Annex A1) it was possible to notice that all of them contained some type of sugar, usually sucrose, and some of them had long lists of excipients including sorbitol and preservatives.

Table 7 - Frequency of initial dosage form to compound suspensions.

Pediatric Hospital/Health Center	Tablets	Capsules	Powders	Injections
IWK (80)	n=36 (78.2%)	n=8 (17.4%)	n=1 (2.2%)	n=1 (2.2%)
NATIONWIDE CHILDREN'S (81)	n=60 (69.8%)	n=19 (22.1%)	n=7 (8.1%)	n=0 (0.0%)
SICK KIDS (82)	n=43 (81.1%)	n=7 (13.2%)	n=1 (1.9%)	n=2 (3.8%)
CHEO (83)	n=23 (85.2%)	n=4 (14.8%)	n=0 (0.0%)	n=0 (0.0%)
MICHIGAN (84)	n=58 (66.7%)	n=20 (23.0%)	n=8 (9.2%)	n=1 (1.1%)

In addition, it was analysed which starting dosage forms were most commonly used to prepare the suspensions. As shown in Table 6, tablets are the most used dosage form to produce suspensions, followed by capsules. The tablets and the contents of the capsules are pulverized into a fine powder using a mortar and pestle. Although suspensions have several disadvantages, especially when used with a feeding tube these results show that these are frequently the most used dosage form.

Annex A2 exemplifies the preparation worksheet of a Tacrolimus 0.5 mg/mL Oral Suspension proposed by the pharmacy of the SickKids Hospital (82). This compounding formula illustrates the preference for suspensions and, at the same time, the use of commercially available vehicles, such as ORA-Plus and the starting dosage form, in this specific case, immediate release capsules.

6 Alternative dosage forms for newborns

As discussed before, the ideal formulation to administer to newborns should have a minimal number of excipients and have a flexible dosage. It should also be safe, easy to administer, stable and, in some cases, palatable. Recently, there has been some progress in pediatric drug development. The biggest effort has been in developing age-appropriate dosage forms, specifically oral solid dosage forms, which enable dose flexibility, ease of administration and overall good acceptance (4).

Since 2008 the oral solid dosage forms have become the recommended pediatric dosage form around the world. Orodispersible tablets or tablets used to prepare liquid formulations have been widely used and accepted in the past years. Solid multiparticulates such as mini tablets, granules or pellets, have been proposed for medicines that require a precise dose measurement (4,85).

Swallowability continues to be the most common complaint regarding oral solid dosage forms, particularly in children younger than 5 years old (86). Orodispersible formulations can be administered without external help, placed inside the mouth, disintegrated, and dissolved fast in the saliva, thus overcoming several disadvantages related with liquid formulations or conventional solid dosage forms (87,88). There are variations on the definition of orally disintegrating tablets (ODTs). but, in general, ODTs are defined as dosage forms that disintegrate or dissolve rapidly without the addition of water, when placed in the oral cavity. After the administration of an ODT, the API dissolves or disperses in the saliva and it is then absorbed after swallowing. ODTs have been widely studied due to their high drug loading as well as their potency to deliver water insoluble drugs (89). These multiple-unit oral systems provide appropriate pediatric dosing, multiplying the dosage units instead of dividing units, as when using tablets. Furthermore, these forms are easy to manufacture, transport, store, dispense and, overall, more convenient than liquid dosage forms (90).

Mini tablets and ODTs are alternatives to conventional solid tablets that provide easier dose flexibility and overcome the swallowing problem (91). These dosage forms are developed by the addiction of superdisintegrants that maintains burst proprieties when in contact with water or saliva. They are prepared using several methods, from conventional to patented technologies. Conventional methods include spray-drying, molding, sublimation, mass-extrusion, direct compression, and freeze-drying, while patented

technologies include Zydis^{VR}, Durasolv^{VR}, Oraquick^{VR} and Flashdose^{VR} (89). Among health care practitioners, ODTs are the second most popular choice to pediatric patients, with liquids being the first (92).

Compared to conventional tablets, ODTs have important advantages as they increase patient compliance, have rapid onset of action and are convenient. ODTs and orally disintegrating mini tablets combine the benefits of oral liquid dosage forms, such as ease of application and dose flexibility, with the benefits of oral solid dosage forms, like high stability and low manufacture and shipping costs. Additionally, these formulations have acceptable taste, increasing treatment compliance with easier drug administration to young children (89).

Polymeric formulations such as viscous solutions, gels, wafers, *in situ* gelling systems and films (Figure 5) are also being studied to be administered to young children. Liquid formulations and gels have several disadvantages like instability, the rapid removal from the buccal cavity and the fact that they are not easy to administer (93). Some studies have tested the use of gels to deliver granules, pellets and minitablets, and concluded that the swallowing was easier and faster due to the smooth texture of the gel vehicle. However, it did not mask the presence of larger solid particles in the buccal cavity (90). On the other hand, solid formulations can be retained in the oral cavity for a longer period. Nowadays, films are the preferred dosage form for transmucosal delivery in children (93). Films have high thinness and flexibility, are comfortable to use, have dose flexibility and are able to achieve high residence times at the application site (94).

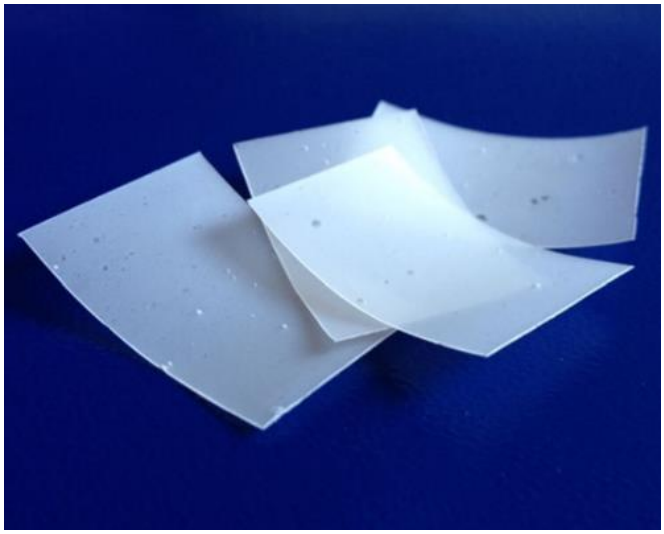


Figure 4 - Orodispersible films with 6 cm^2. Data adapted with permission from (52).

Wafers are another type of dosage form being studied for use in pediatric patients. The use of wafers is still very recent but, just like films, they are able to guarantee easy administration, low residue moisture and higher drug loading capacity (93). Both films and wafers excipients have been studied. To obtain the best adhesion properties the polymers must have high molecular weight, chain flexibility, hydrophilic properties and functional groups capable of forming hydrogen bonds with the mucosa (42,95).

Solid formulations that become liquid upon intake are another possible choice for drug administration in newborns. These might include powder or granules for oral solutions or suspensions that may be packed in multiple dose containers or in single dose containers (i.e., sachet) or soluble tablets that are meant to be dissolved prior to administration (4).

Finally, recently novel types of oral dosage forms have been proposed and studied to administer age-appropriate formulations to newborns. Milk-based liquid preparations have been studied for their ability to dissolve drugs and their stability have also been evaluated. Several studies suggest that the solubility of hydrophobic drugs in milk is higher than in water. Furthermore, reconstituted freeze-dried drug-milk formulations showed superiority regarding solubility and dissolution when compared to conventional capsules of lipophilic drugs (47,96). Another concept is the administration of tablets through a Therapeutic Nipple Shield (Figure 6), which delivers the drug to the breastfeeding child. However, this technology is yet experimental and the risk of interfering with feeding must be carefully evaluated (97).

Figure 5 – Nipple Shield delivery system for oral drug delivery in breastfeeding children (images provided courtesy of http://www.justmilk.org/).

7 Conclusion

Newborns are still “therapeutic orphans” regarding the access to appropriate formulations and drugs. The fact that neonates are such a small fraction of the population, limits the overall ability to provide specific neonatal formulations. However, if neonates are considered during the early steps of formulation design, delays in clinical trials in the newborn population may be avoided. Nevertheless, a lot of fundamental information about this population physiology and characteristics is not yet available to enable the pharmaceutical development (7).

An EMA report from 2017 (98) showed an increased number of clinical studies done in the pediatric population, as well as a large number of submitted PIPs, yet only some PUMAs for drug substances were granted. The shortage of approved medicines for newborns, led to the use of off-label, extemporaneous formulas, magistral preparations, etc., to cover the population needs. However, these types of medicines should always be of the highest quality. A working group at the European Directorate for the Quality of Medicines has been formed to create a pediatric formulary build of predefined specifications, high standard compounding formulas, and well-established preparations. However, the pediatric drug treatment development still presents several gaps (52,56).

New dosage forms, such as orodispersible films and tablets, mini tablets, multiparticulate dosage forms and others, may be a great way to cover the gaps existing in the neonates’ drug treatment. Research is still required to fully understand the impact of particle size, volume and administration to determine the acceptability of these dosage forms in neonates (56), but their use will allow for a more suitable formulation approach and enhance tailored medicines for neonates, as well as a more personalized treatment (5,53,58)

A joint effort between industry, caregivers, regulatory agencies and academia shall be pursued to ensure product availability, dissemination of available information on age-appropriate, evidence-based approach to excipients and their risks and the validation of compounding procedure (5). To conclude, there is still a lot of potential to be explored for product improvement regarding neonatal drug development and formulation.

Bibliography

1. Ward RM, Benjamin D, Barrett JS, Allegaert K, Portman R, Davis JM, et al. Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates. Pediatr Res. 2017;81(5):692–711.

2. EMA EMA. COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) REFLECTION PAPER: formulations of choice for the paediatric population agreed by paediatric working party. 2005;(December 2005). Available from: http://www.emea.europa.eu

3. Lu H, Rosenbaum S. Developmental Pharmacokinetics in Pediatric Populations. J Pediatr Pharmacol Ther. 2014;19(4):262–76.

4. Ivanovska V, Rademaker CMA, Van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: A review of challenges and progress. Pediatrics. 2014;134(2):361–72.

5. Allegaert K. Neonates need tailored drug formulations. World J Clin Pediatr. 2013;2(1):1.

6. European Commission. State of Paediatric Medicines in the EU: 10 years of the EU Paediatric Regulation. DG Heal Consum. 2017;1–17.

7. O'Brien F, Clapham D, Krysiak K, Batchelor H, Field P, Caivano G, et al. Making medicines baby size: The challenges in bridging the formulation gap in neonatal medicine. Int J Mol Sci. 2019;20(11).

8. Noel GJ, Van Den Anker JN, Lombardi D, Ward R. Improving drug formulations for neonates: Making a big difference in our smallest patients. J Pediatr [Internet]. 2012;161(5):947-949.e1. Available from: http://dx.doi.org/10.1016/j.jpeds.2012.07.016

9. Antonucci R, Porcella A. Current pharmacotherapy in the newborn. Res Reports Neonatol. 2012;85.

10. Alcorn J, McNamara PJ. Pharmacokinetics in the newborn. Adv Drug Deliv Rev. 2003;55(5):667–86.

11. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and

mechanisms for pharmacokinetic differences between pediatrie population and adults. Pharmaceutics. 2011;3(1):53–72.

12. Ruggiero A, Ariano A, Triarico S, Capozza MA, Ferrara P, Attinà G. Neonatal pharmacology and clinical implications. Drugs Context. 2019;8:1–9.

13. Tayman C, Rayyan M, Allegaert K. Neonatal Pharmacology: Extensive Interindividual Variability Despite Limited Size. J Pediatr Pharmacol Ther. 2011;16(3):170–84.

14. John van den Anker, MD, PhD, FCP1, 2, 3, Michael D. Reed, PharmD, FCCP, FCP4, Karel Allegaert, MD, PhD3, 5, 6, and Gregory L. Kearns, PharmD, PhD F. Developmental Changes in Pharmacokinetics and Pharmacodynamics.

15. For S, Preparations P. Draft Annex To 46Th Report of the Who Expert Committee on Specifications for Pharmacetical Preparations Development of Paediatric Medicines : Points To Consider in Formulation. 2010;(June):1–34.

16. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384–97.

17. Cuzzolin L. Neonates exposed to excipients: concern about safety. J Pediatr Neonatal Individ Med [Internet]. 2017;7(1):e70112. Available from: www.jpnim.com

18. Cram A, Breitkreutz J, Desset-Brèthes S, Nunn T, Tuleu C. Challenges of developing palatable oral paediatric formulations. Int J Pharm. 2009;365(1–2):1–3.

19. Fasching G, Hiillwarth ME, Schmidt B, Sauer H. Pediatl C Surgery Main topic Necrotizing enterocolitis in very-low-birth-weight infants. 1992;428–30.

20. Arvin Bundhoo, MD and Adam Matson, MD, MS, Division of Neonatology, Connecticut Children's Medical Center, Hartford, CT; Department of Pediatrics, University of Connecticut School of Medicine, Farmington C. National Organization for Rare Disorders [Internet]. 2015 [cited 2021 May 22]. Available from: https://rarediseases.org/rare-diseases/necrotizing-enterocolitis/

21. Ellis ZM, Tan HSG, Embleton ND, Sangild PT, Van Elburg RM. Milk feed osmolality and adverse events in newborn infants and animals: A systematic

review. Arch Dis Child Fetal Neonatal Ed. 2019;104(3):F333–40.

22. (European Medicines Agency). Excipients in the label and 6 package leaflet of medicinal products for human use. 2014;44(January):223–32. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf

23. Committee for Medicinal Products for Human Use (CHMP). Assessment report Propylene glycol in medicinal products for children International. 2014;EMA/175205(March):18. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/03/WC500163989.pdf

24. Turner MA, Duncan JC, Shah U, Metsvaht T, Varendi H, Nellis G, et al. Risk assessment of neonatal excipient exposure: Lessons from food safety and other areas. Adv Drug Deliv Rev [Internet]. 2014;73:89–101. Available from: http://dx.doi.org/10.1016/j.addr.2013.11.003

25. Duro D, Rising R, Cedillo M, Lifshitz F. Association between infantile colic and carbohydrate malabsorption from fruit juices in infancy. Pediatrics. 2002;109(5):797–805.

26. Aires CP, Tabchoury CPM, Del Bel Cury AA, Koo H, Cury JA. Effect of sucrose concentration on dental biofilm formed in situ and on enamel demineralization. Caries Res. 2005;40(1):28–32.

27. Stegink LD, Bell F, Ziegler EE, Krause L. Repeated Ingestion of Aspartame-Sweetened Individuals Heterozygous Beverages: Further Observations for Phenylketonuria in Lewis. 1990;39(10):1076–81.

28. Walker AM, Dreyer NA, Friedlander E, Loughlin J, Rothman KJ, Kohn HI. An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. Am J Public Health. 1982;72(4):376–81.

29. Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. Eur J Pediatr. 2020;179(5):839–47.

30. De Lima Costa HTM, Costa TX, Martins RR, Oliveira AG. Use of off-label and unlicensed medicines in neonatal intensive care. PLoS One. 2018;13(9):1–12.

31. Standing JF, Tuleu C. Paediatric formulations - Getting to the heart of the problem. Int J Pharm. 2005;300(1–2):56–66.

32. Gadge PM, Kenjale PP, Pokharkar VB, Gaikwad VL. Global Pediatric Regulations: An Overview. Ther Innov Regul Sci [Internet]. 2020;54(3):552–8. Available from: https://doi.org/10.1007/s43441-019-00087-1

33. Rose K. The Challenges of Pediatric Drug Development. Curr Ther Res - Clin Exp [Internet]. 2019;90:128–34. Available from: https://doi.org/10.1016/j.curtheres.2019.01.007

34. Nordenmalm S, Tomasi P, Pallidis C. More medicines for children: Impact of the EU paediatric regulation. Arch Dis Child. 2018;103(6):557–64.

35. (CHMP) C for MP for HU, (PDCO) PC. Guideline on pharmaceutical development of medicines for paediatric use [Internet]. EMA/CHMP/QWP/805880/2012 Rev. 2. 2013 [cited 2021 Apr 2]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf

36. Products C for HM. ICH E11(R1) step 5 guideline on clinical investigation of medicinal products in the pediatric population [Internet]. 2017. Available from: https://www.ema.europa.eu/en/ich-e11r1-step-5-guideline-clinical-investigation-medicinal-products-pediatric-population

37. Vieira I, Sousa JJ, Vitorino C. Paediatric Medicines – Regulatory Drivers, Restraints, Opportunities and Challenges. J Pharm Sci. 2021;1–12.

38. UNION TEPATCOTE. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

39. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: The impact of evolving regulations. Adv Drug Deliv Rev [Internet]. 2014;73:2–13. Available from: http://dx.doi.org/10.1016/j.addr.2014.02.003

40. Kimland E, Odlind V. Off-label drug use in pediatric patients. Clin Pharmacol Ther

[Internet]. 2012;91(5):796–801. Available from: http://dx.doi.org/10.1038/clpt.2012.26/nature06264

41. Van Riet Nales DA, Kozarewicz P, Wang S, Saint-Raymond A, Robert JL. Comments on the EMA draft guideline: Final steps towards a harmonized view between regulators and industry. Int J Pharm [Internet]. 2013;457(1):337–9. Available from: http://dx.doi.org/10.1016/j.ijpharm.2013.08.060

42. Linakis MW, Roberts JK, Lala AC, Spigarelli MG, Medlicott NJ, Reith DM, et al. Challenges Associated with Route of Administration in Neonatal Drug Delivery. Clin Pharmacokinet. 2016;55(2):185–96.

43. Montero-Padilla S, Velaga S, Morales JO. Buccal Dosage Forms: General Considerations for Pediatric Patients. AAPS PharmSciTech [Internet]. 2017;18(2):273–82. Available from: http://dx.doi.org/10.1208/s12249-016-0567-2

44. Wasylewicz ATM, van Grinsven RJB, Bikker JMW, Korsten HHM, Egberts TCG, Kerskes CHM, et al. CDSS-Assisted Pharmacy Intervention Reduces Feeding Tube–Related Medication Errors in Hospitalized Patients: A Focus on Medication Suitable for Feeding-Tube Administration. J Parenter Enter Nutr. 2020;

45. White R, Bradnam V. Handbook of Drug Administration via Enteral Feeding Tubes. 3rd ed. UK: Pharmaceutical Press; 2015.

46. Joos E, Verbeke S, Mehuys E, Van Bocxlaer J, Remon JP, Van Winckel M, et al. Medication administration via enteral feeding tube: a survey of pharmacists' knowledge. Int J Clin Pharm. 2016;38(1):10–5.

47. Orubu SEF, Hobson NJ, Basit AW, Tuleu C. The Milky Way: paediatric milk-based dispersible tablets prepared by direct compression – a proof-of-concept study. J Pharm Pharmacol. 2017;69(4):417–31.

48. Batchelor HK, Marriott JF. Formulations for children: Problems and solutions. Br J Clin Pharmacol. 2015;79(3):405–18.

49. Sherwin CMT, Medlicott NJ, Reith DM, Broadbent RS. Intravenous drug delivery in neonates: Lessons learnt. Arch Dis Child. 2014;99(6):590–4.

50. Chen L, Zhang M, Yung J, Chen J, McNair C, Lee KS. Safety of rectal administration of acetaminophen in neonates. Can J Hosp Pharm. 2018;71(6):364–

9.

51. Evans N, Guy RH, Hadgraft J, Parr GD, Rutter N. Transdermal drug delivery to neonates. Int J Pharm. 1985;24(2–3):259–65.

52. Thabet Y, Klingmann V, Breitkreutz J. Drug Formulations: Standards and Novel Strategies for Drug Administration in Pediatrics. J Clin Pharmacol. 2018;58(March):S26–35.

53. Van Riet-Nales DA, Schobben AFAM, Vromans H, Egberts TCG, Rademaker CMA. Safe and effective pharmacotherapy in infants and preschool children: Importance of formulation aspects. Arch Dis Child. 2016;101(7):662–9.

54. Kayitare E, Vervaet C, Ntawukulilyayo JD, Seminega B, Bortel V, Remon JP. Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications. Int J Pharm. 2009;370(1–2):41–6.

55. Swedrowska M, Ingham S, Tomlin S, Forbes B. Recommendations for crushing Circadin® (melatonin) tablets for safe and reliable delivery via pediatric nasogastric tubes. Int J Pharm [Internet]. 2021;594(August 2020):120151. Available from: https://doi.org/10.1016/j.ijpharm.2020.120151

56. Mistry P, Batchelor H. Evidence of acceptability of oral paediatric medicines: a review. J Pharm Pharmacol. 2017;69(4):361–76.

57. Klingmann V, Seitz A, Meissner T, Breitkreutz J, Moeltner A, Bosse HM. Acceptability of Uncoated Mini-Tablets in Neonates—A Randomized Controlled Trial. J Pediatr. 2015;167(4):893-896.e2.

58. Mfoafo KA, Omidian M, Bertol CD, Omidi Y, Omidian H. Neonatal and pediatric oral drug delivery: Hopes and hurdles. Int J Pharm [Internet]. 2021;597(October 2020):120296. Available from: https://doi.org/10.1016/j.ijpharm.2021.120296

59. Magdalena W, Emilia S, Marta S, Katarzyna W. Different Types of Gel Carriers as Metronidazole Delivery Systems to the Oral Mucosa.pdf. Białystok, Poland; 2020.

60. Mahdi MH, Conway BR, Smith AM. Evaluation of gellan gum fluid gels as modified release oral liquids. Int J Pharm [Internet]. 2014;475(1):335–43. Available from: http://dx.doi.org/10.1016/j.ijpharm.2014.08.044

61. Lima G De, Negrini N. Pharmaceutical assistance in the enteral administration of drugs: choosing the appropriate pharmaceutical formulation. Einstein [Internet]. 2009;7:9–17. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Pharmaceutical+assistance+in+the+enteral+administration+of+drugs+:+choosing+the+appropriate+pharmaceutical+formulation#0

62. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: Benefits and limitations of current platforms. Expert Opin Drug Deliv. 2015;12(11):1727–40.

63. European Directorate for the Quality of Medicines, editor. European Pharmacopoeia (Ph. Eur.). 9th Editio. Strasbourg, France: Council of Europe; 2016.

64. Afifi NA. Pharmaceutical Solutions for Oral administration. Pharm Dos Form Des. 2016;1–41.

65. Kulshreshtha AK, Singh ON, Wall GM. Pharmaceutical suspensions: From formulation development to manufacturing. Pharmaceutical Suspensions: From Formulation Development to Manufacturing. 2010. 1–327 p.

66. Khan BA, Akhtar N, Khan HMS, Waseem K, Mahmood T, Rasul A, et al. Basics of pharmaceutical emulsions: A review. African J Pharm Pharmacol. 2011;5(25):2715–25.

67. Pharmaceutical Emulsion: An Overview [Internet]. [cited 2021 Jul 21]. Available from: https://www.pharmapproach.com/pharmaceutical-emulsions-an-overview/

68. Marti-Mestres G, Nielloud F. Emulsions in Health Care Applications—An Overview. J Dispers Sci Technol. 2002;23(1–3):419–39.

69. Zahn J, Hoerning A, Trollmann R, Rascher W, Neubert A. Manipulation of medicinal products for oral administration to paediatric patients at a german university hospital: An observational study. Pharmaceutics. 2020;12(6):1–16.

70. Barber RL, Ekin AE, Sivakumar P, Howard K, O'Sullivan TA. Glucose gel as a potential alternative treatment to infant formula for neonatal hypoglycaemia in Australia. Int J Environ Res Public Health. 2018;15(5):6–8.

71. Rivano M, Albrecht M, Longobardo G, Veneziano C. Galenic Preparation of 40%

Dextrose Gel: A New Approach to the Management of Neonatal Hypoglycemia. Clin Med Insights Endocrinol Diabetes. 2020;13:10–1.

72. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. Drugs R D. 2013;13(1):1–8.

73. Bar-Shalom D. Necessity of rethinking oral pediatric formulations. Clin Ther [Internet]. 2014;36(2):180–3. Available from: http://dx.doi.org/10.1016/j.clinthera.2014.01.010

74. Preckshot J. Pediatric Compounding : Vol. 5. 2001. p. 6–8.

75. Helin-Tanninen M. Compounding of Paediatric Oral Formulations, Extemporaneous nifedipine capsules, powders and suspensions in the hospital pharmacy. Eastern Finland: University of Eastern Finland; 2013.

76. Beckwith MC, Feddema SS, Barton RG, Graves C. A Guide to Drug Therapy in Patients with Enteral Feeding Tubes: Dosage Form Selection and Administration Methods. Vol. 39, Hospital Pharmacy. 2004. p. 225–37.

77. Williams NT. Medication administration through enteral feeding tubes. Am J Heal Pharm. 2008;65(24):2347–57.

78. Gora L, Pharm D, Tschampel MM, Ph R, Visconti JA, Ph D. Techniques and Procedures CONSIDERATIONS OF DRUG THERAPY IN PATIENTS RECEIVING ENTERAL NUTRITION. 2015;105–10.

79. Sari D, Kadifeli D, Akbiyik A, Taşkiran N. Intensive care unit nurses' knowledge of medication administration via enteral tubes. Nurs Crit Care. 2018;23(3):141–6.

80. IWK Compounding Formulas [Internet]. 2019 [cited 2021 Feb 23]. Available from: https://www.iwk.nshealth.ca/page/iwk-compounding-formulas

81. Nationwide Children's Compounding Formulas [Internet]. 2020 [cited 2021 Feb 23]. Available from: https://www.nationwidechildrens.org/specialties/pharmacy-services/compounding-formulas

82. SickKids Hospital Compounding Formulas [Internet]. 2021 [cited 2021 Feb 23]. Available from: https://www.sickkids.ca/en/care-services/for-health-care-providers/compounding-service/

83. CHEO Cmpounding Formulas [Internet]. 2021 [cited 2021 Feb 23]. Available

from: https://www.cheo.on.ca/en/clinics-services-programs/pharmacy.aspx

84. University of Michigan College of Pharmacy. Michigan Pediatric Safety Collaboration - Standardize Compounded Oral Liquids [Internet]. 2021 [cited 2021 Feb 23]. Available from: https://www.mipedscompounds.org/standard-formulations

85. World Health Organization. Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. 2008;(December):1–15. Available from: http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_reportDEC2008.pdf

86. Sastry SV, Nyshadham JR, Fix JA. Recent technological advances in oral drug delivery - A review. Pharm Sci Technol Today. 2000;3(4):138–45.

87. Gulsun T, Akdag Cayli Y, Izat N, Cetin M, Oner L, Sahin S. Development and evaluation of terbutaline sulfate orally disintegrating tablets by direct compression and freeze drying methods. J Drug Deliv Sci Technol [Internet]. 2018;46(April):251–8. Available from: https://doi.org/10.1016/j.jddst.2018.05.014

88. Chinwala M. Recent Formulation Advances and Therapeutic Usefulness of Orally Disintegrating Tablets (ODTs). Pharmacy. 2020;8(4):186.

89. Comoglu T, Dilek Ozyilmaz E. Orally disintegrating tablets and orally disintegrating mini tablets–novel dosage forms for pediatric use. Pharm Dev Technol [Internet]. 2019;24(7):902–14. Available from: https://doi.org/10.1080/10837450.2019.1615090

90. Kluk A, Sznitowska M. Application properties of oral gels as media for administration of minitablets and pellets to paediatric patients. Int J Pharm [Internet]. 2014;460(1–2):228–33. Available from: http://dx.doi.org/10.1016/j.ijpharm.2013.10.052

91. Preis M. Orally Disintegrating Films and Mini-Tablets—Innovative Dosage Forms of Choice for Pediatric Use. AAPS PharmSciTech. 2015;16(2):234–41.

92. Alyami H, Koner J, Dahmash EZ, Bowen J, Terry D, Mohammed AR. Microparticle surface layering through dry coating: impact of moisture content and process parameters on the properties of orally disintegrating tablets. J Pharm

Pharmacol. 2017;69(7):807–22.

93. Costa JSR, de Oliveira Cruvinel K, Oliveira-Nascimento L. A mini-review on drug delivery through wafer technology: Formulation and manufacturing of buccal and oral lyophilizates. J Adv Res [Internet]. 2019;20:33–41. Available from: https://doi.org/10.1016/j.jare.2019.04.010

94. Giordani B, Abruzzo A, Prata C, Nicoletta FP, Dalena F, Cerchiara T, et al. Ondansetron buccal administration for paediatric use: A comparison between films and wafers. Int J Pharm [Internet]. 2020;580(December 2019):119228. Available from: https://doi.org/10.1016/j.ijpharm.2020.119228

95. Sosnik A, Das Neves J, Sarmento B. Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral routes: A review. Prog Polym Sci [Internet]. 2014;39(12):2030–75. Available from: http://dx.doi.org/10.1016/j.progpolymsci.2014.07.010

96. Charkoftaki G, Kytariolos J, Macheras P. Novel milk-based oral formulations: Proof of concept. Int J Pharm [Internet]. 2010;390(2):150–9. Available from: http://dx.doi.org/10.1016/j.ijpharm.2010.01.038

97. Gerrard SE, Baniecki ML, Sokal DC, Morris MK, Urdaneta-Hartmann S, Krebs FC, et al. A nipple shield delivery system for oral drug delivery to breastfeeding infants: Microbicide delivery to inactivate HIV. Int J Pharm [Internet]. 2012;434(1–2):224–34. Available from: http://dx.doi.org/10.1016/j.ijpharm.2012.05.035

98. (PDCO) PC. 10-year Report to the European Commission [Internet]. 2017 [cited 2021 Jun 2]. Available from: https://ec.europa.eu/health/sites/default/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

99. Oral Sweet – Oral Suspending Vehicle [Internet]. 2021 [cited 2021 Feb 25]. Available from: http://www.swissmedicareltd.com/Oral-Sweet.php

100. Oral Plus – Oral Suspending Vehicle [Internet]. 2021 [cited 2021 Feb 25]. Available from: http://www.swissmedicareltd.com/Oral-Plus.php

101. ORA BLEND® Safety Data Sheet [Internet]. 2019 [cited 2021 Feb 25]. Available from: https://www.medisca.ca/ProductFiles/2348/Medisca

Document/SDS/EN/2348.pdf

102. MEDISCA'S ORAL BASES [Internet]. 2021 [cited 2021 Feb 25]. Available from: https://ijpc.com/images/ads/medisca/Oral Bases Sell Sheet Flyer - MUS & MCA.PDF

103. Ora-Plus SDS Medisca [Internet]. 2019 [cited 2021 Feb 25]. Available from: https://www.medisca.ca/ProductFiles/0743/Medisca Document/SDS/EN/0743.pdf

Annex

A1. Vehicle composition

Vehicle	Ingredients
Vehicle 1 (99)	Purified water, Sucrose, Glycerin (E422), Sorbitol (E420), Thickening agent (E466, E415), Buffering agents (E399, E330), Preservatives (E211, E217, E219, E202) and Colour.
Vehicle 2 (100)	Purified water, Sucrose, Thickening agent (E460, E466, E415), Buffering agents (E399, E330), Preservatives (E211, E217, E219, E202) and antifoaming agents: dimethicone.
Vehicle 3 (101)	Trisodium phosphate, Glycerin, Cellulose, Sucrose
Vehicle 4 (102)	Purified water, Sucrose, Glycerin, Sorbitol, Cherry flavor, Microcrystalline cellulose, Carboxymethylcellulose sodium, Xanthan gum, Carrageenan sodium citrate, Citric acid, Potassium sorbate, Methylparaben, Simethicone
Vehicle 5 (103)	Cellulose, Trisodium Phosphate

A2. Compounding Formula: Tacrolimus 0.5 ng/mL Oral Suspension

Ingredients	Manufacturer	Lot	Expiry Date	Quantity	Measured	Checked
Tacrolimus Immediate release 5 mg capsules	Astellas			24 capsules		
Ora-Plus	Perrigo			120 mL		
Simple Syrup	Medisca			120 mL		
Ora-Plus & Simple Syrup Combination	SickKids Pharmacy			q.s. 240 mL		

Equipment:

- Mortar and pestle
- Graduated measure
- Glass stirring rod

Procedure:

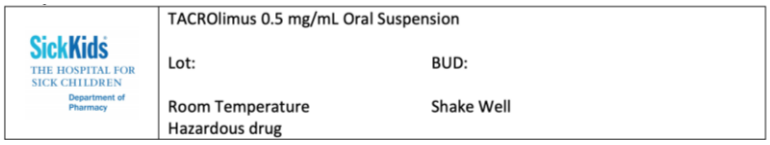
1. Measure 120 mL of ORA-Plus and 120 mL of Simple Syrup into a 250mL graduate and stir well. Stir well again, before triturating and final q.s. as it settles out.
2. Empty contents of capsules into the mortar.
3. Add a small amount of vehicle mixture to powder and levigate into a smooth paste with a pestle. Continue to levigate as vehicle is added in small amounts until a liquid is formed.
4. Transfer liquid contents from mortar to graduate.
5. Use a small amount of vehicle to rinse mortar and add it to graduate.
6. Use vehicle to q.s. to the final volume. Stir well.
7. Transfer to amber bottle.

Quality Control:

Expected Product Appearance	Additional Notes
White Suspension	

Storage: Room temperature
Packaging: Amber Glass/Plastic PET bottles
BUD: 56 days

Sample Label:



Date Made/Prepared By/ Checked By:
