

Manipulations and age-appropriateness of oral medications in pediatric oncology patients in Sweden: Need for personalized dosage forms

Jenny Johannesson^a, Paula Hansson^b, Christel A.S. Bergström^a, Mattias Paulsson^{b,*}

^a Department of Pharmacy, Uppsala University, Uppsala Biomedical Center, P.O Box 580, SE-751 23 Uppsala, Sweden

^b Department of Women's and Children's Health, Uppsala University, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden

ARTICLE INFO

Keywords:

Pediatric
Oncology
Oral medication
Drug manipulation
Age-appropriate
Personalized dosage form

ABSTRACT

Due to the lack of age-appropriate formulations for children, healthcare professionals and caregivers frequently manipulate dosage forms to facilitate oral administration and obtain the required dose. In this study, we investigated drug manipulation and age-appropriateness of oral medications for pediatric oncology patients with the aim of identifying the therapeutic needs for personalized dosage forms. An observational study at a pediatric oncology ward, combined with analysis of the age-appropriateness of the oral medications, was performed. Nurses frequently manipulated solid dosage forms to administer them via enteral feeding tubes. Of the active pharmaceutical ingredients (APIs) assessed for age-appropriateness, 74% (29 of 39) were identified to need personalization, either because of lack of child-friendly dosage form, suitable dosage strength, or both. Most APIs, due to limited solubility, were sensitive to formulation changes, such as drug manipulation. This study demonstrates problems and therapeutic needs regarding oral dosage forms in treatment of children with cancer. Expertise in formulation design, new manufacturing technologies, and patient-centered information are needed to address age-appropriate formulations for children.

1. Introduction

Over the last decade, collaborative effort have been made towards developing child-friendly oral dosage forms to ensure safe and efficient drug therapies in the pediatric patient population. One example of this is the development and marketing of multiparticulate and orodispersible formulations [1,2]. Despite this, healthcare professionals and caregivers often need to manipulate commercially available dosage forms developed for an adult population to facilitate administration or the required dose for a child [3–5]. Pediatric patients (newborns to adolescents) are characterized by gradual growth and developmental changes. The diversity of this population is challenging for the pharmaceutical industry. Acceptability and dose flexibility are key aspects in development of age-appropriate formulations for children [1,2].

Patient acceptability is the overall acceptance of a dosage form determined by the characteristics of both medicinal product and patient [6]. Acceptability of oral dosage forms in young children is often limited by the dosage forms size, shape, texture, taste, and volume/quantity of the medication [7,8]. Furthermore, doses can vary up to 100-fold

throughout childhood and dose adjustments of available dosage forms may be required [9]. Typical procedures for manipulation of oral solid dosage forms are to split or crush tablets, open capsules, and disperse the fragments in liquid or mix with food for administration. Splitting tablets into halves and quarters or extracting a proportion of a dispersed dosage form are associated with risk of inaccurate dosing [10,11]. In addition, manipulations of oral dosage forms can affect the stability, solubility, and bioavailability of the drug [12,13]. Poorly water-soluble drugs can be particularly sensitive to these type of procedures, and data are limited on the clinical outcomes of such drug manipulations. However, the potential risk of suboptimal drug therapy in this vulnerable patient population highlights the requirement for age-appropriate formulations available in a dosage form and strength suitable for children.

In recent years, 3D printing technologies have revolutionized pharmaceutical manufacturing and paved the way for production of personalized drug products [14]. Children are a patient group that benefits from a flexible production platform that can tailor the shape, size, dose, and other attributes of the dosage form to each individual patient. For example, 3D printing of chewable dosage forms in different

Abbreviations: API, active pharmaceutical ingredient; SmPC, summary of product characteristics; BCS, biopharmaceutics classification system; pBCS, pediatric biopharmaceutics classification system; clogP, calculated logP; EMA, European Medicines Agency.

* Corresponding author.

E-mail address: mattias.paulsson@kbh.uu.se (M. Paulsson).

<https://doi.org/10.1016/j.bioph.2021.112576>

Received 7 December 2021; Accepted 20 December 2021

Available online 29 December 2021

0753-3322/© 2021 The Author(s).

Published by Elsevier Masson SAS. This is an open access article under the CC BY license

(<http://creativecommons.org/licenses/by/4.0/>).

doses and flavors have been produced in a clinical setting for treatment of children with maple syrup urine disease, a rare metabolic disease [15]. Furthermore, orodispersible tablets and films, suitable for pediatrics have been manufactured using 3D printing [16,17]. 3D manufacturing technology can also be used to address the low oral bioavailability of many new drugs suffering from poor water solubility [18]. However, 3D printing of pharmaceuticals is still in its beginning and little attention has been given to identify active pharmaceutical ingredients (APIs) where this flexible production platform for personalized dosage forms can be useful for children.

Children suffering from severe diseases such as cancer require lengthy drug treatments with multiple drugs, including oral chemotherapy. Compliance and optimal drug therapies are essential for successful treatment [19]. Manipulation of cytotoxic, often highly potent drugs, poses the risk of sub-therapeutic or toxic doses for the patient, and exposure for the healthcare professionals and caregivers. Pediatric patients and their caretakers would benefit from ready-to-use or personalized medications in the correct dose and appropriate oral dosage form for treatment both at the clinic and at home. In this study, we investigated drug manipulation and age-appropriateness of oral medications in a pediatric oncology population with the aim of identifying therapeutic requirements for child-friendly, personalized oral dosage forms. The study was performed at a university hospital in Sweden on children up to 11 years old. The identification of pediatric therapeutic needs by this study can be used in formulation development of personalized dosage forms by 3D printing.

2. Methods

2.1. Drug manipulation

2.1.1. Study design

A prospective observational study was designed to identify which oral medications are frequently manipulated in pediatric practice and the type of manipulations. The extent of drug manipulation was not the primary aim of this study. The study was carried out at the pediatric hematology and oncology ward at Uppsala University Children's Hospital (12 beds), one of six such centers in Sweden. Inclusion criteria were children up to 11 years old, who were prescribed oral medications at the time of observation. Children whose parents were responsible for handling and administering oral medications during hospitalization were excluded from the study.

2.1.2. Data collection

The study was carried out between December 2019 and February 2020 for a total of 20 days. On these days, pediatric nurses dispensing oral medications were observed in the medication room at the ward. Observations were documented using a standardized protocol by two researchers, both licensed pharmacists. Information collected included: the age of the child, name of medicinal product, dosage form, any procedure used to manipulate the dosage form, and reason for drug manipulation. The administration of drugs to pediatric patients was not observed, but information regarding drug administration via enteral feeding tubes was collected. Time permitting, the nurses were also asked about problems and barriers related to oral drug administration. Repeated dispenses of the same medication to one patient were documented. For the purpose of this study, drug manipulation was defined as any physical alteration of the dosage form not mentioned in the summary of product characteristics (SmPC). This included procedures both to facilitate drug administration and to obtain the required dose.

2.2. Age-appropriateness of oral medications

2.2.1. Data source

The Concise Database hosted by the Swedish eHealth Agency was used to derive data on oral medications used in pediatric oncology

patients. The derived data included oral medicinal products supplied to the pediatric hematology and oncology ward, Uppsala University Children's Hospital (inpatient population) and those prescribed by pediatricians at the same ward to pediatric oncology patients (outpatient population). The medicinal products extracted from the database were sorted by ATC-code and included brand name, dosage form, strength, and package size. Extemporaneous and unlicensed medicines were included in the derived data.

2.2.2. Identification of active pharmaceutical ingredients for development of personalized dosage forms

Age-appropriateness of oral medications in pediatric oncology patients, between January 2019 – December 2020, was studied retrospectively. Oral medications used both in inpatient and outpatient populations were studied, as only a minor part of these patients' drug therapy takes place at the hospital and because drug therapy at home often relies on orally administered medications. In the first step, oral medicinal products derived from the Concise Database for this study were screened. This identified APIs of interest for further analysis of the age-appropriateness of available oral dosage forms. Medicinal products with incomplete ATC-codes, unlicensed medicines, extemporaneous formulations, and duplicates were excluded. The remaining ones were translated to the corresponding number of APIs. Combination products, containing multiple APIs, were recorded as a single API in this study. The APIs were then assessed for their availability as oral liquid dosage forms. APIs for which an oral liquid dosage form was licensed in Sweden were excluded. Finally, APIs not licensed for use in pediatrics, aged 0–11 years, and APIs with rare indications in pediatrics were excluded.

In the second step, APIs identified from the screening step were analyzed and classified on the basis of age-appropriateness of licensed oral medications for pediatric patients 0–11 years. This assessment was based on two aspects: acceptability of dosage form and availability of appropriate dosage strengths (Table S1). Acceptability was assessed as the ability to administer solid dosage forms of the API to children with difficulties swallowing whole tablets or capsules. The ability to manipulate solid dosage forms to facilitate oral administration was evaluated from the information provided in the SmPC. The assessment of dosage strengths was based on whether the recommended dose (as per its SmPC), from the lowest age of pediatric license, could be obtained without the need for manipulation. On the basis of these two investigated aspects, the APIs were classified according to three classes: class I, lack of acceptable dosage form and appropriate dosage strength; class II, lack of either acceptable dosage form or appropriate dosage strength; and class III, age-appropriate pediatric oral formulation available.

2.2.3. Pediatric biopharmaceutics classification system

In a final step, APIs in classes I and II, were categorized according to a pediatric biopharmaceutics classification system (pBCS) [20,21]. A pediatric dose number (D_{op}) was calculated according to the following equation [20]:

$$D_{op} = \frac{M_{op}}{C_s V_{op}} \quad (1)$$

where M_{op} is the pediatric highest dose, C_s is the solubility in water, and V_{op} is the pediatric initial gastric volume. High solubility was considered as a $D_{op} \leq 1$. The calculations were performed based on a single model child, age 6, with a mean weight of 21 kg, and a body surface area of 0.82 m^2 [22,23]. Pediatric dose was obtained from the SmPC or the British National Formulary for Children [22,24]. Water solubility was extracted from the literature and available databases [25–27]. The most conservative solubility values were used. The pediatric initial gastric volume was extrapolated from an adult population according to the following equation [21]:

$$V_{op} = \frac{\text{median weight (kg)} \times 0.56(\text{ml/kg})}{37.1 (\text{ml})} \times 250 (\text{ml}) \tag{2}$$

Permeability was assessed based on the n-octanol/water partition coefficient, log*P*. Calculated log*P* (clog*P*) values were obtained from available database [25]. Metoprolol, clog*P* of 1.8, was used as a reference compound because it is absorbed to a high extent by passive diffusion [21]; high permeability was considered a clog*P* ≥ 1.8.

2.3. Ethical approval

Ethical approval to perform the observational study was granted by the Swedish Ethical Review Authority (ref no. 2019–01358, 27 March 2019). Prior to the study, nurses were informed about the study aim and were given the opportunity not to participate. Data derived from the Concise Database were de-identified to prevent identification of individual pediatric patients or prescribing physicians.

3. Results and discussion

3.1. Drug manipulation

This observational study looked at manipulations of oral medications to pediatric oncology patients at a Swedish hospital. Nineteen pediatric patients, aged 1 month – 11 years were included (Table 1) and a total of 200 observations of nurses dispensing oral medications to pediatric oncology patients were made. Of the dispensed oral medications, 14% (28 of 200) were manipulated before administration. The frequency of manipulations was not the main aim of this study, hence, the limited period of study and small size of the pediatric patient population. The extent of manipulations in our study is in line with similar studies reporting a frequency of manipulations performed outside the information in the SmPC between 14% and 20.8% [3–5]. However, differences in study design and patient population limit direct comparison of the studies.

The percentage of manipulations per age group was highest in infants and toddlers (24%; 7 of 29) and lowest in school children, 6–11 years old (1%; 1 of 70; see Table 1). In a Norwegian study, the highest frequency of manipulations was for school children (29%) and lowest for adolescents (< 2%), indicating that manipulations are frequent in children up to 11 years old [3]. The manipulations in our study included seven APIs exclusively in solid dosage forms (Table 2). The seven APIs belonged to different therapeutic subgroups, including one antineoplastic and immune-modulating agent, tioguanine. The limited number of cytotoxic drugs is probably because chemotherapy was administered

Table 1
Pediatric patients in the observational study, presence of feeding tube, number of observations, and observed manipulations by age group.

Age group	Pediatric patients n (%)	Presence of enteral feeding tubes n (%)	Observations n (%)	Manipulations n (%)
Neonates (0–28 days)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infants and toddlers (1–23 months)	4 (21.1)	4 (33.3)	29 (14.5)	7 (25.0)
Children, pre-school (2–5 years)	10 (52.6)	7 (58.3)	101 (50.5)	20 (71.4)
Children, school (6–11 years)	5 (26.3)	1 (8.3)	70 (35.0)	1 (3.6)
Total	19	12	200	28

Table 2

Observed manipulations, medicinal product, type of drug manipulation, and administration via enteral feeding tube, by age group.

Age group	Medicinal product (API)	Dosage form	Type of manipulation ^a	Administration via enteral feeding tube
Neonates (0–28 days)	–	–	–	–
Infants and toddlers (1–23 months)	Allopurinol Teva (allopurinol)	tablet	split, crush, dispersion in liquid	Yes
	Emend (aprepitant)	capsule, hard	open, dispersion in liquid, proportion of drug dose	Yes
Children, pre-school (2–5 years)	Allopurinol Teva (allopurinol)	tablet	split, crush, dispersion in liquid	Yes
	Celebra (celecoxib)	capsule, hard	dispersion in liquid, proportion of drug dose	Yes
	Emend (aprepitant)	capsule, hard	open, dispersion in liquid	Yes
	Lanvis (tioguanine)	tablet	dispersion in liquid	Yes
	Spiroonolactone Accord (spironolactone)	film-coated tablet	proportion of drug dose	Yes
	Stesolid (diazepam)	tablet	crush, dispersion in liquid	Yes
Children, school (6–11 years)	Probecid (probenecid)	tablet	dispersion in liquid	Yes ^b

Abbreviations: API, active pharmaceutical ingredient.

^a Manipulation procedure outside the information in the summary of product characteristics (SmPC).

^b Caused blockage of enteral feeding tube.

intravenously at the hospital. Previous studies, including a broader pediatric inpatient population, have reported a frequency of manipulation of antineoplastic and immune-modulating agents between 0% and 1.7% [5,28]. Information is limited about the handling and administration of oral chemotherapy to children treated at home, but one study from the United Kingdom investigated problems and perceptions by parents with children receiving oral chemotherapy. Most of the respondent parents had experienced some kind of administration problem when handling oral chemotherapy [19]. Frequently, the child did not like to take their medication. Examples of manipulations reported by parents were crushing tablets or opening capsules and mixing them with food, such as ice cream and corn flakes.

In our study, tablets and capsules were frequently manipulated dosage forms. Manipulations involved crushing tablets or opening capsules, followed by dispersion of the fragments in a small volume of water (Table 2). In some cases, the dosage form was manipulated to obtain the required dose for a child by splitting a tablet or by extracting a proportion of the dispersed formulation. A tablet splitter and a device for crushing tablets (silent knight pill crusher; Medline, Mundelein, IL, USA) were used for manipulations at the studied ward. In addition to differences in practices for dose adjustment, other differences in manipulation procedures between nurses were observed. As example, nurses dispersed the fragmented solid dosage form sometimes in the disposable bag of the tablet crusher device and sometimes transferred the fragments to a medicine cup before dispersion. After dispersion the formulation was withdrawn into an oral syringe. In some cases, the tablet was dispersed directly in an oral syringe, for example Lanvis (tioguanine), to minimize

risk of exposure to the cytotoxic drug.

Dose variability is another previously identified risk with drug manipulations. In a study by Brustugun and colleagues, different manipulation procedures to obtain child-adjusted doses of warfarin tablets were investigated [29]. Splitting tablets were shown to result in a higher variability in dose compared to dispersing tablets and extracting a proportion of the dose. A similar study investigating different types of aspirin tablets, showed that splitting tablets and direct dispersion in an oral syringe gives higher dose recovery than addition of an extra step, such as dispersion in a medicine cup [30]. Overall, the manipulation procedures observed in our study were chosen based on personal experience rather than validated guidelines. This highlights the need for standardized protocols for manipulation procedures and information related to drug manipulation in the SmPC. Furthermore, manipulations are usually not documented in the medical record, making it difficult to evaluate their possible clinical outcomes.

An interesting finding in this study was that all observed manipulations were related to administration via enteral feeding tubes (Table 2). This finding is in line with previous studies showing a high proportion of manipulations related to enteral administration [4,5,31]. Information about enteral administration was not available in the SmPC and hence, this type of administration was considered an off-label use. Enteral administration is associated with several problems, such as blockage of the tube and drug loss [32,33]. To administer solid dosage forms through enteral feeding tubes a tablet needs to be crushed and dispersed in liquid. Our observational study identified several solid dosage forms that were difficult to properly disperse in a limited volume of water

(10–15 ml), one such example was probenecid (Table 2). In summary, drug manipulations were frequent in pediatric oncology practice at the studied Swedish hospital. In particular, administration via enteral feeding tubes was identified as a key problem and hence, an important aspect to consider in drug development of dosage forms intended for this patient group.

3.2. Age-appropriateness of oral medications

3.2.1. Identification of active pharmaceutical ingredients for development of personalized dosage forms

The age-appropriateness of oral medications for pediatric oncology patients was investigated to identify APIs requiring child-friendly, personalized dosage forms. Data were extracted regarding medicinal products supplied to the pediatric oncology ward (inpatient population) and prescribed by pediatricians at the same ward (outpatient population). A flowchart of the screening process, including the stepwise exclusion criteria, is shown in Fig. 1. In total, 676 oral medicinal products used in inpatient (n = 55) and outpatient populations (n = 621) were analyzed. The first step excluded products with incomplete ATC-codes, unlicensed medicines, extemporaneous medicines, and duplicates. The remaining medicinal products (n = 596) corresponded to 159 APIs.

In the next step, 72 APIs were excluded based on the availability of licensed oral liquid dosage forms in Sweden (Table S2). Liquid formulations generally show good acceptability in young children and offer higher dose flexibility than solid dosage forms [34]. These APIs were,

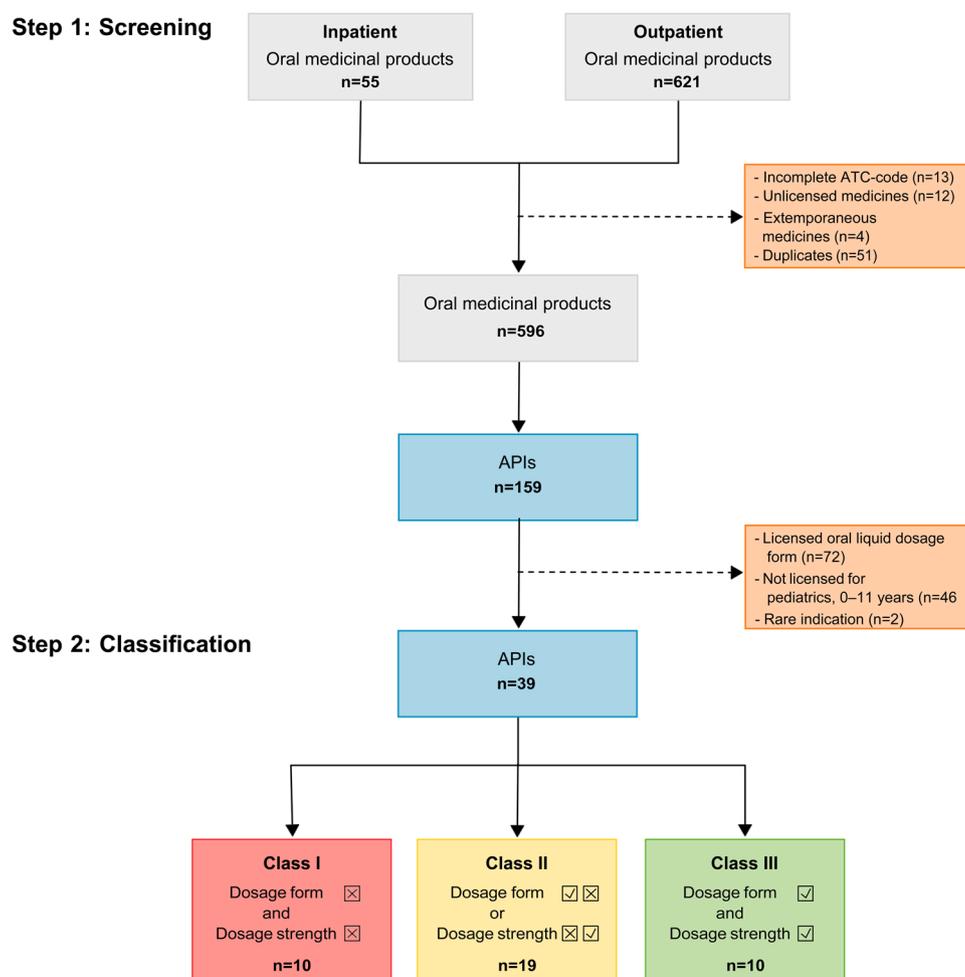


Fig. 1. Screening and classification of active pharmaceutical ingredients (APIs). Screening was performed to identify APIs in need of child-friendly, personalized oral dosage forms.

therefore, not considered high-priority candidates for development of personalized dosage forms. However, even if liquid formulations are considered as the formulation of choice for children, problematic aspects still include stability, use of potentially harmful excipients, and barriers to administration such as taste and volume [8,35,36].

In the third step, 46 APIs were excluded as they were not licensed for use in children, aged 0–11 years, i.e., off-label in this age group (Table S2). Off-label usage is frequent in both inpatient and outpatient pediatric populations in the Nordic countries [37,38]. Off-label usage is associated with several problems, not at least of which is the lack of data supporting safety and efficacy. As our study focused on age-appropriateness related to dosage form, we therefore excluded APIs used off-label. Finally, two APIs were excluded based on their rare hematological indication in pediatrics (Table S2).

After stepwise exclusion, 39 APIs were identified for further analysis of the age-appropriateness of licensed oral dosage forms in Sweden (Fig. 1). The APIs were categorized into three classes based on the acceptability of the dosage form and availability of suitable dosage strengths for pediatrics, aged 0–11 years. APIs in class I-III are listed by ATC-code in Table 3. Overall, 10 APIs were categorized as class I, indicating a lack of both child-friendly dosage form and appropriate dosage strength. Nineteen APIs were classified as class II based on a lack of either child-friendly dosage form or appropriate dosage strength. Ten APIs were categorized as class III, i.e., age-appropriate oral formulation licensed in Sweden. Most APIs were class I or II (29 of 39), indicating that development of child-friendly, personalized oral dosage forms, is highly demanded.

Although the identified APIs (class I-II) belonged to several therapeutic areas, most of them were antineoplastic and immune-modulating agents. Of these, cyclophosphamide, temozolomide, tioguanine, methotrexate, and imatinib have been previously highlighted by the European Medicines Agency (EMA) as APIs with a therapeutic requirement for age-appropriate oral formulations [39]. Our study demonstrates that even if a medicinal product is licensed for the pediatric population, it

may not be age-appropriate regarding dosage form and strength. In a study by van Riet-Nales and colleagues, approximately half of the medications in the Netherlands were authorized for children [35], but like in our study they were not, per definition, available in age-appropriate formulations. The gap between authorization status and age-appropriateness may be explained by the date of marketing authorization. It is only since 2007 that implementation of the European Pediatric Regulation has driven the development and availability of age-appropriate pediatric oral formulations [2,35].

The availability of age-appropriate formulations by age-group (0–11 years) is shown in Fig. 2. The number of APIs licensed for pediatrics increases with patient age. However, the proportion available in an age-appropriate formulation was not higher among schoolchildren (26%; 10

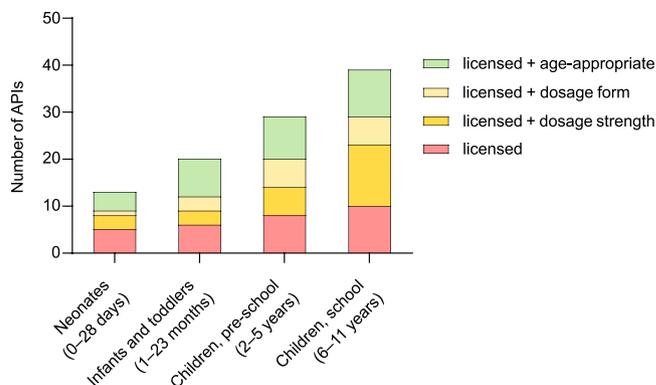


Fig. 2. Number of active pharmaceutical ingredients (APIs), licensed for children (0–11 years old) and available in an age-appropriate oral formulation, by age group. APIs categorized according to: licensed, licensed and available in a child-friendly dosage form, licensed and available in an appropriate dosage strength, licensed and age-appropriate.

Table 3

Classification (I-III) of identified active pharmaceutical ingredients (APIs, n = 39) by ATC-code and age-appropriateness of available medicinal products. Class I, lack of child-friendly dosage form and appropriate dosage strength. Class II, lack of either child-friendly dosage form or appropriate dosage strength. Class III, age-appropriate oral formulation available.

ATC-code		API		
Anatomical group	Therapeutic subgroup	Class I	Class II	Class III
A: Alimentary tract and metabolism	02	metoclopramide	bisacodyl	omeprazole
	03			sterculia gum, lactitol
	06			multienzymes
	09			calcium carbonate, calcium lactate gluconate, zinc sulfate
C: Cardiovascular system	03	metoprolol	spironolactone	
	07		enalapril, losartan	
	09		desmopressin	
H: Systemic hormonal preparations	01	prednisolone	fludrocortisone, hydrocortisone	betamethasone, dexamethasone
	02		tetracycline, nitrofurantoin	
J: Anti-infective for systemic use	01	cyclophosphamide, temozolomide, tioguanine, azathioprine, methotrexate	imatinib, nilotinib	
	04			
M: Musculo-skeletal system	01	gabapentin	diclofenac, naproxen, allopurinol	
	04		clonazepam, diazepam	
N: Nervous system	03	phenylpropanolamine		montelukast
	05		meclizine	
	06		deferasirox	
R: Respiratory system	01	calcium folinate		
V: Various	03			
	03			
Total		10	19	10

of 39) than for neonates (31%; 4 of 13). To develop age-appropriate oral formulations for children, particularly the younger ones, is not a question of one-size-fits-all effort. Typically, several dosage forms and strengths are needed.

In our study, age-appropriateness was determined on the basis of the acceptability of the dosage form and the availability of suitable dosage strengths for children. We based the criterion for swallowability on the high degree of manipulation of solid dosage forms previously reported for children up to 11 years old [5,31]. However, the size of a tablet or capsule affects patient acceptance, with small tablets (2–4 mm) acceptable even in the youngest children [40,41].

The dose in children is often given per bodyweight or body surface area, which demands high dose flexibility. This type of dosing recommendation for fixed dose dosage forms was considered inappropriate for pediatrics, if the SmPC did not provide specific dosing schemes for transforming calculated doses to available dosage strengths. In summary, our analysis of oral medications in pediatric oncology patients revealed a lack of age-appropriate oral formulations for most of the assessed APIs, and within several therapeutic groups. These results further confirm the need for development of personalized dosage forms,

especially within oncology.

3.2.2. Pediatric biopharmaceutics classification system

The biopharmaceutics classification system (BCS) has been established to allow early predictions of drug absorption based on in vitro solubility and intestinal permeability; is extensively used in pharmaceutical development [42]. To address the physiological and developmental differences between children and adults, work has been initiated to develop a pediatric BCS [43]. The APIs in class I and II ($n = 29$) with an identified need for age-appropriate pediatric oral formulations were examined for their preformulation related characteristics and then classified according to the pBCS (Table 4). Overall, five APIs were identified as class I (high solubility and permeability), nine APIs as class II (low solubility, high permeability), eight APIs as class III (high solubility, low permeability), and seven APIs as class IV (low solubility and permeability).

The solubility classification was based on dose number, which relates solubility to the highest dose and initial gastric volume. In this study, dose number was calculated for a 6-year-old child, i.e., in the middle of the studied age range. Solubility is a key factor for drug absorption, and

Table 4

Patient and preformulation related characteristics of class I and II active pharmaceutical ingredients (APIs) ($n = 29$).

API	Patient		Preformulation			
	Therapeutic needs	Dose ^a	Water solubility (mg/ml) ^b	Dose number (D_{op}) ^c	$\log P^d$	pBCS class ^e
allopurinol	child-friendly dosage form	100 mg, three times per day	0.569	2.22	-0.41	IV
azathioprine	child-friendly dosage form, dose flexibility	1–4 mg/kg/day	0.124	8.55	0.84	IV
bisacodyl	child-friendly dosage form	5 mg/day	0.00127	49.7	4.71	II
calcium folinate	child-friendly dosage form, dose flexibility	250 µg/kg/day	0.297	0.22	-0.46	III
clonazepam	child-friendly dosage form	3–6 mg/day	0.1	0.76	2.76	I
cyclophosphamide	child-friendly dosage form, dose flexibility	3 mg/kg/day	40	0.02	0.76	III
deferasirox	dose flexibility	7–21 mg/kg/day	0.4	14.0	4.01	II
desmopressin	child-friendly dosage form	0.1–0.2 mg, three times per day	0.11	0.02	-1.0	III
diazepam	child-friendly dosage form	5 mg/day	0.05	1.26	2.63	II
diclofenac	child-friendly dosage form	25 mg, two times per day	0.00237	133	4.98	II
enalapril	child-friendly dosage form	2.5 mg/day	16.4	0.002	0.19	III
fludrocortisone	child-friendly dosage form	0.05–0.1 mg/day	0.11	0.01	1.35	III
gabapentin	child-friendly dosage form, dose flexibility	10–35 mg/kg/day	4.49	2.07	-1.9	IV
hydrocortisone	dose flexibility	8–10 mg/m ² /day, in 3 doses	0.32	0.11	1.79	I
imatinib	dose flexibility	340 mg/m ² /day	0.0146	241	3.47	II
losartan	child-friendly dosage form	25 mg/day	0.00822	38.4	4.5	II
meclizine	child-friendly dosage form	12.5 mg/day	1.0	0.16	5.59	I
methotrexate	child-friendly dosage form, dose flexibility	10–15 mg/m ² , once per week	2.6	0.06	-0.05	III
metoclopramide	child-friendly dosage form, dose flexibility	0.1–0.15 mg/kg/day	0.2	0.2	2.18	I
metoprolol	child-friendly dosage form, dose flexibility	0.5 mg/kg/day	0.402	0.33	1.8	I
naproxen	child-friendly dosage form	125 mg, two times per day	0.0159	99.3	3.29	II
nilotinib	dose flexibility	230 mg/m ² , two times per day	0.00201	1 185	4.51	II
nitrofurantoin	dose flexibility	3 mg/kg/day, in 2 doses	0.0795	5.0	0.03	IV
phenylpropanolamine	child-friendly dosage form	25 mg, two times per day	149	0.002	0.57	III
prednisolone	child-friendly dosage form, dose flexibility	1–2 mg/kg/day	0.215	2.47	1.66	IV
spironolactone	dose flexibility	1–3 mg/kg/day in 1–2 doses	0.022	36.2	3.1	II
temozolomide	child-friendly dosage form, dose flexibility	150–200 mg/m ² /day	5.09	0.41	-0.28	III
tetracycline	child-friendly dosage form	250 mg, four times per day	0.231	13.7	-0.56	IV
tioguanine	child-friendly dosage form, dose flexibility	60–200 mg/m ² /day	0.834	2.48	-0.36	IV

^a The dose for children (≥ 6 years old) was obtained from the summary of product characteristics (SmPC) and the British National Formulary for Children [22,24].

^b Water solubility was extracted from the literature and available databases [25–27].

^c Pediatric dose number for a child, age 6 years old (weight: 21 kg, body surface area: 0.82 m², initial gastric volume: 79.2 ml) [21–23].

^d Calculated $\log P$ values were obtained from the DrugBank database [25].

^e Pediatric biopharmaceutical classification system (pBCS): High solubility $D_{op} \leq 1$, High permeability $\log P \geq 1.8$ (reference compound metoprolol) [21]. Class I: High solubility and permeability, class II: Low solubility, high permeability, class III: High solubility, low permeability, class IV: low solubility and permeability.

highly influenced by the volume and composition of the gastrointestinal fluid. In our study, the BSC adult volume of 250 ml was extrapolated to pediatric gastric volume based on body weight as described previously [20,21]. However, a fixed reference value of 25 ml for all pediatric age groups or volume related to body surface area has also been suggested, highlighting the lack of agreement in this matter [43,44]. The composition of the gastrointestinal fluid is another key factor affecting drug solubility, for which there are differences in gastric pH and bile salt composition between neonates and adults [45]. A study by Maharaj and colleagues investigated solubility of seven BCS class II compounds using biorelevant age-specific pediatric media [46]. For six of the seven studied compounds, solubility fell outside (80–125%) the adult value for at least one pediatric medium, demonstrating the impact of age-related changes in gastrointestinal fluid composition on drug solubility.

For children two years and older, intestinal permeability is generally assumed to be equivalent to that in adults [47]. In our study, permeability class was based on clogP. Therefore changes in BCS and pBCS class derive from the estimated solubility class. Of the 29 investigated APIs, 16 were identified as class II or IV, indicating low solubility (Table 4). A previous study found 24.5% of their study compounds had an unfavorable change in BCS class, i.e. from high to low solubility [20]. This indicates the considerable influence of age-related volume on BSC solubility class. Of the APIs explored in our study, allopurinol, diazepam, enalapril, fludrocortisone, hydrocortisone, methotrexate, prednisolone, and tioguanine have been previously reported to change solubility class in the pBCS [20,21]. In summary, most APIs in our study were low-solubility drugs according to the pBCS. This classification can further be used to identify low-solubility APIs sensitive to formulation changes such as manipulation processes.

3.3. General discussion

The observational study was carried out for 20 days, at a single pediatric oncology ward and hence, on a limited pediatric patient population. Children 1 month – 11 years old were included, but no neonates. Nevertheless, the high number of manipulations in this study and in similar ones, on broader pediatric patient populations, indicates that drug manipulations would occur in other pediatric subpopulations [4,5,31]. Our observations were made in connection with nurses dispensing oral medications. Barriers to drug administration and clinical outcomes, e.g., adverse events linked to manipulations, were not investigated. Administration of oral solid dosage forms via enteral feeding tubes was identified as the main problem associated with drug manipulation to severely sick children. Hence, barriers to oral administration, e.g. swallowability, taste, texture, and volume or quantity, were not possible to evaluate. Neither did we address manipulations that occurred in an outpatient setting. However, previous studies have shown that drug manipulations in outpatient care are frequent, demonstrating the need of age-appropriate formulations to ensure safe and adequate drug treatments in children treated at home [4,8].

To more thoroughly explore the therapeutic needs of severely sick children, we analyzed the age-appropriateness of commercially available oral medications. In this part of the study, oral medications in outpatient care were assessed. The evaluation of age-appropriateness, with regard to acceptability of solid dosage forms used, was based exclusively on age, i.e., that children, aged 0–11 years are not able to swallow whole tablets or capsules, which is not an absolute criterion. In addition, information about dispersibility of the dosage form in liquid or compatibility with food is not always available in the SmPC. The dose in children was mainly based on the information in the SmPC when available; however, additional data sources for dosing are often used in the clinic.

A stepwise exclusion approach was used to screen the APIs. The exclusion steps were not absolute and some excluded APIs may still be of interest for development of personalized dosage forms. One such example is aprepitant, licensed in Sweden as hard capsules and as a

powder for oral suspension. Since the liquid formulation is licensed, it was excluded for further analysis. However, at the time of the study, the liquid oral dosage form was not available in Sweden, which is why it was identified in our observational study as a frequently manipulated drug. Thus, the license status of a medicinal product is not directly linked to its availability on the ward. Among the APIs excluded for lack of pediatric license (0–11 years), several were cancer drugs and opiates (Table S2). These therapeutic groups have previously been highlighted for their need of child-friendly, personalized dosage forms [48].

The drug manipulations and lack of age-appropriate oral medications demonstrates the need for developing oral formulations suitable for children with regard to dosage form and dose. 3D printing has previously been used for production of child-friendly, personalized dosage forms, such as orodispersible and chewable ones [15,17,49]. Visser and colleagues studied the use of oral medications to children in the Netherlands to identify APIs suitable for inkjet printing of orodispersible films [50]. Of the examined APIs (n = 34) only one, montelukast, was sufficiently water-soluble for inkjet printing of films in therapeutically effective doses. A number of poorly water-soluble drugs were identified in our study (Table 4). During the observational study, low-solubility drugs like aprepitant and probenecid were observed difficult to disperse in a small volume of water. A combined approach is therefore needed to successfully address the demand of personalized medicines to severely sick children. This approach would combine formulation strategies to circumvent low drug solubility together with the use of 3D printing technologies to personalize dosage forms [51–54].

4. Conclusion

The present study highlights problems and needs related to oral solid dosage forms used in the treatment of children with cancer. Drug manipulation of solid dosage forms to enable administration via enteral feeding tubes was identified as the main problem. Different procedures for manipulation were identified, demonstrating the lack of validated guidelines. The analysis of age-appropriateness of oral medication showed that 74% (29 of 39) of the APIs licensed for children (0–11 years) needed for personalized dosage forms, because of a lack of child-friendly dosage form, suitable dosage strength, or both. In our evaluations using a pBCS model, most of these APIs had low solubility with risk of low oral bioavailability. These APIs may also be sensitive to formulation changes, such as dispersion of crushed tablets. In summary, the study identified a lack of age-appropriate formulations in pediatric oncology. To allow successful, safe and convenient treatment of these patients, a patient-centric approach, combined with expertise within formulation design and application of novel manufacturing technologies, is needed.

CRedit authorship contribution statement

Jenny Johannesson: Conceptualization, Methodology, Investigation, Writing – original draft, Visualization. **Paula Hansson:** Methodology, Investigation, Writing – review & editing. **Christel Bergström:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Mattias Paulsson:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Conflict of interest statement

The authors declare no conflicts of interest.

Data Availability

Data will be made available on request.

Acknowledgements

The authors would like to warmly thank the nurses at the pediatric hematology and oncology ward, Uppsala University Children's Hospital for their participation and the opportunity to carry out the observational study on drug manipulations. The authors would also like to thank Prof. Gustaf Ljungman and Dr. Gunnar Liminga at Uppsala University Children's Hospital for their valuable clinical input in this study. Funding by the Erling-Persson Family Foundation (2017) is gratefully acknowledged.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.biopha.2021.112576](https://doi.org/10.1016/j.biopha.2021.112576).

References

- [1] K.A. Mfofo, M. Omidian, C.D. Bertol, Y. Omid, H. Omidian, Neonatal and pediatric oral drug delivery: hopes and hurdles, *Int. J. Pharm.* 597 (2021), 120296, <https://doi.org/10.1016/j.ijpharm.2021.120296>.
- [2] R.G. Strickley, Pediatric oral formulations: an updated review of commercially available pediatric oral formulations since 2007, *J. Pharm. Sci.* 108 (2019) 1335–1365, <https://doi.org/10.1016/j.xphs.2018.11.013>.
- [3] K. Bjerknes, S. Bøyum, S. Kristensen, J. Brustugun, S. Wang, Manipulating tablets and capsules given to hospitalised children in Norway is common practice, *Acta Paediatr.* 106 (2017) 503–508, <https://doi.org/10.1111/apa.13700>.
- [4] A.C. Vossen, L. van der, Al-Hassany, S. Buljac, J.-D. Brugma, A.G. Vulto, L. M. Hanff, Manipulation of oral medication for children by parents and nurses occurs frequently and is often not supported by instructions, *Acta Paediatr.* 108 (2019) 1475–1481, <https://doi.org/10.1111/apa.14718>.
- [5] J. Zahn, A. Hoerning, R. Trollmann, W. Rascher, A. Neubert, Manipulation of medicinal products for oral administration to paediatric patients at a German University hospital: an observational study, *Pharmaceutics* 12 (2020) 583, <https://doi.org/10.3390/pharmaceutics12060583>.
- [6] EMA, 2014. Guideline on pharmaceutical development of medicines for paediatric use. EMA/CHMP/QWP/805880/2012. (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf) (Accessed 8 June 2021).
- [7] P. Mistry, H. Batchelor, SPaEDD-UK project (Smart Paediatric Drug Development - UK), Evidence of acceptability of oral paediatric medicines: a review, *J. Pharm. Pharmacol.* 69 (2017) 361–376, <https://doi.org/10.1111/jphp.12610>.
- [8] R. Venables, H. Batchelor, J. Hodson, H. Stirling, J. Marriott, Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population, *Int. J. Pharm.* 480 (2015) 55–62, <https://doi.org/10.1016/j.ijpharm.2015.01.023>.
- [9] R.H. Richey, C. Hughes, J.V. Craig, U.U. Shah, J.L. Ford, C.E. Barker, M. Peak, A. J. Nunn, M.A. Turner, A systematic review of the use of dosage form manipulation to obtain required doses to inform use of manipulation in paediatric practice, *Int. J. Pharm.* 518 (2017) 155–166, <https://doi.org/10.1016/j.ijpharm.2016.12.032>.
- [10] D. Abu-Geras, D. Hadziomerovic, A. Leau, R.N. Khan, S. Gudka, C. Locher, M. Razaghikashani, L.Y. Lim, Accuracy of tablet splitting and liquid measurements: an examination of who, what and how, *J. Pharm. Pharm.* 69 (2017) 603–612, <https://doi.org/10.1111/jphp.12671>.
- [11] C. Watson, E.A. Webb, S. Kerr, J.H. Davies, H. Stirling, H. Batchelor, How close is the dose? manipulation of 10 mg hydrocortisone tablets to provide appropriate doses to children, *Int. J. Pharm.* 545 (2018) 57–63, <https://doi.org/10.1016/j.ijpharm.2018.04.054>.
- [12] H. Batchelor, A.M. Kaukonen, S. Klein, B. Davit, R. Ju, R. Ternik, T. Heimbach, W. Lin, J. Wang, D. Storey, Food effects in paediatric medicines development for products co-administered with food, *Int. J. Pharm.* 536 (2018) 530–535, <https://doi.org/10.1016/j.ijpharm.2017.05.011>.
- [13] J. Martir, T. Flanagan, J. Mann, N. Fotaki, Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review, *J. Pharm. Pharm.* 69 (2017) 384–397, <https://doi.org/10.1111/jphp.12635>.
- [14] I. Seoane-Viãno, S.J. Trenfield, A.W. Basit, A. Goyanes, Translating 3D printed pharmaceuticals: from hype to real-world clinical applications, *Adv. Drug Deliv. Rev.* 174 (2021) 553–575, <https://doi.org/10.1016/j.addr.2021.05.003>.
- [15] A. Goyanes, C.M. Madia, A. Umerji, G. Duran Piñeiro, J.M. Giraldez Montero, M. J. Lamas Diaz, M. Gonzalez Barcia, F. Taherali, P. Sánchez-Pintos, M.-L. Couce, S. Gaisford, A.W. Basit, Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: first single-centre, prospective, crossover study in patients, *Int. J. Pharm.* 567 (2019), 118497, <https://doi.org/10.1016/j.ijpharm.2019.118497>.
- [16] D.-T. Eduardo, S.-E. Ana, B. José, F. A micro-extrusion 3D printing platform for fabrication of orodispersible printlets for pediatric use, *Int. J. Pharm.* 605 (2021), 120854, <https://doi.org/10.1016/j.ijpharm.2021.120854>.
- [17] H. Öblom, E. Sjöholm, M. Rautamo, N. Sandler, Towards printed pediatric medicines in hospital pharmacies: comparison of 2D and 3D-printed orodispersible warfarin films with conventional oral powders in unit dose sachets, *Pharmaceutics* 11 (2019) 334, <https://doi.org/10.3390/pharmaceutics11070334>.
- [18] O. Jennotte, N. Koch, A. Lechanteur, B. Evrard, Three-dimensional printing technology as a promising tool in bioavailability enhancement of poorly water-soluble molecules: a review, *Int. J. Pharm.* 580 (2020), 119200, <https://doi.org/10.1016/j.ijpharm.2020.119200>.
- [19] N. Christiansen, K.M.G. Taylor, C. Duggan, Oral chemotherapy in paediatric oncology in the UK: problems, perceptions and information needs of parents, *Pharm. World Sci.* 30 (2008) 550–555, <https://doi.org/10.1007/s11096-008-9208-5>.
- [20] J.-M. del Moral-Sanchez, I. Gonzalez-Alvarez, M. Gonzalez-Alvarez, A. Navarro, M. Bermejo, Classification of WHO essential oral medicines for children applying a provisional pediatric biopharmaceutics classification system, *Pharmaceutics* 11 (2019) 567, <https://doi.org/10.3390/pharmaceutics11110567>.
- [21] R. Shawahna, Pediatric biopharmaceutical classification system: using age-appropriate initial gastric volume, *AAPS J.* 18 (2016) 728–736, <https://doi.org/10.1208/s12248-016-9885-2>.
- [22] BNF for Children, British Medical Association, Royal Pharmaceutical Society, Pharmaceutical Press, London, 2020.
- [23] K.A. Wikland, Z.C. Luo, A. Niklasson, J. Karlberg, Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference, *Acta Paediatr.* 91 (2002) 739–754, <https://doi.org/10.1111/j.1651-2227.2002.tb03322.x>.
- [24] FASS Allmänhet - Startside. (<https://www.fass.se/LIF/startpage>) (Accessed 19 April 2021).
- [25] PubBank. (<https://go.drugbank.com/>) (Accessed 24 April 2021).
- [26] PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) (Accessed 19 April 2021).
- [27] S.H. Yalkowsky, Y. He, P. Jain, Handbook of Aqueous Solubility Data, second ed., CRC Press, Boca Raton, 2010.
- [28] R.H. Richey, U.U. Shah, M. Peak, J.V. Craig, J.L. Ford, C.E. Barker, A.J. Nunn, M. A. Turner, Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence, *BMC Pediatr.* 13 (2013) 1–8, <https://doi.org/10.1186/1471-2431-13-81>.
- [29] J. Brustugun, E. Birkedal Aas, I. Tho, K. Bjerknes, Comparing two methods of tablet manipulation to adjust the warfarin dose in paediatric care, *Pharmaceutics* 12 (2020) 375, <https://doi.org/10.3390/pharmaceutics12040375>.
- [30] J. Brustugun, N. Notaker, L.H. Paetz, I. Tho, K. Bjerknes, Adjusting the dose in paediatric care by dispersing fragments of four different aspirin tablets, *Acta Paediatr.* 109 (2020) 2394–2401, <https://doi.org/10.1111/apa.15216>.
- [31] K. Bjerknes, S. Bøyum, S. Kristensen, J. Brustugun, S. Wang, Manipulating tablets and capsules given to hospitalised children in Norway is common practice, *Acta Paediatr.* 106 (2017) 503–508, <https://doi.org/10.1111/apa.13700>.
- [32] M. Rautamo, K. Kvarnström, M. Siven, M. Airaksinen, P. Lahdenne, N. Sandler, A focus group study about oral drug administration practices at hospital wards—aspects to consider in drug development of age-appropriate formulations for children, *Pharmaceutics* 12 (2020) 109, <https://doi.org/10.3390/pharmaceutics12020109>.
- [33] R. White, V. Bradnam, Handbook of Drug Administration via Enteral Feeding Tubes, third ed., Pharmaceutical Press, London, 2015.
- [34] D.A. van Riet-Nales, J.A. Ferreira, A.F.A.M. Schobben, B.J. de Neef, T.C.G. Egberts, C.M.A. Rademaker, Methods of administering oral formulations and child acceptability, *Int. J. Pharm.* 491 (2015) 261–267, <https://doi.org/10.1016/j.ijpharm.2015.06.047>.
- [35] D.A. van Riet-Nales, K.E. de Jager, A.F.A.M. Schobben, T.C.G. Egberts, C.M. A. Rademaker, The availability and age-appropriateness of medicines authorized for children in the Netherlands, *Br. J. Clin. Pharm.* 72 (2011) 465–473, <https://doi.org/10.1111/j.1365-2125.2011.03982.x>.
- [36] J. Walsh, A. Cram, K. Woertz, J. Breikreutz, G. Winzenburg, R. Turner, C. Tuleu, Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients, *Adv. Drug Deliv. Rev.* 73 (2014) 14–33, <https://doi.org/10.1016/j.addr.2014.02.012>.
- [37] J. Olsson, E. Kimland, S. Pettersson, V. Odling, Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care – a nationwide study, *Acta Paediatr.* 100 (2011) 1272–1275, <https://doi.org/10.1111/j.1651-2227.2011.02287.x>.
- [38] A. Teigen, S. Wang, B.T. Truong, K. Bjerknes, Off-label and unlicensed medicines to hospitalised children in Norway, *J. Pharm. Pharm.* 69 (2017) 432–438, <https://doi.org/10.1111/jphp.12581>.
- [39] EMA, 2014. Draft inventory of paediatric therapeutic needs: Paediatric oncology. EMA/PDCO/381728/2014. (https://www.ema.europa.eu/en/documents/other/draft-inventory-paediatric-therapeutic-needs-paediatric-oncology_en.pdf) (accessed 11 June 2021).
- [40] V. Klingmann, A. Seitz, T. Meissner, J. Breikreutz, A. Moeltner, H.M. Bosse, Acceptability of uncoated mini-tablets in neonates—a randomized controlled trial, *J. Pediatr.* 167 (893–896) (2015), e2, <https://doi.org/10.1016/j.jpeds.2015.07.010>.
- [41] D.A. van Riet-Nales, B.J. Neef, A.F.A.M. de, Schobben, J.A. Ferreira, T.C.G. Egberts, C.M.A. Rademaker, Acceptability of different oral formulations in infants and preschool children, *Arch. Dis. Child.* 98 (2013) 725–731, <https://doi.org/10.1136/archdischild-2012-303303>.
- [42] G.L. Amidon, H. Lennernäs, V.P. Shah, J.R. Crison, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, *Pharm. Res* 12 (1995) 413–420, <https://doi.org/10.1023/A:1016212804288>.
- [43] S.M. Abdel-Rahman, G.L. Amidon, A. Kaul, V. Lukacova, A.A. Vinks, G.T. Knipp, Summary of the national institute of child health and human development—best pharmaceuticals for children act pediatric formulation initiatives

- workshop–pediatric biopharmaceutics classification system working group, Clin. Ther., S. 34 (2012) S11–S24, <https://doi.org/10.1016/j.clinthera.2012.09.014>.
- [44] S.V. Gandhi, W. Rodriguez, M. Khan, J.E. Polli, Considerations for a pediatric biopharmaceutics classification system (BCS): application to five drugs, AAPS PharmSciTech 15 (2014) 601–611, <https://doi.org/10.1208/s12249-014-0084-0>.
- [45] J. Van Den Abeele, M. Rayyan, I. Hoffman, E. Van de Vijver, W. Zhu, P. Augustijns, Gastric fluid composition in a paediatric population: age-dependent changes relevant for gastrointestinal drug disposition, Eur. J. Pharm. Sci. 123 (2018) 301–311, <https://doi.org/10.1016/j.ejps.2018.07.022>.
- [46] A.R. Maharaj, A.N. Edginton, N. Fotaki, Assessment of age-related changes in pediatric gastrointestinal solubility, Pharm. Res. 33 (2016) 52–71, <https://doi.org/10.1007/s11095-015-1762-7>.
- [47] H.K. Batchelor, R. Kendall, S. Dessel-Brethes, R. Alex, T.B. Ernest, Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients, Eur. J. Pharm. Biopharm. 85 (2013) 833–842, <https://doi.org/10.1016/j.ejpb.2013.04.015>.
- [48] M. Rautamo, K. Kvarnström, M. Sivé, M. Airaksinen, P. Lahdenne, N. Sandler, Benefits and prerequisites associated with the adoption of oral 3d-printed medicines for pediatric patients: a focus group study among healthcare professionals, Pharmaceutics 12 (2020) 229, <https://doi.org/10.3390/pharmaceutics12030229>.
- [49] I. El Aita, J. Rahman, J. Breitzkreutz, J. Quodbach, 3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing, Eur. J. Pharm. Biopharm. 157 (2020) 59–65, <https://doi.org/10.1016/j.ejpb.2020.09.012>.
- [50] J.C. Visser, L. Wibier, O. Kiefer, M. Orlu, J. Breitzkreutz, H.J. Woerdenbag, K. Taxis, A pediatrics utilization study in the netherlands to identify active pharmaceutical ingredients suitable for inkjet printing on orodispersible films, Pharmaceutics 12 (2020) 164, <https://doi.org/10.3390/pharmaceutics12020164>.
- [51] E.A. Clark, M.R. Alexander, D.J. Irvine, C.J. Roberts, M.J. Wallace, J. Yoo, R. D. Wildman, Making tablets for delivery of poorly soluble drugs using photoinitiated 3D inkjet printing, Int. J. Pharm. 578 (2020), 118805, <https://doi.org/10.1016/j.ijpharm.2019.118805>.
- [52] J. Conceição, X. Farto-Vaamonde, A. Goyanes, O. Adeoye, A. Concheiro, H. Cabral-Marques, J.M. Sousa Lobo, C. Alvarez-Lorenzo, Hydroxypropyl- β -cyclodextrin-based fast dissolving carbamazepine printlets prepared by semisolid extrusion 3D printing, Carbohydr. Polym. 221 (2019) 55–62, <https://doi.org/10.1016/j.carbpol.2019.05.084>.
- [53] J. Johannesson, J. Khan, M. Hubert, A. Teleki, C.A.S. Bergström, 3D-printing of solid lipid tablets from emulsion gels, Int. J. Pharm. 597 (2021), 120304, <https://doi.org/10.1016/j.ijpharm.2021.120304>.
- [54] K. Vithani, A. Goyanes, V. Jannin, A.W. Basit, S. Gaisford, B.J. Boyd, A proof of concept for 3D printing of solid lipid-based formulations of poorly water-soluble drugs to control formulation dispersion kinetics, Pharm. Res. 36 (2019) 102, <https://doi.org/10.1007/s11095-019-2639-y>.