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Research Article

Pediatric Biopharmaceutical Classification System: Using Age-Appropriate Initial Gastric Volume

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Abstract. Development of optimized pediatric formulations for oral administration can be challenging, time consuming, and financially intensive process. Since its inception, the biopharmaceutical classification system (BCS) has facilitated the development of oral drug formulations destined for adults. At least theoretically, the BCS principles are applied also to pediatrics. A comprehensive age-appropriate BCS has not been fully developed. The objective of this work was to provisionally classify oral drugs listed on the latest World Health Organization's Essential Medicines List for Children into an age-appropriate BCS. A total of 38 orally administered drugs were included in this classification. Dose numbers were calculated using age-appropriate initial gastric volume for neonates, 6-month-old infants, and children aging 1 year through adulthood. Using age-appropriate initial gastric volume and British National Formulary age-specific dosing recommendations in the calculation of dose numbers, the solubility classes shifted from low to high in pediatric subpopulations of 12 years and older for amoxicillin, 5 years, 12 years and older for cephalexin, 9 years and older for chloramphenicol, 3–4 years, 9–11 and 15 years and older for diazepam, 18 years and older (adult) for doxycycline and erythromycin, 8 years and older for phenobarbital, 10 years and older for prednisolone, and 15 years and older for trimethoprim. Pediatric biopharmaceutics are not fully understood where several knowledge gaps have been recently emphasized. The current biowaiver criteria are not suitable for safe application in all pediatric populations.

KEY WORDS: BCS; initial gastric volume; pediatric; permeability; solubility.

INTRODUCTION

Recently, there has been a growing emphasis on enhancing pediatric accessibility to quality essential drugs which subsequently has raised the number of drug formulations tested in and labeled for use in pediatric populations (1). Accordingly, health regulatory authorities in the USA and Europe have incentivized the pharmaceutical industry to devote more resources and research toward developing optimized pediatric formulations. Such incentives include 6 months of added exclusivity and additional support from public funding agencies for pediatric drug discovery and clinical testing (2–4). Unfortunately and despite these incentives, children have remained largely "therapeutic orphans" (2, 5).

Development of optimized pediatric formulations for oral administration can be challenging, time consuming, and financially intensive process (1). Furthermore, generation of detailed biopharmaceutic data in pediatric population is often hampered by ethical, technical, and logistic constraints that limit recruitment and inclusion of children in clinical trials (2, 6, 7). Due to these hurdles, and despite incentives, pediatric biopharmaceutics has remained a recognized under-researched area with several accepted knowledge gaps where additional research is highly required (2, 8, 9). In practice, pediatric formulations are often derived from adult formulations after necessary extrapolation and modeling (10–12). Following the guidance documents published by the Food and Drug Administration (FDA) and the International Conference on Harmonization (ICH), extrapolation from adult data into pediatric population can be justified when the course of disease and response to therapeutic intervention are sufficiently similar in adults and children (10–12). However, while extrapolation can be done with respect to efficacy, there remain challenges with regard to predicting safety or the need for dose adjustments (1).

Using principles founded in the biopharmaceutical classification system (BCS), initial predictions of the intestinal absorption characteristics of an active pharmaceutical ingredient (API) are frequently based upon its solubility in the gastrointestinal (GI) milieu and its permeability across the enterocyte membrane (13–16). The BCS categorizes drug

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molecules into four classes based on their aqueous solubility and intestinal permeability. Today, the BCS is widely used in support of waivers (biowaivers) of *in vivo* bioequivalence (BE) studies for immediate release (IR) solid oral formulations containing BCS class I (high solubility and high permeability) and, more recently, class III (high solubility low permeability) drugs (17, 18). Health regulatory authorities allow the use of *in vitro* dissolution testing as a surrogate for conducting *in vivo* BE trials for highly soluble compounds. Accordingly, biowaivers reduce regulatory burden, processing, and approval time, thus providing economic benefits while maintaining high drug quality standards for therapeutic equivalence (19).

Although the BCS is implicitly based upon the GI physiology of adults, it is uncertain how such classifications may translate to the same drugs when administered in pediatric patients. Theoretically, the basic concepts should be applicable irrespective of patient age (2). However, fundamental differences exist between adult and pediatric populations in terms of developmental changes from birth to adolescence which contribute to age-associated variation in drug absorption, distribution, metabolism, and elimination of drugs (9). The initial gastric volume (V_0) is one of these clear differences. According to regulatory guidelines, a drug is classified as highly soluble when the maximal dose strength is soluble in 250 mL of aqueous media whose pH values range from 1.0 to 6.8 (17) or 1.0–7.5 (20). The volume of 250 mL was derived from a typical BE study protocol in which oral drugs are administered to adult volunteers with a glass of water (about 8 oz). However, BE standards in pediatric populations have not been established and recommendations are still needed (2).

Solubility of drugs in adult GI milieu is expected to be different from those in pediatrics due to differences in GI fluid composition and volume occurring over time with age and development. Hence, children are more of a heterogeneous population and solubilities of drugs are expected to differ with age and development status of the child. Therefore, age-appropriate pediatric BCS (PBCS) criteria are needed to properly classify traditional and novel therapeutic agents in pediatric populations (2). However, classification of traditional drugs into BCS classes using age-appropriate gastric volumes across pediatric age populations was not previously performed.

Since the introduction of BCS, there has been growing interest in provisional BCS classifications of drug lists and databases like the top 200 drugs in different countries and the World Health Organization's (WHO) Essential Medicines List (EML) for adults (21–25). These investigations used molecular properties like the *n*-octanol/water partition coefficient (Log*P*), the pH-dependent partition coefficient (Log*D*) at certain pH points, and the polar surface area (PSA) as indicators for intestinal permeability to judge if molecules can be assigned a high- or a low-permeability BCS class. The PBCS Working Group of the National Institute of Child Health and Human Development provisionally classified 56 commonly used pediatric drugs based on their aqueous solubility and predicted *n*-octanol/water partition coefficient (cLog*P*) values as indicators of their intestinal permeability (9). Gandhi *et al* extended the work of the PBCS Working Group and attempted to classify five drugs commonly used in pediatric populations into PBCS applying pediatric biopharmaceutical considerations (8). Recently, Charoo *et al* assessed the risks of extending the BCS-based biowaiver decision on IR oral dosage forms of fluconazole in adults to pediatric population and concluded that it can be safely granted a biowaiver provided using safe excipients (26). Previous studies neither included the drugs listed on the WHO's EML for children nor classified drug molecules into age-appropriate PBCS for all children groups capable of swallowing solid oral medications (8, 9, 26).

The present study emphasizes the care that must be taken with assigning BCS solubility classes in pediatric populations. Considerable heterogeneity is obvious among pediatric populations as the V_0 varies with age and body size. Because the solubility class is assigned based on the solubility of the drug in a volume equivalent to the V_0, misjudgments regarding the solubility class can arise when considering pediatric populations as a homogenous group and not using age-appropriate V_0 values.

This study aims to investigate the effects of variable age based V_0 on the BCS solubility class of oral drugs particularly available on the WHO's EML for children. Oral drugs available on the WHO's EML for children are also provisionally classified into PBCS on the basis of their dose number (D_0) values in pediatric populations. The results of this study extend those started by the PBCS Working Group of the National Institute of Child Health and Human Development.

MATERIALS AND METHODS

Drugs List

The latest EML for Children (fourth list, 2013) was used in this study. The list is available at the WHO's website (http://www.who.int). Only drugs available in solid oral dosage forms were selected for this provisional classification.

Permeability

Although a compound's permeability classification can be influenced by paracellular transport or by transporter activity, for the purpose of this evaluation, drug permeabiity solely from the perspective of transmembrane transport was considered. Accordingly, permeability was determined on the basis of the *n*-octanol/water partition coefficient as calculated (cLog*P*) using ALOGPS (The Virtual Computational Chemistry Laboratory, VCCLAB, Germany) software package. The experimentally determined *n*-octanol/water partition coefficient (Log*P*) values were obtained from (27). Correlation of human jejunal permeability with partition coefficients and the use of benchmark reference drug molecule were carried out as previously described (9, 21, 23). Detailed correlations are shown in the supplementary materials.

Initial Gastric Volume for Adults

According to the FDA, EMA, and WHO guidelines, drugs are administered to adult healthy volunteers with a glass of water that has a volume of 250 mL (17, 18, 28).

Therefore, a drug would be considered a high-solubility class if the highest dose strength was soluble in 250 mL or less of water over the pH range specified by the regulatory guidelines at 37 ± 1°C. The FDA, EMA, and WHO used to have different pH ranges, but in the recent guidance draft, the FDA revised the pH range and proposed a range of 1–6.8 which is similar to the range used in the EMA and the WHO guidelines (17, 18, 28). A V_0 of 250 mL was used in calculating the D_0 of drugs to account for their aqueous solubility in adults.

Initial Gastric Volume for Pediatric Subpopulations

In the US, children as young as 4 years old could be taught to ingest oral tablets (29). However and although this might vary depending on the child, generally, the age at which children can safely take tablet and capsule dosage forms is around 6 years (30, 31). Therefore, children of 6 years old and above might be prescribed oral solid dosage forms and younger children might be prescribed oral suspensions. In this study, age-based V_0 calculations of D_0 values were made for neonates, 6-month-old infants, and infants and children 1 year old and above.

Initial Gastric Volume in Pediatrics

Two fundamental parameters are key factors in determining the solubility of a compound in a medium; these two parameters are composition and volume. In general, it is widely accepted that the gastric pH in children above 2 years of age is similar to that in adults (7, 32). The age-related gastric volumes in children were not intensively investigated. The fasted gastric volume in children was reported to range from 0.40 to 0.56 mL/kg (33–35). This volume is equivalent to 28.0–37.1 mL/kg in a 70-kg fasted male (9). The fasted gastric volume was typically reported as 40 mL in a 70-kg fasted male (36).

To extrapolate to children, median weights of neonates, infants 6 months old, infants and children aging from 1 to 17 years were obtained from the Centers for Disease Control and Prevention growth charts (37). Extrapolating the 250-mL V_0 value used in adults to pediatric subpopulation based on the 0.56 mL/kg value was done according to Eq. 1 (9, 33–36). The median weight in different age groups, gastric volumes, and normalized V_0 are shown in Table I

$$Normalized\ V_0 = \frac{(\text{median child weight in kg}) \times 0.56\ \text{mL}}{37.1\ \text{mL/kg}} \times 250\ \text{mL} \quad (1)$$

A drug would be considered a high-solubility class if the highest dose strength was soluble in a volume of water equivalent to or less than the normalized V_0 in children over the specified pH range at 37 ± 1°C.

Maximum Pediatric Dose Strength

The maximum dose strengths (in milligrams) for all drugs available in solid oral dosage forms were obtained from the WHO's EML for Children. The maximal per oral dose for each pediatric subpopulation was taken from the British National Formulary for Children (38). The British National Formulary for Children expressed dosing recommendations for many drugs in terms of mg/kg and for some drugs in μg/kg. However, in many cases, a maximal dose in milligrams or micrograms was specified for different pediatric subpopulations. When specified, the maximal dose for each subpopulation was used; otherwise, dosing recommendations in terms of mg/kg or μg/kg and median weights of neonates, infants 6 months old, infants and children aging from 1 to 17 years obtained from the Centers for Disease Control and Prevention growth charts (37) were used to derive age-specific doses. The age-specific maximal dose strength (M_0) was used to calculate D_0 as shown in Eq. 2.

Solubility

Experimental aqueous solubility data in (mg/mL) were obtained from Yalkowsky & He (39) and DrugBank databases (27); data were originally from (40) in the former database. The most conservative data measures were used. Data were preferred when the pH and temperature at which the aqueous solubility was measured were mentioned.

Dose Number

D_0 was calculated according to the following equation (22, 24, 41):

$$D_0 = \frac{M_0}{C_s V_0} \quad (2)$$

where D_0 is the dose number, M_0 is the maximum dose strength, C_s is the saturated solubility, and V_0 is the initial gastric volume. If a medication was available in different strengths, then the highest strength was used to calculate the D_0.

RESULTS

Permeability Class

When the experimentally determined Log*P* values were plotted against software calculated (cLog*P*) values, the plot showed a high linear correlation ($R^2 = 0.92$) for 35 drugs. The linear correlation plot and the correlation of human jejunal permeability values with partition coefficients are shown in the supplementary materials. Permeability classification based on cLog*P* of metoprolol as a benchmark for high/low permeability showed that 20 (52.6%) of the 38 drugs were assigned to high permeability class, whereas the rest of 18 (47.4%) of the 38 drugs were assigned to low permeability class. Classification of the 38 drugs into high and low permeability classes is shown in the supplementary materials.

Dose Number and Solubility Class

Drugs with $D_0 \leq 1$ were classified as high-solubility-class drugs and, conversely, drugs with $D_0 > 1$ were classified as low-solubility-class drugs.

Table I. Median weight, gastric volume, and normalized initial gastric volume in neonates, 6-month-old infants, infants, and children aging from 1 to 17 years

Age (years)	Median weight (kg)	Gastric volume (mL)	Normalized V_0 (mL)
Newborn (neonate)	3.95	2.21	14.9
0.50 (6-month-old infant)	7.90	4.42	29.8
1	10.3	5.77	38.9
2	12.7	7.11	47.9
3	14.3	8.01	54.0
4	16.0	8.96	60.4
5	18.5	10.4	69.8
6	21.0	11.8	79.2
7	23.0	12.9	86.8
8	26.0	14.6	98.1
9	29.0	16.2	109
10	32.0	17.9	121
11	36.0	20.2	136
12	40.5	22.7	153
13	45.5	25.5	172
14	51.0	28.6	192
15	56.0	31.4	211
16	61.0	34.2	230
17	65.0	36.4	245

Drugs that did not change solubility class in pediatrics

Calculated D_0 values showed that 29 (76.3%) of the 38 drugs would be assigned to either high- or low- solubility class and did not change the assigned solubility class when calculated using age-appropriate D_0. These drugs are presented in Table II.

Drugs that change solubility class in pediatrics

The following compounds are shown to be affected by age-associated changes in M_0 and gastric volume: amoxicillin, cephalexin, chloramphenicol, diazepam, doxycycline, erythromycin, phenobarbital, prednisolone, and trimethoprim. For each of these compounds, their age-specific solubility classes, based on their calculated D_0 values, are provided in Table II. In some cases, as age (and therefore V_0) increased, the drug went from being classified as low solubility (youngest group) to high solubility as the child matures (Table II).

Provisional BCS and PBCS Classifications

The orally administered drugs listed on the WHO's EML for children were provisionally classified into BCS and PBCS classes on the basis of their D_0 values which were calculated based on various V_0 and their cLog*P* values. Table III displays provisional classifications of the 38 drugs based on V_0 in pediatrics and adults.

DISCUSSION

In this study, solubility data and a commonly used simple molecular descriptor (cLog*P*) were used to provisionally classify drugs available in IR oral dosage forms on the WHO's EML for children. The majority of the drugs classified in this provisional classification were anti-infective and anthelmintic agents (Table II). This might reflect their urgent need in maintaining healthcare delivery and might reflect treatment priorities in primary healthcare settings.

Permeability Class

Data pertaining to pediatric biopharmaceutics are still scarce. Despite the lack of complete understanding, it is generally accepted that intestinal permeability of drugs in children ages 2 years or older are equivalent to that observed in adults (7, 9). Therefore, in this work, adult standards of intestinal permeability were used to designate the drugs as being high or low permeability. However, it is important to note that greater paracellular permeability is expected in younger pediatric subpopulations. Although this could be a limitation of this study, similar standards were used in the provisional classification of the PBCS Working Group of the National Institute of Child Health and Human Development (9). Software-predicted cLog*P* values were used to assign a high or low permeability class to each drug with metoprolol serving as the benchmark for differentiating between high/low intestinal permeability. This reference drug was consistently used in previous studies (9, 21, 23). Partition coefficients are easily accessible molecular descriptors that can be calculated using validated software packages (9, 21, 23–25). The use of this benchmark was validated by correlating human P_{eff} data of a set of 28 drugs including 14 drugs which were recommended by the FDA as reference compounds for permeability (20, 21, 23). In this study, correlation between the software calculated cLog*P* to the experimentally determined Log*P* values are provided in the supplementary materials. The high level of correlation observed between observed and predicted values suggest that software-predicted cLog*P* values can be applied with some confidence in the prediction of intestinal permeability.

Table II. Dose number (D_0) in neonates, infants, and children of 1 year old through adulthood

Drug	Therapeutic class	Dose number (D_0)																			
			Age (years)																		
		Newborn (neonate)	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Adult (18 years and above)
Albendazole	Anthelminthic	Not given to this subpopulation			417	741	663	573	505	461	408	366	331	294	262	233	208	189	174	163	160
Amitriptyline	Anti-depressant	Not given to this subpopulation			21.5	19.1	17.1	14.8	13.0	11.9	10.5	9.4	8.5	56.9	50.5	45.0	40.1	36.6	33.6	31.5	30.9
Amoxicillin	Anti-bacterial	2.44	1.22	1.88	1.52	1.35	1.21	1.04	1.84	1.68	1.49	1.33	1.21	1.07	**0.95**	**0.85**	**0.76**	**0.69**	**0.63**	**0.59**	**0.58**
Azithromycin	Anti-bacterial	Not given to this subpopulation	2.65	5.15	4.17	3.71	3.31	2.86	2.52	2.30	3.06	2.74	2.48	2.94	2.62	2.91	2.60	2.37	2.17	2.04	2.00
Carbamazepine	Anti-epileptic	299	299	291	236	209	187	162	143	130	115	103	93.6	83.2	73.9	132	117	107	98.2	92.1	45.2
Cefalexin	Anti-bacterial	4.69	2.34	1.80	1.46	1.29	1.16	**1.00**	1.76	1.61	1.42	1.28	1.16	1.03	**0.91**	**0.81**	**0.73**	**0.66**	**0.61**	**0.57**	**0.56**
Chloramphenicol	Anti-bacterial	1.33	1.33	1.33	2.09	1.85	1.66	1.43	1.26	1.15	1.02	**0.91**	**0.83**	**0.74**	**0.65**	**0.58**	**0.52**	**0.47**	**0.43**	**0.41**	**0.40**
Ciprofloxacin	Anti-bacterial	0.13	0.18	0.21	0.17	0.15	0.14	0.12	0.11	0.10	0.08	0.08	0.07	0.06	0.05	0.05	0.04	0.04	0.04	0.03	0.03
Clindamycin	Anti-bacterial	52.0	86.6	86.6	86.6	90.8	81.2	70.2	61.9	56.5	50.0	44.8	40.6	36.1	32.1	28.5	25.5	23.2	21.3	20.0	19.6
Cloxacillin	Anti-bacterial	603	302	231	375	333	298	258	227	207	183	164	298	265	235	210	187	170	156	147	144
Cyclizine	Antiemetic	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.25	0.23	0.21	0.18	0.33	0.29	0.26	0.24	0.22	0.20	0.20
Dexamethasone	Anti-inflammatory	0.99	0.75	0.58	0.47	0.42	0.37	0.32	0.28	0.26	0.23	0.21	0.19	0.17	0.15	0.13	0.12	0.11	0.10	0.09	0.18
Diazepam	Anticonvulsant	1.33	1.33	1.29	1.04	**0.93**	**0.83**	1.43	1.26	1.15	1.02	**0.91**	**0.83**	**0.74**	1.31	1.16	1.04	**0.95**	**0.87**	**0.82**	**0.80**
Diethylcarbamazine	Anti-filarial	0.11	0.05	0.04	0.03	0.03	0.03	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Doxycycline	Anti-bacterial	Not given to this subpopulation													2.08	1.85	1.65	1.50	1.38	1.29	**0.63**
Erythromycin	Anti-bacterial	4.19	2.10	1.61	2.61	2.32	2.07	1.79	1.58	1.44	2.55	2.28	2.07	1.84	1.64	1.46	1.30	1.18	1.09	1.02	**1.00**
Ethosuximide	Anti-epileptic	0.14	0.14	0.16	0.13	0.12	0.11	0.09	0.08	0.07	0.07	0.06	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.03	0.03
Fluoxetine HCl	Anti-depressant	Not given to this subpopulation										0.004	0.003	0.003	0.003	0.002	0.002	0.002	0.002	0.002	0.002
Ibuprofen	Analgesic	63.1	379	123	99.4	88.2	78.9	273	240	219	194	174	158	140	187	166	148	135	124	116	114
Ivermectin	Anti-filarial	5.30	5.30	5.30	5.30	5.56	4.97	4.30	3.79	3.46	3.06	2.74	2.48	2.21	1.96	1.75	1.56	1.42	1.30	1.22	1.20
Levamisole HCl	Anthelminthic	0.048	0.024	0.018	0.015	0.013	0.012	0.010	0.009	0.008	0.007	0.007	0.006	0.005	0.005	0.004	0.004	0.003	0.003	0.003	0.003
Loratadine	Anti-allergic	Not given to this subpopulation			9485	8423	7528	6511	5736	5237	4633	8307	7528	6692	5948	5295	4724	4302	3949	3706	3636
Mebendazole	Anthelminthic	Not given to this subpopulation	47.0	36.1	146	130	116	100	88.5	80.8	71.5	64.1	58.1	51.6	45.9	40.8	36.4	33.2	30.5	28.6	28.1
Metronidazole	Anti-bacterial	0.21	0.21	0.21	0.88	0.78	0.70	0.60	0.53	0.49	0.43	0.38	0.35	0.31	0.28	0.25	0.22	0.20	0.18	0.17	0.21
Midazolam	Sedative	5.52	5.52	5.36	4.35	3.86	3.45	2.98	2.63	2.40	2.12	1.90	2.76	2.45	2.18	1.94	1.73	1.58	1.45	1.36	2.50
Morphine	Analgesic	0.18	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.56	0.49	0.44	0.39	0.35	0.32	0.29	0.27	0.27
Niclosamide	Anthelminthic	4141	4141	4141	4141	4141	4141	4141	3943	3601	3185	2856	2588	2300	2045	1820	1624	1479	1358	1274	1250
Nitrofurantoin	Anti-bacterial	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	7.33	6.54	5.95	5.46	5.13	5.03
Oxamniquine	Anti-schistosomal	4.85	4.85	4.85	4.85	4.85	4.85	4.37	3.85	3.51	3.11	2.79	2.52	2.24	1.99	1.78	1.58	1.44	1.32	1.24	1.22
Paracetamol	Analgesic	0.58	0.29	0.22	0.27	0.24	0.21	0.25	0.22	0.21	0.18	0.33	0.30	0.26	0.23	0.21	0.19	0.17	0.16	0.15	0.14
Phenobarbital	Anti-epileptic	1.19	1.19	1.19	1.88	1.67	1.49	1.29	1.14	1.04	**0.92**	**0.82**	**0.75**	**0.66**	**0.59**	**0.52**	**0.47**	**0.43**	**0.39**	**0.37**	**0.36**

Table II. (continued)

Drug	Therapeutic class	Dose number (D_0)																			
		Age (years)																			
		Newborn (neonate)	0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Adult (18 years and above)
Phenoxymethylpenicillin	Anti-bacterial	0.42	0.21	0.32	0.26	0.23	0.21	0.18	0.16	0.29	0.25	0.23	0.21	0.18	0.16	0.15	0.13	0.12	0.11	0.10	0.10
Phenytoin	Anti-epileptic	210	105	80.4	65.2	57.9	51.8	44.8	39.4	36.0	31.9	28.6	25.9	23.0	20.4	18.2	16.2	14.8	13.6	12.7	12.5
Praziquantel	Anthelminthic	26.5	26.5	26.5	27.8	24.8	21.5	18.9	17.3	15.3	13.7	12.4	11.0	9.8	8.7	7.8	7.1	6.5	6.1	6.0
Prednisolone	Anti-inflammatory	7.52	3.76	2.88	2.34	2.08	1.86	1.61	1.41	1.29	1.14	1.02	**0.93**	**0.83**	**0.73**	**0.65**	**0.58**	**0.53**	**0.49**	**0.46**	**0.45**
Sulfamethoxazole	Anti-bacterial	10.4	6.60	10.12	8.21	7.29	6.52	5.64	4.96	7.56	6.68	5.99	5.43	4.83	4.29	3.82	3.41	3.10	2.85	2.67	5.25
Trimethoprim	Anti-bacterial	13.4	6.71	5.15	4.17	3.71	3.31	2.86	2.52	2.30	2.04	1.83	1.66	1.47	1.31	1.16	1.04	**0.95**	**0.87**	**0.82**	1.60
Valproic acid	Anti-epileptic	25.8	12.9	9.90	8.03	7.13	6.37	5.51	4.85	4.43	3.92	3.51	3.19	2.83	2.52	2.24	2.00	1.82	1.67	1.57	1.54

Italicized drugs are the drugs that did not change their solubility class; drugs in bold are the drugs that change their solubility class. Dose number (D_0) values were calculated based on age-specific initial gastric volume (V_0) values. Drugs having a $D_0 \leq 1$ are considered high-solubility drugs and drugs having $D_0 > 1$ are considered low-solubility drugs

Solubility Class

Drug solubility within the GI milieu is a key factor determining the bioavailability of a drug molecule. In the present study, drugs were considered highly soluble when the calculated D_0 was ≤1 using various V_0 adopted for different pediatric subpopulations as well as for adults. Although the findings of this study showed that this shift did not affect the solubility classification for the majority of drugs, interestingly, the solubility class showed a shift for amoxicillin, cefalexin, chloramphenicol, doxycycline, diazepam, erythromycin, phenobarbital, prednisolone, and trimethoprim (Table II). The effect of the V_0 used in the calculation of D_0 on the assignment of the solubility class was highlighted previously (9, 42). It was suggested that in case the administered dose is also reduced in certain populations, the overall effect of the reduced V_0 on the D_0 and subsequently the BCS solubility class might remain minimal (9, 42). However, in this study, the maximal dose strength given to each pediatric subpopulation along with the corresponding V_0 were used for calculation of age-appropriate D_0. It is important to note that in this classification, experimental solubility data recorded at ambient temperature were used and, as the solubility of a compound is expected to increase at 37°C, the solubility classification used in this study could be conservative.

In the GI milieu, solubility of a drug molecule depends on the volume as well as the composition of the GI luminal fluid. The composition of the GI luminal fluid shows marked compositional changes with development (43). In a recent study, Maharaj *et al* assessed the solubility of seven BCS II drugs using biorelevant media reflective of age-specific pediatric populations (43). Using the ratio of solubility in pediatrics to solubility in adults as an indicator, six of the seven drugs studies fell outside the BE criterion of 0.8–1.25 in at least one of the developed age-specific pediatric media. Extrapolating what was seen in Maharaj *et al*'s study, it is highly probable that the solubility of some drugs would show discrepancies in some pediatric subpopulations. Taking a conservative approach in using the BCS-based biowaiver principles, more risk is considered when the solubility class of a drug shifts from high to low than *vice versa*. To account for possible discrepancies in solubility of drugs in pediatric subpopulations, percentages by which experimental solubility used in this study might change to shift the solubility class from high to low were calculated. For some drugs, percentages were as low as 1% in some pediatric subpopulations, especially neonates, and as high as 99.8% in older pediatric subpopulations. These percentages are shown in the supplementary materials.

Provisional Classifications

Using adult standards for solubility, 18 (47%) drugs used in this study belonged to the high-solubility class (BCS I and III) in at least one population (Table III). As expected, more drugs belonged to the low-solubility BCS classes (BCS II and IV) when the V_0 decreased. This could have implications on the performance of the formulations in the GI environment.

Globally, age-appropriate formulations are urgently needed as, according to some estimates, off-label use of drugs in children ranges from 60 to 90% (1, 44, 45). These estimates

Table III. Pediatric and adult biopharmaceutical classification system of the 38 oral drugs used in the study

	Biopharmaceutical classification system																		
	Newborn (neonate)	Age (years)																	Adult
		0.5	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Albendazole	Not given to this subpopulation			II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Amitriptyline	Not given to this subpopulation			II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Amoxicillin	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	**III**	**III**	**III**	**III**	**III**	**III**	**III**
Azithromycin	Not given to this subpopulation	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Carbamazepine	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Cefalexin	IV	IV	IV	IV	IV	IV	**III**	IV	IV	IV	IV	IV	IV	**III**	**III**	**III**	**III**	**III**	**III**	**III**
Chloramphenicol	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**
Ciprofloxacin	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Clindamycin	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
Cloxacillin	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Cyclizine	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Dexamethasone	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Diazepam	II	II	II	II	**I**	**I**	II	II	II	II	**I**	**I**	**I**	II	II	II	**I**	**I**	**I**	**I**
Diethylcarbamazine	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Doxycycline	Not given to this subpopulation													IV	IV	IV	IV	IV	IV	**III**
Erythromycin	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	**I**
Ethosuximide	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Fluoxetine HCl	Not given to this subpopulation										I	I	I	I	I	I	I	I	I	I
Ibuprofen	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Ivermectin	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Levamisole HCl	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I
Loratadine	Not given to this subpopulation			II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Mebendazole	Not given to this subpopulation	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Metronidazole	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Midazolam	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Morphine	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Niclosamide	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Nitrofurantoin	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
Oxamniquine	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
Paracetamol	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Phenobarbital	IV	IV	IV	IV	IV	IV	IV	IV	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**
Phenoxymethylpenicillin	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
Phenytoin	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Praziquantel	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
Prednisolone	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**	**III**
Sulfamethoxazole	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV
Trimethoprim	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	IV	**III**	**III**	**III**	IV
Valproic acid	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II

Italicized drugs are the drugs that did not change their solubility class; drugs in bold are the drugs that change their solubility class

suggest that in practice, drug therapy in children is still largely empirical (1). Probably, there is no single formulation that is ideal for pediatric population of all ages. Considering all age groups from birth through adulthood, the magnitude of doses may vary 100-folds, and theoretically, a range of different strengths of a dosage form should be available to permit simple, accurate and safe administration of drugs in pediatric populations (46). Development of age-appropriate formulations is highly desirable to include all age groups (47). It was suggested that a PBCS should at least consider six age groups which are (a) neonates (≤40 weeks post-conception), (b) infants (0–6 months), (c) infants (6–12 months), (d) toddlers (1–3 years), (e) children (4–6 years), (f) children (7–12 years), and (g) adolescents (13–18 years) (2, 48). However, more categories were said to be needed which could be physiologically meaningful for a more comprehensive evaluation (48). For more comprehensive classification, drugs in this study were classified in neonates, 6-month-old infants, and age–year-wise from the age of 1 year to adulthood (Tables II and III).

Focus on orally administered solid oral dosage forms is important as recent findings suggested that there was no significant difference in refusal rates when children were to receive liquid or solid formulations (49). Nahirya-Ntege *et al* showed that children as well as their providers preferred oral tablets over syrups when administering anti-retroviral drugs (50). Furthermore, palatability of oral liquid dosage forms could

be an issue affecting refusal rate and pediatric patient compliance (1). In practice, oral drugs are often diluted in beverages to enhance palatability and patient acceptance in pediatrics. This practice could compromise their efficacy. Moreover, long-term storage, storage, and transport under extreme temperatures can be issues compromising the efficacy of liquid oral dosage forms, especially in developing countries (51). Therefore, flexible solid oral dosage forms provide advantages over liquid oral dosage forms in these circumstances. Development of drugs for pediatric populations is obligatory in the USA and Europe. The US Pediatric Research Equity Act and the European Pediatric Investigation Plan are required by the FDA and EMA, respectively (52–54). BE of the pediatric formulation to that in adults is recommended but not required.

Findings of this study could be important in managing formulation bridging. In practice, it is common to undertake a relative bioavailability study, or it might be surrogated by an *in vitro* dissolution testing in healthy adult volunteers to ensure that the pharmacokinetic profile is equivalent for two formulations (7). Subsequent extrapolation to pediatrics is followed by a dose determination/confirmation study (7). In BCS-based biowaiver, bridging can be performed without conducting *in vivo* pharmacokinetic studies, especially for IR formulations containing BCS I and more recently BCS III drugs (7, 17, 18). The US Pediatric Formulation Initiative (PFI) workshop has emphasized the use of BCS in children (55). The PFI has identified several knowledge gaps that need research including (a) drug metabolism and transport in the GI tract, (b) age-relevant changes in the physiology of the GI tract, (c) changes in permeability and fraction absorbed in children, and (d) developing and validating pediatric physiologic and population-based pharmacokinetic databases (2). In addition to the difference in the V_0 between adults and pediatrics, key factors like gastric and intestinal pH, gastric emptying, intestinal residence time, volume of gastric fluids, immaturity of secretion and activity of bile and pancreatic fluid, expression of influx and efflux transporters, metabolizing enzymes, and membrane permeability differ in pediatric compared to adult populations (56–58). Therefore, the pharmacokinetics and drug disposition in pediatrics might be fundamentally different from that in adults. Despite these differences, in general, studies are often conducted in adults assuming absence of drug absorption differences between children aging 2 years and above and adult population because accurate measures of intestinal absorption in children compared to adults are lacking (1, 7, 9).

Development of a definitive PBCS requires deeper understanding of the GI physiology and intestinal permeability in pediatric populations. Age-based changes in the GI fluid composition, volume, and pH are essentially critical for the prediction of age-based solubilities.

CONCLUSION

Taken together, the results of this study show that considerations for adult BCS do not apply directly to pediatric subpopulations and the regulations that allow waiver of BE studies based on *in vitro* dissolution studies instead of *in vivo* BE studies might not be appropriately applied on pediatric formulations. Standardization in conducting BE studies for pediatric formulations in pediatrics and adults might assist in understanding how drugs perform across age groups (9). Deeper understanding of the GI environment in children is needed before developing predictive dissolution testing in pediatric populations. More investigations are needed to establish age-specific PBCS that would serve as a framework in the development of formulations for the target age population.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interests None

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