# ORIGINAL ARTICLE

# Biopharmaceutical optimization in neglected diseases for paediatric patients by applying the provisional paediatric biopharmaceutical classification system

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## AIMS

Unavailability and lack of appropriate, effective and safe formulations are common problems in paediatric therapeutics. Key factors such as swallowing abilities, organoleptic preferences and dosage requirements determine the need for optimization of formulations. The provisional Biopharmaceutics Classification System (BCS) can be used in paediatric formulation design as a risk analysis and optimization tool. The objective of this study was to classify six neglected tropical disease drugs following a provisional paediatric BCS (pBCS) classification adapted to three paediatric subpopulations (neonates, infants and children).

## METHODS

Albendazole, benznidazole, ivermectin, nifurtimox, praziquantel and proguanil were selected from the 5th edition of the Model List of Essential Medicines for Children from the World Health Organization. Paediatric drug solubility classification was based on dose number calculation. Provisional permeability classification was based on log $P$ comparison versus metoprolol log $P$ value, assuming passive diffusion absorption mechanisms and no changes in passive membrane permeability between paediatric patients and adults. pBCS classes were estimated for each drug, according to different doses and volumes adapted for each age stage and were compared to the adult classification.

## RESULTS

All six drugs were classified into provisional pBCS in the three paediatric subpopulations. Three drugs maintained the same classification as for adults, ivermectin and benznidazole changed solubility class from low to high in neonates and proguanil changed from low to high solubility in all age stages.

## CONCLUSION

Provisional pBCS classification of these six drugs shows potential changes in the limiting factors in oral absorption in paediatrics, depending on age stage, compared to the adult population. This valuable information will aid the optimization of paediatric dosing and formulations and can identify bioinequivalence risks when comparing different formulations and paediatric populations.

**WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT**
- BCS has demonstrated to be an essential development tool for adult medication but its application to paediatric development requires further research in child physiology.
- In the case of neglected diseases, the lack of commercial preparation worsens this situation and the pharmacist practitioner needs tools for dosing decisions and compounding.

**WHAT THIS STUDY ADDS**
- This study adds the provisional classification of six drugs based in a proposed paediatric BCS.
- The study highlights the knowledge gaps for paediatric BCS classification and shows how this classification can be used as a tool for pharmaceutical compounding decisions.
- The design of harmonized national paediatric formularies should be done with pBCS in mind as a bioequivalence risk tool.

## Introduction

The World Health Organization (WHO) defines as "Neglected tropical diseases" (NTDs) a group of infectious diseases in tropical and subtropical regions spanning across 149 countries. The populations affected are mainly those living in poverty without adequate sanitation and in contact with infectious vectors and animals (domestic and livestock) [1]. Initially, the NTD term grouped a set of infectious diseases caused by helminths, bacteria and protozoa. Today, the list includes more than 40 diseases including viral, fungal and ectoparasitic infection pathways [2].

In usual clinical practice and especially in the field of NTDs, paediatric formulations are frequently derived from adult formulations. It is broadly accepted that there is a need for development of paediatric formulations [3–5]. Paediatric patients represent a varying and dynamic population with significant differences in ADME processes (absorption, distribution, metabolism and excretion), as compared to adult patients [5]. Furthermore, children need age-appropriate formulations that: (a) fit with changes derived from ageing and gaining weight, (b) have acceptable safety, and (c) are adapted for their growth and ability to take medication [3].

The paediatric population requires galenic preparations different from adults, mostly tablets and capsules, which do not allow adjusting the appropriate dose. Therefore, proper treatment is hampered due to their special conditions of swallowing abilities, organoleptic properties and dosage requirements [6].

The Biopharmaceutics Classification System (BCS) is a theoretical scheme that categorizes drugs into four classes (Figure 1) considering their solubility and permeability [7]. Both are fundamental parameters controlling the absorption of any drug administered orally [7]. The BCS has gained broad acceptance in the pharmaceutical industry and has significantly impacted adult drug development [5, 8]. This system, applied to paediatrics, can be an excellent guide for the industry and for pharmacists dedicated to compounding and could benefit the paediatric population as it allows the identification of drugs that need a specific formulation for children at different stages of growth. In addition, the BCS improves regulatory approval processes in terms of efficiency by contributing to universal public health [9]. Nevertheless, BCS classification is based on adult data, and cannot be extrapolated to children because of developmental issues. These differences suggest the need for a specific paediatric Biopharmaceutics Classification System (pBCS).

Some international programmes and initiatives have been launched to improve the current situation in drug paediatric development, for instance the European Paediatric Formulation Initiative [10] and the US Paediatric Formulation Initiative [11]. These initiatives have recognized the potential utility of a pBCS for pediatric development [5]. Professional associations have organized workgroups to address the paediatric drug development needs as the "Paediatric Formulations Task Force" from the American Association of Pharmaceutical Scientists [6]. In the area of NTD-related treatments there have been examples of successful projects like the Paediatric Praziquantel Consortium [12], in which, by applying BCS concepts, a paediatric formulation tablet of praziquantel was developed to combat schistosomiasis in children. The "Drugs for Neglected Diseases initiative (DNDi)" is another example of a collaborative non-profit drug research organization that is developing new treatments for neglected diseases [13]. All these activities are aligned with the new regulatory frameworks in the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) that include the requirement for a Pediatric Investigation Plan (PIP) or Pediatric Study Plan (PSP) in drugs that could be used in children [14, 15].

Since 2007, the World Health Organization (WHO) has provided the WHO Model List of Essential Medicines for Children [16], a core list of minimum medicine needs for a basic healthcare system, listing the most efficacious, safe and cost-effective medicines for priority conditions in children up to 12 years old. From this list, six oral drugs that are used to treat NTDs were selected for the present work. In addition, the selected compounds are marketed as tablets, which are not suitable for paediatric administration.



| Class 1 High permeability High solubility | Class 2 High permeability Low solubility |
| --- | --- |
| Class 3 Low permeability High solubility | Class 4 Low permeability Low solubility |

**Figure 1**
Different BCS drug classes proposed by Amidon *et al.* [7]

The objective was to provisionally classify six NTDs drugs following a proposal of pBCS adapted to three paediatric subpopulations, namely neonates, infants and children. Albendazole, benznidazole, ivermectin, nifurtimox, praziquantel and proguanil (Figure 2) were selected as they meet the above requirements and because there are no clear recommendations about their dosage, safety, efficacy and formulation for the different paediatric stages. In addition, three of them (albendazole, benznidazole and nifurtimox) were listed on the report "Best Pharmaceuticals for Children Act (BPCA) Priority List of Needs in Pediatric Therapeutics, NIH" [17].

# Methods

## *Paediatric solubility classification*
Paediatric drug solubility classification was determined via paediatric dose number calculation. The following equation was used to obtain the dose number [18]:

$$Dop = \frac{M_{0p}/V_{0p}}{C_s}$$

where $M_{0p}$ is the paediatric highest dose strength (in milligrams), $V_{0p}$ is the water volume taken with a dose (in millilitres), and $C_s$ is the solubility in milligrams per millilitre.

A paediatric dose number requires a paediatric dose as well as a paediatric reference volume, so there would not be a single pBCS classification boundary as several subpopulations exist within the paediatric population.

A paediatric reference volume ($V_{0p}$) was calculated for each of the three subpopulations: neonates (0–1 month), infants (1–24 months) and children (2–12 years). For each subpopulation, the volume was calculated based on body surface area (BSA), relative to the adult volume of 250 ml [19] and adult BSA of 1.73 m². Subpopulation BSA was calculated [20] from:

$$BSA\ (m^2) = \frac{\sqrt{Height\ (cm) \times Weight\ (kg)}}{60}$$

where height and weight were taken to be the 50th percentile of boy values in the WHO growth charts for ages 0.5 months and 12.5 months [21] and Center for Disease Control and Prevention (CDC) charts for age 7 years [22].

$M_{0p}$ for each subpopulation was obtained from the WHO Model Prescribing Information: Drugs Used in Parasitic Diseases [23, 24] and, on the other hand, with common clinical equations including Fried's Rule, Clark's Rule and BSA Method.

$$Fried's\ Rule : \frac{Age\ (months)}{150} \cdot Adult\ dose$$

$$Clark's\ Rule : \frac{Weight\ (pounds)}{150\ pounds} \cdot Adult\ dose$$

$$BSA\ Method : \frac{BSA\ patient\ (m^2)}{1.73 m^2} \cdot Adult\ dose$$

Fried's Rule is a modification of Clark's Rule (used for children from 2 to 7 years old) that can be used for newborns and infants. This method is based on the age and maturational development. Given that age cannot be the only variable taken into account for dose estimation [25], these formulas are not commonly used but may be useful when referenced doses are not available.

For the dose calculation with BSA Method, the 50th percentile BSA of boy values in the WHO growth charts [21] (for ages 0.5 months and 12.5 months) and CDC charts [22] (for age 7 years) were used. For reference drug doses expressed in mg kg$^{-1}$, the 50th percentile weight as in the calculation of BSA was used to calculate the total dose.

Since three different methods were used to calculate the dose in the three paediatric populations, the obtained values were compared to the referenced dose when available. The
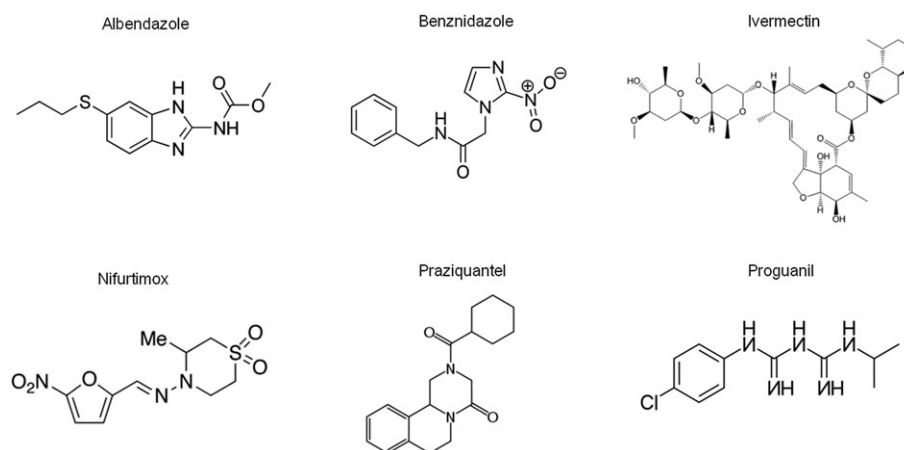


**Figure 2**
Chemical structures of the selected drugs

referenced dose is assumed to be the gold standard as it is based on clinical use and thus has adequate risk/benefit ratio.

Drug solubility data (mg ml$^{-1}$) were obtained from several bibliographic sources. Nevertheless, in order to obtain a solubility classification, the solubility values were obtained from "The International Pharmacopoeia" [26] and "Merck Index" [27]. The most conservative data of solubility were used. When specific solubility values were not available, a value was assigned according to Table 1. Solubility values in the range of physiological pHs were considered for classification in the case of ionizable compounds (weak acid or bases). The pH fluctuation that occurs in the gastrointestinal tract with paediatric development since birth [4, 28, 29] is, in our view, one of the principal factors that can cause variation in drug absorption and clinical efficacy. For instance, gastric pH in the newborn is neutral (pH 6–8) at birth. During the first 24–48 hours of life, it descends to adult values (pH 1–3) thanks to an overproduction of gastric acid and then ascends back to values close to neutrality for 20–30 days [28, 29]. From that moment, pH progressively descends until reaching adult levels by 2 years of age [4].

These variations in pH may influence ionizable drugs, affecting absorption by changes in the relative amount of unionized drug available [30]. Lower levels of gastric pH might be involved in the enhanced bioavailability of weak bases by increasing their solubility [31, 32]. Conversely, weak acids in a more acid environment are less ionized, so dissolution is decreased and absorption is thus reduced [29, 32].

## Permeability classification

Permeability data were considered as if drugs were transported across biological membranes by passive transcellular diffusion, even though carrier-mediated mechanisms might coexist [33]. Log $P$ ($n$-octanol/water partition coefficient) values were obtained from Chemicalize [34], an online platform for chemical calculations. The classification was based on the relationship between human intestinal permeabilities and log $P$ values. Similarly to other studies [35–37], metoprolol was selected as the reference compound for permeability because it is known to be absorbed up to 95%. Thereby, drugs with estimated log $P$ values greater than or equal to 1.76 were rated as high-permeability drug and,

conversely, drug values lower than 1.76 were rated as low-permeability drugs.

# Results

## Classification of drug solubility

The estimated parameters for the three paediatric subgroups used for all six NTD drugs to calculate the solubility are indicated in Table 2. Drugs with estimated dose number of ≤1 were classified as high-solubility drugs, conversely, drugs with estimated dose number of >1 were classified as low-solubility drugs. All the reported values of solubility of the studied NTD drugs are summarized in Table 3.

## Classification of drug permeability

The data found in the literature was used to propose a provisional classification for each compound according to paediatric characteristics (Table 4).

## Albendazole pBCS provisional classification

Albendazole is a benzimidazole anthelmintic drug, particularly active in echinococcosis. It has a very high affinity for the beta-tubulin of the parasite. Albendazole binds with beta-tubulin units of the parasite inhibiting their

## Table 2

Shared parameters to obtain pBCS classification

|  | Neonate (0.5 months) | Infant (12.5 months) | Child (7 years) |
|---|---|---|---|
| **P50th weight (kg)** [21, 22] | 3.7 | 9.8 | 23 |
| **P50th length (cm)** [21, 22] | 52.5 | 77.0 | 122.0 |
| **BSA (m$^2$)** | 0.23 | 0.46 | 0.88 |
| **Normalized V$_{0P}$ (ml)** | 33.57 | 66.16 | 127.58 |

## Table 1

Solubility definitions [35]

| Descriptive term (solubility definition) | Parts of solvent required for one part of solute | Solubility range (mg ml$^{-1}$) | Solubility assigned (mg ml$^{-1}$) |
|---|---|---|---|
| **Very soluble (vs)** | <1 | >1000 | 1000 |
| **Freely soluble (fs)** | from 1 to 10 | 100–1000 | 100 |
| **Soluble (s)** | from 10 to 30 | 33–100 | 33 |
| **Sparingly soluble (sps)** | from 30 to 100 | 10–33 | 10 |
| **Slightly soluble (ss)** | from 100 to 1000 | 1–10 | 1 |
| **Very slightly soluble (vss)** | from 1000 to 10 000 | 0.1–1 | 0.1 |
| **Practically insoluble (pi)** | >10 000 | <0.1 | 0.01 |

## Table 3

Solubility values of selected NTD drugs

| | Reported values (mg ml$^{-1}$) | Estimated solubility by log $S$ in the most unfavourable condition of the physiological pH range (mg ml$^{-1}$)* [34] | Solubility assigned for provisional pBCS (mg ml$^{-1}$) |
|---|---|---|---|
| Albendazole | pi in water [26] <br> pi in water [27] <br> 0.01 (in water) [53] | 0.011 *(log S at pH 6)* | 0.01 |
| Benznidazole | pi in water [26] <br> 0.4 [35] <br> 0.04 (in buffer at pH 7.4) [54] <br> 0.237 (in water at 25°C) [55] <br> 0.236 (in simulated gastric fluid at pH 1.2) [55] <br> 0.244 (in simulated enteric fluid at pH 6.8) [55] | 1.404 *(log S at pH 3.2)* | 0.01 |
| *Ivermectin* | 0.004 (in water) [27, 35] <br> 0.0007 (in simulated intestinal fluid at pH 6.5) [56] <br> 0.12 (in fasted-state simulated intestinal fluid at pH 6.5) [56] | 158 341.953 *(log S at pH range 1–6)* | 0.004 |
| Nifurtimox | pi in water [26] <br> s in water [27] | 0.158 *(log S at pH 3)* | 0.01 |
| *Praziquantel* | vss in water [26] <br> 0.4 (in water) [27, 35] <br> 0.215 (in water at 37°C) [57] | 0.008 *(log S at pH range 1–6)* | 0.1 |
| *Proguanil* | ss in water [26] <br> 0.156 (in water) [58] | 253.73 *(log S at pH range 1–6)* | 1 |

Drugs whose solubility values do not vary in the range of physiological pH are given in italics.

*Values to be taken with caution as they differ greatly from the experimental ones.

pi, practically insoluble; vss, very slightly soluble; ss, slightly soluble; s, soluble

polymerization into microtubules and, consequently, disrupts the absorption of nutrients by the parasite [38].

Albendazole is a weak base at physiological pH range with a strongest basic pKa of 4.2 and a minimum estimated solubility value at pH 6 [34]. Practically insoluble in water, a solubility of 0.01 mg ml$^{-1}$ was assigned that is similar in comparison with the other experimental or estimated values from literature (Table 3). It was classified as a high-permeability drug with a log $P$ of 3.2.

Safety and efficacy of oral albendazole have not been established in children up to two years. Therefore, $M_{0p}$ of neonates and infants were estimated by clinical formulas in order to have a provisional estimation of the dose in those stages. For children over 2 years old, referenced $M_{0p}$ = 400 mg [23] was used. Table 4 lists $M_{0p}$ for every dosage method, the estimated paediatric dose number and pBCS classification for each defined paediatric stage.

### Benznidazole pBCS provisional classification

Benznidazole is a 2-nitroimidazole derivative which has an inhibitory effect on protein synthesis and ribonucleic acid synthesis in *Trypanosoma cruzi* cells. It is used in Chagas disease [39] at a paediatric dose of 5 mg kg$^{-1}$ [23].

Benznidazole is a weak base at physiological pH range (strongest basic pKa of 4.21). pH 3.2 is the minimum estimated solubility value [34], and it is practically insoluble according to WHO Pharmacopoeia [26]. A solubility of

0.01 mg ml$^{-1}$ was chosen that, in comparison with the other values in Table 3, is a conservative estimate. It was classified as a low-permeability drug with a log $P$ of 1.64.

Table 4 lists $M_{0p}$ for every dosage method, the estimated paediatric dose number and pBCS classification for each defined paediatric stage.

### Ivermectin pBCS provisional classification

Ivermectin is a semisynthetic acaracide drug, which is produced by fermentation by using *Streptomyces avermitilis*. It binds selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria. This binding causes an increase in the permeability of the cell membrane to chloride ions and results in hyperpolarization of the cell, leading to paralysis and death of the parasite [40].

Safety and efficacy of oral ivermectin have not been established in paediatric patients weighing less than 15 kg. Because of this, the referenced dose of 200 µg kg$^{-1}$ [23] was used only for children with a weight greater than 15 kg in the 50th percentile.

Ivermectin is a neutral base at physiological environment and its solubility does not change with pH variations [34]. The WHO Pharmacopoeia does not collect ivermectin data. The Merck Index [27] provides a solubility data of 0.004 mg ml$^{-1}$ (Table 3). It was classified as a high-permeability drug with a log $P$ of 5.83.

## Table 4

Provisional pBCS of the six selected drugs with formulation recommendations

| | Neonate (0.5 months) | | | Infant (12.5 months) | | | Child (7 years) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fr-R | BSA-R | Ref | Fr-R | BSA-R | Ref | Cr-R | BSA-R | Ref |
| *Albendazole* | | | | | | | | | |
| $M_{0p}$ | 1.33 | 53.71 | – | 33.33 | 105.86 | – | 135.22 | 204.13 | 400.00 |
| Dop | 3.97 | 160.00 | – | 50.38 | 160.00 | – | 105.98 | 160.00 | 313.53 |
| Permeability | High-permeability drug | | | | | | | | |
| pBCS | 2 | 2 | – | 2 | 2 | – | 2 | 2 | 2 |
| aBCS | | | | | 2 | | | | |
| | BCS Class 2: Absorption limited by solubility and dissolution. Pancreatic and biliary development with age will improve absorption, formulation in a digestible lipid vehicle will improve oral absorption | | | | | | | | |
| **Benznidazole** | | | | | | | | | |
| $M_{0p}$ | 0.33 | 13.43 | 18.50 | 8.33 | 26.46 | 49.00 | 33.80 | 51.03 | 115.00 |
| Dop | 0.99 | 40.00 | 55.11 | 12.60 | 40.00 | 74.06 | 26.50 | 40.00 | 90.14 |
| Permeability | Low-permeability drug | | | | | | | | |
| pBCS | 3 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| aBCS | | | | | 4 | | | | |
| | BCS Class 3–4 depending on dose. Low permeability and low solubility at high dose. More frequent dosing of solubilised drug will improve absorption | | | | | | | | |
| **Ivermectin** | | | | | | | | | |
| $M_{0p}$ | 0.05 | 1.88 | – | 1.16 | 3.71 | – | 4.73 | 7.14 | 4.6 |
| Dop | 0.34 | 14.00 | – | 4.41 | 14.00 | – | 9.27 | 14.00 | 9.01 |
| Permeability | High-permeability drug | | | | | | | | |
| pBCS | 1 | 2 | – | 2 | 2 | – | 2 | 2 | 2 |
| aBCS | | | | | 2 | | | | |
| | BCS Class 2 (1 at lowest doses). May be Class 4 due to high molecular weight. Digestible lipidic solubilisation vehicle would improve absorption. | | | | | | | | |
| *Nifurtimox* | | | | | | | | | |
| $M_{0p}$ | 0.83 | 33.57 | 18.50 | 20.83 | 66.16 | 49.00 | 84.51 | 127.58 | 115.00 |
| Dop | 2.48 | 100.00 | 55.11 | 31.49 | 100.00 | 74.06 | 66.24 | 100.00 | 90.14 |
| Permeability | Low-permeability drug | | | | | | | | |
| pBCS | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| aBCS | | | | | 4 | | | | |
| | BCS Class 4 | | | | | | | | |
| *Praziquantel* | | | | | | | | | |
| $M_{0p}$ | 5.83 | 234.97 | – | 145.83 | 463.13 | – | 591.57 | 893.07 | 575.00 |
| Dop | 1.73 | 70.00 | – | 22.04 | 70.00 | – | 46.37 | 70.00 | 45.07 |
| Permeability | High-permeability drug | | | | | | | | |
| pBCS | 2 | 2 | – | 2 | 2 | – | 2 | 2 | 2 |
| aBCS | | | | | 2 | | | | |
| | BCS Class 2. Absorption limited by solubility and dissolution, digestible lipid vehicles aid absorption. | | | | | | | | |
| **Proguanil** | | | | | | | | | |
| $M_{0p}$ | 1.33 | 53.71 | 25.00 | 33.33 | 105.86 | 50.00 | 135.22 | 204.13 | 100.00 |
| Dop | 0.04 | 1.60 | 0.74 | 0.50 | 1.60 | 0.76 | 1.06 | 1.60 | 0.78 |

*(continues)*

## Table 4

(Continued)

| | Neonate (0.5 months) | | | Infant (12.5 months) | | | Child (7 years) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Fr-R | BSA-R | Ref | Fr-R | BSA-R | Ref | Cr-R | BSA-R | Ref |
| Permeability | High-permeability drug | | | | | | | | |
| pBCS | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 1 |
| aBCS | | | | | 2 | | | | |
| | BCS Class 2–1: high to low dose. Absorption of high doses aided by lipid vehicle. | | | | | | | | |

Drugs with the same pBCS classification as adult BCS is given in italics.
Drugs in bold-italics indicate some variation in pBCS classification to the adult BCS.
Drugs in bold indicate changes in pBCS classification in all stages.
Fr-R, Fried's Rule dosage; BSA-R, Body Surface Area Rule dosage; Ref, Referenced dose; aBCS, adult BCS

Table 4 lists $M_{0p}$ for every dosage method, the estimated paediatric dose number and pBCS classification for each defined paediatric stage.

### Nifurtimox pBCS provisional classification

Nifurtimox is a 5-nitrofuran derivative whose mechanism of action appears to be related to its metabolism via partial reduction to chemically reactive radicals that cause production of toxic-reduced products of oxygen [41]. It is mainly used to treat Chagas disease in early stages at a paediatric dose of 5 mg kg$^{-1}$ [23].

Nifurtimox is a weak base at physiological pH range with a strongest basic pKa of 0.34 and a minimum estimated solubility value at pH 3. The most conservative solubility definition (Table 3) was practically insoluble in water [26]. Thus, a solubility of 0.01 mg ml$^{-1}$ was considered. It was assigned to the group of low-permeability drugs with a log $P$ of −0.27.

Table 4 lists $M_{0p}$ for every dosage method, the estimated paediatric dose number and pBCS classification for each defined paediatric stage.

### Praziquantel pBCS provisional classification

Praziquantel is used to treat cestodiasis. It produces a change in the calcium permeability of the parasite membranes, causing serious injury to the tegument, massive contraction, paralysis, disruption of metabolism and death [42].

Safety and efficacy of oral praziquantel in children less than 4 years old has not been established. Consequently, $M_{0p}$ of neonates and infants was estimated by clinical formulas. For children stage, we used $M_{0p} = 25$ mg kg$^{-1}$ [23].

Praziquantel is a neutral base and therefore, the solubility does not change at physiological pH range. The most conservative solubility definition was very slightly soluble in water [26], so a solubility of 0.1 mg ml$^{-1}$ was assigned. The chosen value was similar to reported values but greater than the estimated value in the most disadvantaged pH condition (Table 3). It was classified as a high-permeability drug with a log $P$ of 2.3.

Table 4 lists $M_{0p}$ for every dosage method, the estimated paediatric dose number and pBCS classification for each defined paediatric stage.

### Proguanil pBCS provisional classification

Proguanil is used for prophylaxis against *Plasmodium falciparum* and *Plasmodium vivax*. Proguanil itself is a prodrug and must be metabolized to cycloguanil for antimalarial activity. Cycloguanil inhibits nucleic acid synthesis by inhibiting plasmodial dihydrofolate reductase [43].

Referenced doses for proguanil are: 25 mg for neonates, 50 mg for infants and 100 mg for children [23].

Proguanil is a neutral base in physiological environment; consequently its solubility is not affected. The most conservative solubility definition was slightly soluble in water [26], so a solubility of 1 mg ml$^{-1}$ was selected (Table 3). It was classified as high-permeability drug with a log $P$ of 2.38.

Table 4 lists $M_{0p}$ for every dosage method, the estimated paediatric dose number and pBCS classification for each defined paediatric stage.

## Discussion

The main reason for developing a pBCS is to encourage the design of specific NTD drugs medications for paediatric populations. Secondly, the risks of reformulating adult medication for administration to children could be predicted based on the changes of classification between adults and children. Finally, pBCS might help to estimate the risk of non-bioequivalence across different compounding formulations prepared at different hospital pharmacies.

### Formulation

In many cases when paediatric formulation is not available, the demand is met by compounding preparations, as viscous suspensions formulated from commercial adult tablets or capsules by incorporating other excipients [4]. This process of adapting the formulation can modify BCS parameters, especially the solubility. Excipients are not necessarily inert substances for children as is often assumed, and their use has resulted in severe adverse effects in children [44]. Excipients used in adult medicines cannot always be supposed to have the same effect in children. Furthermore, effects may differ between different age groups because of age-related changes. For example, children from earlier stages

may not be able to metabolize or eliminate them as an adult [45, 46]. Therefore, the selection of excipients is an important stage in paediatric formulation development [46] and it is always better to use the minimal amount and number of excipients [5]. pBCS can be used as a tool to predict the complexity of infant formulation, as paediatric Class I and III compounds (i.e. high solubility) are expected to need less excipients, whereas Class II/IV may need, for instance, solubilizing agents.

The flavour profile will be closely related to therapeutic non-compliance, making organoleptic additives and bitter taste-masking technologies very important [47]. The unanswered question is whether or not the physical changes associated with these technologies affect the drug release compared with a conventional adult formulation and how this comparison could be made on a meaningful in vitro test representing the gastrointestinal tract of children. Again, the paediatric BCS could be envisaged as a tool to decipher whether a conventional dissolution apparatus could be used to predict and compare paediatric product performance, as in adult BCS Class I/III, or whether new dissolution devices reflecting children pH profiles, volumes and transit times would be necessary.

## Permeability

Our objective was to classify six NTDs drugs into a provisional pBCS. This classification is defined as provisional, as absolute human permeability data are not available for the studied age stages and the doses and volume used are also estimations. It is known that intestinal permeability decreases progressively during the first week after birth, when it is described as being high [28]. But drug permeability within paediatric populations is under-researched. Therefore, log $P$ values were used to perform a provisional permeability classification as lipophilicity of the drug is one of the main determinants of the drug membrane permeability by passive diffusion. However, this factor is one of the main limitations of the present study. Classification of drug permeability is based on comparison with metoprolol, as its fraction absorbed in adults is higher than 90%. If metoprolol absorption is similar in paediatric populations, it is adequate to use this compound as a cutoff for provisional classification, but the best model compound would be a drug with a known oral fraction absorbed in each paediatric subgroup.

## Solubility

As well as permeability, a limitation for performing the pBCS classification is the availability of experimental solubility values. Intestinal absorption of drugs depends directly on the dissolution of the compound and the subsequent passage through the gastrointestinal mucosa. The solubility of a compound in physiological fluids is an essential requirement for it to become absorbed since only dissolved drugs can be absorbed [28]. Drug dissolution depends on its physicochemical and physiological characteristics [29]. Age-related changes in the composition of gastrointestinal fluids, particularly pH, will result in changes in drug solubility, gastrointestinal dissolution and absorption [48].

## pH, solubility and absorption age differences in paediatric population

Albendazole, benznidazole and nifurtimox are among the drugs selected for this study whose solubility is affected in the acid pH range (pH 1–6) [34]. We can assume that absorption will be influenced by growth due to changes in gastrointestinal pH that occur from birth to approximately 2 years of age [28, 32].

If the solubility data used to calculate the provisional pBCS is analysed and compared with reported values of water solubility (Table 3), it can be seen that, in all of the drugs, the most conservative data has been used. With respect to the estimated solubility by log $S$ [34] in the most disadvantaged condition of the physiological pH range, there are many discrepancies with literature values. For example, the log $S$ predicted values from Chemicalize are higher than the values reported in the literature. The exceptions are albendazole and praziquantel for which predicted values are in accordance with literature values. The estimated solubility data of ivermectin and proguanil were unexpectedly high compared with the reported values, so the predictions were not considered reliable [34].

## Paediatric reference volume

Another limitation that we have found for the definition of pBCS classification limits is the determination of the volume of administration. In adults it is determined in 250 ml of water [19], but not for the paediatric population or in its stages. As discussed by Batchelor *et al.* [49], the pBCS working group used a provisional estimate of 25 ml as reference volume for each paediatric stage [5]. Currently in the literature there are authors who choose to calculate the relative volume based on the volume of gastric fluids and extrapolate it to the 250 ml used for adults [50, 51]. For this case the range of volumes goes from 13.2 ml in neonates to 56.6 ml up to 3 years old. Another option is to estimate the administered volume based on the extrapolated BSA of each development stage from the volume administered in adults [52]. BSA extrapolation leads to the higher volume estimations and so is a less conservative option. For the present work, these different volumes would only affect to the solubility class of proguanil in neonates and infants with the referenced doses that would be classified as low solubility with Batchelor *et al.* [49] and Shawahna *et al.* [51] volumes.

## The lack of referenced doses

The fourth limitation we found is the lack of referenced doses, mainly in neonates and infants. Albendazole, ivermectin and praziquantel do not have referenced doses for these stages and the only option to classify them is via clinical empirical formulas. Large differences have been detected between calculated dosages by Clark's and Fried's rules and the BSA rule. Given this assumption, when no referenced doses are available, we may be overdosing or underdosing. For example, in the case of benznidazole in infants and children (Table 4), Fried's Rule calculated dose is much lower than the BSA Rule one, which is approximately half of the referenced dose. In the case of nifurtimox, both Fried's Rule and Clark's Rule doses are lower that the referenced dose. In the case of proguanil, the BSA Rule dose is twice the referenced one. The only cases in which the referenced dose and the dose

calculated with Clark's Rule are very similar were in the population of children with the drugs ivermectin and praziquantel (Table 4).

The notable differences between doses for the same stage may lead to the classification of the drug into a different group of pBCS according to the selected dosage. For example, using Fried's Rule for benznidazole leads to a pBCS class 3, while the other dosages result in a pBCS class 4 (Table 4). These variations can also be observed for ivermectin and proguanil. Note that Dop values are very close to 1 in the case of benznidazole obtained with Fried's Rule for neonates and proguanil obtained with Clark's Rule for children.

### Provisional pBCS classification

Regarding permeability, four of the six compounds were classified as highly permeable (albendazole, ivermectin, praziquantel and proguanil). In terms of solubility (based on the paediatric dose number), low-solubility classification predominates. None of the drugs were classified in pBCS class 3 and only proguanil was classified in pBCS class 1 with some dosages. Table 4 summarizes the different paediatric classifications in comparison with the adult classification.

Benznidazole dose with Fried's Rule is assigned to a different class (pBCS class 3) (Table 4). The other example is ivermectin in which $M_{0p}$ by Fried's rule is so small compared to the others, that there is a change in the solubility classification from low to high solubility. Albendazole, nifurtimox and praziquantel maintain the same pBCS classification for their different dosages at any stage and with respect to adult BCS classification. Proguanil is the only one that presents changes in all stages (Table 4).

Taking as the most relevant dose the referenced one, it can be observed that there is a switch from class 2 in aBCS to class 1 in pBCS in the three paediatric stages. There is an improvement in solubility that makes it be classified in a more favourable class. This change would decrease the formulation development risks and it would ease the demonstration of bioequivalence among different formulations but additionally could lead to a higher fraction absorbed in children and thus a higher exposure.

What are the implications for compounding pharmaceutical preparations with these drugs? Being class 2 or 4 drugs means solubility and dissolution are important factors affecting fraction absorbed and absorption rate. Excipients and dosage form may change dissolution rate and in consequence harmonized formulations would be desirable to ensure the same performance in different clinical units of hospitals. pBCS can be used as a tool to identify when formulation could be critical to ensure performance similar to the adult formulation and similarity across compounded formulas, but, as we have pointed out in this study, there is a need to increase our knowledge of children's gastrointestinal system, in particular fluid volumes and composition, to use the right parameters for pBCS classification.

## Conclusion

In summary, provisional pBCS classification of these six drugs shows potential changes in the limiting factors in oral absorption in paediatrics compared to the adult population. This valuable information could serve as a formulation tool during paediatric development and to minimize the potential risks when developing formulations for paediatric use by pharmaceutical compounding. The need for standardization of these formulations would be higher in those unfavourable classification changes from adult BCS to paediatric BCS as for instance from classes 3–1 to 2–4, which could be more sensitive to the effect of excipients.

## Competing Interests

There are no competing interests to declare.

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