Research Article

Regional-Dependent Intestinal Permeability and BCS Classification: Elucidation of pH-Related Complexity in Rats Using Pseudoephedrine

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Abstract. Based on its lower Log *P* value relative to metoprolol, a marker for the low/high-permeability (P_{eff}) class boundary, pseudoephedrine was provisionally classified as BCS low-permeability compound. On the other hand, following oral administration, pseudoephedrine fraction dose absorbed (F_{abs}) and systemic bioavailability approaches 100%. This represents a challenge to the generally recognized P_{eff}–F_{abs} correlation. The purpose of this study was to elucidate the underlying mechanisms behind the confusion in pseudoephedrine's BCS classification. Pseudoephedrine's BCS solubility class was determined, and its physicochemical properties and intestinal permeability were thoroughly investigated, both *in vitro* and *in vivo* in rats, considering the complexity of the whole of the small intestine. Pseudoephedrine was found to be unequivocally a high-solubility compound. All of the permeability studies revealed similar phenomenon; at any given intestinal segment/pH, the permeability of metoprolol was higher than that of pseudoephedrine, however, as the intestinal region becomes progressively distal, and the pH gradually increases, pseudoephedrine's permeability rises above that of metoprolol in the former segment. This unique permeability pattern likely explains pseudoephedrine's complete absorption. In conclusion, pseudoephedrine is a BCS Class I compound; no discrepancy between P_{eff} and F_{abs} is involved in its absorption. Rather, it reflects the complexity behind P_{eff} when considering the whole of the intestine. We propose to allow high-permeability classification to drugs with P_{eff} that matches/exceeds the low/high class benchmark *anywhere* throughout the intestinal tract and not restricted necessarily to the jejunum.

KEY WORDS: BCS classification; biowaiver; intestinal absorption; regioselective absorption; segmental-dependent permeability.

INTRODUCTION

Amidon *et al.* (1) revealed that the two key parameters governing the fraction of dose absorbed (F_{abs}) following oral administration are the permeability (P_{eff}) through the gastrointestinal (GI) wall and the solubility/dissolution of the drug dose in the GI milieu. Based on extensive research, it was determined that an excellent correlation exists between the human jejunal P_{eff} measured using intestinal perfusion and the F_{abs} obtained from pharmacokinetic or mass-balance studies in humans (2–7). Indeed, drug regulatory agencies worldwide, including the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have been using P_{eff} as a surrogate for F_{abs}, and implemented this P_{eff}–F_{abs} correlation in BCS-based biowaiver decisions.

The commonly used decongestant pseudoephedrine is a sympathomimetic agent that acts predominantly on the α-adrenergic receptors. Based on its significantly lower Log

P value relative to metoprolol, a widely used marker for the low/high-permeability class boundary, pseudoephedrine was provisionally classified as a low-permeability, BCS Class III compound (8). On the other hand, following oral administration, pseudoephedrine F_{abs} and systemic bioavailability approaches 100% (9). Pseudoephedrine undergoes no presystemic metabolism, less than 1% of the dose is metabolized by the liver (9), and up to 96% of the dose is excreted unchanged in the urine (10). Hence, considering its high solubility, it was classified as Class III also according to the biopharmaceutics drug disposition classification system (BDDCS) (11). As noted above, a match is expected between high F_{abs} and high P_{eff}; the FDA and EMA definitions for high permeability is $F_{abs}>90\%$ and $F_{abs}>85\%$, respectively. It is generally recognized, therefore, that a high F_{abs} drug must exhibit high P_{eff} in the human intestine, even though actual permeability data may not be available. The intestinal absorption of pseudoephedrine, however, allegedly represents a case of discrepancy between P_{eff} and F_{abs}. This directly affects its BCS classification, which in turns dictates whether a generic immediate-release (IR) oral drug product containing pseudoephedrine may be eligible for a BCS-based biowaiver. This is therefore a question of considerable scientific and financial importance that involves public health policy aspects as well (12). This alleged P_{eff}–F_{abs} disparity

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emphasizes that the intestinal permeability, considering the whole of the intestine, is more complex than generally recognized, as will be further discussed in this paper (13).

The purpose of this study was to elucidate the underlying mechanisms behind the confusion in pseudoephedrine's BCS classification. We have determined the solubility class of pseudoephedrine, and thoroughly investigated its physico-chemical properties and intestinal permeability, both *in vitro* and *in vivo* in rats, taking into consideration the complexity of the whole of the small intestine. The results were compared with metoprolol, the FDA reference drug for the low/high-permeability class boundary. We then performed a thorough theoretical physicochemical analysis of pseudoephedrine *vs.* metoprolol, to further clarify the mechanistic explanation behind the experimental data. Overall, this study points out a unique intestinal absorption pattern through elucidation of the solubility and permeability class membership of pseudoe-phedrine and highlights the underlying complexity and the care that must be taken when interpreting intestinal perme-ability data.

MATERIALS AND METHODS

Materials

Pseudoephedrine hydrochloride, metoprolol tartrate, phenol red, potassium chloride, potassium phosphate mono-basic, sodium chloride, octanol, hexadecane, and trifluoro-acetic acid (TFA) were purchased from Sigma Chemical Co. (St. Louis, MO). Acetonitrile, methanol and water (Merck KGaA, Darmstadt, Germany) were ultra-performance liquid chromatography (UPLC) grade. All other chemicals were of analytical reagent grade.

Solubility Studies

The solubility class membership of pseudoephedrine was determined according to the FDA's BCS guidance for industry (14). The equilibrium solubility of the drug was determined at both 37°C and at room temperature (25°C), in phosphate buffer at pH 7.5, acetate buffer at pH 4.5, and maleate buffer at pH 1.0, using the shake-flask method, as previously reported (15–17). Briefly, excess amounts of pseudoephedrine were added to glass vials containing the different buffers. Solution pH was verified after addition of the drug to the buffer. The vials were tightly closed and placed in a shaking (100 rpm) water bath at 37°C or 25°C. Establishment of equilibrium was confirmed by comparison of 48- and 72-h samples. Prior to sampling, the vials were centrifuged (10,000 rpm for 10 min) and the supernatant was carefully withdrawn and immediately assayed by UPLC.

Determination of Octanol–Buffer Partition Coefficients

Experimental octanol–buffer partition coefficients, Log *D*, for pseudoephedrine and metoprolol at pH 6.5, 7.0, and 7.5 were determined using the traditional shake-flask method (18,19). Briefly, solutions of pseudoephedrine or metoprolol were prepared in octanol-saturated phosphate buffers with pH values of 6.5, 7.0, and 7.5. These aqueous solutions were then equilibrated at room temperature with an equivalent

volume of buffer saturated octanol for 48 h. The octanol and aqueous phases were then separated by centrifugation, and the drug concentration in the aqueous phase was determined by UPLC. The drug concentration in the octanol phase was obtained by mass balance. From these data, the apparent octanol/buffer partition coefficient was determined. Experi-mental octanol–buffer partition coefficients of the unionized form, Log *P*, for pseudoephedrine and metoprolol were determined at pH 13 solution, using the same method described above.

Parallel Artificial Membrane Permeability Assay

Permeability studies through artificial membrane were carried out in two different methods: the hexadecane-based parallel artificial membrane permeability assay (PAMPA) and the pre-coated PAMPA assay (BD Gentest™).

The hexadecane-based permeability studies were carried out as previously described with minor modifications (20,21). Briefly, three solutions of pseudoephedrine or metoprolol were prepared with different ratios of potassium phosphate monobasic and sodium phosphate dibasic, to give pH values of 6.5, 7.0, and 7.5. Osmolality (290 mOsm/L) and ionic strength were similar in all buffers. Millipore (Danvers, MA) 96-well MultiScreen-Permeability filter plates with 0.3 cm^2 polycarbonate filter support (0.45 μm) were used. The filter supports were impregnated with 15 μl of a 5% hexadecane in hexane solution, and were then allowed to dry for 1 h, during which the hexane was completely evaporated resulting in a uniform layer of hexadecane. Then, the donor wells were filled with the different pseudoephedrine solutions (200 μl), the receiver wells were filled with blank buffers (300 μl), and the PAMPA sandwich was incubated at room temperature. Receiver plates were collected hourly for 4 h.

The pre-coated PAMPA experiments (BD Gentest™, BD Biosciences, Bedford, MA) were carried out according to the manufacturer instructions, with the addition of tracking the transport rate, as described for the hexadecane-based PAMPA. Receiver plates were collected hourly for 5 h.

Apparent permeability coefficient (P_{app}) values for both PAMPA methods were calculated from the linear plot of drug accumulated in the acceptor side *vs.* time using the equation:

$$P_{app} = \frac{dQ/dt}{A \cdot C_0}$$

where dQ/dt is the steady-state appearance rate of pseudoe-phedrine/metoprolol on the receiver side, C_0 is the initial concentration of the drug in the donor side (250 μM in all experiments), and A is the membrane surface area (0.048 cm^2). Linear regression was carried out to obtain the steady-state appearance rate of the drugs on the receiver side.

Rat Intestinal Perfusions

The *in situ* effective permeability coefficient (P_{eff}) of pseudoephedrine *vs.* metoprolol was determined using the single-pass rat intestinal perfusion model. All animal experi-ments were conducted using protocols approved by the Ben-Gurion University of the Negev Animal Use and Care Committee (Protocol IL-60-11-2010). The animals (male Wistar rats weighing 270–300 g, Harlan, Israel) were housed

and handled according to the Ben-Gurion University of the Negev Unit for Laboratory Animal Medicine Guidelines.

The experimental procedure followed previous reports (22,23). Briefly, anesthetized rats were placed on a heated (37°C) surface (Harvard Apparatus Inc., Holliston, MA), and a midline abdominal incision of 3–4 cm was made. To account for the complexity of the whole of the small intestine, permeability was determined in three different 10-cm segments; a proximal jejunal segment (starting 2 cm below the ligament of Treitz), mid-small intestinal segment (isolated between the end of the upper and the beginning of the lower segments), and a distal ileal segment (ending 2 cm above the cecum). Each intestinal segment (approximately 10 cm) was cannulated on two ends, and was rinsed with blank perfusion buffer. All solutions were incubated in a 37°C water bath.

Three perfusion buffers containing pseudoephedrine, metoprolol and phenol red (a non-absorbable marker for water flux measurements) were prepared with different ratios of potassium phosphate monobasic and sodium phosphate dibasic, to give pH values of 6.5, 7.0, and 7.5, while osmolality (290 mOsm/L) and ionic strength were similar in all buffers. The permeability in each intestinal segment was measured at the pH that corresponds to the physiological pH of that region: (1) proximal jejunum, pH 6.5; (2) mid-small intestine, pH 7.0; and (3) distal ileum, pH 7.5 (24,25). The perfusion buffer was first perfused for 1 h, to ensure steady-state conditions, followed by additional 1 h of perfusion with samples taken every 10 min. The pH of the collected samples was measured at the outlet, to verify that there was no pH change throughout the perfusion. All samples were immediately assayed by UPLC. At the end of the experiment, the length of each perfused intestinal segment was accurately measured.

The effective permeability (P_{eff}; in centimeters per second) through the rat gut wall was determined according to the following equation:

$$P_{\text{eff}} = \frac{-Q ln(C'_{\text{out}}/C'_{\text{in}})}{2\pi RL}$$

where Q is the perfusion buffer flow rate (0.2 mL/min), $C'_{\text{out}}/C'_{\text{in}}$ is the ratio of the outlet and the inlet concentration of drug that has been adjusted for water transport (26–28), R is the radius of the intestinal segment (set to 0.2 cm), and L is the length of the perfused intestinal segment.

Physicochemical Analysis

The theoretical fraction extracted into octanol (f_e) was calculated using the following equation from Winne (29) and Wagner and Sedman (30):

$$f_e = \frac{f_u P}{1 + f_u P}$$

where P is the octanol–water partition coefficient of the unionized form of the drug and f_u is the fraction unionized of the drug at a given pH. The f_u vs. pH was plotted according to the Henderson–Hasselbalch equation, using the following literature pK_a values: 9.68 for metoprolol (31) and 9.86 for pseudoephedrine (32).

Ultra-Performance Liquid Chromatography

UPLC experiments were performed on a Waters (Milford, MA) Acquity UPLC H-Class system equipped with photodiode array detector and Empower software. The simultaneous determination of pseudoephedrine, metoprolol and phenol red was achieved using a Waters (Milford, MA) Acquity UPLC BEH C_{18} 1.7-μm 2.1× 100 mm column. The mobile phase consisted of 90:10 going to 20:80 (v/v) water:acetonitrile (both with 0.1% TFA) over 5 min (flow rate, 0.5 mL/min). The detection wavelengths and retention times for pseudoephedrine, metoprolol and phenol red were 256, 275, and 285 nm and 2.5, 3.1, and 3.6 min, respectively. Injection volumes for all UPLC analyses ranged from 2 to 50 μL.

Statistical Analysis

Log D and Log P determinations were performed in triplicates. All other in vitro experiments were replicated with $n=4$, and all animal experiments were replicated with $n=5$. Values are expressed as means±standard deviation (SD). To determine statistically significant differences among the experimental groups, the nonparametric Kruskal–Wallis test was used for multiple comparisons and the two-tailed nonparametric Mann–Whitney U test for two-group comparison where appropriate. A p value of less than 0.05 was termed significant.

RESULTS

Solubility Studies

The solubility of pseudoephedrine in the three pH values of 1.0, 4.5, and 7.5, at both 37°C and at room temperature, is presented in Table I. The data indicate that pseudoephedrine is unequivocally a high-solubility compound; taking 60 mg as the highest single unit dose strength, the minimal dose number (D_0) at 37°C is 0.00034, indicating a BCS high-solubility class membership.

Octanol–Buffer Partition Coefficients

The Log D values for pseudoephedrine and metoprolol at the three pH values of 6.5, 7.0, and 7.5, representing the conditions throughout the small intestine, are presented in Fig. 1. It can be seen that at any given pH, the octanol–buffer partition coefficient of metoprolol is higher than that of pseudoephedrine. However, pseudoephedrine's Log D value at 7.5 approximately equals that of metoprolol at 6.5. The octanol–buffer partition coefficient values of the unionized form, Log P, for pseudoephedrine and metoprolol were determined to be 1.5 and 2.3, respectively (Table II).

Permeability Studies

The accumulated amount transported vs. time plots of pseudoephedrine and metoprolol in the hexadecane-based PAMPA and the Pre-coated PAMPA assay, at the three pH values of 6.5, 7.0, and 7.5, are presented in Figs. 2 and 3, respectively. The in situ effective permeability coefficient

Table I. The Solubility (in Milligrams per Milliliter) of Pseudoephedrine in the Three pH Values 1.0, 4.5, and 7.5, at 37°C and at Room Temperature (25°C)

	pH 1.0	pH 4.5	pH 7.5
37°C	835±33	743±18	700±9
25°C	428±2	250±1	213±1

Data presented as mean±SD; *n*=3

(P_{eff}) values of pseudoephedrine *vs.* metoprolol determined using the single-pass rat intestinal perfusion model, in the three small intestinal segments the proximal jejunum (pH 6.5), mid-small intestine (pH 7.0), and the distal ileum (pH 7.5), are presented in Fig. 4. It can be seen that all of these permeability studies revealed a similar phenomenon; at any given intestinal segment/pH, the permeability of metoprolol was higher than that of pseudoephedrine, however, as the intestinal region was progressively more distal, and the pH of that region was gradually increasing, pseudoephedrine's permeability rose above that of metoprolol in the former segment. This results in the unique phenomenon in which the permeability of pseudoephedrine at pH 7.0 was higher than that of metoprolol at pH 6.5, and the permeability of pseudoephedrine at pH 7.5 was higher than that of metoprolol at pH 7.0.

Physicochemical Analysis

The theoretical f_{u} and f_{e} plots as a function of pH for pseudoephedrine and metoprolol are presented in Fig. 5. The physicochemical properties used for these analyses are summarized in Table II. The f_{u} of the basic compounds pseudoephedrine and metoprolol is negligible at low pH, and increases as the pH rises, resulting in the classic sigmoidal shape. For both drugs, the f_{e} *vs.* pH plot follows a similar pattern, but with a shift to the left (lower pH values). The shift magnitude equals to Log(P-1) at the midpoint of the f_{e} and f_{u} sigmoidal curves (29,30). Both drugs have approximately similar pK_{a}; however, because of pseudoephedrine's
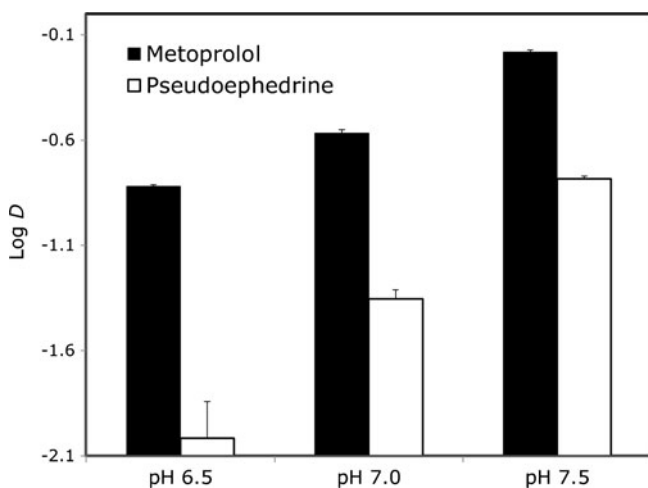

Fig. 1. The octanol–buffer partition coefficients, Log *D*, for pseudoephedrine and metoprolol at the three pH values 6.5, 7.0, and 7.5. Data are presented as the mean±SD; *n*=3 in each experimental group
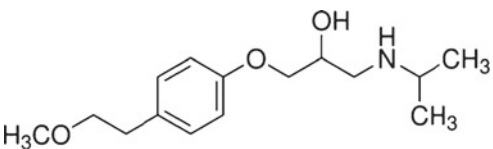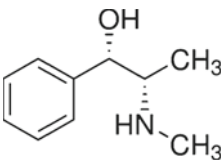
lower Log *P* the rise in its f_{e} occurs at higher pH values in comparison to metoprolol. Experimental octanol–buffer partitioning of the drugs at the three pH values of 6.5, 7.0, and 7.5 are also presented in Fig. 5 and were in good agreement with the theoretical plots.

DISCUSSION

While in the FDA guidance for industry regarding BCS solubility classification there is an explicit recognition of the changes in this parameter along the GI tract, demonstrated in the requirement to show that the drug dose is dissolved in 250 mL of aqueous media in all luminal conditions, that is pH 1–7.5 (14), the permeability classification does not consider the changes along the intestine and requires only the value in the jejunum. This policy misses the complexity behind the permeability measure, considering the whole of the intestine; permeability is location dependent, and pertaining to each point throughout the GI tract. In fact, even the P_{eff} values we report here for the different segment, proximal jejunum, mid-small intestine, and distal ileum, are average values; these values were calculated based on perfusion through a 10-cm intestinal segment, over which the permeability may change locally at any point, and hence the overall value represents the *average* permeability in this 10-cm segment. Within a 10-cm intestinal segment with approximately similar characteristics the local P_{eff} changes may be small, but when considering the many parameters that vary significantly from one region to another throughout the entire intestine, looking merely at one segment can lead to misjudgment regarding P_{eff} and F_{abs}, potentially impacting decisions regarding drug discovery, formulation design, drug development and regulation. The comparison of pseudoephedrine and metoprolol presented in this paper emphasizes this point and its consequences.

When evaluating P_{eff} data, one must first define the borderline for the low/high-permeability class membership; the completely absorbed β-blocker metoprolol is a widely used and acceptable marker for this purpose (3,33,34). However, as can be seen in Fig. 4, metoprolol's permeability increases significantly as the drug travels along the small intestine and the pH rises; the next question is, therefore, which P_{eff} value of metoprolol should be taken as the low/high class benchmark, the proximal jejunal value, or the higher value at the distal ileum? A careful examination of the oral absorption of IR metoprolol reveals that 80–90% of the dose is absorbed from the upper 50 cm, i.e., the proximal jejunum, in both human (35) and rats (36). It follows, hence, that metoprolol's P_{eff} in the proximal jejunum is the value that allows its high absorption, and that the values in more distal segments are in fact not relevant for the absorption of an IR dose of metoprolol. This analysis establishes metoprolol's P_{eff} in the proximal jejunum as the marker for the low/high-permeability class boundary. In light of this point, the results we present here for the intestinal permeability of pseudoephedrine become critical; although showing low permeability in the upper small intestine, pseudoephedrine's P_{eff} values in the subsequent small intestinal regions are comparable/higher than the benchmark of metoprolol's permeability in the proximal jejunum. As a result, it is evident that an IR oral dose of pseudoephedrine is under

Table II. Pseudoephedrine and Metoprolol Physicochemical Properties Used for the Fraction Unionized (f_u) and Fraction Extracted into Octanol (f_e) Analyses

	Chemical structure	pK_a	Log P
Metoprolol		9.68	2.3 ± 0.03
Pseudoephedrine		9.86	1.5 ± 0.01

Log P values were experimentally determined in this study; data presented as mean±SD; n=3. The pK_a values were taken from the literature, for both metoprolol (31) and pseudoephedrine (32)

high-permeability conditions throughout the majority of the small intestinal transit time, which allows for its complete absorption. It should be noted that this phenomenon was revealed by all of the experimental methods used in this study (Log D, hexadecane-based PAMPA, pre-coated PAMPA, *in vivo* rat intestinal perfusion, and the theoretical physicochemical analysis). It can be concluded, therefore, that

pseudoephedrine is a BCS Class I compound, and that no discrepancy between P_{eff} and F_{abs} is involved in its intestinal absorption; rather, the confusion in its BCS classification was a reflection of the complexity behind the permeability measure when considering the whole of the intestinal tract. When making a case for a BCS classification, looking solely at the jejunum can be misleading, for the solubility class, as
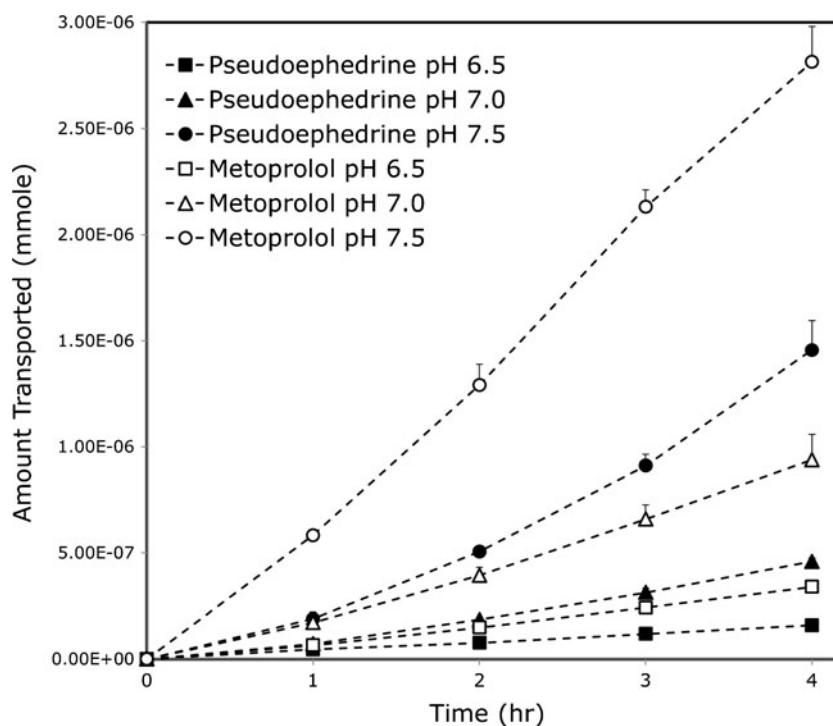

Fig. 2. The mass transfer of pseudoephedrine and metoprolol at the three pH values 6.5, 7.0, and 7.5 in the hexadecane-based PAMPA assay. Data are presented as the mean±SD; n=4 in each experimental group
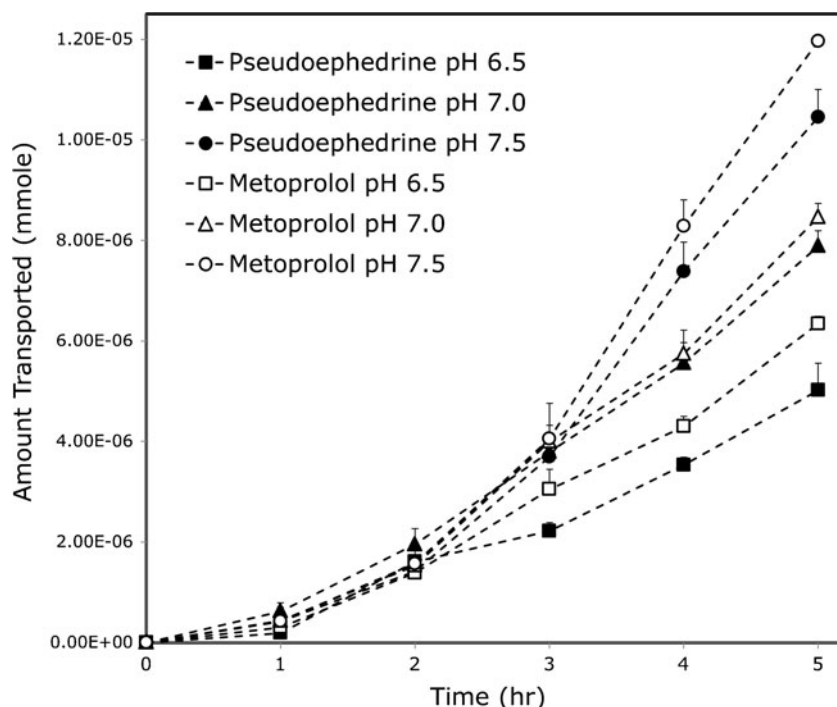
Fig. 3. The mass transfer of pseudoephedrine and metoprolol at the three pH values 6.5, 7.0, and 7.5 in the pre-coated PAMPA experiments (BD Gentest™). Data are presented as the mean±SD; *n*=4 in each experimental group

explicitly recognized by the FDA guidelines, but also for the permeability class assignment, as evident by the data presented here. We therefore suggest the following extension to the current high-permeability criterion: setting metoprolol's P_{eff} in the proximal jejunum as the low/high-permeability class boundary, and, if the permeability of the tested compound matches/exceeds this benchmark *anywhere* throughout the intestinal tract, i.e., not necessarily in the jejunum, then this compound should be classified as high permeability. This extension may allow a scientifically justified Class I classification for compounds that according to the current BCS guideline fail to meet the high-permeability criterion due to segmental-dependent permeability. Naturally, regulatory changes cannot be based on animal studies only, and additional human data are needed.
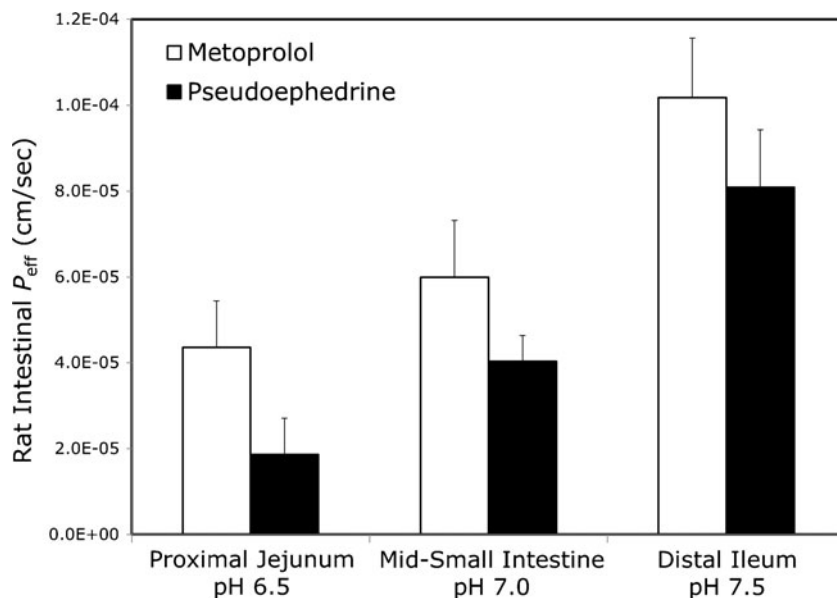

Fig. 4. Effective permeability values (P_{eff}; in centimeters per second) obtained for pseudoephedrine and metoprolol after *in situ* single pass perfusion to the rat proximal jejunum at pH 6.5, mid-small intestine at pH 7.0, and to the distal ileum at pH 7.5. Data are presented as the mean±SD; *n*=5 in each experimental group
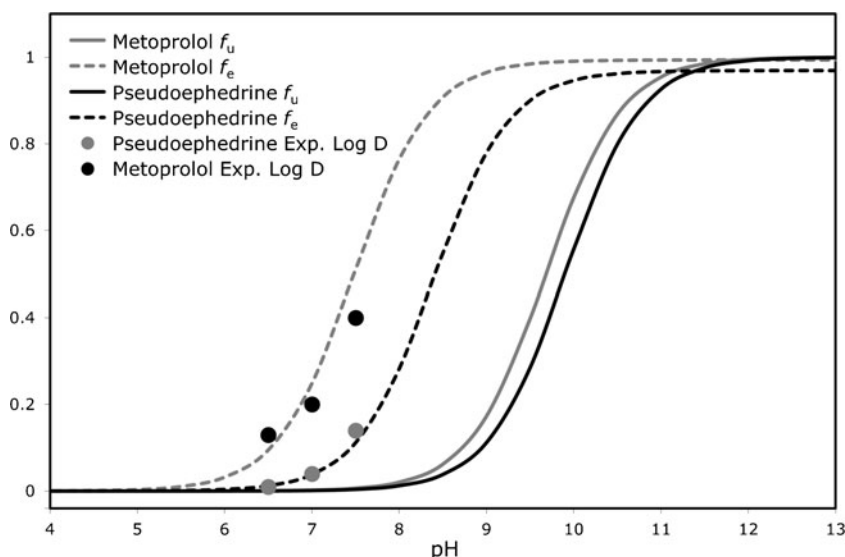
Fig. 5. The theoretical fraction unionized (f_u) and fraction extracted into octanol (f_e) plots as a function of pH for pseudoephedrine and metoprolol, and experimental buffer–octanol partitioning of the drugs in the three pH values 6.5, 7.0, and 7.5 (plotted as fraction extracted into octanol)

To a large extent, the regional-permeability is determined by the interplay between the physicochemical properties of the drug and the function of the membrane (4,22,37–40). Intestinal segments may differ from each other in many aspects, including the total surface area of the membrane, tight junctional resistance, enzyme activities, amount and capacity of transporters, unstirred water layer, capillary blood flow, etc. In the pseudoephedrine case presented in this paper, the segmental-dependent permeability is attributable mainly to the pH changes along the intestine, as evident by the high correlation between the PAMPA and the *in vivo* studies, by the good agreement of the experimental and the theoretical analyses (Fig. 5), and by previous reported studies (41–43). The increasing pH along the intestine may result in this unique absorption pattern for a whole class of molecular entities; we have previously shown that the β-blocker sotalol follows a similar permeability pattern, starting as low-permeability in the proximal GI sections, increasing gradually with the pH increase throughout the small intestine, and becomes a high-permeability compound as the pH rises above 7.5 in the ileum, which allows for complete absorption of this drug (24). While pseudoephedrine includes the basic secondary amine as a sole ionizable center, sotalol is an amphoteric molecule that contains the acidic methanesulfonamide functionality and the basic secondary amine. Sotalol's isoelectric point is, however, beyond the pH range relevant to the small intestine, and hence it behaves essentially as a weak base, leading to the observed absorption pattern. It can be concluded, hence, that a molecule must contain a basic functionality to present with this phenomenon, but it does not necessarily have to be the sole ionizable center.

The study reported in this paper emphasizes the underlying complexity and the care that must be taken with interpretation of intestinal permeability data. While the wrong impression of low permeability may be received for pseudoephedrine when looking merely at the proximal jejunum, the correct high-permeability classification is revealed when the permeability is more thoroughly assessed. Overall, therefore, the scientifically justified BCS classification for this compound is Class I. As noted above, pseudoephedrine undergoes no presystemic metabolism, less than 1% of the dose is metabolized by the liver (9), and up to 96% of the dose is excreted unchanged in the urine (10). Therefore, its BDDCS classification would be Class III (11). Pseudoephedrine hence represents a case of disagreement between the BCS and the BDDCS, and a deviation from the P_{eff}–F_{met} (fraction metabolized) correlation proposed by the BDDCS. Thus, while the extent of drug metabolism may be useful in supporting permeability classification under certain circumstances, the data presented in this paper demonstrate the care that must be taken with intestinal permeability/extent of absorption determinations (12,24,44).

CONCLUSIONS

In conclusion, this study provides evidence to indicate that pseudoephedrine is a BCS Class I compound. No discrepancy between P_{eff} and F_{abs} is involved in its absorption, rather, it reflects the complexity behind P_{eff} when considering the whole of the intestinal tract. As an extension to the current high-permeability criterion, we propose to allow high-permeability classification to drugs with P_{eff} that matches/exceeds the low/high class benchmark *anywhere* throughout the intestinal tract, i.e., not necessarily only in the jejunum.

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