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Evaluating student understanding of core pharmacokinetic concepts

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ABSTRACT

Both educators and graduates have expressed concern about a perceived pharmacology knowledge gap that includes difficulty applying fundamental principles to clinical and research problems. Consequently, we sought to determine the extent to which current students can explain the meaning of, and appropriately apply, a subset of core concepts, and to identify any misconceptions arising from the responses. Of the twenty-four pharmacology core concepts arising from the recent international collaboration, four pharmacokinetic concepts were chosen, namely *drug bioavailability, drug clearance, volume of distribution, and steady-state concentration*. A total of 318 students from 11 universities across seven countries chose to participate in this study. Expert analysts identified the essential elements for each concept, then independently assessed each student's response. Teams of two experts compared their evaluations to reach a consensus and grouped misconceptions thematically. For each core concept, less than 30% of students provided responses that encompassed all essential elements. Participants found drug clearance most challenging, generally conflating it with the rate of elimination, whereas they

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demonstrated a better understanding of *drug bioavailability*. There were 34 misconception themes coded in a total of 813 statements, with *volume of distribution* and *drug clearance* producing the highest numbers (13 and 12, respectively). Overall, results suggest that students found it easier to apply the concept than to explain its meaning, which might reflect the shift from didactic to active learning approaches. These findings may be useful for educators who are developing introductory pharmacokinetic courses by providing conceptual focus and revealing common misconceptions to explicitly address.

1. Introduction

1.1. Statement of the problem

Students learn pharmacology for a wide range of reasons, including as part of health profession programs or within science curricula. The extent and quality of their pharmacology learning may impact their success as graduates; indeed, there is evidence that a lack of pharmacology knowledge has contributed to poor patient outcomes in some contexts (World Health Organization, 2023). A study of 895 final-year medical students from 17 European medical schools showed that the students lacked essential prescribing competencies, as well as certain crucial knowledge of pharmacological drug interactions and contraindications (Brinkman et al., 2017). These findings align with those of the EQUIP study, which explored the experiences of medical students and junior doctors and highlighted a *"lack of learning opportunities related to safe and effective use of medicines"* (Dornan et al., 2009). One study found that a lack of pharmacology knowledge acquisition and application in nursing education contributed to their perceived lack of preparedness to administer oral medication (Cleary-Holdforth and Leufer, 2020). Similarly, a report of the perceptions of 1741 nursing students identified *"relatively low pharmaceutical care knowledge scores"* (De Baetselier et al., 2022). This was reinforced by a recent systematic review of nurse prescribing education, which identified pharmacology education as the most urgent need (Tan et al., 2023). Thus, there is a risk that graduates who deal with the safe and effective use of medicines, or their discovery and development, are not fully prepared for the workplace (Dornan et al., 2009; Harding et al., 2010; Heaton et al., 2008; Lum et al., 2013; Omer et al., 2021; Ross and Maxwell, 2012; Roberts et al., 2023).

Given the exponential growth in our collective understanding of pharmacology, educators must carefully choose the knowledge, skills, and attitudes that graduates must possess. A recent international collaboration under the banner of the International Union of Basic and Clinical Pharmacology (IUPHAR) Education Section (IUPHAR-Ed) (White et al., 2023) identified 24 core concepts of pharmacology using a Delphi process. The IUPHAR-Ed team then defined each of the 24 core concepts and identified the sub-concepts that provided the conceptual foundation on which each core concept stood (Guilding et al., 2024). To date, the extent to which students understand and can apply these core concepts is unexplored.

1.2. Proposed solution - core concepts and concept inventories

Over the past few decades, many science disciplines such as physics, statistics, physiology, biology, and chemistry have developed *concept inventories* - tests that determine whether students can understand and apply the core concepts of the discipline (Allen et al., 2004; Epstein, 2013; Hestenes et al., 1992; Krause et al., 2004; McFarland et al., 2017; McGinness and Savage, 2016; Porter et al., 2019; Stefanski et al., 2016; Veilleux and Chapman, 2017). Although there is no single approach to their creation (Netere et al., 2024a), these inventories have produced many benefits (Furrow and Hsu, 2019), as they provide a rigorous and validated mechanism to help instructors and students know whether they have attained the fundamental concepts of their discipline. They also enable the testing of the effectiveness of innovations in teaching and learning, for example, the evidence-based move to (inter)active learning has been gained on the back of evidence from concept inventories (Freeman et al., 2014; Hake, 1998).

1.3. Concept inventory design and misconceptions

Now that the core concepts of pharmacology have been identified, the process of producing multiple-choice questions that test attainment of these concepts has begun (Netere et al., 2024a,b). A crucial element of the rigorous testing of students' application of core concepts is the use of validated misconceptions in the creation of multiple-choice questions (MCQs), using student wording as options (distractors) (Klymkowsky and Garvin-Doxas, 2020). In most disciplines, the process of exploring student understanding of a topic, and identifying misconceptions, begins with open-ended questions in interviews (Rye et al., 1997), focus groups, or surveys, before proceeding to the development of MCQs (Netere et al., 2024a,b).

To explore student understanding of the core concepts of pharmacology and to identify problematic alternative conceptions or misconceptions that students hold about a subset of pharmacology core concepts, we designed a study to address the following research questions.

1.4. Research questions

RQ1. What do students understand the pharmacokinetic core concepts *drug bioavailability, drug clearance, steady-state concentration and volume of distribution* to mean?
RQ2. To what extent do student conceptions of these core concepts align with expert understandings of those concepts?
RQ3. To what extent are students able to apply these core concepts to predict outcomes or solve novel problems?
RQ4. Which of these concepts are most prone to misconceptions? What are the most common misconceptions held by students?

2. Methodology

2.1. Overall study design and methodology

A pilot study identified the most challenging core concepts. The authors developed conception and application tasks for each core concept, then produced and refined the analytical methodology. The graphical abstract shows the steps taken to answer the four research questions posed in this study (Fig. 1).

2.2. Human ethics approval

The project "Core Concepts of Pharmacology – testing student understanding" was approved by the Monash University Human Research Ethics Committee under Project ID 37467, which included all the universities involved in the study. The following universities required institutional approval in addition to the Monash overarching approval: University of Galway (Project ID 2023.11.009), University of New England (HRE23-007), University of Surrey (Project ID FHMS 23–24 038), East Tennessee State University (Project ID 0623.18e-ETSU), and Nazarbayev University (NU-IREC ID: 752/21082023). The remaining universities did not require additional ethics approval.

2.3. Participant recruitment

Students enrolled in medical, pharmacy, veterinary medicine, science, biomedical science, and pharmaceutical science programs were asked to participate by authors (MA, AMB, CG, MH, TH, JK, JPK, KK, NK, WL, JM, JN, CR) who taught into them. Students were informed that participation was entirely voluntary and would not count towards their mark or grade for any of their coursework. Students received an explanatory statement, and completion of the survey was taken as an indication of their consent to participate in the study.

2.4. Pilot – fourth year pharmacy students

A pilot study in 2023 involving 10 pharmacy student volunteers at Monash University in Melbourne, Australia, was used to identify the eight most difficult concepts from the list of 24 previously defined and unpacked concepts (Guilding et al., 2024). The purpose of the pilot study was to identify core concepts that would form the basis/focus of the quiz; later studies will explore the remaining 16 core concepts. Students were asked *"What does the term [insert core concept] mean to you?"* Student responses were compared to IUPHAR-Ed expert group definitions and evaluated using an agreed evaluation scheme, overseen by author PJW. The four pharmacokinetic core concepts with which students had the most difficulty were selected as the focus for this quiz, namely, *drug bioavailability, drug clearance, steady-state concentration, and volume of distribution.*

2.5. Quiz design and delivery

Quiz Development: A 15-minute quiz was developed to i) explore students' ability to understand and apply the core concepts of pharmacology, and ii) identify misconceptions held regarding the concept in question.

Quiz Structure: Participants were asked a series of demographic questions, followed by two questions for each of the four core concepts.

Quiz Tasks: The first of the two quiz tasks for each core concept asked participants to explain what they understood the core concept to mean. This task was intended to provide an open-ended opportunity for participants to use their own words to explain the meaning of the core concept and was intended to address RQ1 (i.e. *to what extent do students understand the core concept)*.

The second of the two tasks asked participants to analyse a simple scenario that required them to successfully employ the core concept to answer the question. An example is shown below. Responses to both questions were intended to explore RQs1-4.

Example – Core Concept: steady-state concentration

1. Explain what you understand the term 'Steady-state concentration' to mean.
2. KinetiCut is an experimental drug that transiently and selectively suppresses memory for pharmacokinetics equations. If you wanted to maintain a steady-state plasma KinetiCut concentration, what factors would you need to consider?

Quiz Delivery: Participants completed a short (15-min) quiz to assess their understanding of the four selected core concepts of pharmacology. The tool was constructed in Qualtrics and delivered via hyperlink or QR code. In some institutions, students were offered food while they completed their survey or were entered into a raffle for books or university merchandise after demonstrating proof of survey completion, while in other institutions no incentives were provided.

2.6. Data analysis

2.6.1. Text mining (N-grams) analysis

Responses to each question were analysed using text mining to reveal common terms and ideas that were combined to produce a corpus. Specifically, an online N-grams analyser, http://guidetodatamining.com/ngramAnalyzer/, was used to identify and quantify the most frequent words and word strings within the corpus. The top 10 monograms (nouns or verbs) were identified, excluding words contained in the original question or the core concepts themselves. These were then organised thematically, and bi-grams, tri-grams, 4-grams, and 5-grams were explored to reveal context.

2.6.2. Identifying 'essential elements' of each core concept

To determine the extent of alignment of student and expert understanding of the core concept, participant responses to the task *"Explain what you understand the term 'Core Concept' to mean"* were compared to expert definitions of the core concept in the form of essential elements

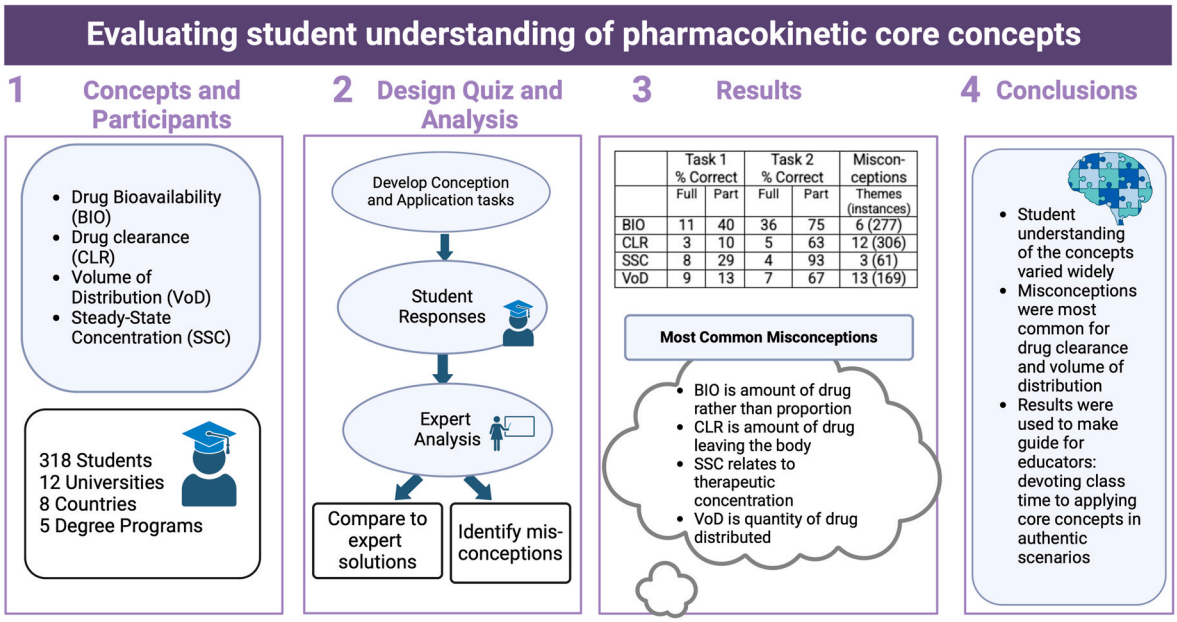

Fig. 1. Overview of the study design, methods, and results.

(EEs). The research team examined the definitions of the core concepts from Guilding et al. (2024), and identified EEs of the core concept, defined as "*discrete ideas present in the IUPHAR-Ed definition of the core concept*". PW and KV performed the initial drafting of the EEs of the core concept, which were later refined following feedback from the research team and the pair of experts who analysed responses for that core concept.

2.6.3. Analysis of the responses to prompts asking participants to "Explain what you understand the term 'insert core concept' to mean"

A team of experts (authors AMB, AS, CR, ED, JM, JK, KK and ST) conducted the analysis of the questions. Analysts were provided with Excel spreadsheets containing the participant responses and core concepts with their associated EEs, then completed the following tasks. First, in pairs, analysts made any refinements necessary to the EE for the core concept under consideration to analyse responses using a shared understanding of these elements. Next, analysts individually read each student's response and determined whether it contained the EE in full, partially, or not at all. Following this step, the two analysts came together to discuss and reach consensus on all discrepancies.

Analysts highlighted any underlying misconceptions for each student's response, defined as "*an illogical or unclear presupposition incongruent with the current state of scientific knowledge/professional standard*" (Olde Bekkink et al., 2016). Analysts were given a misconception from the discipline of physics, as an example. It considered a student's explanation that a buried object is not affected by gravity: "*Because when it's buried, gravity usually doesn't get under the ground*". This statement indicates a misconception that the effects of gravity are confined to objects above ground.

2.6.4. Analysis of responses to questions asking participants to apply each core concept in a novel scenario or context

In pairs, analysts assigned to specific core concepts collaborated to produce an indicative answer to the associated application question that was accurate, logical, and reasonable. Analysts then selected one of the following options from a drop-down list to assess the quality of each response: *Not sure*; *Off track or incorrect response; Correct but surface level; Partly correct but some errors or misconceptions; Accurate and logical response with reasoning provided.*

2.6.5. Which core concepts are most prone to misconceptions? What are the most common misconceptions held by students?

For each student response, analysts highlighted any text they believed to be incorrect, and identified any underlying misconceptions as defined earlier. Two experts independently assessed each student's response to tasks related to a given core concept, and coded misconceptions in Excel spreadsheets initially using a single label (misconception). These individual misconceptions were then grouped into broader emergent categories as reported by Rye et al. (1997).

3. Results

3.1. Demographics and prior experience of participants

A total of 318 students participated in the quiz (see Table 1). The majority (66%) reported English as their first language, with 28 other languages nominated as alternative first languages. Most students were in their second year of study (73%) in a medicine (39%) or pharmacy (35%) program. All students had completed a pharmacology course previously, of whom 60% had completed one prior course, and 28% had completed two.

3.2. Essential element analysis of responses

Each response was analysed by two independent coders as to whether it included the three pre-determined EEs of the IUPHAR-Ed definition of the core concepts. Fig. 2 shows the percentage of responses determined to include each EE.

Table 1
Demographics and response rates of participants.

Element	Details	N	%
Program	Medicine	125	39
	Pharmacy	110	35
	Pharm. Sci.	54	17
	Vet. Med.	20	6
	Biomed. Sci.	4	1
Year of study	1	10	3
	2	233	73
	3	32	10
	4	37	12
University	Monash	124	39
	Galway	110	35
	N. England	28	9
	Surrey	14	4
	UFSC	14	4
	Nazarbayev	11	3
	Sydney	6	2
	ETSU	4	1
	Newcastle	3	1
	UNIFAE	2	1
	Hong Kong	1	<1
	UFAM	1	<1
1st Language	English	210	66
	Not English*	95	30
	Not provided	13	4
Prior pharmacology courses	1	192	60
	2	88	28
	3	19	6
	4	9	3
Number of responses to questions	Drug bioavailability – conception	274	86
	Drug bioavailability – application	280	88
	Drug clearance – conception	273	86
	Drug clearance – application	267	84
	Steady-state concentration – conception	265	83
	Steady-state concentration – application	271	86
	Volume of distribution – conception	263	83
	Volume of distribution – application	272	86

3.3. Application of core concepts

A total of 276 participants responded to at least one of the questions that required application of the core concepts in a novel context or scenario. Fig. 3 shows the expert ratings of the responses to the application tasks for each core concept as: *off track or incorrect response; partly correct but some errors or misconceptions; correct but surface level; accurate and logical response with reasoning provided.*

3.4. Drug bioavailability - student understanding and misconceptions

The first question on this concept sought to determine students' understanding of *drug bioavailability*. A total of 274 participants provided their own explanation of this concept in response to the survey question.

An inductive analysis (N-grams) was performed by identifying the most frequent 1–5 word strings in the collective corpus of participant responses, which were then grouped by emergent themes (Table 2). This analysis highlighted the following themes: amount/how much of the drug; drug reaching the blood/systemic circulation; amount of the drug absorbed or reaching other compartments; and related to metabolism.

The EEs of this core concept, as identified by experts, are shown in Fig. 2. Analysis of participant responses indicated that 19 students (7%) included both EE1 and EE2 in their response, while 31 students (11%) included only EE1 as part of their explanation (Fig. 2). In the case of EE2, 96 students only partially addressed this by either mentioning the

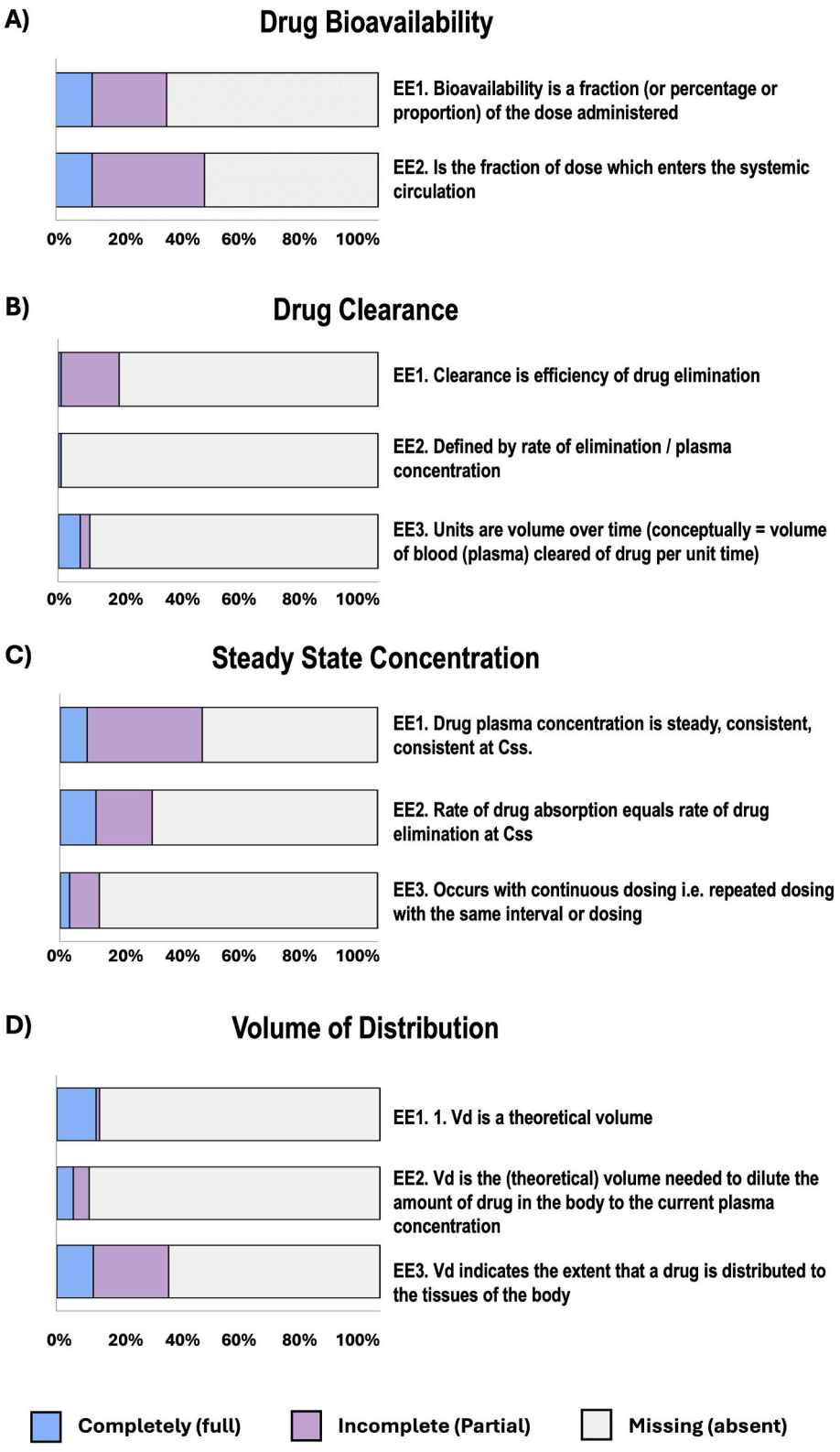

Fig. 2. Ratings of participant responses to the conception task. Answers were coded as complete (full), incomplete (partial), or missing (absent) for each essential element. Vd - *volume of distribution*; Css - steady-state concentration; EE - essential element.

fraction (or proportion) of dose or the systemic circulation, but not both elements. The top three misconceptions identified in student explanations (Table 3) included: bioavailability as an amount rather than a proportion or fraction; the drug must reach the target or have an effect; and the drug needs to reach the bloodstream rather than the systemic circulation.

To further evaluate student understanding of *drug bioavailability* in context, the following conceptual application question was asked: *"The pharmacokinetic properties of several new compounds are studied in phase II clinical trials. Healthy volunteers were administered each of the drugs orally*

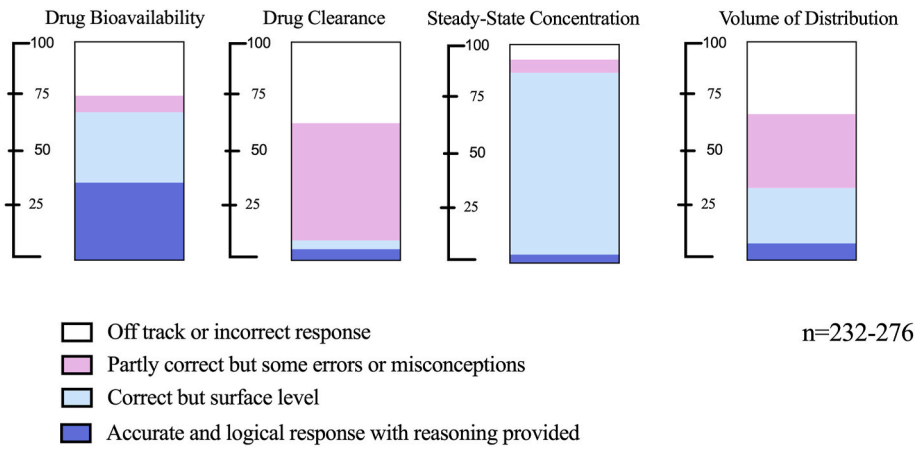

Fig. 3. Expert ratings of the responses to the application tasks for each core concept. n=232-276.

Table 2
N-gram analysis of participant questions – drug bioavailability and drug clearance.

PK Concept	Common Themes	Common Terms (n) – Conception	Common Terms (n) – Application
drug bioavailability	quantity of drug	*How much of the drug…* (19) *The amount of the drug…*(15)	*lowest amount* (3)
	comparison to administered dose	*Percentage of (a) drug…* (9) *Proportion of (the) drug…* (5)	*proportion* (7) *percentage of (the) drug* (5)
	access circulation	*bloodstream* (21) *reaches the systemic circulation* (5)	*circulation* (107) *systemic* (97)
	absorption	*…is absorbed…* (17)	
	metabolism	*metabolism* (26) *first-pass metabolism* (12)	
drug clearance	drug removal	*removed from the body* (26) *cleared from the body* (25)	
	elimination/excretion	*eliminated* (33) *excreted* (10)	
	rate	*time (e.g. time it takes, per unit time)* (93) *rate (e.g. of removal)* (58)	*clearance is a rate (22)*
	volume	*volume of blood/plasma cleared* (4)	
	quantity		*clearance is the amount* (16)

Table 3
Drug bioavailability misconceptions.

Misconception (n)	Source Question*	Exemplar
The bioavailability is an amount (quantity) rather than a proportion (fraction/percentage) (130)	conception	*"Is the quantity of the drugs [sic] that truly reaches the circulation."*
The drug must reach the target or have an effect (89)	conception	*"It would be the way the drug is available so it can have an effect."*
The drug needs to reach the bloodstream rather than the systemic circulation (34)	conception	*"The proportion of the drug that reaches the bloodstream."*
The drug needs to move throughout the body or tissues (15)	conception	*"…percentage of the drug that reaches the tissues"*
The drug needs to reach the system rather than systemic circulation (6)	conception	*"The amount of a drug available to the system."*
The drug needs to avoid first-pass metabolism (3)	conception	*"How much survives first pass through liver."*

* Note: no misconceptions were identified from the application question

and intravenously in separate sessions. Mean results are shown in the table below. Which drug has the lowest bioavailability? Indicate your choice (Drug A-D) and explain your choice below."

(*continued on next column*)

(*continued*)

Drug	Dose, oral (mg)	Amount of the drug reaching the systemic circulation (mg)
Drug	Dose, oral (mg)	Amount of the drug reaching the systemic circulation (mg)
A	45	30
B	70	65
C	90	45
D	60	40

A similar number of participants answered this question (n = 276) compared to the conception question, most of whom provided correct responses but at a surface level (Fig. 3). Common terms identified from the N-gram analysis of the conception question also arose from responses to the application question (Table 2), with a key focus on access of the drug to the circulation.

3.5. Drug clearance - student understanding and misconceptions

Two hundred and seventy-three students responded to the prompt "*Explain what you understand the term drug clearance to mean*". A variety of themes emerged during the N-grams analysis, the predominant of which were the idea of removal of drug from the body using a variety of terms, and notions of *"rate"* and *"time"* (Table 2), while only four students addressed the volume of blood/plasma cleared, which is an EE. Common misconceptions were then identified during the qualitative analysis, the most frequent of which were the route by which a drug was

eliminated and the time over which an amount of drug was removed (Table 4).

Analysis of participant responses indicated that 17 students articulated EE3 (6%), whereas EE2 was included in only three responses (1%) (Fig. 2). In the case of EE1, although 45 students (16%) partially articulated it, only 4 students included it fully. The top 3 misconceptions identified in student explanations (Table 4) largely related to focusing on one method of drug elimination (e.g. renal) or confusing elimination and clearance.

To further evaluate student understanding of *drug clearance* in context, the following conceptual application question was asked: *"Drug clearance and drug elimination half-life are related concepts. Briefly explain what differentiates between them."* Two hundred and fifty-three participants answered this question, of whom 34% provided a response rated as partly correct with some misconceptions and 33% were off track or incorrect (Fig. 3). The top 3 misconceptions identified in student answers for this question related to the view that clearance refers to the drug leaving the body rather than being cleared from the plasma (Table 4). The N-grams analysis of the application question highlighted 2 themes that were shared with the conception question, each of which was related to the amount of drug, either directly, or in the context of a rate (Table 2).

3.6. Steady-state concentration - student understanding and misconceptions

The first task sought to determine students' conceptions of this term by asking them to explain what they "*understand 'steady-state concentration' to mean*". A total of 265 participants submitted responses for this concept. The N-grams analysis included the eponymous concentration of drug in the blood, ideas of the amount of drug being administered or absorbed, the perception of "*being equal to*", and the notion of the amount being eliminated (Table 5). Twenty-three responses included EE1 (9%), 30 included EE2 (11%) and 8 included EE3 (3%) as part of their explanation (Fig. 2). Only one student responded with all three elements in full. In the case of EE1, 96 students (36%) only partially addressed this and commonly identified blood or circulation instead of specifying plasma concentration. Regarding EE3, 233 students (88%) did not mention continuous or repeated dosing. The top 3 misconceptions identified (Table 6) focussed on the action or effectiveness of the drug and confusion about the meaning of "steady-state".

To further evaluate student understanding of steady-state concentration in context, the following conceptual application question was asked: *"KinetiCut is an experimental drug that transiently and selectively suppresses memory for pharmacokinetics equations. If you wanted to maintain a steady-state plasma KinetiCut concentration, what factors would you need to consider?* Two hundred and thirty-two participants answered this question, and the vast majority of responses (83%) were coded as correct, though superficial (Fig. 3). No misconceptions were identified in students' answers to this question.

Table 4
Drug clearance misconceptions.

Misconception (n)	Source Question	Exemplar
Drug clearance is the amount of drug leaving the body or the rate at which it does so (159)	conception & application	*"Clearance is the constant rate at which a drug is cleared from the body…"* *"The rate at which a drug is removed from the body so it not longer [sic] has a biological effect."* *"How much of the drug is cleared from the body."*
Clearance is the route by which a drug is eliminated from the body (73)	conception	*"Drug Clearance [sic] is the rate at which a drug is removed from the circulation either via the kidneys, liver or other pathways."*
Clearance is the permanent removal of the drug from the body (21)	conception	*"The permanent elimination of the drug from the body, eg. [sic] renal clearance."*
Clearance represents the time required to remove a drug from the body (15)	conception	*"The time it takes a drug to be removed from an amount of liquid in the body."*
Clearance is the ability of your body to remove a drug (8)	application	*"Drug clearance is the ability of your body to get rid of a drug from your system."*
Clearance relates to the inactivation of the drug (4)	application	*"Clearance refers to the inactivation of the drug, whereas elimination refers to its removal from the body entirely."*

3.7. Volume of distribution - student understanding and misconceptions

Students were asked first to explain the meaning and then to apply the concept of volume of distribution. A total of 263 survey participants chose to provide a meaning for this concept, and their responses were subjected to inductive analysis (N-grams) (Table 5). Almost half of the students reiterated the concept as an answer and the primary emergent theme was the notion of quanta of drug, be it amounts, concentrations, or volumes. A secondary theme was the location in which the drug would be found, either more generally (e.g. tissues, compartments), or specifically (e.g. plasma, blood, circulation). Two of the elements considered essential by the expert group were generally absent from student answers (Fig. 2). Few students acknowledged that the volume of distribution is theoretical rather than actual, and that it reflects the extent to which the drug would be diluted to achieve the observed plasma concentration. Approximately half of the students recognised that the concept involves the distribution of a given drug around the body. However, the explanations were generally incomplete and tended to focus on the ability to access a tissue (e.g. penetration). The most common misconception was that the volume of distribution pertained to the quantity of the drug, rather than the volume in which it is diluted (Table 7).

Students were then asked to apply their knowledge to the question, *"Does a larger body volume result in a higher volume of distribution? Please explain your response below."*. Of the 248 students who responded, most supplied a partially correct, if somewhat superficial explanation (Fig. 3). The N-grams analysis showed that students generally associated a larger body volume with a larger volume of distribution (Table 5), reinforcing the pattern seen in the responses to the request for an explanation of the meaning of the term. Three fundamental misconceptions were identified, the most common of which was the idea that volume of distribution is an actual rather than theoretical value (Table 7).

3.8. Summary of misconceptions findings

The tables above show only the most frequent 3–5 misconception themes. Supplementary Table 1 provides the complete list of apparent misconceptions identified by the analysis team. Overall, there were 34 misconception themes coded in a total of 813 instances. For *drug bioavailability*, there were 6 themes in total, all of which arose from the conception task (coded 277 times). Evaluation of the responses for *drug clearance* led to the identification of 12 themes in total, with 9 themes arising from the conception task and 3 themes from the application task (coded 306 times). For *steady-state concentration*, there were 3 themes in total, all of which arose from the conception task (coded 61 times). Finally, for the *volume of distribution*, there were 13 themes in total, 10 of which were associated with the conception task and 3 for the application task (coded 169 times).

Table 5
N-gram analysis of participant questions – steady-state concentration and volume of distribution

PK Concept	Common Themes	Common Terms (n) – Conception	Common Terms (n) – Application
steady-state concentration	systemic concentration	*drug concentration* (21) *plasma concentration* (17) *concentration in blood* (3)	
	administered or absorbed	*absorbed/absorption* (27) *administered/administration* (23)	*absorption* (14)
	equivalence	*equal* (31) *is same as* (19)	
	drug loss	*eliminated/elimination* (35) *being cleared* (6) *metabolised* (7)	*clearance (e.g. drug clearance, clearance rate)* (77) *elimination* (29) *metabolism* (31)
	constant/stable	*constant* (46) *stable* (7)	
	related to therapeutic window	*therapeutic window* (22)	
	influencing factors		*bioavailability* (43) *distribution* (30) *half-life* (22) *absorption* (14)
volume of distribution	quantity of drug volume drug location theoretical volume distribution influencing factors	*amount* (70) *concentration* (48) *volume of drug* (17) *dose* (12) *volume* (161) *volume of the body* (6) *plasma* (47) *blood/bloodstream* (47) *circulation* (13) *theoretical volume* (18) *distributes/distribution* (90)	*larger body volume results in larger volume of distribution (62)* *larger body volume due to greater area to distribute in* (11) *protein binding* (6) *pharmacokinetic properties* (3) *drug clearance* (2)

Table 6
Steady-state concentration misconceptions

Misconception (n)	Source Question*	Exemplar
Relates to the concentration required for a therapeutic effect, or the need for the concentration to be within the therapeutic window (48)	conception	*"The concentration of drug needed for the drug to be effective."*
The concentration cannot fluctuate (11)	conception	*"Steady state is when the concentration of drug is relatively stable and is not fluctuating up or down, usually occurs after 3-4 half-lives."*
Relates the concentration of drug to that binding to receptors (2)	conception	*"The concentration which [sic] evens out over time/flattens as the receptor occupancy maxes out and no more binding occurs."*

* Note: no misconceptions were identified from the application question

Table 7
Volume of distribution misconceptions

Misconception (n)	Source Question	Exemplar
Volume of distribution is the quantity of drug, as amount, volume, or concentration, distributed throughout the body (66)	conception	*"Quantity of the drug that is spread throughout the body."*
Volume of distribution reflects the body volume or size (44)	conception & application	*"…a larger body volume would lead to an increase in the body's water volume, consequently, it would increase the distribution."* "*The size of the individual or living animal, for example humans have a higher volume of distribution than mice*."
Volume of distribution represents the body's ability to distribute a drug or the efficiency with which it does so (10)	conception	*"It's a pharmacokinetic profile that's got to do with how well the body distributes a drug."*
Volume of distribution represents the ease with which a drug penetrates a tissue (8)	conception	*"Volume of distribution is the extent to which a drug leaves the bloodstream and enters the tissues."*
Volume of distribution represents the proportion of drug in the circulation compared to the proportion in the tissues (8)	conception	*"Vd is ratio in which [sic] the drug concentration is compared to whether it is localised in the blood or the tissue."*
Volume of distribution is only related to the physicochemical properties of the drug (7)	application	*"Only factors like physicochemical properties will affect Vd."* *"…the volume of distribution relates only to the drug your [sic] administering, not the patient."*

3.9. Student performance by course of study, first language and prior exposure to pharmacology

This study was not designed to test hypotheses regarding possible relationships between programs of study, first language, or the number of pharmacological courses that participants had previously taken. In order to inform future studies, we binned the data using these variables and present means and standard deviations in Supplementary Tables 1–6. There were relatively few differences between the groups. Pharmacy students appeared to outperform medical students for some of the EE comparisons and application tasks. Students whose first language was not English performed similarly on EE conception and application tasks compared to students whose first language was English. Students who had taken two or more courses of pharmacology performed similarly on both tasks to students who had only taken one course (Supplementary Tables 1–6).

4. Discussion

4.1. Summary of major findings

Based upon the cohort of learners who participated in the questionnaire, our data suggest that a minority of students understand the core pharmacology concepts *drug bioavailability, drug clearance, steady-state concentration,* and *volume of distribution* in a way that aligns with the expectations of an international group of pharmacology experts. Overall, fewer than 50% of participants identified the EEs for all but one of these core concepts, namely EE3 of *volume of distribution*. Alignment between student and expert responses was least frequent for *drug clearance*, followed by *steady-state concentration* and *volume of distribution*, whereas it was strongest for *drug bioavailability*. The extent to which students' answers reflect a true lack of comprehension is unclear. Nonetheless, similar patterns were identified across institutions and training programs. Consequently, this study identified that students have a wide variety of understandings of what *volume of distribution, steady-state concentration, drug bioavailability,* and *drug clearance* mean (RQ1), and these perceptions do not align well with expert understanding (RQ2). Students did perform slightly better when applying the core concepts to novel problems or using them to predict outcomes (RQ3), although numerous misconceptions were identified in the responses to the tasks (RQ4). Although it might not be surprising that students who were not afforded an opportunity to prepare for this task performed relatively poorly, it is somewhat concerning that students who have taken one or more units that include introductory pharmacokinetic concepts have trouble explaining their meaning and show many misconceptions. It is unclear whether the misconceptions identified in this study would be directly responsible for prescribing or dispensing errors by health professionals. However, it is quite possible that fundamental misunderstanding of clinical parameters such as volume of distribution (as an amount of drug) and steady-state concentration (as the concentration required for a therapeutic effect) could lead to errors in clinical practice or drug discovery and development. Moreover, errors in application of the core concepts in context were quite common - 25, 33 and 37% of participants provided incorrect answers to the application questions for *drug bioavailability*, *volume of distribution*, and *drug clearance* respectively. Pharmacokinetic principles could become clearer when graduates begin to use these principles in their daily practice, particularly given the underpinning value of *steady-state concentration* and *drug clearance* knowledge for drug monitoring and prescribing. A study of interns involving the same tasks would be of interest. For students, we suggest that greater use of authentic cases and problems within curricula will better prepare them for their professional context.

It is noteworthy that these four pharmacokinetic core concepts are pharmacokinetic parameters rather than pharmacokinetic processes. Instead, they are concepts that have meaning in the mathematical models describing pharmacokinetic processes. This raises the question of whether some of the difficulty in articulating understanding relates to the mathematical aspect of these core concepts.

4.2. Understanding of PK core concepts

4.2.1. Drug bioavailability

Students correctly linked the concept of *drug bioavailability* to the pharmacokinetic process of absorption; however, very few were able to explain it fully and precisely, which revealed misconceptions when attempting to articulate their thinking. By contrast, students were more successful at the application task, although at a relatively surface level.

The most common misconceptions students have about *drug bioavailability* are related to the misapprehension that this concept correlates with an amount of drug present within the systemic circulation, rather than a fraction or percentage of the administered dose. Concepts of ratio, proportion, and related multiplicative reasoning are known to be an area that students find difficult (Koenig and Pike, 2014; Tariq, 2008), with proportional reasoning identified as a threshold concept in other disciplines (Lloyd and Frith, 2013). Furthermore, the term *"amount"* is problematic in that it can be used to mean mass or volume (Rees and Bruce, 2022) and is generally poorly defined and understood. Taken together, it is possible that a weakness in foundational mathematical concepts could affect the understanding of pharmacological concepts. For some educators, it might be a bit challenging to teach pharmacokinetics in a way that ensures that students learn to *"choose suitable mathematics to use and at the appropriate level as required by the context/situation, apply the mathematics competently and confidently, and ensure that the solution fits the situation"* (Bell et al., 2020). One approach to address this is collaborative pedagogy, in which discipline experts work with literacy/numeracy experts to create enhanced learning opportunities for students (Frith, 2011).

Additionally, many students related *drug bioavailability* to the ability of the drug to reach its target or be efficacious, rather than simply the proportion of the administered dose that reaches the systemic circulation. There is a parallel here with the observations for similar misconceptions regarding *steady-state concentration* (see below) in that students related *steady-state concentration* to a therapeutic effect. It is tempting to speculate that this could arise if these concepts are primarily taught within the context of calculating dosing regimens or at least a therapeutic application. Although it is common to use clinical scenarios or vignettes to improve students' motivations to study a subject that might be considered daunting and challenging (Cook and Artino, 2016), it can potentially skew students' perceptions of the content.

4.2.2. Drug clearance

Of the four core concepts, overwhelmingly, students grappled most with *drug clearance*, conflating it with both the route and rate of elimination, as well as the time required to accomplish the removal of the drug from the body. Although it is recognised that the concepts of clearance and half-life are linked, the ability to differentiate between them was challenging for those respondents who tackled the application question.

Contemporary approaches to teaching might have contributed to the students' misinterpretation, however. More emphasis could be placed on the distinction between clearance as a pharmacokinetic parameter and elimination as a pharmacokinetic process, with clearance providing a quantitative estimate of the efficiency of the process of elimination. Additionally, clearance is sometimes explained using metaphors or analogies, which usually provides a valuable bridge to understanding (Low, 2008; Mouraz et al., 2013), but for students who are already struggling, it could potentially compound their perplexity (Chew and Laubichler, 2003).

4.2.3. Steady-state concentration

As with *drug bioavailability*, students had difficulty articulating the meaning of *steady-state concentration* with sufficient detail. By contrast, they were able to relate it in a vague manner to the concentration remaining relatively constant, occasionally recognising that it occurs when the rate of absorption equals the rate of elimination. Unlike the core concept of *drug bioavailability*, however, only 8% of students provided partial or complete responses for the application question.

The most common misconception about *steady-state concentration* was that it was related to a therapeutic effect or a requirement to be in an appropriate treatment range. Students may have been taught about steady state in the context of determining an appropriate dose and dosing interval, creating a focus on treatment management. Similarly, they may have associated steady state with the therapeutic window, without intending to imply that this concentration had to be within that window. A smaller percentage of students indicated that *steady-state concentration* cannot fluctuate, which while true for an intravenous infusion, is not the case for multiple dosing paradigms. Consequently, more emphasis on this core concept along with active learning

modalities that involve problem sets and computer simulations, which have been successfully employed to illustrate pharmacokinetic principles, including steady-state plasma concentrations, may be beneficial (Gabrielsson et al., 2014; Mehvar, 2001).

4.2.4. Volume of distribution

Volume of distribution plays an important role in determining and monitoring treatment regimens, as well as assessing the influence of physiological changes, such as age-related changes, pregnancy, and oedema (Feghali et al., 2015; Huang et al., 2020; Jaehde and Sörgel, 1995). Despite this, it is a concept with which students regularly struggle, as evidenced by the limited meanings supplied by survey participants and the contrast between those students for whom English is their first language versus their second (Supplementary Table 2). Students were only able to articulate the third of the 3 EEs, namely the extent to which a drug distributes throughout the body, approximately 50% of the time. Additionally, the primary meaning-associated misconception was a focus on the quantity of drug rather than the theoretical volume in which it is diluted. Similar to responses for *drug bioavailability*, students lacked precision in the use of words relating to the amount of substance, quantity, volume, proportion, or percentage.

By contrast, approximately half of the students correctly applied this concept to the question of the relationship between body size and *volume of distribution*. It is noteworthy that the explanations were generally superficial, often 1–3 words and lacking a rationale for their response. Students may have assimilated this concept to the extent that their understanding is primarily implicit, and therefore, more readily applied than explained. This is not a consistent finding in the literature, however, as some students appear to be better at answering 'know' questions than 'know how' questions (Wilhelmus and Drukarch, 2020). Alternatively, this response pattern may reflect the pedagogical shift from rote memorisation to active learning in tertiary institutions (Freeman et al., 2014; Prince, 2004), though the gains have not been uniform (Andrews et al., 2011), and students are often resistant to this approach (Finelli et al., 2018; Tharayil et al., 2018). Additionally, it has been argued that students do not require foundation fact-based knowledge to engage effectively with higher order learning (Agarwal, 2019) and therefore, the choice of tasks asking for terms to be explained may not align with current teaching practices. Consequently, moving forward, it would be valuable to probe this possibility with students using approaches such as think-aloud interviews (Altalhi et al., 2021; Eccles and Arsal, 2017; Jenkins and Shoopman, 2019; Reinhart et al., 2022).

4.3. Influence of course/first language and prior learning

As mentioned, this study was not designed to compare student performance based on program of study, first language, or number of prior pharmacology courses taken. The pharmacy students who engaged in this study did appear to outperform medical students from other universities across a range of tasks, however this could be due to many factors that are unrelated to their degree of study. These findings are nonetheless consistent with a previous study of over 600 pharmacy and medical students (Keijsers et al., 2014), which found that *"pharmacy students had better knowledge of basic pharmacology than medical students"*.

4.4. Limitations

Whilst there were over 300 participants from 11 universities across 7 different countries, a large proportion were sourced from two institutions. Consequently, it is possible that the findings of this study may not be fully representative of the diversity of pharmacology education programs globally and may not reveal the degree of variability that no doubt exists. Knowledge gaps and misconceptions may arise due to differences in time since teaching, instructional methods, and curriculum design between courses. Of particular interest would be the potential impact of stand-alone courses versus an integrated curriculum, as the latter has been shown to reduce understanding of pharmacokinetic concepts (Pandit et al., 2021). Similarly, although there is evidence that pharmacy students are exposed to almost twice as much pharmacology teaching across their program than medical students (Lloyd et al., 2013), they might not necessarily receive more pharmacokinetics-specific instruction. This study was not designed to test hypotheses regarding causal relationships between these factors, and hence we did not control for or report them explicitly, though future studies could. Nevertheless, this study provides a significant first step towards a clearer understanding of the misconceptions and alternative conceptions surrounding pharmacokinetic core concepts that could be used to refresh both the pharmacology curriculum and approaches to assessment.

Since participation was voluntary, there might have been a self-selection bias that favoured participation by motivated and/or confident students, or those for whom an incentive was provided. Additionally, the proportion of participants from under-represented groups is unknown and certain cohorts of students might disproportionately struggle with the numeracy and quantitative aspects of the subject (Koenig, 2011). Consequently, those who find these areas challenging may have opted not to participate, a possibility reinforced by the fact that 12–17% of participants chose not to answer certain questions. This self-selection bias could result in an overrepresentation of students who are more comfortable with pharmacokinetics, potentially skewing the findings and underestimating the true extent to which misconceptions and knowledge gaps occur within the broader student population.

Misconceptions might arise from a variety of sources, including previous coursework, textbooks, or even the phrasing of the assessment questions (Taylor and Kowalski, 2014; Erman, 2017); therefore, it is challenging to account for the contextual factors that may influence how a student might respond to the question sets. Also, pharmacokinetic concepts are often interrelated and therefore, students might understand a concept better in the context of a broader pharmacological framework rather than in isolation. Differences in how pharmacokinetics is taught, as well as by whom and how many, might also impact students' ability to articulate and apply concepts (Hattie, 2003; Hughes et al., 2018; Jones and Harris, 2012; Kheir et al., 2015).

Although expert analysts identified EEs and assessed responses, there is always a degree of subjectivity in qualitative evaluation, which could influence the consistency and reliability of assessments. Additionally, the process of thematically grouping misconceptions is inherently subjective and therefore, different experts might categorise and interpret misconceptions differently, affecting the conclusions drawn.

4.5. Guide to educators

Participant responses were used to identify the fundamental knowledge gaps and common misunderstandings regarding the core concepts *drug bioavailability*, *steady-state concentration*, *volume of distribution*, and *drug clearance*. On this basis, we propose a set of suggestions for teaching each of these core concepts (Table 8). A valuable future direction will be to identify evidence-based educational resources that support these suggestions, the creation of which is an integral component of the IUPHAR-Ed collaboration.

5. Conclusions

This study has, for the first time, revealed the extent to which students understand and can apply the core concepts *drug bioavailability, drug clearance, steady-state concentration, and volume of distribution.* The gaps in student understanding reported here, as exemplified by their misconceptions or alternative conceptions, may provide educators with a valuable guide to the concepts upon which to focus their teaching to have the greatest potential impact on student learning. Identifying misconceptions is an important first step in improving teaching quality and encouraging students to think deeply about these concepts. Indeed, physics educators found that the performance of students from top

Table 8
Suggestions for teaching pharmacokinetic core concepts

Topic	Suggestions
Teaching pharmacokinetic parameters	Be aware of the mathematical demands of the subject and that some of the numerical concepts are threshold concepts that university students are known to find difficult. Collaborative pedagogy including pharmacology and mathematics educators may provide useful interventions for student success. It can be helpful to introduce the pharmacokinetic processes first (i.e. absorption, distribution, and elimination) and then relate these to the pharmacokinetic parameters (i.e. drug bioavailability, volume of distribution, and drug clearance, respectively) to facilitate students' ability to distinguish between the roles of the various concepts. As concepts can be taught in different ways, agreement amongst instructors on a consistent approach can avoid students' confusion.
Drug bioavailability	The role of the route of administration in determining the proportion of the dose that gains access to the systemic circulation should be emphasised, as well as the factors that determine drug bioavailability. Active learning activities can be designed to demonstrate that while the dose administered, and by extension the resulting plasma concentration can change, the proportion of the drug that gains access to systemic circulation remains the same.
Drug clearance	Students often confuse elimination and clearance, and therefore, consider introducing elimination as a process that involves a route and a rate, which link mass and time. The elimination rate varies as plasma drug concentration changes, whereas clearance is a flow rate (i.e. volume per time) that is constant under conditions in which the rate of elimination is proportional to the plasma concentration. Creating active learning sessions to help students to understand the relationship between clearance and elimination, and distinguish between them can reduce confusion between these concepts.
Steady-state concentration	Demonstrate how the plasma drug concentration versus time graph from a single dose relates to that from multiple doses for which the plasma drug concentration accumulates, and illustrate this for varying dose intervals at the same dose rate. Design an active learning task to allow students to explore fluctuations in the steady-state concentrations over time resulting from changes in dose (e.g. missed dose, doubled dose) or clearance, to establish that the steady-state concentration increases with increasing dose rate and decreases with increasing clearance.
Volume of distribution	Remind students of the relationship between the mass of drug, volume it is dissolved in, and concentration. Use this to clearly distinguish between the role of plasma drug concentration in helping to calculate the volume of distribution and the independence of this volume from the quantity of drug. Engage students in an activity in which they calculate the body size that would result from small versus profoundly large volumes of distribution, to emphasise that volume of distribution is an apparent and not a real volume.

universities on conceptual tests was poor, and included the same misconceptions as primary school students, which led to a transformation of the discipline and a focus on the application of concepts. Misconceptions identified in this study will also be used as distractors in creating the first pharmacology concept inventory, currently in development.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No additional relationships to declare. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2025.177256.

Data availability

Data will be made available on request.

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