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PROGRAMME DESCRIPTION

Using GastroPlus to teach complex biopharmaceutical concepts

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Abstract

Context: In response to the COVID-19 pandemic, many educational adjustments had to be made to move in-person teaching to online classrooms. This report showcases the use of the software GastroPlus at an undergraduate level pharmacy course. **Programme description:** This course aimed for the students to learn how to perform mechanistically based simulation to predict the oral absorption pattern, pharmacokinetics and biopharmaceutics properties of compounds in humans. The computer simulation offered the opportunity to teach concepts about bioavailability providing all kinds of experience with major biopharmaceutic determinants that affect systemic drug exposure. **Evaluation:** The advantage of this approach was seen by the enhanced performance on the biopharmaceutics questions on the final exam compared with the previous year where the laboratory was not implemented: An increase from 2019 (where no laboratory was implemented) through 2021 in correct scores from 52, 76 to 75%, respectively. **Conclusion:** There is great benefit in using computer programs and simulations as a technique to enhance active learning and to educate pharmacy students in salient aspects of biopharmaceutics.

Context

In response to the COVID-19 pandemic, many adjustments were required to be undertaken to move from in-person didactic lectures and bench laboratories to teaching via online classrooms (Chandrasekaran, 2020). In many circumstances, this pivot was challenging, especially for wet laboratory demonstrations. On the other hand, this online environment yielded an opportunity for innovative learning approaches to be developed, implemented and assessed for their efficacy. There is an increasing number of anecdotes, case reports, and publications on how instructors tackled the challenge of delivering course content while engaging the students to provide the best learning experience under the given circumstances (Chandrasekaran, 2020).

As reported by Delgado, creative online laboratory alternatives can provide students with valuable learning experiences such as data analysis and critical thinking skills to solve scientific problems, which can be applied in their future careers (Vasiliadou, 2020; Delgado, Bhark, & Donahue, 2021). Additionally, this platform can facilitate the ability to undertake group laboratory work, which is an important part of the students' learning experience with respect to pedagogy and roles with a healthcare team, while also enabling social interaction and collaboration. Furthermore, as pointed out by Dustman and colleagues, the student's retention of information and their comprehension of fundamental concepts can be positively impacted by virtual in silico simulations (Dustman, King-Keller, & Marquez, 2021). Another advantage of using online tools is the ability of students to learn at their own pace and to adjust the learning to their individual needs (Quesada, 2020; Dustman *et al*., 2021).

A review of the biomedical literature databases (Pubmed, Embase, Google Scholar) revealed that the use of various multimedia simulation software had been incorporated into the pharmacy curriculum (Romero *et al*., 2020). Indeed, there is a significant experience at the University of Alberta for the effective utilisation of simulation programs in the undergraduate pharmacokinetic course (uSimPK) (Brocks, 2015; Brocks

& Hamdy, 2020). However, to date, there is a paucity of a report in the literature on simulation software being utilised in pharmaceutics, which is a key component of the curriculum in accredited pharmacy programs and national licensing examinations.

The pedagogical experiences of the authors showcase the use of the software GastroPlus (Simulations Plus, Lancaster, CA) in a Pharmaceutics course (PharmD program at the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta). GastroPlus is a mechanistically based simulation software package that simulates drug absorption through various routes of administration and can model salient aspects of biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals with a user-friendly interface (Romero *et al*., 2020).

In this course, foundational pharmaceutical principles with respect to the concepts of bioavailability were previously taught with traditional didactic methods in a limited way. For instance, the authority style semi-formal chalk and talk descriptional lectures with no active learning component such as multimedia or hands-on experience. This only covers the definition of the concepts which were unable to be fully expanded into contextual extensions of pertinent variables that determine the rate and extent of absorption, which encompasses bioavailability. The learning objectives for this lecture were for the pharmacy students to be able to define the fundamental parameters of the biopharmaceutical classification system (BCS) and demonstrate knowledge of *in vitro* and *in vivo* correlation and bioavailability. The computer simulation program offered the opportunity to teach these concepts in an active learning multimedia environment with discussion in a hybrid facilitator demonstrator style.

Furthermore, GastroPlus is software used both in the pharmaceutical industry and regulatory agencies around the globe; hence the opportunity for the students to be exposed to this tool is invaluable. Since there is a raising need for trained scientists in modelling and simulation (M&S) using this and other similar software, this course is beneficial from a knowledge perspective as well as a career-enhancing and skill-training opportunity (Romero *et al*., 2020).

Description of the In-silico Laboratory

The pharmaceutics course was identical to previous years (i.e. same instructor and the material covered during the in-class lectures for over a decade) except for the firm active learning commitment to using GastroPlus as a multimedia approach. In this paper, the authors describe how the computer laboratory was conducted.

All sessions were carried out using the online Zoom meeting platform. Prior to the computer laboratory session, a Zoom seminar was provided outlining the following topics: learning objectives, introduction to GastroPlus and its functionality. A case study was discussed to contextualize the important aspects, underlying absorption covered previously in the lectures given in class, and finally, a detailed laboratory assignment description was undertaken.

The computer laboratory course's aim was to "learn how to perform mechanistically based in silico simulation to predict the oral absorption, pharmacokinetics and biopharmaceutics properties of a given compound in humans". The focus was given on the following parameters:

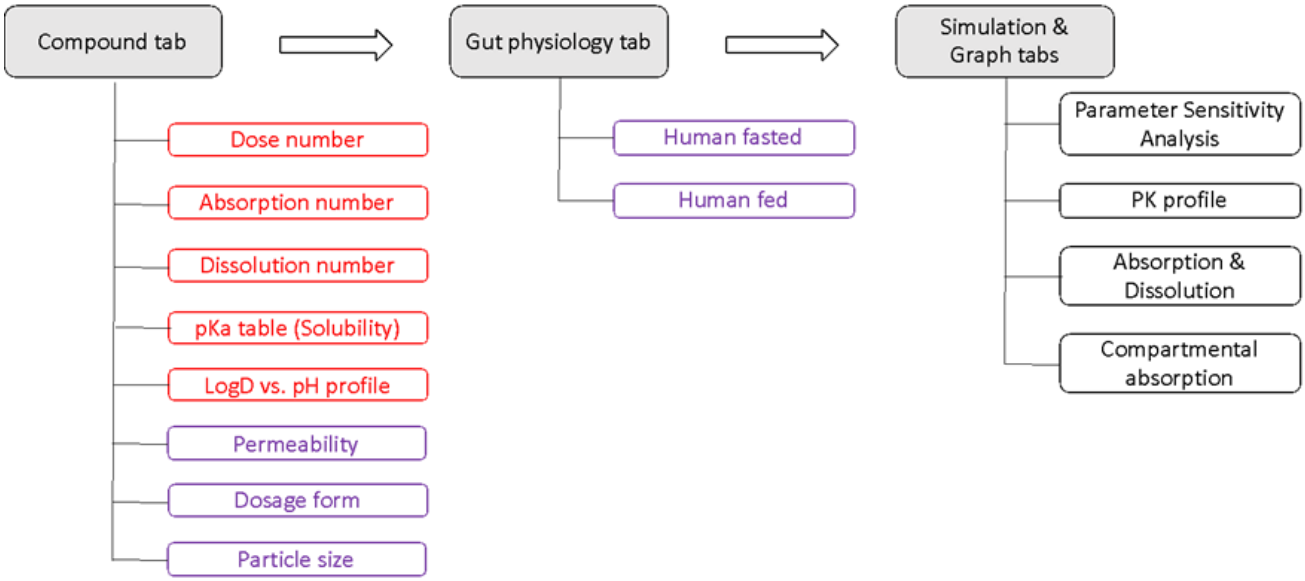
- Particle size;
- Log D (the diffusivity water: Octanaol partition coefficient at a specific pH);
- Dissolution;
- Solubility;
- Dosage form – Immediate Release *vs* Controlled Release: Gastric Retention /CR: Dispersed;
- Gastrointestinal physiology (pH and gastrointestinal transit time).

The pre-laboratory seminar was important to introduce the pharmacy students to the software's interface and to show its applicability, which provided the students with a conceptual framework of ideas as to what to expect from the laboratory session. Using this approach, students could then optimally utilise the assigned laboratory time period and have a meaningful and engaging learning experience. If a new technological variable was to be introduced and conducted on the day of the laboratory, many students would most likely be anxious and overwhelmed.

The class was divided into groups of a dozen students, each with an assigned laboratory date. During the first 15 minutes of the laboratory session, the 12 students remained as one group while the teaching assistant (TA) gave a brief demonstration of the computer software Gastroplus. Subsequently, the students were divided into three breakout rooms. Each group was given a unique medicinal compound to understand the factors that affect its absorption and perform a pharmaceutical development assessment using computer simulations. The students provided electronically shared digital screenshots of their simulations to answer questions with respect to concepts related to bioavailability, absorption,

solubility, permeability, physicochemical properties, and dosage form analysis, as shown in the attached laboratory report. The students accessed the software via an Amazon cloud server, and each student was provided with a personal login name to access. The sessions were moderated by both the instructor and the TA to guide students during the laboratory exercise.

The software GastroPlus is composed of different tabs (a clickable area at the top of a window that allows access to another page or area on each topic), namely: Compound, Gut Physiology, Pharmacokinetics, Simulation and Graph. The individual tabs which were used by the students are described below. In the compound tab, the students could find information about the drug particle (e.g. solubility and intestinal permeability) and were also able to change parameters such as dosage form and particle size. In the Gut physiology tab, there is an array of species and conditions the student can choose from. In this laboratory, the focus was to analyze human physiology under both fasted and fed states. Since the students were using a demo database, the pharmacokinetic (PK) parameters of the compound of interest were already set; in this way, the default parameters were used. In the Simulation tab, the students performed both single simulations (to analyse the PK profile, absorption & dissolution, and compartmental absorption) and parameter sensitivity analysis. The flowchart in Figure 1 captures the steps taken by the students during the computer laboratory exercise.



Note: Red: Parameters analysed by the students to understand the physicochemical properties of the compound. Purple: Parameters the student could change to assess the impact on the pharmacokinetics.

Figure 1: Flowchart to run simulations using GastroPlus

The laboratory report manual provides questions that guide the students through the simulated drug development process along with a representation of the software screen that students will be viewing. The subheading functions highlighted in red are the dependent variable parameters analysed by the students to help in understanding the physicochemical properties of the compound. While those in purple are the independent variable parameters, the student could change them to assess their impact on the pharmacokinetic outcome measure.

Section 1 – Compound tab (Figure 2)

1) What can you tell about the drug's solubility and permeability based on the Dose number, Absorption number, Dissolution number (Figure 2), pKa table, LogD profile (Figure 3)?
2) When using solid oral dosage forms, immediate release is usually the simplest and most preferrable type of formulation. However, other dosage forms may be a better approach to increase drug absorption. Would you consider CR: Gastric Release as a better alternative dosage form to IR: Tablet? Please explain.

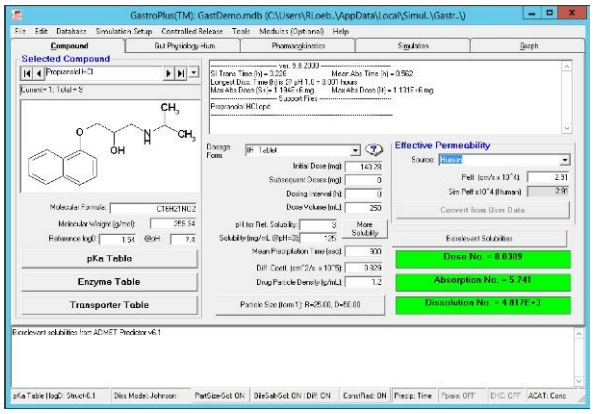


Figure 2: Compound tab

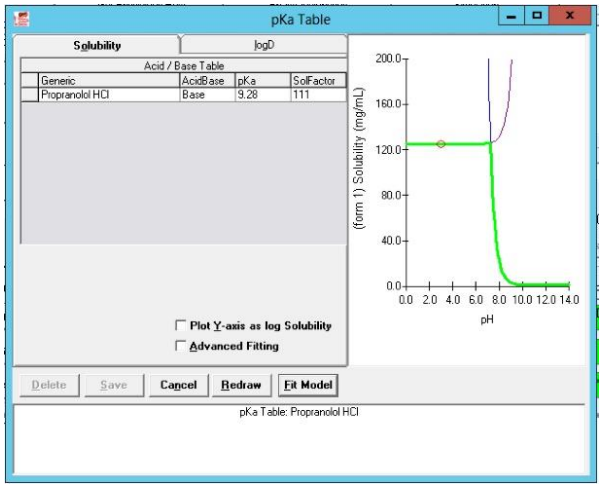


Figure 3: pKa table – Solubility

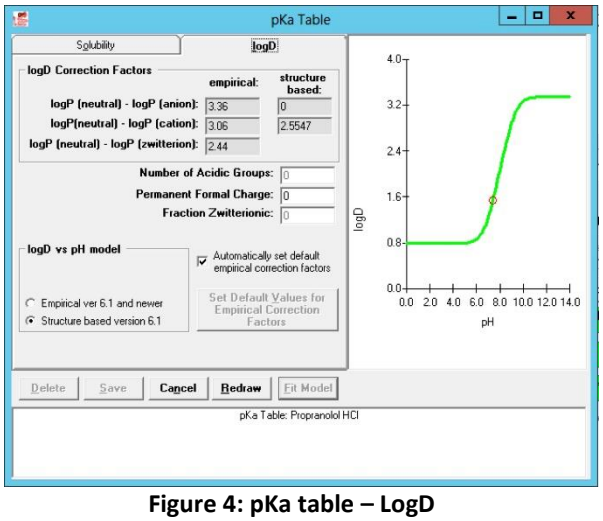


Figure 4: pKa table – LogD

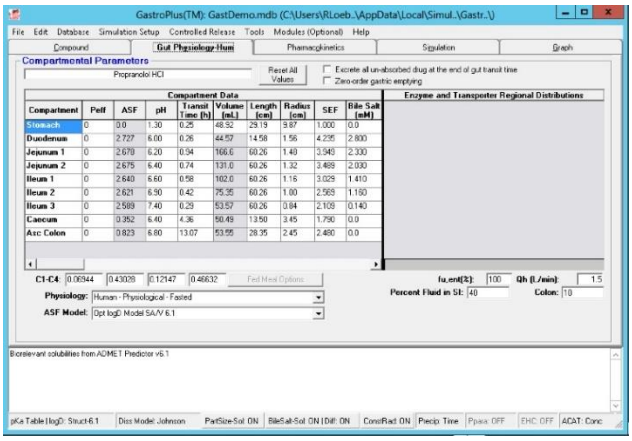


Figure 5: Gut physiology tab

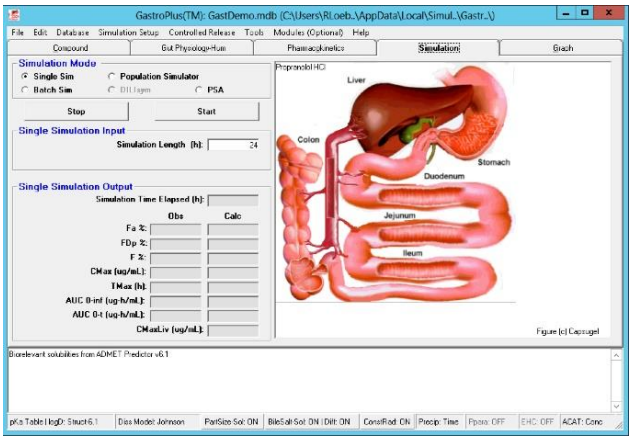


Figure 6: Simulation tab

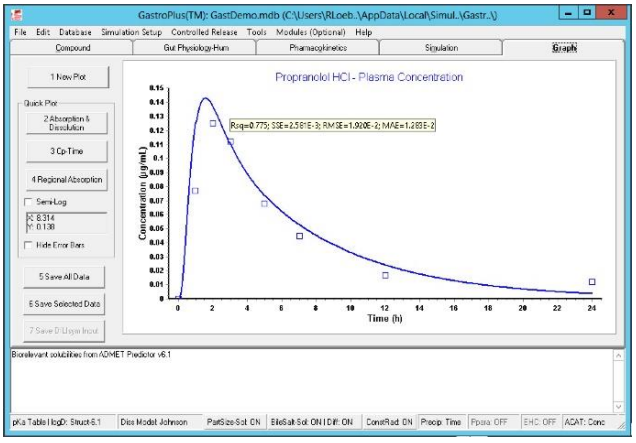


Figure 7: Graph tab – Plasma curve

Section 2 – Simulation and graph tabs

1) Run a simulation using the default parameters (IR: Tablet; Fasted physiology) – see Figure 5, Figure 6 and Figure 7.

Based on the "Absorption and Dissolution" (Figure 8):

a) What is controlling the absorption pattern of the drug?

b) What can you tell about the metabolism of the drug based on the total amount in the systemic circulation?

Compare the "Regional Distribution" graph of (Figure 9):

c) Fasted *vs* Fed state physiologies (using IR: Tablet as dosage form).

d) CR: Gastric Release *vs* IR: Tablet (using fasted physiology).

e) CR: Dispersed *vs* IR: Tablet (using fasted physiology).

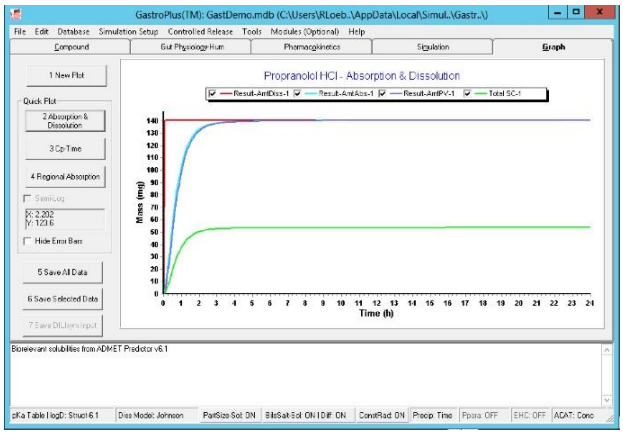


Figure 8: Graph tab – Absorption and Dissolution

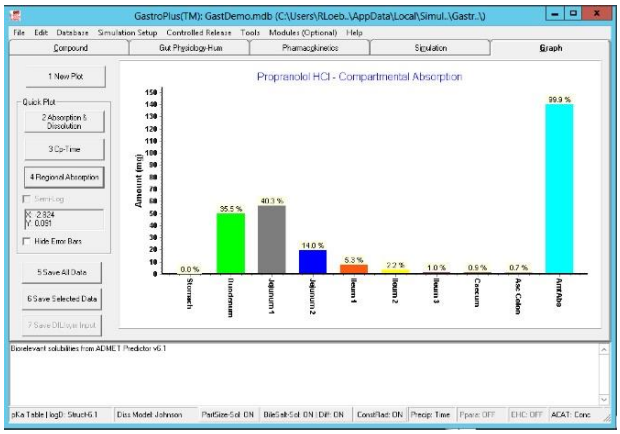


Figure 9: Graph tab – Regional Absorption

Section 3 – Parameter sensitivity analysis (Figure 10 and 11)

1) Run a PSA with parameter(s) that you think would affect the pharmacokinetics of the drug. Explain.

2) Run a PSA with one parameter that you think would not affect the PK. Explain.

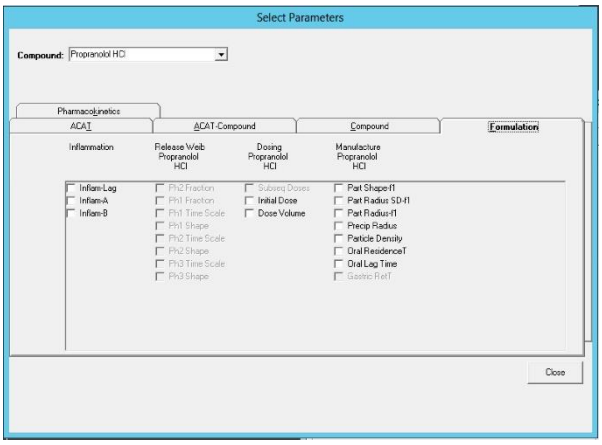


Figure 10: Parameter Sensitivity Analysis – Select parameters

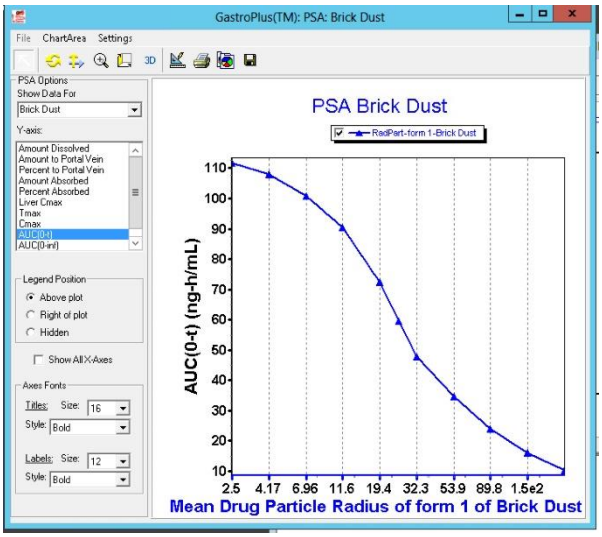


Figure 11: Parameter Sensitivity Analysis – Impact of particle size on Area Under the Curve (AUC) for brick dust

The following laboratory report by one of the groups showcases how well they were able to grasp the concepts taught in the course by using GastroPlus.

Section 1 – Compound Tab

1) What can you tell about the drug's solubility and permeability based on the Dose Number, Absorption Number, Dissolution Number, pKa table, LogD profile?

   a) Dose Number. 10.4343 - The dose number >1 indicates that piroxicam IR tablets will not dissolve completely in 250mL and will have low solubility.

   b) Absorption Number. 20.668 - The absorption number >1 indicates that all of the drugs will

be absorbed during transit through the small intestine and have high permeability.

c) Dissolution Number. 0.236 - Since the dissolution number is <1, it indicates that all of the doses will not be dissolved during transit through the small intestine. The dissolution number is primarily affected by the particle size and solubility. We can change the dissolution by decreasing the particle size.

d) Pka table - Piroxicam has 2 pKa values; acidic (5.46), and basic (1.86) (Figure 12).

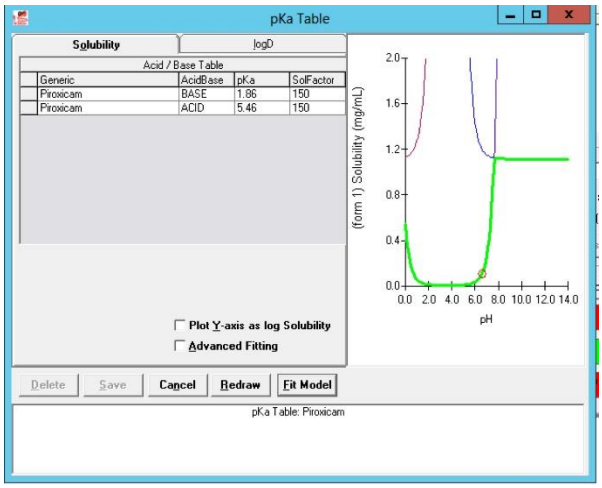


Figure 12: pKa table showing pKa values of acidic and basic groups of piroxicam

i. At pH less 1.86, the acidic group and basic groups both will be protonated (pH < pKa). Therefore, the charged basic group contributes to the solubility of the drug at pH less than 1.86.

ii. Between pH values 1.86 and 5.46, the acidic group will be protonated (pH < pKa) and the basic group will be deprotonated (pH > pKa). Therefore, the uncharged acidic and basic group makes the drug less soluble at this pH range.

iii. At pH values above 5.46, the acidic group will be deprotonated (pH > pKa) and basic group will be deprotonated (pH > pKa). Therefore, the charged acidic group contributes to the solubility of drug at pH above 5.46.

e) LogD profile – When the solubility is low, the lipophilicity increases until pH 5, which indicates that piroxicam molecules are more permeable. Between pH 5 and 8, the lipophilicity and permeability of the drug is decreasing while solubility is increasing.

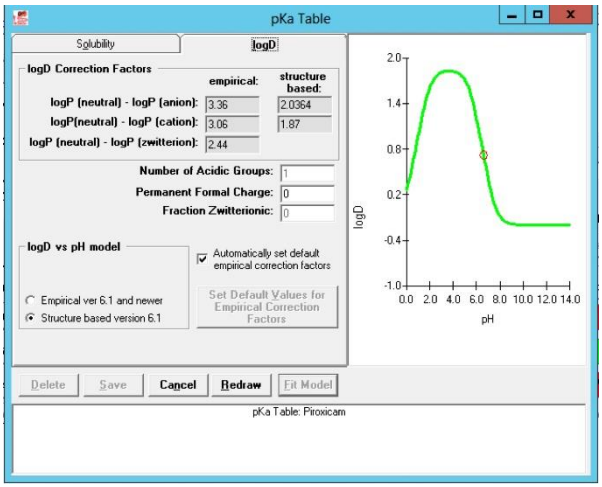


Figure 13: logD *vs* pH of piroxicam

2) When using solid oral dosage forms, immediate release is usually the simplest and most preferrable type of formulation. However, other dosage forms may be a better approach to increase drug absorption. Would you consider CR:Gastric Release as a better alternative dosage form to IR: Tablet? Explain.

Yes, immediate release tablets were absorbed throughout the gastrointestinal tract. However, the gastric release dosage form was predominantly absorbed in the duodenum (i.e. the first segment of the small intestine; small intestine is the major absorption site). This indicates that the gastric release dosage forms will be in the stomach for a longer period of time, thereby allowing it to dissolve more at a pH below 2. Consequently, it creates a super saturated solution that can be readily absorbed at the duodenum.

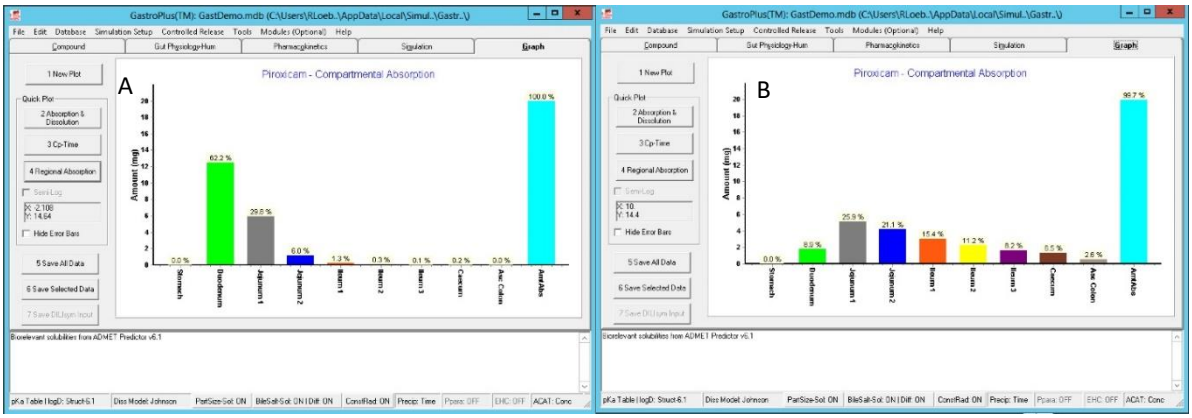


Figure 14: Compartmental absorption of Piroxicam CR: Gastric release (A) and Piroxicam IR: Immediate release tablets (B) tablet along the gastrointestinal tract

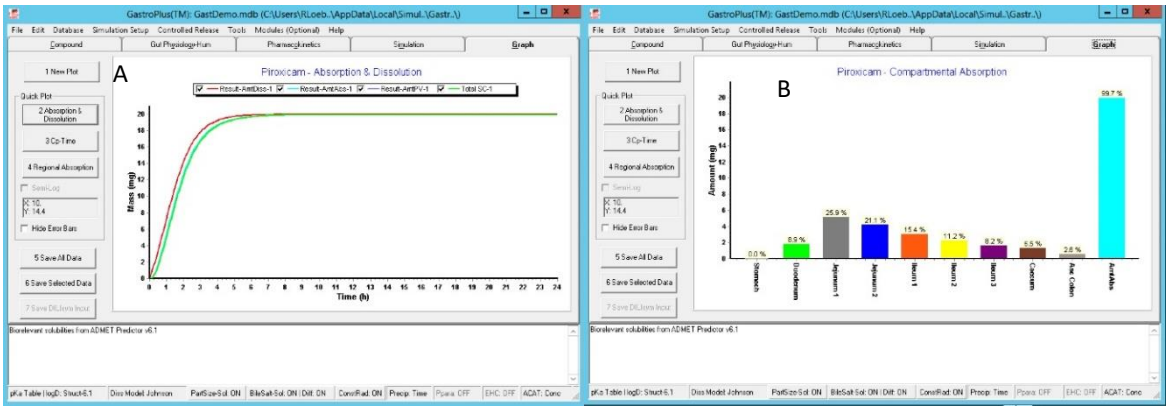
Section 2 – Simulation and graph tabs

1) Run a simulation using the default parameters (IR: Tablet; Fasted physiology…)

Based on the "Absorption and Dissolution":

a) What is controlling the absorption pattern of the drug?

The absorption and dissolution graphs of the piroxicam IR tablets superimpose, thereby indication that the drug is controlled by dissolution (Figure 15A). Furthermore, it is absorbed throughout the intestinal tract (Figure 15B).



(A) Absorption and dissolution profile of piroxicam IR tablets; (B) Compartmental absorption of Piroxicam IR tablets tablet along the gastrointestinal tract

Figure 15: Simulation results using default parameters for IR: immediate-release tablets of piroxicam

b) What can you tell about the metabolism of the drug based on the total amount in the systemic circulation?

The total systemic circulation and the absorption lines on the graph are superimposable (Figure 16) suggesting that as the drug passes through the liver, there is very minimal first pass metabolism.

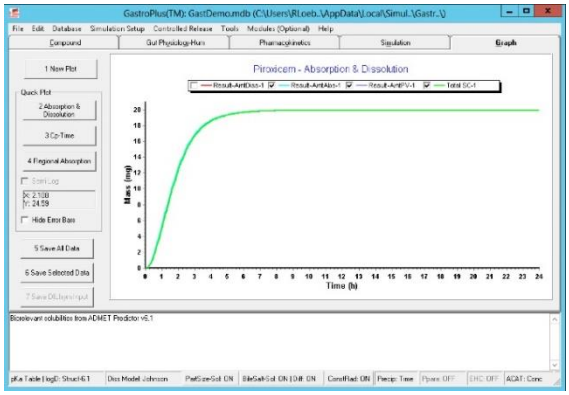


Figure 16: Mass *vs* time graph showing absorption profile and total systemic circulation of piroxicam IR tablets

Compare the "Regional Distribution" graph of:

c) Fasted *vs* Fed state physiologies (using IR: Tablet as dosage form).

d) CR: Gastric Release *vs* IR: Tablet (using fasted physiology).

e) CR: Dispersed *vs* IR: Tablet (using fasted physiology).

The absorption profiles of the drug in the Fasted and Fed state physiologies are very similar. The difference between the total absorbed is very minimal (0.2%) indicating that the presence of food does not affect the bioavailability of the medication (Figure 17).

The type of dosage form affects the region of absorption of the drug as mentioned above in Q.2a. The gut physiology does not affect the bioavailability of piroxicam (Figure 18 and Figure 19).

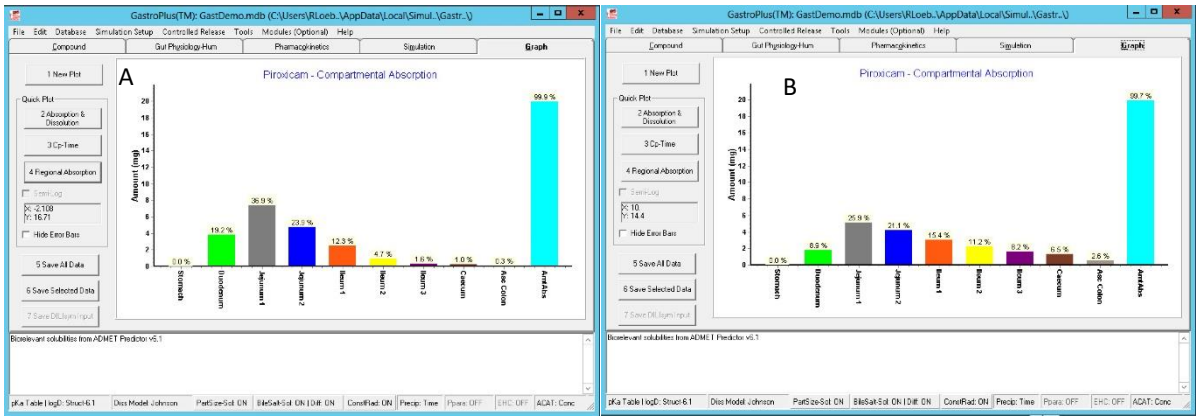


Figure 17: Compartmental absorption of Piroxicam IR: immediate-release tablets along the gastrointestinal tract at Fed state (A) and Fasted state (B) physiologies

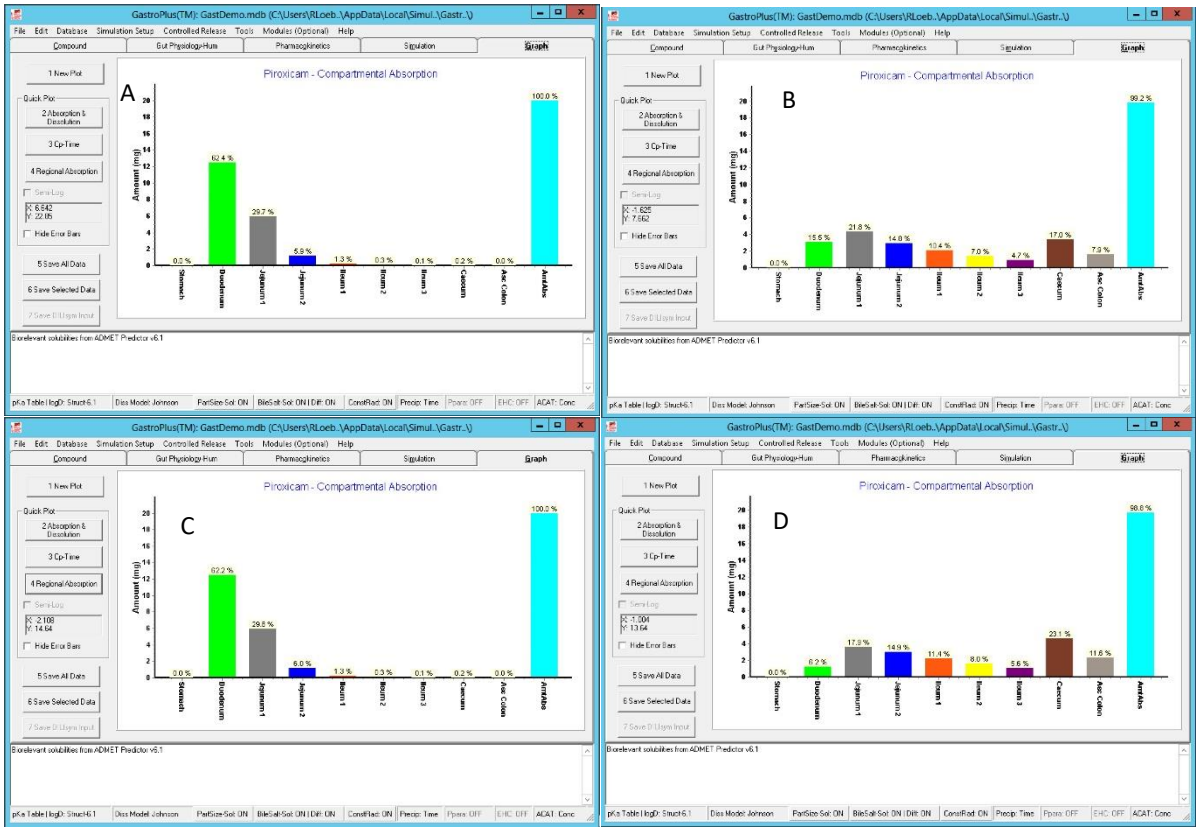


Figure 18: Compartmental absorption of (A) Piroxicam CR: gastric release tablets at fed state physiology, (B) Piroxicam CR: dispersed tablets at fed state physiology, (C) Piroxicam CR: gastric release tablets at fasted state physiology and (D) Piroxicam CR: dispersed tablets at fasted state physiology along the gastrointestinal tract

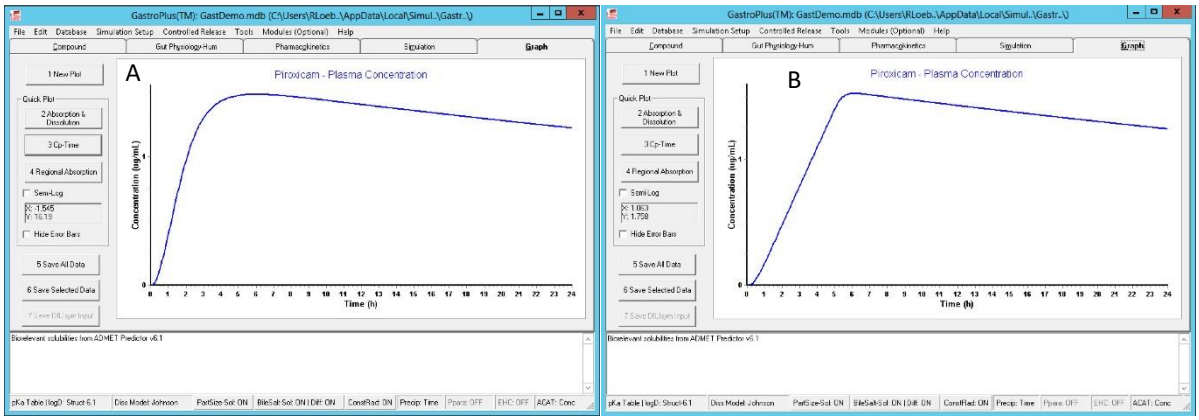
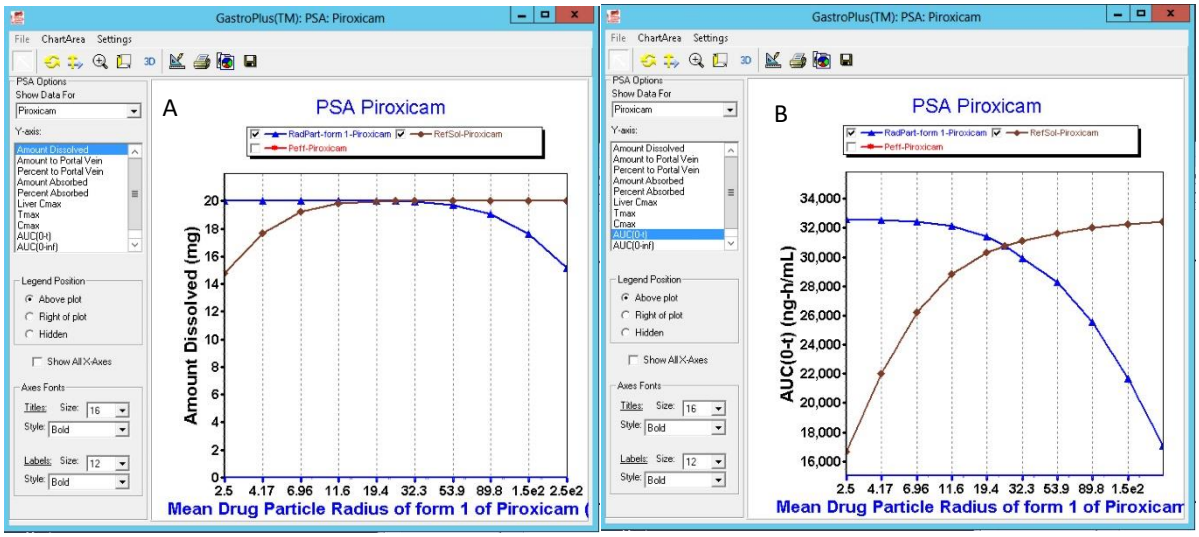


Figure 19: PK profile for IR: Tablet (A) and CR:Gastric release (B)

In this example, the students could see that the PK profile for CR:Gastric release (right side) followed the dissolution profile they loaded. Not much information could be retrieved when looking solely at the PK profile of IR (left side) *vs* CR: Gastric release, whereas a more mechanistic understanding was obtained when looking into the simulated regions of absorption within the gastrointestinal tract).

Section 3 – Parameter sensitivity analysis

1) Run a PSA with parameter(s) that you think would affect the pharmacokinetics of the drug. Explain.



(A) Effect of particle radius and drug solubility of amount dissolved; (B) Effect of particle radius and drug solubility of AUC

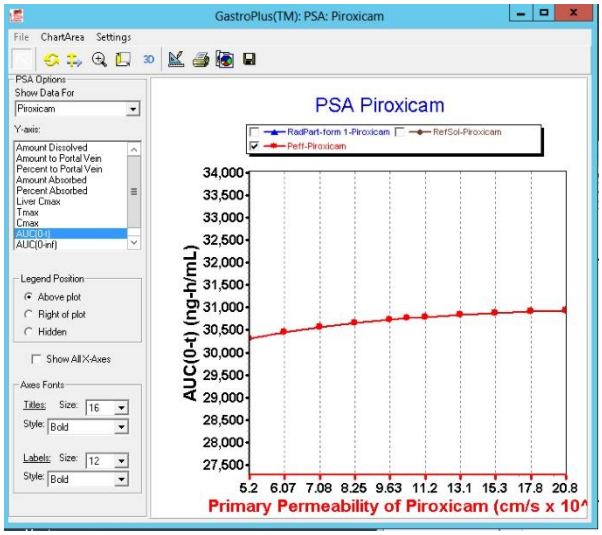
Figure 20: Parameter sensitivity analysis (PSA) of Piroxicam IR: immediate release tablets using particle radius (blue) and drug solubility (brown) parameters

Particle radius affects the pharmacokinetics of the drug. As the particle size increases, there is a decrease in the amount dissolve and the AUC. The other parameter that affects the pharmacokinetics of the drug is solubility. As the solubility increases, the amount dissolved, and AUC also increase. This further indicates that our drug is controlled by dissolution.

The particle size can be reduced in order to increase the solubility of the drug. Since, piroxicam absorption is controlled by dissolution, increasing the solubility of the drug could potentially help improve its bioavailability.

2) Run a PSA with one parameter that you think would not affect the PK. Explain.

The permeability of the drug does not affect the pharmacokinetics such as AUC (Figure 21).



Note: Effect of drug permeability on AUC

Figure 21: Parameter sensitivity analysis (PSA) of Piroxicam IR: immediate release tablets using drug permeability (red line) parameter

The pre-laboratory seminar prepared the students for the computer laboratory exercise and experience. Meanwhile, the post laboratory assignment and quiz allowed the instructors to assess the students' learning of the in-silico laboratory material. During the laboratory sessions, the students were challenged with various scenarios making choices and receiving feedback through the process. This had a positive impact on students' engagement through discussion, reflection, and collaborations amongst themselves.

This laboratory was also important for the pharmacy students to begin the development of decision-making skills. Through the instantaneous feedback provided by the software when they changed independent variable parameters, they could immediately see the impact of their decisions on choices for a specific parameter (e.g. the impact of different dosage forms on drug absorption) and thus draw conclusions based on causality accordingly. This type of education simulation program is an important tool and an excellent opportunity to engage students with biopharmaceutic modelling and simulation (using GastroPlus). This is an important component of the current drug development process in the pharmaceutical industry and is utilised by pharmaceutical companies in decision making and by regulatory agencies in the evaluation of new chemical entities in the drug approval process.

Simulation Plus allowed the University of Alberta Faculty of Pharmacy & Pharmaceutical Sciences to try the use of their software technology for educational purposes and provided access to the pharmacy students during the duration of their training. Moreover, as of October 2021, Simulations Plus has launched the University Program that offers one-year access to Simulations Plus software for use in academic courses at accredited universities worldwide. The goal of this initiative is to increase education and publications promoting the next generation of scientists. More than 100 universities in 32 countries have gained access to the software tools through the aforementioned program. This is a strong indication of the added value of the laboratory described in this work. This is a notable leadership service commitment to pedagogy and training of healthcare professionals that the authors believe is mutually beneficial, and the authors encourage other software providers in the pharmaceutical industry to follow suit.

Evaluation and future plans

An evaluation of the success of this laboratory in the students' learning was undertaken, comparing their performance on the biopharmaceutics questions on the final examination of the course in the years of 2020 and 2021 (with active learning component added) compared with the previous year where the laboratory was not utilised: 76% (2020); 75% (2021) *vs* 52% (2019), respectively. Hence, the students learned the concept better than they did in the past. This holds true even in a pandemic scenario, where teaching and learning have been made even more challenging. Since this was the first two times that this laboratory had been implemented, the measurement of student learning is only at a preliminary stage of assessment. In future iterations of the course, a short pre-laboratory seminar assessment quiz to further engage the students is planned to be implemented, which will serve as a strong baseline to assess any learning gains.

The comments from the students were positive regarding their access to the Gastroplus program, which they could further supplement with lecture notes and reading of their textbooks. Utilising active learning and multimedia approaches have been woven through the curriculum so seamlessly that, indeed, there was no negative feedback. In future iterations of this course, the authors will endeavour to examine and expand on our ability to assess in greater detail to weigh usage of this and other tools as it would provide additional strength. Due to the pandemic, it was impossible to have in-person laboratories. The computer lab was, therefore, a suitable replacement for a wet-lab exercise, which would have been cancelled. Due to the short planning time available, the authors overlooked a more robust assessment as other needs took priority. The authors realise that this is a

shortcoming that can be improved upon to help empower educators to assess these impact and outcome aspects when implementing such course changes.

However, given the apparent initial success and positive feedback from students, the instructors understand that the computer laboratory should be maintained even in a post-pandemic scenario. This is in accordance with the latest American Association of Colleges of Pharmacy (AACP) report, which suggests that "*future research and scholarly activities should be conducted to determine if evidence supports continuing pandemic-related adaptations for curricular and student engagement to advance pharmacy education"* (Bzowyckyj *et al.,* 2021). In conclusion, this simulation lab proved to be an important mechanistic learning tool for students. The lab will be part of teaching biopharmaceutics within the curriculum.

Previously, this important subject which underpins the pharmaceutical performance of products, was taught only by providing definitions of the biopharmaceutical concepts during the lectures. While still valid, this approach was limited in enabling the students to apply and translate the knowledge to solve "*real case*" scenarios. The use of an active learning component, such a GastroPlus, enabled the students to contextualize the concepts and integrate the knowledge, which would have been an intimidating task and more difficult for some learners if only relying on the definitions given in the lectures. The course was structured in a similar manner as in previous years (e.g. same instructor and material covered during the lectures as required to fulfil national accreditation standards) except for the additional introduction and use of GastroPlus. The students learned the concepts in a different stylistic approach and manner than they did in the past and appeared to better grasp the underpinning concepts and their application. Our results have been replicated in other pharmacy learning examples that involved different pharmaceutical subject areas (Gleason, B. L., *et al*. 2011; Lucas, K. H., *et al*. 2013; Tatachar, A., *et al*. 2016).

In conclusion, this simulation laboratory proved to be an important mechanistic learning tool for students. The in-silico laboratory will continue to be part of teaching biopharmaceutics within the curriculum.

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Conflict of interest

The authors declare no conflicts of interest related to this work.

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