Pharmacy Education (2020) 20(2) 124 - 135
https://doi.org/10.46542/pe.2020.202.124135

COVID-19 SPECIAL COLLECTION

RESEARCH ARTICLE

Using in silico process simulation tools in pharmacy education: Considerations for pivoting to online learning

Deirdre M D'Arcy[1,4], Thi Thanh Van Pham[1], Marina Navas Bachiller[1,4], Nikoletta Fotaki[2], Tim Persoons[3,4]

[1]School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Ireland
[2]Deptartment of Pharmacy and Pharmacology, University of Bath, United Kingdom
[3]Department of Mechanical, Manufacturing and Biomedical Engineering, Trinity College Dublin, Ireland
[4]SSPC, The Science Foundation Ireland Research Centre for Pharmaceuticals

Keywords
In silico Simulations
Dissolution
Online Learning
Biopharmaceutics

Correspondence
Deirdre D'Arcy
School of Pharmacy and Pharmaceutical Sciences
Trinity College Dublin
Dublin 2
Ireland.
ddarcy@tcd.ie

Abstract

The COVID-19 pandemic has required identification of pharmaceutical learning content and teaching methods which can support attainment of learning outcomes through online delivery. In silico, or computer based, process simulations are ideal tools for incorporation into online programme elements, however the scaffolding of learning with in silico tools requires a structured approach. A previously developed face-to-face workshop, which used in vitro and in silico dissolution testing, was pivoted to an online learning element using an in-house dissolution simulation programme. The learning element was developed through trial and evaluation of experiences of novice, competent and expert user(s). The delivery of the learning element was planned to address three stages of simulation learning according to the Belton model, with accompanying tools developed to aid scaffolding and assessment of competency milestones. The proposed delivery and assessment is suitable for both synchronous and asynchronous learning, and is suitable for incorporation into an Advanced Pharmaceutics module.

Introduction

The COVID-19 pandemic has affected delivery of higher education globally, from early 2020. Many universities pivoted their teaching to online delivery (Crawford *et al*., 2020). In the field of pharmacy education, as in others, this required identification of material which could be more easily adapted to online delivery, through to identification of material which should be prioritised for in-person teaching where possible (e.g. certain laboratory and clinical skills assessments). An *in silico* process simulation tool, tailored specifically to teach pharmaceutically relevant content, could be an ideal candidate to aid online teaching. Notwithstanding that, every pivot to fully online delivery of teaching content brings its own challenges (Crawford *et al*., 2020; Ma *et al*., 2020). Furthermore, in the ongoing context of students undertaking mostly- or fully-online programmes, there is the challenge of maintaining student engagement while learning remotely and likely in relative isolation (Nordmann *et al*., 2020).

Dissolution testing is used in pharmaceutical drug development to characterise active pharmaceutical ingredients (API), for formulation development and in quality control testing (Abend *et al*., 2018). In recent years there has been a focus on the use of dissolution testing to establish a safe design space, where acceptance criteria for dissolution/drug release are informed by in vivo performance (Abend *et al.*, 2018). Clinically relevant dissolution testing refers to dissolution testing conditions and acceptance criteria that can identify and reject product batches not expected to be bioequivalent with pivotal clinical batches (Abend *et al*., 2018). In order for the pharmaceutical students to reach the stage of understanding and being able to apply the concept of clinically relevant dissolution testing, they must first attain and synthesise knowledge about formulation design, drug dissolution/release testing, absorption processes and relevant physiology (e.g. gastrointestinal tract for oral delivery), pharmacokinetic processes and modelling approaches to produce absorption profiles and statistical and quality aspects relevant to the concept of a design space. It is implicit, therefore, that learning about clinically relevant dissolution applied to formulation design is an advanced pharmaceutics topic.

There are many subjects within pharmaceutical sciences education which could be well represented through *in silico* simulations; various *in silico* approaches and packages are employed in pharmacokinetics and pharmacodynamics teaching for example (Brocks, 2015; Gabrielsson *et al.*, 2014; Hara *et al.*, 2020), and similarly there are reports of *in silico* methods used in medicinal chemistry applications (Hall, 2018; Rodrigues *et al*., 2015). *In silico* process simulations can represent mechanistic processes used in engineering applications relevant to pharmaceutical technology in particular, such as fluid flows, drying, mixing and dissolution. As simulations relevant to pharmaceutical processing will often be dynamic simulations, it can be helpful to consider the definition presented by Rakic and colleagues where a model represents the system itself, while a simulation represents the functioning of the system over time (Rakić, Rosić, & Boljat, 2020).

In silico modelling and simulation tools are increasingly used in pharmaceutical drug development, with significant collaborative research ongoing to optimise the application of *in silico* tools in biopharmaceutical applications (Ahmad *et al.,* 2020). Therefore, students of pharmacy and pharmaceutical sciences should be familiar with types of modelling approaches (e.g. empirical versus mechanistic), regulatory views on levels of risk associated with model applications (ICH Quality Working Group, 2012), and common types of modelling software that are available (e.g. statistical packages and physiologically based biopharmaceutics and pharmacokinetics (PBBP/ PBPK) modelling software platforms).

Whilst it would be unusual for pharmacy/pharmaceutical sciences students to be taught simulation techniques, such as how to assimilate the relevant equations and write the code for process simulation, it is essential that there is a clear focus on what any *in silico* model does. Students should have an understanding of the underpinning equations being simulated; what assumptions are in the model applications; what is not included in the simulation and what might result in erroneous output. In summary, efforts should be made to minimise the 'black box' effect in using process simulations in education (Roman, Delgado, & García-Morales, 2020). Care should be taken with reduced-order models (ROM), which aim to approximate physical phenomena from their complete three-dimensional behaviour into one- or zero-dimensional elements. ROMs can provide powerful tools for rapid assessment of the transient behaviour of complex systems, however only if used with expertise (Chen *et al*., 2020).

To that end, we have developed the in-house dissolution simulation programme, Simdisso, as a collaborative effort between staff from the pharmacy and engineering diciplines. The mass transfer simulation is based on the Ranz-Marshall correlation which relates mass transfer, fluid velocity, density and viscosity, particle size, velocity and drug diffusivity. Particle velocity requires an additional particle motion simulation, and other inputs reflecting choice of dissolution apparatus, medium volume and drug solubility are used to generate dissolution simulations (D'Arcy & Persoons, 2019). The method has been detailed in the literature and its performance in simulating dissolution of non-agglomerating particulate systems has been presented elsewhere (D'Arcy & Persoons, 2011; Serrano *et al*., 2016; D'Arcy & Persoons, 2019).The simulation programme runs on the Matlab platform (www.mathworks.com), and in current versions users can view the code and comments. This allows users, without engaging in the programming of the code, exposure to code syntax and presentation of relevant equations in the code, and to anticipate how the code can evolve with altering defined inputs and outputs. The focus of Simdisso is on flexibility, in order to replicate multiple aspects of processes involved in *in vitro* dissolution testing (particle motion, apparatus, medium etc.) as are considered relevant to any particular application. It is therefore, particularly useful to illustrate parameter sensitivity to dissolution testing variables.

Simdisso has been used recently in post-graduate workshop education in the School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin (SOPPS, TCD), co-delivered with the Department of Pharmacy and Pharmacology, University of Bath. The workshop was designed for ten to fifteen students, and combined training in in-vitro dissolution testing, dissolution simulation and an introduction to the concepts of Physiologically Based Biopharmaceutics (PBBP) modelling. The workshop was formative in nature, with a strong focus on early-stage postgraduate research students to support their skills development. In that instance, student engagement was optimised through enabling simulation of the dissolution tests which the students had just completed and comparison between real and observed results. As the workshop was on campus the students had access to the simulation programme run on Matlab combined with face-to-face real time interaction with instructors, both in the in-vitro dissolution and *in silico* simulation exercises. Based on instructor and student feedback the workshop approach was successful, however the adaptation of this learning experience to fully online teaching is not straightforward.

The aim of the current work was to develop an online learning element using Simdisso to enable an understanding of the use of *in silico* tools to support interpretation of the role of dissolution testing in advanced biopharmaceutics. The objectives were:

i) to pivot a combined in-person in vitro and *in silico* post-graduate workshop plan to development of a fully online learning element, being cognisant of challenges of online teaching and learning during the COVID-19 pandemic, through trialling and developing delivery of the learning element to support a Master of Science (MSc.) graduate project,

ii) to identify appropriate scaffolding and assessment approaches to ensure that meeting competency milestones can be formally evaluated, with a view to the learning element ultimately being suitable for incorporation in an Advanced Pharmaceutics module on the integrated Pharmacy programme in SOPPS, TCD.

Methods

This study was deemed exempt from the requirement for ethical review.

The learning element was developed and trialled using an MSc. student (novice user), Ph.D. student (competent user) and academic staff (expert user) experiences to ensure technological suitability of the approach to delivery. The experience, evaluation and feedback of the single-novice-user trial with competent and expert users as educators was used to inform the design and development of the presented online learning element.

Remote learning technology

Meetings were arranged between the novice, competent and expert users, to build a personal rapport and establish familiarity with using online communication tools. Microsoft Teams was used for video calls, screencasting/ screensharing and as a repository to store relevant documentation.

The proposed delivery methods were selected based on the facilities available in the institutional virtual learning environment (VLE), which is currently Blackboard Learn (www.blackboard.com), other VLEs have a similar range of tools. In addition to supporting a document repository for the teaching element, the following VLE capabilities were considered for use at the different stages of the learning element: Synchronous video interactions and screencasting through Blackboard collaborate, including one-to-one and group elements; recorded instructor presentations or screencasts through Panopto in Blackboard; possibility of students uploading presentations or screenshots to instructor; moderated discussion boards.

Flexibility in delivery

The design of the pivot to online and remote learning focussed on ensuring that the learning could be met with minimal resources and possibly unreliable internet connectivity. For each stage in the learning process, alternative methods for flexibility in online delivery were identified to support difficulty in accessing resources and lack of real time interactions.

Adaptation of workshop to fully online learning element

Context: Whereas the face to face postgraduate workshop described was a valuable template on which to develop the learning element, it was necessary to devise an approach to support student engagement in the absence of the contemporaneous in vitro dissolution testing experience, and in the absence of face-to-face, and possibly real time, instructor interaction.

In order to support student engagement, pre-existing medications under investigation in clinical trials for the treatment of COVID-19 were used as a hook in the

simulated cases. The simulated learning element was designed to illustrate how dissolution testing could be used to identify boundaries for critical process parameters (CPPs) during manufacturing, to ensure that manufactured product fell within a safe design space. Therefore the first part of the exercise involved setting specific objectives and providing background learning content to contextualise the learning aims. An online presentation and written instruction were used to replace the in-person workshop introduction in the face to face lab. Screencasting was used in the original in-person computer lab to introduce the Simdisso interface on Matlab, and online screen-casting was used for the same purpose in the online element. In the current trial, hands-on user experience of Simdisso was replicated through the user detailing simulation inputs to the competent user (who accessed the software), and the simulation being run via screencasting. This could be synchronous or asynchronous and recorded for the user to visualise. In-person discussion on the application of the simulation and interpretation of outputs and results in the face to face lab was replicated through online discussion (synchronous and asynchronous) and the development of a series of flexible tools to support clear scaffolding of learning at different stages of the learning element. These tools are also the basis of the proposed assessment methods.

There were three pillars underpinning the development of the dissolution Simulation Online Learning Element (SOLE):

1. That the learning element incorporated relevant content and context including: methodological aspects of in vitro dissolution testing, bio-pharmaceutical aspects relating to Quality by Design (QbD) and PBBP modelling, and exposure to running simulations through the Simdisso interface.

2. That the learning element was developed based on the proposed learning model for process simulation pedagogy presented by Belton (2016). This study focussed on the teaching of process simulation, and through thematic analysis of student evaluation and feedback, three learning stages were identified: i) early phase focussed on introductory and expository learning; ii) late phase focussed on discovery/ inquiry-based learning; iii) 'future' phase potentially leading to the development of proficiency or expertise.

3. That the learning element was suitable for use in postgraduate pharmaceutical sciences teaching and furthermore, in particular, suitable for integration into a Year 5 Advanced Pharmaceutics module in the five year integrated pharmacy programme in SOPPS, TCD. The learning element in the Advanced Pharmaceutics module should dovetail with teaching on PBBP/PBPK modelling and clinically relevant dissolution testing, and more broadly to support relevant integration across the pharmacy programme, and be suitable for online delivery. The relevant learning outcome within the Year 5 Advanced Pharmaceutics module is:

   'Describe the concept and applications of in vivo predictive dissolution testing and in vivo-in vitro correlations, as well as biopharmaceutics-relevant modelling and simulation approaches'.

It should be noted that the Advanced Pharmaceutics module also builds on earlier biopharmaceutics learning in accordance with the integrated programme approach.

The consideration of the three pillars was employed at each of the learning stages as follows:

Early phase learning

Context: Specific objectives were highlighted to ensure that the students would access and assimilate the relevant information to appropriately contextualise the simulation programme learning element outlined in the first pillar, e.g. that use of dissolution in safe design space could be discussed and that the mechanistic approach to dissolution simulation using Simdisso could be outlined. In order to consider patient and study types to which to project would be applicable, pharmaceutical QbD (Yu *et al*., 2014) and the Biopharmaceutics Risk Assessment Roadmap (BioRAM) (Dickinson *et al*., 2016; Selen *et al.,* 2014) were consulted. As the current learning element focussed on using medications being studied for COVID-19 treatment, a further objective was that medications undergoing trials for COVID-19 were identified. The learning was contextualised through guiding the user to relevant background reading websites, and prior learning material.

Expository learning: The use of the simulation programme for dissolution simulation was presented through a screensharing session between the expert user (academic staff) and the novice user. An example of the interface where parameter values are entered in the programme is presented in Figure A. Initial simulations were conducted in a similar manner. The competent and novice users interacted through screensharing and sharing input data and outputs.

Late stage learning

Discovery/inquiry: Following introductory learning and initial expository simulations, further discussion, hypotheses generation, novel simulations, analysis and evaluation of results took place between the competent and novice user, partly through screencasting of the simulation tool interface, and partly through the novel results being presented via Microsoft Teams and discussed initially between the novice and competent user, and then summarised and presented to the expert user.

'Future' learning

Suggestions for further development of the simulation methodology to better predict certain scenarios was the final part of the novice user learning. Although the novice user would not be expected to reach a point of expertise following an introductory programme, the inclusion of an element requiring the student to suggest both alterations to the simulations conducted and improvements to the model employed, reflects the potential for students to present their understanding of the role and limitations of applications of the simulation tool.

Assessment and Evaluation

In order to scaffold the development of the learner through the competency milestones associated with each stage, critical points and methods, including assessment tools, for instructor feedback and debriefing were identified at each learning stage, based on novice user progress and feedback. The progression of the novice user through the various competency levels was considered preliminary validation of the delivery approach at this single-user level. Novice-user evaluation was presented as feedback on methods used during the project, and was used to inform the recommended delivery methods and associated assessment and scaffolding tools. This process was iterative in the novice user discussing utility of the various tools developed, with the competent and expert users as the project progressed.

Results

Remote learning technology

Generation of an online repository was sufficient for sharing relevant learning content (e.g. lecture notes, relevant literature), along with written documentation outlining the objectives for introductory learning and contextualisation. This was supported with a synchronous video discussion to present the tasks. Following the introductory learning/contextualisation of the process, for the expository element in the early phase learning, screensharing or screencasting was successful in introducing the student to the simulation programme interface, the simulation options available therein and the Matlab platform on which it was run. A screenshot of the inputs stage of the simulation programme is shown in Figure A. As the code can be seen by the user, it can be highlighted how the various steps and conditions in the dissolution testing process are represented in the simulation code. With respect to the late phase discovery/inquiry-based learning, the competent and novice users successfully employed the programme for advancing simulation options, and online video calls for synchronous discussions about presented results, and emails/discussion boards for asynchronous discussion. It should be noted that this teaching took place with the novice and competent users based in a different country and time zone, with the team involved in delivery of the learning element located in four countries and two time-zones, one hour apart. Results were presented to the expert user through brief reports and results templates. A synchronous video call was employed for the final debriefing discussion at the 'future' competency milestone. The tools used to assess user progress at each stage will be presented.

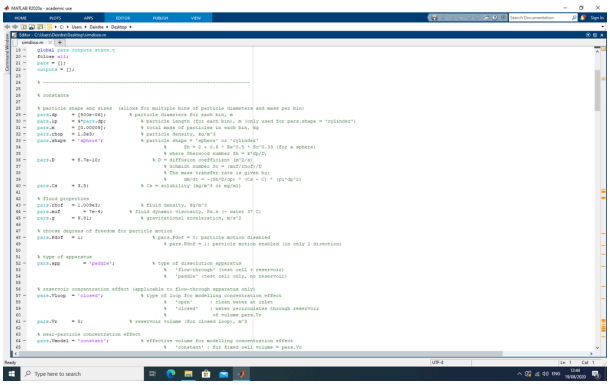

Figure A: Screenshot of inputs section in Simdisso. Code and syntax associated with inputs are visible, along with commenting approach and Matlab interface

Introduction and context (early phase learning)

The learning was contextualised through guiding the user to relevant background reading (research publications and regulatory documents) relating to clinically relevant

dissolution testing and the use of the simulation programme in research applications (D'Arcy & Persoons, 2019). Clinical trials databases were consulted to identify drugs under investigation, with a focus on pre-existing medical products with varying biopharmaceutical properties, i.e. class I-III and II-IV of the biopharmaceutics classification system (BCS) (Amidon *et al.*, 1995). As BCS class II-IV drugs have low solubility, the potential for CPPs to affect the compliance of dissolution testing with safe space acceptance criteria would likely be greater for these drugs, providing an opportunity for the student to apply biopharmaceutics knowledge to interpretation of simulated results. To provide a framework to systematically consider how the simulation approach could be used at different points of product development and for different patient types, resources on pharmaceutical QbD and BioRAM (QbD-BioRAM), were consulted. This also supports integration within the Advanced Pharmaceutics module and the Integrated Pharmacy Programme (Selen *et al.*, 2014; Yu *et al.*, 2014; Dickinson *et al.*, 2016; Ryan *et al.*, 2019). The drugs selected for use were hydroxy-chloroquine sulfate (BCS class III) and Lopinavir (BCS class IV), which were being investigated for use in treating COVID-19 in the World Health Organisation (WHO) Solidarity trial at the time the current work was undertaken (WHO, 2020). However, the same approach could be used for other drugs with varying BCS classes, in particular high versus low solubility to emphasise dissolution-dependent effects.

Alignment with the process simulation pedagogy model (Belton, 2016)

Expository learning

Initial simulations of dissolution of selected APIs were conducted using standard published dissolution conditions. Students at SOPPS, TCD currently have access to Matlab, however it is not commonly used in the pharmacy programme and students would not be expected to be familiar with its installation or use. This could be envisaged as a barrier to the learning resource when delivering the learning remotely, and if only used for one workshop. Therefore, while direct access of the user to the software would be optimal, it was considered a more fool-proof option to trial screencasting of operation of the programme, which again could be recorded if necessary, ensuring equitable and self-paced access to the relevant resources. Conversely, if the teaching element was expanded to an advanced exercise focussing on the late phase discovery/inquiry-based learning, it could be of greater benefit to students to invest the time in installing Matlab on their own computer. Similarly if remote access was available to the novice user through the online platform, or eg a cloud application (as has become the case in SOPPS, TCD since the time of this project), this would be encouraged.

Late phase discovery/inquiry-based learning

The user input template (Figure B) was developed, which was shared in the online document repository, facilitating the accurate running of simulation options by the competent user, based on the previous simulation evaluation of the novice user. This input template would also support group work output, in the form of further simulations a group may wish to pursue following preliminary results. Examples of discovery/inquiry-based simulation options included simulation of particle motion using different API particle sizes, which then determined whether a particle would sink (stationary) or be suspended (move with the fluid); this difference in behaviour notably affects particle dissolution behaviour, and thus could impact on whether a certain set of particle characteristics would result in particle dissolution being within the safe design space or not. Simulating particle motion before simulating its dissolution, in order to select appropriate velocity values for dissolution simulation, is therefore very useful in illustrating the potential shortcomings of a model when parameters are not accounted for or 'default' values used without their impact being understood.

Through bookending application of the QbD-BioRAM approach at the introductory stage of early phase learning and at the conclusions following the discovery/inquiry phase, the user systematically considered relevant biopharmaceutical aspects. In the context of the learning cases in this simulation online learning element, the varying impact of CPPs on dissolution of APIs with different biopharmaceutical properties was hypothesised, through particle size effects. These effects were then illustrated using Simdisso and potential manufacturing challenges to formulating a product within the safe design space were identified. Furthermore, underpinned by QbD-BioRAM and in consideration of a likely patient cohort of geriatric or critically ill patients with possible difficulties in solid oral dosage form administration, the patient-focussed relevance of the results could be highlighted. Although a wide range of simulations were conducted at this stage, it was not necessary for both users to be present while the simulations were running, which enabled their engagement with outputs at different times suiting their availability and again supporting the concept of equitable access to the learning resource.

Future phase

For the future phase of learning, the novice user suggested enhancements of the simulation approach which could further improve the flexibility of the simulation programme in representing real in-vitro dissolution processes. Incorporating a requirement for such suggestions from the novice user facilitates the educator in accurately interpreting how well the student understood the application of the simulation. Therefore, this is considered a crucial debriefing point from the expert user.

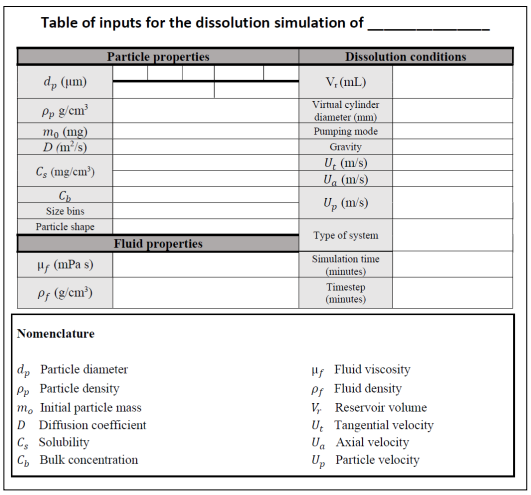

Table of inputs for the dissolution simulation of _____

Particle properties		Dissolution conditions	
d_p (μm)		V_r (mL)	
ρ_p g/cm^3		Virtual cylinder diameter (mm)	
m_0 (mg)		Pumping mode	
D (m^2/s)		Gravity	
C_s (mg/cm^3)		U_t (m/s)	
		U_a (m/s)	
C_b		U_p (m/s)	
Size bins			
Particle shape		Type of system	
Fluid properties			
μ_f (mPa s)		Simulation time (minutes)	
ρ_f (g/cm^3)		Timestep (minutes)	

Nomenclature

d_p	Particle diameter	μ_f	Fluid viscosity
ρ_p	Particle density	ρ_f	Fluid density
m_o	Initial particle mass	V_r	Reservoir volume
D	Diffusion coefficient	U_t	Tangential velocity
C_s	Solubility	U_a	Axial velocity
C_b	Bulk concentration	U_p	Particle velocity

Figure B: Tool 1- Inputs template tool developed during the project to support remote and/or asynchronous online learning, and scaffolding of user competence development

	Milestones	Scaffolding approaches
Competency milestones and developmental scaffolding methods	Novice user -understands background and simulation tool interface	Check user inputs table for source of values and how they will be input, and why these inputs were selected. Check initial simulation outputs to ensure simulated results can be generated. Can be compared to pre-run simulation for accuracy, included as diagnostic aid for student. Use QbD-BioRAM tool to check context
	Competent user- correctly selects and adjusts simulation parameters to test hypotheses	Present simulated results, adjusted inputs table, reasoning for adjustment and updated simulations.Use simulation process flow tool to assess understanding. Clarify "muddiest point" with student. Discussion on reasoning and application via video call or virtual whiteboard in real time, or discussion board and Process flow template report if asynchronous.
	Expert user –can use simulation tool to troubleshoot a problem or can identify specific model limitations and suggest improvements to explore complex problems	Critical debriefing point. Scaffolding to ensure that "black box" conceptualisation is avoided; model limitations identified and points at which adjustment to the model might impact the dynamic simulation outputs. Presentation of a more complex case scenario, and discussion of model application. Supported by all three tools especially for formative assessment.

Figure C: Competency milestones and suggested developmental scaffolding approaches supporting remote/online application

User evaluation, and scaffolding learner development

The points in the exercise identified as competency milestones are presented in Figure C, along with suggested developmental scaffolding methods. Regular engagement between the novice, competent and expert users facilitated scaffolding method development based on ongoing user feedback.

User evaluation of the learning element

Based on novice-user progress and feedback and competent-user feedback, three tools were developed to scaffold learning and also to serve as templates for assessment. These were the inputs table (Figure B), the QBD-BioRAM tool (Figure D), and the simulation process flow tool (Figure E).

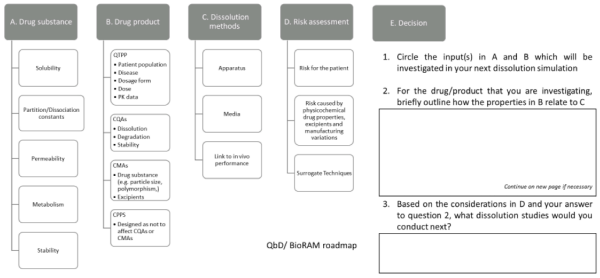

Figure D: Tool 2- QbD-BioRAM tool to assess contextualisation of dissolution testing and simulation programme application to biopharmaceutics scenarios

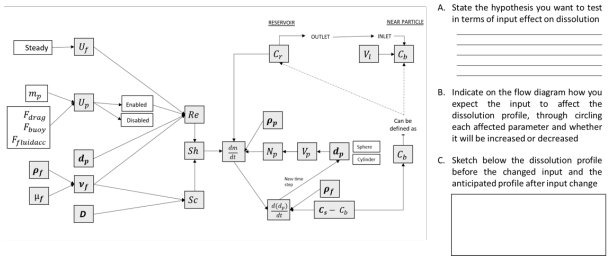

Figure E: Tool 3- Simulation process flow tool to facilitate discussion around the effects of input changes and as an assessment tool to evaluate understanding of the simulation and its applications, at both discovery/inquiry and future learning stages.

Nomenclature as detailed in Figure 2. Additionally: Cr reservoir concentration; m mass; Np number of particles; Re Reynolds number; Sc Schmidt number; Sh Sherwood number; Uf fluid velocity; Vl layer volume; Vp particle volume

Scaffolding of learning

As the background context was also the source of the initial user inputs for the first simulations, a point for instructor-student feedback was identified to support the student proceeding to integrate the background knowledge and its application to the process. The input

table (Figure B) was developed, where appropriateness of initial simulation inputs could be assessed, and the quality-by Design QBD-BioRAM tool (Figure D) has been developed to assess initial contextualisation.

The second instructor-student feedback point is at the end of the late phase discovery/inquiry-based learning. At this point the user should be able to present simulated dissolution results, hypothesise on how different dissolution conditions/API properties could affect these results, present adjusted input tables to reflect the hypotheses and novel simulation outputs. Furthermore, the user should be able to interpret results with respect to the given context, and make preliminary suggestions on the role of dissolution testing in safe design space for different APIs. The simulation process flow tool (Figure E) was developed both to facilitate discussion around the effects of input changes and as an assessment tool to determine the milestone attainment of 'competent user' in combination with the input table (Figure B). It is suggested that the instructor can take a 'muddiest point' (Angelo & Cross, 1993) approach in clarifying any aspects of simulation application and interpretation to support the evolution of the learner to scaffold learning at the end of the late phase.

The third scaffolding point is the final debriefing. The user would not be expected to gain expert competency level without notable familiarity with the software, however, a point identified towards future competence is that the user can identify and discuss model limitations, suggest improvements and suggest when a model may or may not be suitable for troubleshooting a complex problem. This debriefing stage checks the reasoning for the student's suggestions and ensures the avoidance of the 'black box' effect with simulations where the user is aware of inputs and outputs but lacks clarity on how the simulation dynamics operate. The simulation process flow tool (Figure E) can be used at this point to discuss and assess user understanding of how the simulated process could be adjusted, potentially in combination with the QBD-BioRAM tool (Figure D) to illustrate situations where the simulation programme might be required for more complex scenarios.

The tools developed through the user feedback process for scaffolding and assessment of learning were used to scaffold novice-user learning and support their interaction with the competent and expert users. Based on this process, Question sections were added to Figures D (Q1-3) and E (QA-C) to formalise their adaptation as assessment tools through discussion with the academic staff from TCD and University of Bath.

Flexibility in online/remote delivery

Whereas for this project the student was guided towards the introductory information sources, this point of the exercise could be expanded or reduced, to align with limited time/resource accessibility or learning objectives. For example, a pre-recording or explanatory document could be made available with the relevant information rather than requiring the student to source the information. To replicate student-educator interaction, the current work used several pre-arranged live video calls to discuss the context of the simulation learning element, and also to teach the mechanistic mass transfer element on which the simulation is based, through screen sharing (screencasting). Live teaching for group work can be facilitated through synchronous presentations, using for example virtual whiteboards to capture student discussion. However, in the case of unreliable internet connection or time-zone challenges, this live teaching can be replaced with recorded presentations and, for example, moderated discussion board or student-to-instructor recorded screencasting to facilitate troubles-hooting, group learning and student-educator interaction. These teaching modalities are available through the VLE which will be used for the Advanced Pharmaceutics module. Similarly, for the assessment of correct inputs, in the trial, student understanding was assessed via a written report incorporating the inputs tool, and real time video discussion. Alternative approaches could include student(s) completing the inputs table, and discussion on appropriateness of inputs via a discussion board. For a smaller workshop, initial inputs could be provided via this tool, and their source and purpose presented. Adjusted inputs, simulation outputs and hypotheses, using the simulation process flow tool, can be deposited in shared repositories for asynchronous evaluation in addressing the late phase learning milestone. Considering the findings of Frandsen & Lehn-Christiansen, (Frandsen & Lehn-Christiansen, 2020), we suggest that ideally the final debriefing would be a synchronous activity, fostering a positive semi-structured environment to promote student questioning and clarify learning objectives at that point.

With respect to the third pillar, it is intended that the simulation online learning element could be implemented within a Year 5 Advanced Pharmaceutics module. In line with the integrative teaching and learning approach in the SOPPS, TCD, it was necessary that the element could be integrated within the programme. The school employs an integration approach based on five cross-cutting themes which are also aligned with the Pharmaceutical Society of Ireland's competency framework (Ryan *et al.*, 2019). All

module descriptors on the integrated pharmacy programme detail vertical and horizontal links with content in other modules, in addition to the integrative themes which apply to that module. Figure F details the presentation of the integration of the relevant bio-pharmaceutics element of the Advanced Pharmaceutics module with other modules in the programme. The relevant learning outcome (detailed in Figure 6) is currently examined as part of a formal exam, and the proposed assessment following introduction of the online learning element is through completion of the tool templates as appropriate to the biopharmaceutics case studies presented. Furthermore, the curricular themes 'Safe and Rational use of Medicines' and 'Medicines Sourcing, Production and Use' are associated with the advanced pharmaceutics module. Therefore, the simulation-based learning element is clearly well positioned for this module and supports integration of learning content in the other programme modules as detailed.

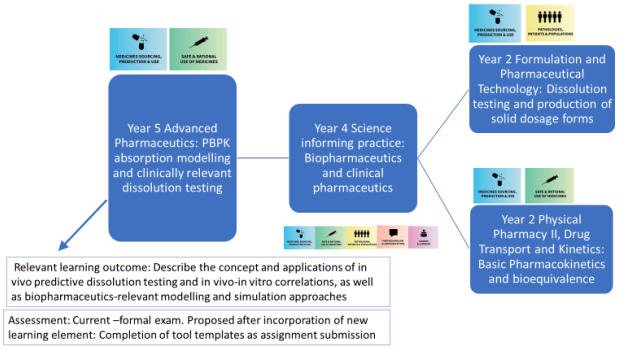

Figure F: Integration of the current relevant teaching content in the Advanced Pharmaceutics module within the pharmacy programme where the new learning element would be implemented along with proposed change to assessment, supporting use of earlier learning in contextualising knowledge and its application.

The pharmacy curriculum is integrated across five cross- cutting curricular themes:

Medicines Sourcing, Production and Use

Safe and Rational Use of Medicines

Pathologies, Patients and Populations;

Professionalism and Communications

Leaders and Learners

Discussion

The pivot to online learning has resulted in students and educators alike being required to deliver learning content online which was not originally envisaged for this delivery mode. Students had not necessarily elected to pursue an online programme, nor had the possibility to choose an optimal situation from which to access the online material (i.e. many undergraduate students were required to return to their original family home). In these instances, there may have been limited access to computer resources, workspaces conducive to effective learning or reliable internet connectivity. Furthermore, it is likely that challenges would be exacerbated in less affluent sociodemographic environments. In order to maintain equitable access to the educational tools being developed, the process of developing the simulation-based learning element ensured that flexibility of technological and learning needs was embedded in the content development. It is also recognised (Lewin, Seider, & Seader, 2002; Belton, 2016) that a multimedia approach is valuable to support self-paced learning.

There is widespread use of simulation-based education in healthcare programmes, in particular relating to clinical skills and competencies (JRCPTB/NHS Health Education England, 2016; Ferguson *et al*., 2020). The value and challenges of such approaches, have been broadly reported in clinical education literature (Croft *et al.,* 2019; Sarfati *et al*., 2019; Ferguson *et al.*, 2020). However, the use of *in silico*, or computer-based process simulations tends to be reported more in educational literature relating to physical sciences, for example, chemical engineering (Li & Huang, 2017; Rasteiro & Urbano, 2017; de Lucas-Consuegra, Serrano, & Llanos, 2018; Golman & Yermukhambetova, 2019; Moodley, 2020; Nachtigalova *et al.*, 2020; Roman *et al.,* 2020).

In silico simulation tools are not only useful as a substitute for 'real life' or in vitro laboratory experience, but in some cases have been shown to actually improve performance in conceptual questions (Finkelstein *et al*., 2005). Advantages of process simulations include being able to break processes down to component parts to facilitate understanding, and to explore effects which cannot be replicated in real life (Rakić *et al.*, 2020). An example in the simulation programme discussed in the current work is the possibility to explore the effect of applying or disabling gravitational force in the simulation. Developing the simulation learning element as a pivot to online learning in the context of the current pandemic exploits these advantages of *in silico* simulation based learning, while also being cognisant of ensuring equity of access to all students, through identifying simple and asynchronous methods of delivery.

Furthermore, the absence of a sophisticated user interface for the presented simulation programme results in providing the user with 'behind the scenes' insight into simulation code. While not engaging in programming the code, this insight can be considered valuable to the user in terms of understanding the fundamentals of an in-silico simulation approach. The need to engage students with the simulation code/basic equations and therefore the fundamental principles underpinning the process simulation, in order to mitigate concerns relating to superficial learning using process simulation tools, has been recognised (Roman *et al*., 2020).

Using the example of medications investigated for COVID-19 treatment was successful in engaging user interest in the project, and was sufficiently versatile to enable multiple API examples and dissolution conditions to be investigated, applicable to each of the three learning stages. Combining this versatility with the QbD-BioRAM approach of risk assessing formulation development requirements suggests a rich opportunity for the learning element to be integrated into the pharmacy programme, in addition to biopharmaceutics-based modules in other postgraduate pharmaceutical sciences programmes in the authors' universities.

The structure of the element in terms of the Belton model for simulation pedagogy (Belton, 2016) facilitated the identification of milestone competencies and scaffolding opportunities during user development, and thus could also be delivered as individual elements, e.g. an introductory novice user level or a more advanced level supporting inquiry-based learning. The authors propose that this flexibility supports the use of the presented learning element in a range of teaching scenarios to postgraduate pharmaceutical sciences students, dependent on the target competency level and time available for delivery. In terms of assessment, the scaffolding opportunities suggested are considered largely formative in nature, however the developed assessment tools potentially present opportunity for either diagnostic and formative assessment (using the tools as a basis for discussion) or summative assessment (using the tools as a template for assignment submission). Nonetheless we suggest that combination of the tools with a reflective learning element following instructor feedback would optimise advanced user assessment at the advanced 'Future' competency milestone.

Future work: Implementation and Evaluation

Despite the successful development of the learning element, challenges were identified.

Regardless of all efforts to ensure equitable access, an *in silico* simulation tool is visual and dynamic, and requires at least the resources to access and download pre-recorded videos or screencasts. Asynchronous text discussion of complex process dynamics can be unwieldy, and more study is required to identify optimal online instructor-educator interactions in potentially resource poor settings or with unreliable internet connectivity. Appropriate debriefing is critical, and online interactions are not always optimal for supporting informal student questioning to identify areas of suboptimal learning.

Future plans include a focus on QbD-BioRAM in earlier (Year 4) learning in the integrated pharmacy programme in SOPPS, TCD, in order to support a focussed delivery of the presented learning element in Year 5 Advanced Pharmaceutics module. The learning element presented in the current work was trialled with a single novice user. Although flexible approaches to delivery of the learning element were identified, their value beyond single or small user groups has not been established. Evaluation of the learning element and assessment tools delivered as a structured workshop to groups of students should then be undertaken to validate delivery of the learning element beyond single-user training; in particular evaluation of which combination of the suggested delivery methods (synchronous, asynchronous, etc.) would be most acceptable or user-friendly to students engaged in remote online learning. Expanding evaluation to different expert/academic staff users in different institutions would provide notable value in further developing and refining the learning element.

In conclusion, in the current work, the use of the simulation programme in teaching was pivoted to develop an online learning element. Through use of an engaging cognitive hook, that of exploration of manufacturing challenges of pre-existing medicines being investigated as therapeutic agents for COVID-19, remote learning of the process simulation software was achieved across different countries and time zones. The learning element was successfully aligned with the three stages of competency in simulation pedagogy outlined by Belton (2016), and the learning element design was scaffolded through identification of competency milestones and development of associated assessment tools, based on iterative user feedback and discussion. In recognition of the advanced biopharmaceutics knowledge required for application of the learning element, intentional, directed preparatory work at earlier stages of the pharmacy programme is suggested. Alternative methods for online delivery and interaction are proposed to address resource limitations. Nonetheless challenges remain in identifying

optimal user-instructor interactions, and further study is suggested to optimise online asynchronous delivery or engagement with large student groups.

References

Abend, A., Heimbach, T., Cohen, M., Kesisoglou, F., Pepin, X., & Suarez-Sharp, S. (2018). Dissolution and translational modeling strategies enabling patient-centric drug product development: the M-CERSI workshop summary report. Springer. https://doi.org/10.1208/s12248-018-0213-x

Ahmad, A., Pepin, X., Aarons, L., Wang, Y., Darwich, A.S., Wood, J.M., *et al* .(2020). IMI-Oral biopharmaceutics tools project-Evaluation of bottom-up PBPK prediction success part 4: Prediction accuracy and software comparisons with improved data and modelling strategies. *European Journal of Pharmaceutics and Biopharmaceutics*, **156**, 50-63. https://doi.org/10.1016/j.ejpb.2020.08.006

Amidon, G.L., Lennernäs, H., Shah, V.P., & Crison, J.R. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research*, **12**(3), 413-420. https://doi.org/10.1023/A:1016212804288

Angelo, T.A., & Cross, K.P. (1993). Classroom assessment technique examples. Classroom assessment techniques: A handbook for college teachers. Jossey-Bass, 2nd edition

Belton, D.J. (2016). Teaching process simulation using video-enhanced and discovery/inquiry-based learning: Methodology and analysis within a theoretical framework for skill acquisition. *Education for Chemical Engineers*, **17**, 54-64. https://doi.org/10.1016/j.ece.2016.08.003

Brocks, D.R. (2015). uSIMPK. An Excel for Windows-based simulation program for instruction of basic pharmacokinetics principles to pharmacy students. *Computer methods and programs in biomedicine*, **120**(3), 154-163. https://doi.org/10.1016/j.cmpb.2015.04.006

Chen, B., Harp, D.R., Pawar, R.J., Stauffer, P.H., Viswanathan, H.S., & Middleton, R.S. (2020). Frankenstein's ROMster: Avoiding pitfalls of reduced-order model development. *International Journal of Greenhouse Gas Control*, **93**. https://doi.org/10.1016/j.ijggc.2019.102892

Crawford, J., Butler-Henderson, K., Rudolph, J., Malkawi, B., Glowatz, M., Burton, R., *et al*. (2020). COVID-19: 20 countries' higher education intra-period digital pedagogy responses. *Journal of Applied Learning & Teaching*, **3**(1), 1-20. https://doi.org/10.37074/jalt.2020.3.1.7

Croft, H. A., Glass, B., Gilligan, C., Rasiah, R., & Levett-Jones, T. (2019). Integrated simulation-based skills assessment for evaluating pharmacist competence: A scoping review. *Pharmacy Education,* **19**, 381-396

D'Arcy, D.M., & Persoons, T. (2011). Mechanistic modelling and mechanistic monitoring: simulation and shadowgraph imaging of particulate dissolution in the flow-through apparatus. *Journal of Pharmaceutical Sciences*, **100**(3), 1102-1115. https://doi.org/10.1002/jps.22337

D'Arcy, D.M., & Persoons, T. (2019). Understanding the potential for dissolution simulation to explore the effects of medium viscosity on particulate dissolution. *AAPS PharmSciTech*, **20**(2), 47. https://doi.org/10.1208/s12249-018-1260-4

de Lucas-Consuegra, A., Serrano, A., & Llanos, J. (2018). Use of process simulator to enhance the teaching-learning process of flow of fluids for engineering students. C*omputer Applications in Engineering Education*, **26**(4), 980-993. https://doi.org/10.1002/cae.21949

Dickinson, P.A., Kesisoglou, F., Flanagan, T., Martinez, M.N., Mistry, H.B., Crison, J.R., *et al.* (2016). Optimizing clinical drug product performance: applying biopharmaceutics risk assessment roadmap (BioRAM) and the BioRAM scoring grid. *Journal of Pharmaceutical Sciences*, **105**(11), 3243-3255. https://doi.org/10.1016/j.xphs.2016.07.024

Ferguson, J., Astbury, J., Willis, S., Silverthorne, J., & Schafheutle, E. (2020). Implementing, embedding and sustaining simulation-based education: What helps, what hinders. *Medical Education*, **54**(10), 915-924. https://doi.org/10.1111/medu.14182

Finkelstein, N. D., Adams, W. K., Keller, C., Kohl, P. B., Perkins, K. K., Podolefsky, N. S., *et al*. (2005). When learning about the real world is better done virtually: A study of substituting computer simulations for laboratory equipment. *Physical review special topics-physics education research*, **1**(1). https://doi.org/10.1103/PhysRevSTPER.1.010103

Frandsen, A., & Lehn-Christiansen, S. (2020). Into the black-box of learning in simulation debriefing: A qualitative research study. *Nurse Education Today*, **88**. https://doi.org/10.1016/j.nedt.2020.104373

Gabrielsson, J., Andersson, K., Tobin, G., Ingvast-Larsson, C., & Jirstrand, M. (2014). Maxsim2-Real-time interactive simulations for computer-assisted teaching of pharmacokinetics and pharmacodynamics. *Computer methods and programs in biomedicine*, **113**(3), 815-829. https://doi.org/10.1016/j.cmpb.2013.12.006

Golman, B., & Yermukhambetova, A. (2019). An Excel VBA-based educational module for simulation and energy optimization of spray drying process. *Computer Applications in Engineering Education*, **27**(5), 1103-1112. https://doi.org/10.1002/cae.22139

Hall, B.L. (2018). Development of a Computationally-Based Medicinal Chemistry Course at a Small, Primarily Undergraduate Institution. *The FASEB Journal*, **32**, 663.14

Hara, I., Suzuki, H., Kusakari, S., & Matsuoka, M. (2020). Practical training of pharmacokinetics with an web-based simulation application. Nihon Yakurigaku zasshi. *Folia Pharmacologica Japonica*, **155**(1), 51-55. https://doi.org/10.1254/fpj.19057

ICH Quality Working Group (2012). Points to consider for ICH Q8/Q9/Q10 guidelines. London, United Kingdon: European Medicines Agency

JRCPTB/NHS Health Education England (2016). Enhancing UK Core Medical Training through simulation-based education: an evidence-based approach. Available at: https://www.jrcptb.org.uk/sites/default/files/HEE_Report_FINAL.pdf

Lewin, D.R., Seider, W.D., & Seader, J. (2002). Integrated process design instruction. *Computers & Chemical Engineering*, **26**(2), 295-306. https://doi.org/10.1016/S0098-1354(01)00747-5

Li, X., & Huang, Z.J. (2017). An inverted classroom approach to educate MATLAB in chemical process control. *Education for Chemical Engineers*, **19**, 1-12. https://doi.org/10.1016/j.ece.2016.08.001

Ma, C., Wong, L., Wen, A., Arndt, R., Katz, A.R., Richardson, K., *et al*. (2020). Evaluation of distance facilitation and technology in an interprofessional simulation exercise. *Currents in Pharmacy Teaching and Learning*, **12**(7), 776-785. https://doi.org/10.1016/j.cptl.2020.02.007

Moodley, K. (2020). Improvement of the learning and assessment of the practical component of a Process Dynamics and Control course for fourth year chemical engineering students. *Education for Chemical Engineers*, **31**, 1-10. https://doi.org/10.1016/j.ece.2020.02.002

Nachtigalova, I., Finkeova, J., Krbcova, Z., & Souskova, H. (2020). A spreadsheet-based tool for education of chemical process simulation and control fundamentals. *Computer Applications in Engineering Education*, 28(4), 923-937. https://doi.org/10.1002/cae.22271

Nordmann, E., Horlin, C., Hutchison, J., Murray, J.-A., Robson, L., Seery, M., & MacKay, J. (2020). 10 simple rules for supporting a temporary online pivot in higher education. *PLOS Computational Biology*, **16**(10). https://doi.org/10.1371/journal.pcbi.1008242

Rakić, K., Rosić, M., & Boljat, I. (2020). A Survey of Agent-Based Modelling and Simulation Tools for Educational Purpose. *Tehnički Vjesnik*, **27**(3), 1014-1020. https://doi.org/10.17559/TV-20190517110455

Rasteiro, M.G., & Urbano, D. (2017). Evaluation of on-line simulation tools to teach Chemical Processes. Paper presented at the 2017 4th Experiment@ International Conference (exp. at'17). https://doi.org/10.1109/EXPAT.2017.7984397

Rodrigues, R.P., Andrade, S.F., Mantoani, S.P., Eifler-Lima, V.L., Silva, V.B., & Kawano, D.F. (2015). Using free computational resources to illustrate the drug design process in an undergraduate medicinal chemistry course. *Journal of Chemical Education*, **92**(5), 827-835. https://doi.org/10.1021/ed500195d

Roman, C., Delgado, M.A., & García-Morales, M. (2020). Using process simulators in Chemical Engineering education: Is it possible to minimize the 'black box' effect? *Computer Applications in Engineering Education*, **28**(5), 1369-1385. https://doi.org/10.1002/cae.22307

Ryan, T.J., Grimes, T., Henman, M.C., Ní Sheachnasaigh, E., O'Dwyer, M., Roche, C., Ryder, S.A., Sasse, A., Walsh, J.J., D'Arcy, D.M. (2019). Design and implementation of an integrated competency-focused pharmacy programme: a case report. *Pharmacy*, **7**(3), 121. https://doi.org/10.3390/pharmacy7030121

Sarfati, L., Ranchon, F., Vantard, N., Schwiertz, V., Larbre, V., Parat, S., *et al*. (2019). Human-simulation-based learning to prevent medication error: A systematic review. *Journal of evaluation in Clinical Practice*, **25**(1), 11-20. https://doi.org/10.1111/jep.12883

Selen, A., Dickinson, P.A., Müllertz, A., Crison, J.R., Mistry, H.B., Cruañes, M.T., *et al*. (2014). The biopharmaceutics risk assessment roadmap for optimizing clinical drug product performance. *Journal of Pharmaceutical Sciences*, **103**(11), 3377-3397. https://doi.org/10.1002/jps.24162

Serrano, D.R., Persoons, T., D'Arcy, D.M., Galiana, C., Dea-Ayuela, M.A., & Healy, A.M. (2016). Modelling and shadowgraph imaging of cocrystal dissolution and assessment of in vitro antimicrobial activity for sulfadimidine/4-aminosalicylic acid cocrystals. *European Journal of Pharmaceutical Sciences*, **89**, 125-136 http://dx.doi.org/10.1016/j.ejps.2016.04.030

WHO [World Health Organisation]. (2020). Solidarity clinical trial for COVID-19 treatments. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

Yu, L.X., Amidon, G., Khan, M. A., Hoag, S. W., Polli, J., Raju, G., & Woodcock, J. (2014). Understanding pharmaceutical quality by design. The AAPS journal, 16(4), 771-783. https://doi.org/10.1208/s12248-014-9598-3