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Published in:
Multimodal Technologies and Interaction

DOI:
10.3390/mti5030010

Publication date:
2021

Document Version
Author accepted manuscript

Citation for published version (Harvard):
Abuhammad, A, Falah, J, Alfalah, SFM, Abu-Tarboush , M, Tarawneh , RT, Drikakis, D & Charissis, V 2021, '"MedChemVR": a virtual reality game to enhance medicinal chemistry education', *Multimodal Technologies and Interaction*, vol. 5, no. 3, 10. https://doi.org/10.3390/mti5030010

Multimodal Technologies and Interaction

Article

"MedChemVR": A Virtual Reality Game to Enhance Medicinal Chemistry Education

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Abstract: Medicinal chemistry (MC) is an indispensable component of the pharmacy curriculum. The pharmacists' unique knowledge of a medicine's chemistry enhances their understanding of the pharmacological activity, manufacturing, storage, use, supply, and handling of drugs. However, chemistry is a challenging subject for both teaching and learning. These challenges are typically caused by the inability of students to construct a mental image of the three-dimensional (3D) structure of a drug molecule from its two-dimensional presentations. This study explores a prototype virtual reality (VR) gamification option, as an educational tool developed to aid the learning process and to improve the delivery of the MC subject to students. The developed system is evaluated by a cohort of 41 students. The analysis of the results was encouraging and provided invaluable feedback for the future development of the proposed system.

Keywords: medicinal chemistry; virtual reality; gamification; e-learning; education; human-computer interaction; inclusive education

Citation: Abuhammad, A.; Falah, J.; Alfalah, S.F.M.; Abu-Tarboush, M.; Tarawneh, R.T.; Drikakis, D.; Charissis, V. "MedChemVR": A Virtual Reality Game to Enhance Medicinal Chemistry Education. *Multimodal Technol. Interact.* **2021**, *5*, 10. https://doi.org/10.3390/mti5030010

Academic Editors: Christoph W. Borst and Cristina Portalés Ricart

Received: 31 December 2020
Accepted: 22 February 2021
Published: 4 March 2021

1. Introduction

Pharmacists have long been recognized as the medication experts who provide therapeutic counselling to patients and other health care professionals. Knowledge of the chemistry of drug molecules is what sets pharmacists apart as chemical experts in the healthcare system and helps them accomplish this role [1,2].

Medicinal chemistry (MC) is the unique interdisciplinary component of the pharmacy curriculum that plays an important role in the construction of this specific knowledge [2]. The International Union for Pure and Applied Chemistry (IUPAC) defines MC as a "chemistry-based discipline, also involving aspects of biological, medical, and pharmaceutical sciences. The IUPAC is directing the activities in the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships" [3].

The study of chemical structures of drugs and their receptors provides students with a thorough understanding of drug mechanisms of action, structure-activity relationships (SAR), physicochemical properties, drug-drug interactions, side effects, and pharmacokinetic properties. The importance of MC education for pharmacy students and its clinical relevance has been well emphasized by experts and pharmacy educators [1,4–6]. It has also been adopted by many medicinal chemistry courses around the world. Furthermore, classical textbooks of medicinal chemistry have been recently tailored to satisfy this trend [2,7,8].

The majority of drugs are organic small molecules, thus organic chemistry is a fundamental prerequisite to study medicinal chemistry. Although pharmacy students consider organic chemistry to be highly important and relevant to the pharmacy profession, they still perceive it as complex and difficult [9–11]. This is evident by the steady decrease of specialist chemists and pharmacologists graduating [12]. To counteract this decline in student numbers in the particular disciplines, many medical and applied health schools have reduced the prerequisite for acquiring specialist pharmacology knowledge with consequent detrimental effects in the new generation of medical and allied health professionals [12].

Adhering to the above issues, this paper presents an alternative solution to 2D and traditional teaching methods. The proposed system is designed to entice the new generations of students through teaching by gamification the ability to immerse the student in the digital classroom and laboratory environments with the use of virtual reality (VR). These two components (i.e., games and VR) were deemed essential to provide the desired knowledge to the students while aiming to reduce the aforementioned anxiety and course-related fears. Both methods and technologies have been successfully used in previous studies to mitigate similar student performance issues in medical school and junior doctors' training [13,14]. The proposed VR system, be-spoke human-computer interaction (HCI) design, and gamification methods could provide a new paradigm framework that could accommodate, similar to medical chemistry, multidisciplinary modules, and courses.

In particular, this research aims to combine the above technologies and offers a simplified yet immersive system explicitly developed for the medical chemistry courses, which currently lack or have limited support from similar applications. In addition, this work presents the design rationale and the development process of the proposed system. In turn, the paper discusses the evaluation process and results of a 41 student cohort. Finally, the paper explores the benefits and drawbacks of the VR teaching game and offers a tentative plan of future work that will enhance the context and interaction with prospective students in this thematic area.

2. Background

2.1. Current Issues

In many pharmacy schools, students pass the organic chemistry class a year or more before taking the MC course, resulting in a poor recall of the basic knowledge needed to comprehend the subject [11]. Due to the complexity of the subject of organic chemistry, there is widespread anxiety among students [15,16]. This attitude is developed either as a reaction to previous poor experiences in chemistry or secondary to the pre-perceived notion that chemistry is very difficult as determined by second-hand experiences and associated perceptions [16–21]. This "chemophobia" impedes the engagement of students with MC classes, reduces their interest in the topic, and makes learning tedious and unsuccessful [10,11]. Therefore, many students start the MC class with much apprehension and fear. In reality, drug molecules are three-dimensional (3D) entities usually presented to the students in books and lectures as a two-dimensional (2D) structural formula. The 3D representation contains information, such as general conformation, stereochemistry, bond angles, and torsion angles, which are absent in the 2D presentation and already used extensively in this field's research [22]. Therefore, the visualization of the 3D structure has been reported to enhance students' understanding of chemical structures.

2.2. Current Solutions

In the last two decades, the extensive development of new information technology has been successfully employed in MC education [23,24]. The use of 3D visualization and computer molecular modeling tools have been shown to improve students' achievement and attitudes toward MC [9,24]. Other methods that have been successfully implemented to augment traditional lectures in MC include active-learning, case-based learning, e-learning activities, and lately the 3D printing of enzymes and ligands [25–30]. Nevertheless, the 3D representation of structures in a virtual and immersive environment has been used extensively in other medical-related disciplines such as the teaching of anatomy, pathology, and surgical rehearsal for various specializations [31–34]. These cases required the student to develop a 3D mental map for understanding the positioning and interaction between different physical structures. Such a task was not possible with the use of existing teaching methods and tools, which presented the information primarily in a two-dimensional manner. Initial attempts to develop 3D structures were implemented with the use of physical mock-up models, which offered some support to the students learning process [35].

Yet, these 3D models required physical space to experiment with and could not cover all the possible versions, cases, and iterations encountered in real-life [13,31]. As such, the 3D visualization and in extent the virtual and/or augmented reality (VR/AR) could mitigate this issue. The latter emerging technologies could offer be-spoke material and various options for the learning and teaching of such complex courses. Preliminary studies and some initial commercial attempts that utilized the visualization of the 3D structure have been reported to enhance students' understanding of chemical structures. In the last two decades, the extensive development of new information technology has been successfully employed in MC education [19,20]. The use of 3D visualization and computer molecular modeling tools have been shown to improve students' achievement and attitudes toward MC [9,30].

3. Proposed Solution Rationale, Design, and Development

3.1. Smart Phones and Tablets

The upsurge in the popularity of smartphones, the drop in their cost, and the improved computing ability has made them valuable learning tools. They can provide convenient ubiquitous access to education since they are in the students' possession throughout the day [36,37]. A large number of chemistry applications are currently available on smartphones and other portable electronic devices to support chemistry students [38,39]. This accessibility, both in space and time, was deemed essential for the development of the proposed teaching MC application. As such, the proposed system was developed primarily for use in Android smart devices, with a view to expanding in iOS and Windows-based mobile systems, as presented in Figure 1.

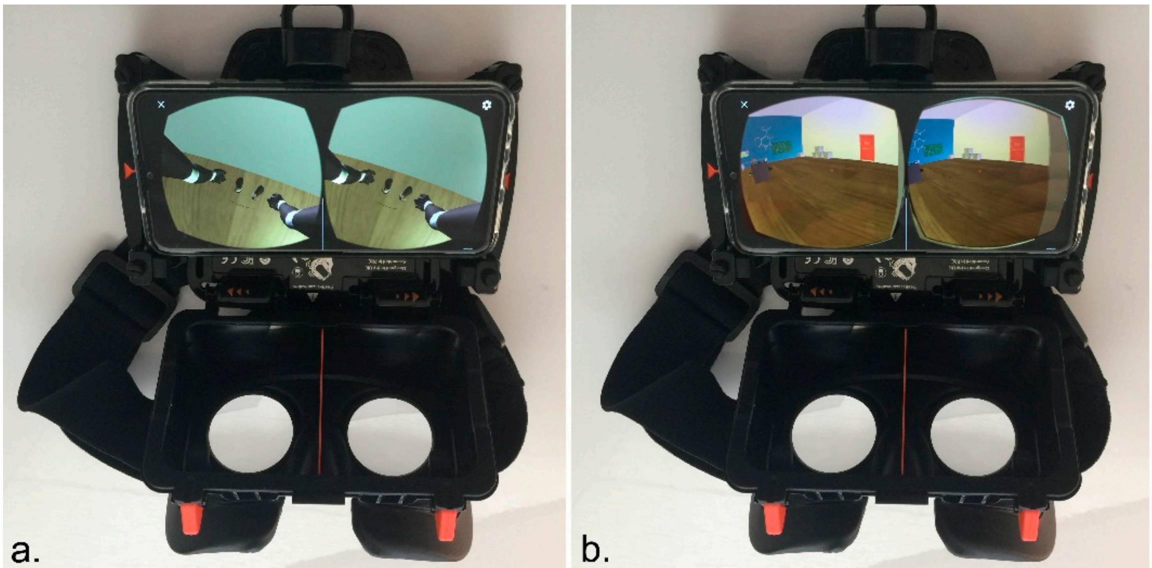

Figure 1. Screenshots of the system operating in a smartphone embedded in a head-mounted display (HMD): (**a**) Image of the user's digital body representation in the virtual reality (VR) environment. (**b**) Image of the virtual classroom with the hovering molecular structures under investigation.

3.2. The Gamification Approach

Several applications have employed gamification methods to appeal to the majority of the student ages [40,41]. The use of online games as part of teaching applications has been shown to encourage learning, enhances student interest, boosts retention, and improves learning outcomes [39,42]. Learning and teaching computer-games proved to be effective vehicles for demonstrating the relevance of chemical principles and SAR to therapeutic decision-making and patient care in pharmacy education [43].

Similarly, the gamification approach is being used in numerous other subjects that the students tend to find difficult, not interesting or exceptionally complex. The gamification approach offers the advantage of making learning enjoyable and can employ interaction methods, which could enable the students to learn through simulated action and experiencing the subjects [41–44].

3.3. Virtual Reality

Virtual reality (VR) offers an immersive experience that is very different from using a standard 3D visualization software typically represented in 2D screens and monitors [31,45]. The ability to fully immerse the user in realistic or fantasy environments has been a major point of interest for various developers as the users are more enticed to participate, use, and purchase such applications [46–49]. This capacity has the potential to help the mental health of users in adverse conditions such as the current pandemic, which requires the users to interact remotely in virtual common spaces [50,51].

As VR technologies increasingly become more available and affordable, several teaching and learning applications have emerged to support students. This current teaching trend has also been applied to chemistry where various VR applications and serious games became available, as presented in Table 1. However, most of these games introduce simple chemical concepts and target primarily high school students.

The provision of VR serious games on smartphones offers a unique combination of emerging technologies that enable the users to train on their own time and space while experiencing a real environment remotely and with the use of an inexpensive and accessible device such as a smartphone. Current smartphones present an ideal conduit for the presentation and interaction with VR applications as they utilize the high-speed 3D graphics processing units (GPU) capacity in high-resolution screens.

The interaction can be embedded with the use of eye-tracking or with external controllers typically included with a head-mounted display (HMD) device. The latter is used as a cost-effective shell that accommodates the smartphone (i.e., google cardboard or inexpensive plastic HMD versions) in contrast to a full VR head-mounted display such as Occulus Rift, Quest, and HTC Vive, etc., that have embedded screens and GPUs in some cases.

The above capabilities of VR devices and applications have recently spurred the interest of medicinal chemists and drug designers both in academia and industry. Molecular Rift is a virtual reality environment (VRE) steered with hand movements [52,53]. The particular application has been developed to help drug designers with the potential to be used in education [54–56].

Recently, a VR toolkit has been developed to allow the interactive exploration of chemical space populated by DrugBank compounds in VR with the potential to be used as teaching aids [54]. To the best of our knowledge, there are no VR games intended solely for the learning and education of the drug chemical structure or MC for pharmacy students.

Table 1. Current VR educational applications for chemistry.

Game	System	Target Users	Description	Molecules	Reference/Site
VR Chemist	SteamVR, VR room	High-School Chemistry	Students pick up the atoms and bindings using controllers and then attach them to form the molecules.	H_2O, CO_2, H_2O_2	Stenshagen https://brage.bibsys.no/xmlui/handle/11250/2502558 (accessed on 3 March 2021)
Chemistry VR-Cardboard	iOS Android		Use elements of the Mendeleev Table to build simple chemical structures using cardboards and magnet	Simple molecules such as: H_2O.	Google Play
MEL Chemistry VRLessons	*Google Cardboard* Samsung Gear VR	K–12 students	Basic chemistry principles. The structure of an atom, what an electron orbital is, and what an isotope is.	Simple molecules such as: H_2O, sugar, and simple alkanes.	https://melscience.com/vr/lessons/molecules/ (accessed on 3 March 2021)
Molecule VR	*Google Cardboard*	Biology, and medicinal chemistry students	Basic concepts of cell communication and signalling.	Selected protein structures from the Protein Data Bank.	https://play.google.com/store/apps/details?id=com.AppMinded.MoleculeVR&hl=en (accessed on 3 March 2021)
EduChem VR	Google Cardboard, Android and iOS	University courses and advanced high-school levels	Organic chemistry concepts.		http://educhem-vr.com (accessed on 3 March 2021)
Learning Carbons VR				Explore different carbon forms,	
Learning MacroMol VR				explain the concept of stereochemistry,	
Learning Stereo ChemVR				explore macromolecular structures.	
Chemistry WebVR	Web-based			Basic concepts such as orbitals, hybridization, stereochemistry, and molecular geometries.	

3.4. Proposed VR Learning and Teaching Applications

Based on the aforementioned facts and observations, this work presents a prototype educational VR game, namely "MedChemVR". This VR application is an interactive visualization tool for drug chemical structures presented in an immersive virtual classroom environment similar to an existing space in the University of Jordan. This latest version of the VR game was developed using one class of drugs, the nonsteroidal anti-inflammatory drugs (NSAIDs), which is a popular class and prerequisite knowledge in several examinations. This game allows the students to navigate through the chemical structures from all aspects and interact with the molecules in the simulated virtual environment. Such experience aims to help them grasp the structures' geometry and understand their properties, as well as improve their engagement and motivation toward the subject.

3.5. Gamification and HCI Rationale

The MedChemVR game was developed using the Unity3D engine based on users' requirements and in-depth medicinal chemists' consultation. A preliminary evaluation of the Alpha version of the game was previously performed with a focus group and provided encouraging results, as well as enlightening feedback, which was utilized to improve the current version of the application as illustrated in Figure 2.

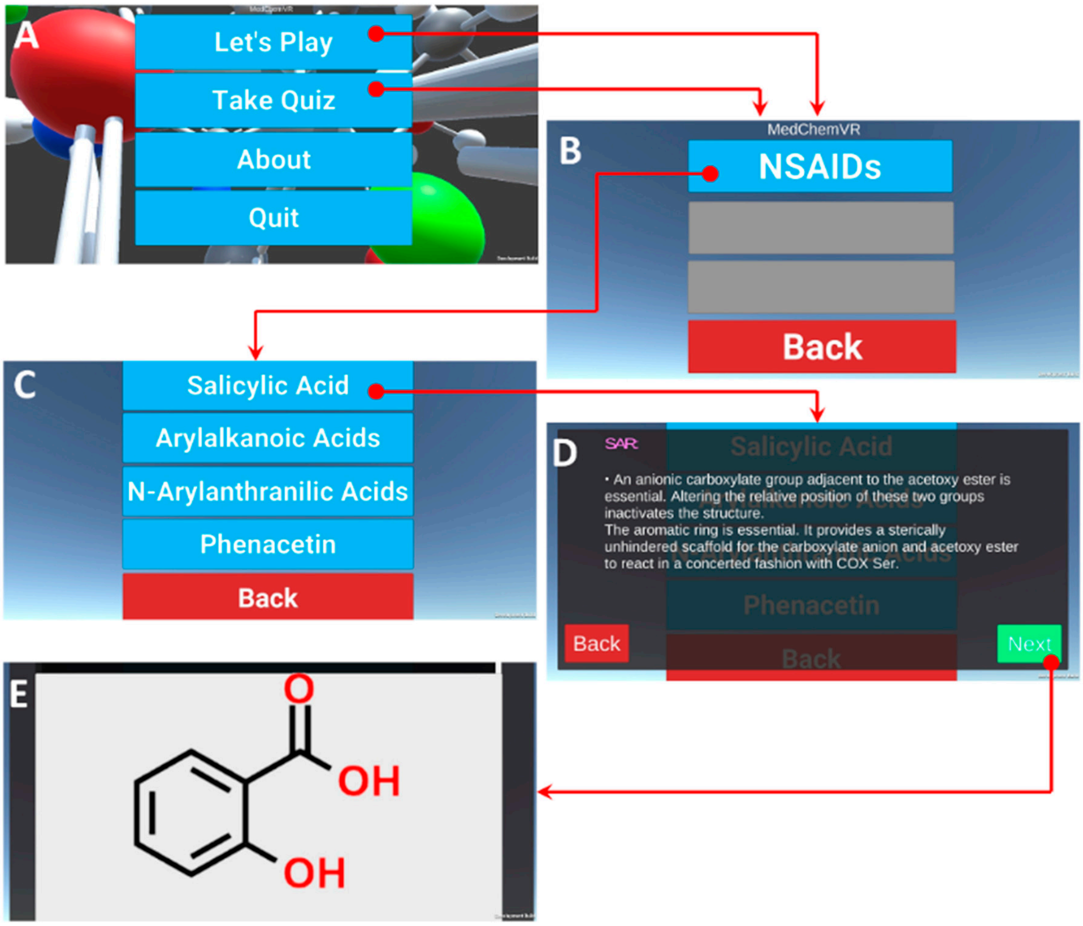

Figure 2. The consecutive interfaces of the MedChemVR. (**A**) The start screen. (**B**) The second interface in either the "Let's Play/Take a Quiz" mode takes the student to the next interface. (**C**) The chemical sub-classes to which drugs belong. (**D**) The structure-activity relationships (SAR) of each subclass. (**E**) Visualization of the two-dimensional (2D) structure of each drug, by clicking on the 2D structure, the student will be guided to the VR classroom.

The interface design of the MedChemVR game was supplemented with several consecutive interfaces to simplify the navigation through the 3D chemical structures of drugs. In particular, the main interface guides the student to either the play mode "Let's Play" or the quiz mode "Take a Quiz" as well as information on the game and an option to quit the game, as presented in Figure 2. The second interface in the "Let's Play/Take a Quiz" mode provides a menu of different pharmacological classes of drugs. A selection of any of these classes will take the student to the next interface, as shown in Figure 2.

In this prototype system, we have implemented a single class of drugs, the NSAIDs. The next interface shows the sub-classified chemical of each drug class as present in the main teaching textbook of MC [7]. Upon selection of a subclass, a screen will be displayed showing the SAR information to help the student relate the drug structure to its SAR. The following interface is the one that allows the students to select a particular drug and visualize it in a 2D format, as illustrated in Figure 2.

3.6. *"Let's Play" Mode—Rationale*

The main element of the proposed application is the fusion of critical learning and teaching information in a game environment. In this case, it was deemed essential to transfer the existing curriculum through gamification in an immersive space where the user/student could experience the surroundings of a classroom, yet can isolate and concentrate on the taught material. For this reason, *gamification* was selected as the best option in contrast to *serious games*.

Gamification is typically employed in existing content, which requires a more enticing conduit to present information to the learner. This can be achieved by utilizing game theory and mechanics to engage users and enrich the learning experience [57,58]. In contrast, the serious games' method, embeds specific learning outcomes in the design of the game and the learning objectives are met through playing and/or completing the game. Such games are designed with a defined learning specification in mind and the game is developed keeping the learning goals at its core. Serious games typically offer training and/or simulation as part of the gameplay [59]. The latter method could be utilized primarily in subjects that could replicate real-life situations and scenarios (i.e., engineering subjects, human anatomy/pathology, and surgical rehearsal, etc.). As the molecular structures of chemical compounds are not visible and do not offer a hands-on experience in real-life, their structural characteristics and interactions are visualized in a way that could imitate large objects and be manipulated within the VR environment. Previous work on the VR interaction and manipulation of medical anatomy and pathology provided the baseline for the design and implementation of the proposed system [13,14,34,60,61]. The movement in the VR space is minimal, restricting the user to focus on the virtual 3D molecular model and prevents him/her from wandering aimlessly in the VR classroom.

Notably, the typical affordances of 3D learning environments defined as spatial knowledge representation, engagement, experiential, contextual, and collaborative learning are the five key-element tasks that could be provided to the user to enhance knowledge acquisition [62]. Yet, the presentation of the 3D learning environment experienced in a desktop computer has some inherited limitations, which can be eliminated by the fully immersive environment provided by the use of HMD and smartphones. The latter combination offers a 3D and VR environment that could be experienced in a cost-effective, mobile, and immersive manner. The proposed VR application entails all the aforementioned affordances of 3D learning except the collaborative learning element. The collaborative environment will be further explored in the future version of the VR application to further support the social coherence of the class particularly in situations similar to the current pandemic that prohibits social interaction [18].

The spatial knowledge representation was achieved with the 3D visualization of the molecular scaffolding and color-coded spheres that the user can interact and navigate with typical 3D functions, such as pan, zoom, and rotate on its axis, activated by the hand controllers provided with every HMD set. Beyond the mechanics of VR interaction, the particular gamification process also offers an interesting learning environment for the student populations which as *digital natives* are more comfortable to adapt and follow this learning process [63]. Yet, the gamification of the MedChem system was produced without the distraction of an elaborate gameplay which could dilute the learning process. As such, the students play and learn by automatically evaluating their efforts against the correct molecular structures and the provided time to completion. This is a typical scoring approach that is used in entertainment games in which the player builds up the individual score and ability while uncovering new levels [64,65].

3.7. "Let's Play" Mode—Game Activity

In the "Let's Play" mode, by clicking on the 2D structure, the student will be guided to the VR classroom, where the 3D structure is displayed as a ball-and-stick molecular model in front of the atoms' holder depicted as colored spheres, as presented in Figure 3. The standard Corey-Pauling-Koltun (CPK) color convention was used to allow distinguishing the atoms of different chemical elements in molecular models [56]. The CPK color scheme includes: White for hydrogen, grey for carbon, red for oxygen, yellow for sulfur, blue for nitrogen, and green for the halogens (F, Cl, Br, I). Other factors such as the design of the class environment, as well as the color and texture of the different parts within the class are optimized to ensure enjoyability, flexibility, and ease of use. The degree of enjoyability directly correlates with the duration and frequency of the gameplay, enforcing the resultant learning process.

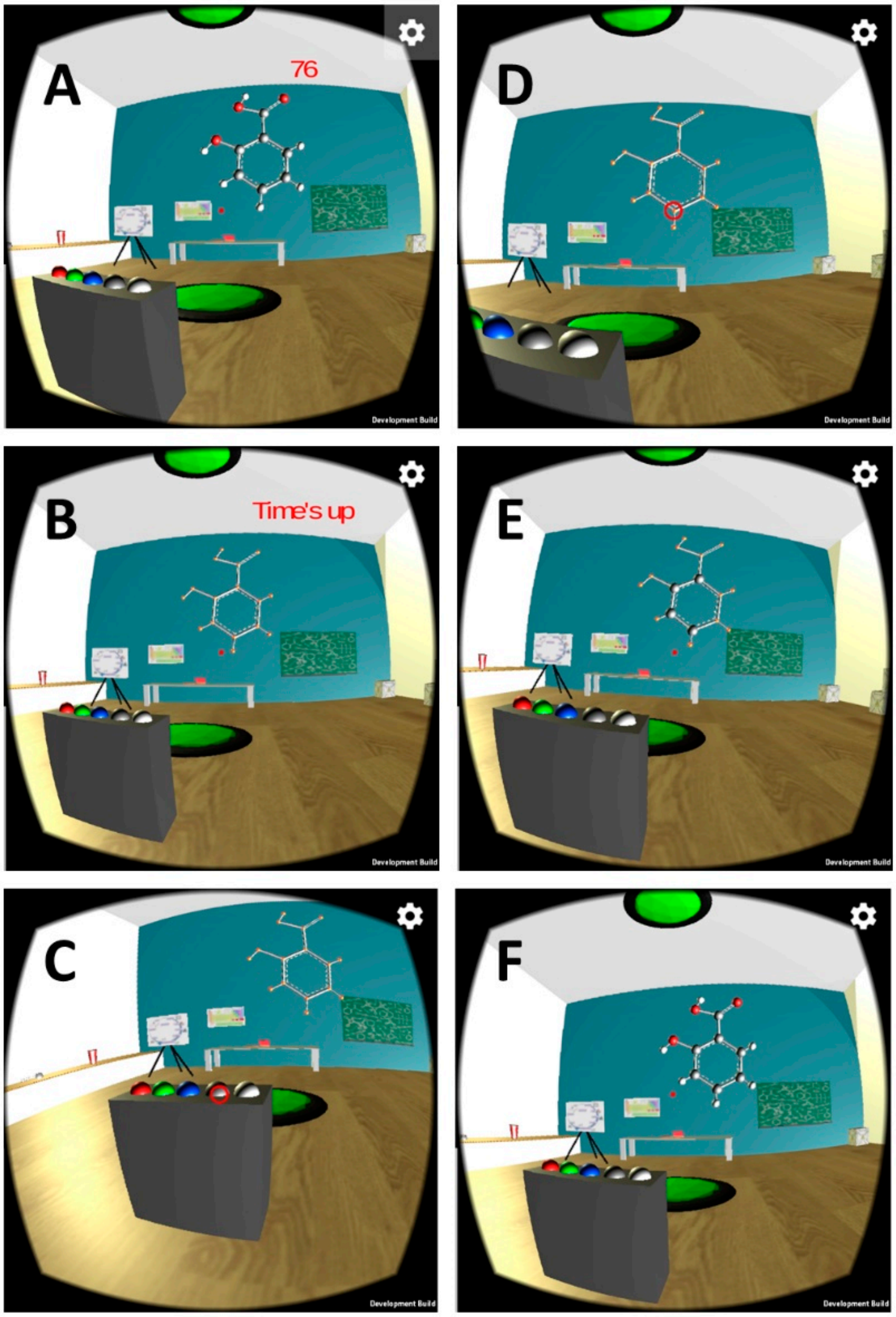

Figure 3. A selection of screenshots of the actual VR classroom of MedChemVR game, presenting the different learning and teaching activities the "Let's Play" mode. (**A**) presentation fo complete structure for 90 s (**B**) End of the countdown (**C**) Main scaffolding with no atoms. (**D**) Selection of atom position (**E**) positioning atoms (2D) complete structure by the student, (**F**) atoms are accepted in the structure only in the correct positions.

While in the "Let's Play" mode, the student would be able to visualize the 3D structure from different viewpoints aided by the supplemented remote lever to move forward and backwards. The system allows the timing of 90 s to revise the structure, after which the atoms (balls/spheres) will disappear leaving only the skeleton of bonds (sticks), as illustrated in Figure 3. Then, the student will be allowed to try and rebuild the structure by adding the atoms (using the colored spheres) back to their correct position.

The remote controller is needed for the atom installation using the shoot button. In the "Let's Play" mode, the system will accept the atom only if the correct element has been placed in the right position. The different stages and requirements of the game in the "Let's Play" mode are presented below:

a. The system allows the student to examine, navigate, and review the structure for 90 s (the timer is on the right top corner) only in the "Let's Play" mode. The student can examine the structure from all sides by moving around while wearing the glasses. Zooming in and out can be achieved using the Bluetooth remote controller lever.
b. When the time is up, the student will get a message "Time's up", the spheres representing the atoms will disappear, and the skeleton of bonds will remain displayed.
c. The student can start playing by selecting the correct atom they want to re-install, by pointing the cursor (red circle) at the correct sphere on the atom holder, and clicking on the shoot button on the front of the remote controller. As an example, the carbon (grey sphere) is selected in Figures 3 and 4.
d. The atom's position on the drug skeleton is selected by pointing the cursor towards it.
e. Atoms are added back by clicking on the shoot button on the front of the remote controller.
f. The student can add all atoms of the same type before selecting another type of atom (different colored spheres) until they re-build the molecular structure of the drug. In the "Let's Play" mode, the system will accept the sphere only if the right atom is placed in the right position. The student will return to the main interface when they finish building the structure.

Notably, the above stages were developed based on feedback from the students during the system evaluation. The latter is described further in the following sections.

3.8. "Take a Quiz" Mode

The quiz mode is used to ensure the student remembers the correct elements and their positions in the molecular model. The student is expected to be able to rebuild the structure by adding the atoms (balls) back to their correct positions.

Unlike the play mode, the quiz mode will accept any atom the student adds until the student submits their model, as depicted in Figure 4.

Upon submission of the model, the student will get either a "Success" or "Try again!", depending on whether or not they manage to rebuild the correct chemical structure, as illustrated in Figure 4. The student can exit the classroom anytime and return to the main interface by pointing the cursor at the fire exit door in the corner of the class, either on the "Let's Play" or "Take a Quiz" mode, as presented in Figure 4. Finally, the timing of both playing and quiz sessions was provided to enable the student to have ample experience of the system, yet to comply with the examination requirements. The latter was a condition that was considered important for the preparation of students for future exams. The different stages and requirements of the game in the "Take a Quiz" mode are presented below:

a. In this mode, the skeleton with no atoms will be displayed in the class, and the timer starts immediately (120 s).
b. The student can select atoms, and install them back into the structure in the same way as in the "Let's Play" mode.
c. In the quiz mode, the system will accept the sphere regardless of its color, and they will not be able to change the atom once placed on the skeleton.
d. If any of the atoms are placed in the wrong position, the student will get a message "Try again!" at the end of the allowed time.
e. If the student gets all atoms to their right positions, they will get the message "Success".
f. The student can quit the game, leave the VR classroom, and return to the main interface by pointing the cursor at the fire exit door in the corner of the class and also by clicking the shoot button of the remote controller. This option is also present in the "Let's Play" mode.

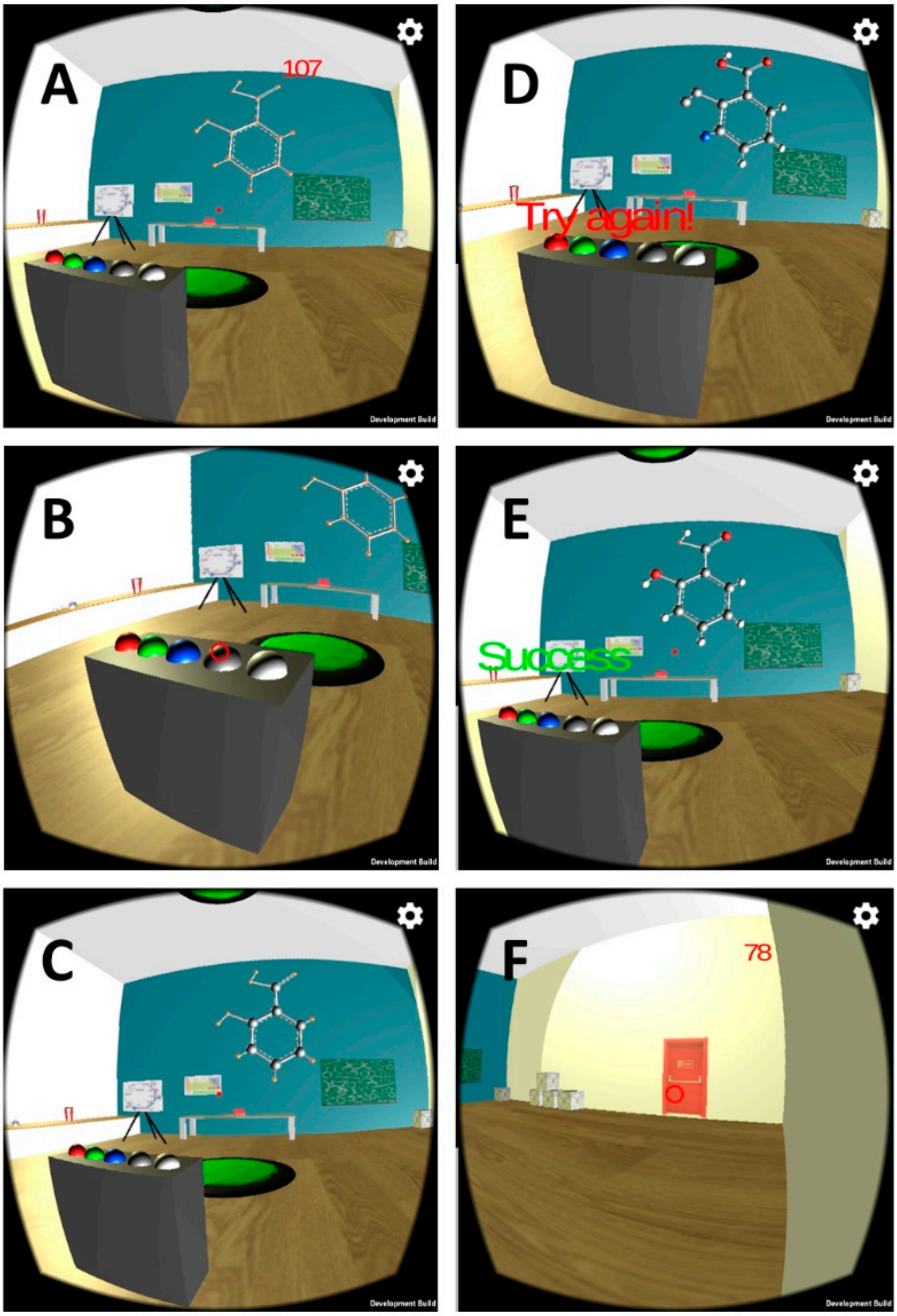

Figure 4. Screenshots of the real-life MedChemVR game in the "Take a Quiz" mode. The screenshots present different activities aiming to evaluate the user's knowledge. (**A**) Main scaffolding with no atoms, (**B**) installing atoms in the scaffolding, (**C**) positioning the atoms, (**D**) "Try Again" message appears when the atoms are incorrectly positioned, (**E**) "Success" message appears when the atoms are correctly positioned (2D) complete structure by the student, (**F**) Exiting the VR room and the testing part of the application back to the main menu.

4. Methodology

4.1. Software and Hardware Requirements

For the development of the application, a group of software packages were employed. The 3D environment and objects were modeled with the use of the Autodesk Maya 3D visualization software. In turn, the 3D models were introduced to the Uni-ty3D game engine where the interactivity with the objects was developed. Finally, the complete computer game was exported as a VR Android compatible application. For an evaluation of the application, the experimenters used the Samsung Galaxy S7 Edge mobile smartphone and a pair of BOBOVRZ4 virtual reality glasses with BlueTooth remote control. The system was also tested with other HMD brands in Jordan and the UK, as illustrated in Figure 1.

4.2. Participants

In this study, the student-sample used to evaluate the MedChemVR game consisted of Pharmacy and PharmD students at the School of Pharmacy in the University of Jordan, in their fourth, fifth or sixth year of study (for PharmD students). A sample of 41 students volunteered to try the game and complete an electronic questionnaire immediately after evaluating the game. All 41 students are familiar with the topic of MC and have at least finished one course of MC. Both Pharmacy and PharmD programs include three courses of MC making a total of eight credit hours. The number of students in each class can range from 40 to 60 students. The evaluation was carried out for two weeks.

4.3. Evaluation Rationale and Structure

The students were provided with information on the study procedure and received no compensation for their participation. Before trying the game, the students were informed verbally of the game rules and use of the remote controller. Each participant wore the VR glasses and experienced the MedChemVR classroom environment for 30–45 min to try both play and quiz modes using a drug molecule of their choice. Following the interaction session, the participants completed the short electronic survey prepared using Google Forms as can be seen in Table 2.

Table 2. Students' feedback—questionnaire part 2.

	Please Answer the Following Questions Where: (1) Strongly Disagree, (2) Disagree, (3) Moderate, (4) Agree, (5) Strongly Agree
Q5.	Drug chemical structures are easy to understand and memorize using the MedChem VR game.
Q6.	I think the MedChemVR learning tool is flexible enough for training.
Q7.	Understanding the structure-activity relationship (SAR) from the drug chemicalthe structure is easy.
Q8.	Visualizing and deriving conclusions from a drug's structure is easy.
Q9.	I can easily recognize and navigate through the 3D structure of drugs from different perspectives.
Q10.	I feel that I will be well prepared for the exams.
Q11.	The MedChemVR game is an enjoyable learning tool
Q12.	I think the MedChemVR game integration into teaching and learning is very important for students.
Q13.	Using virtual reality saves the time required to learn the chemical structures in medicinal chemistry.
Q14.	I believe there are advantages to using virtual reality technology in our course(s).
Q15.	I believe that MedChemVR provides an immersive learning environment where students can become engaged in learning as we explore the virtual environment.
Q16.	Using the application of 3D models would be easier for me than traditional methods to learn chemical structures in medicinal chemistry.
Q17.	Using virtual models is useful for me since it will increase my knowledge and help me see the 3D structure model of a drug from several viewing positions.

Table 2. *Cont.*

	Please Answer the Following Questions Where: (1) Strongly Disagree, (2) Disagree, (3) Moderate, (4) Agree, (5) Strongly Agree
Q18.	The experiment content helps me better understand and memorize the chemical structure of a drug.
Q19.	Visualizing and rotating 2D and 3D structures of a drug is helpful in medicinal chemistry studies.
Q20.	It would be helpful to incorporate virtual reality as computerized visual aids during medicinal chemistry lectures.
Q21.	I think my academic achievement will be enhanced by embedding MedChemVR as a learning tool.
Q22.	I would consider using virtual reality visual aids to aid my personal studies outside the classroom.

First, a two-fold questionnaire was presented to the users. The first part of the questionnaire was concerned with the demographic information of the group, which was covered by the first four questions.

The second part of the questionnaire aimed to acquire students' subjective feedback that could highlight the benefits and drawback of the proposed MedChem VR teaching game-application, as shown in Table 2. Moreover, their responses could further inform the development of supplementary options that could be included in future MedChemVR versions.

5. Evaluation Results

The evaluation of the game by 41 Pharmacy/PharmD (22/19) students showed that the majority of them were not satisfied with the traditional teaching tools used in MC classes. The students agreed on the need for new technologies such as VR to impact and improve their attitude towards the topic. The students showed consensus on the enjoyability of the game and its ability to enhance their engagement. These findings highlight the potential of further exploring the use of VR in MC education. The analysis of the sample shown out of 41 participants were 38 females and three males. This distribution is consistent with the ratio of females to males in the School of Pharmacy at the University of Jordan. Moreover, this result is similar to preliminary studies with 405 students who were consulted before the development of this application.

5.1. Reliability Test

The Cronbach alpha is a value typically considered when multiple-item measures/values of a concept are used [41]. The reliability of the derived data can be confirmed when the Cronbach alpha value exceeds 70% (0.7). In this experiment, the Cronbach alpha value is A = 0.929. Moreover, if an item is deleted, the Cronbach alpha could vary between 0.915–0.938.

5.2. Frequencies

In all the questions (Q5 to Q22), the value of the mean indicates agree and strongly agree on all questions where the values varied between 0.5122–1.1951, while the sample answers were spread around the mean within two standard deviations $+/-$ mean. The values of the standard deviation varied between (1.00547–1.12076). The NB frequency distribution indicates the percentage of answers in each category.

5.3. Correlation Test

To test the correlations between the different indices, two indexes were developed by incorporating sets of related questions, as described below. An index called Q23 (MedChemVR as a learning tool) was computed by adding Q13, Q16, Q17, Q18, and Q22. Moreover, an index called Q24 (attitude toward MedChemVR) was computed by adding Q5, Q6, Q7, Q8, and Q9 to test the relationships between the two indices, and it was calculated as 0.817 and found significant at the 0.001 level. The calculated correlation of Q23 with variables Q13, Q16, Q17, Q18, and Q22 were presented to be highly correlated. The Pearson value ranged from 0.692–0.782 and was found significant at the 0.001 level, which means that all the questions are highly correlated with the other group. The computed correlation of Q24 with variables Q5, Q6, Q7, Q8, and Q9 resulted in a Pearson value that ranged from 0.351–0.804, in which all the correlations were found significant at the 0.01 level, except Q7, where the correlation was 0.351 and found significant at the 0.05 level.

5.4. Additional Regression Analysis

The ANOVA analysis shows that the five questions (Q13, Q16, Q17, Q18, and Q22) together explain any changes in the dependent variable Q23, where the F value was 16.091 and found significant at the 0.0001 level. However, the coefficients indicate that the t-test of each independent item of only Q17 is very important. Yet, if all the variables are taken together, they affect the dependent variable.

On the other hand, Q24 was affected by the independent variables (Q5, Q6, Q7, Q8, and Q9). The most important questions were Q5, Q6, and Q9, since their t-value was above 1.97. When taking all five variables together, the ANOVA model showed an F value of 23.136 and was found significant at the 0.0001 level. The Likert scale results in percentages are presented in Table 3 and analyzed in detail in the following sections.

Table 3. Likert scale results.

Questions	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Q5	0	9.76	12.2	26.83	51.22
Q6	0	14.63	17.07	34.15	34.15
Q7	0	24.39	24.39	26.83	24.39
Q8	0	14.63	24.39	34.15	26.83
Q9	0	19.51	12.2	34.15	34.15
Q13	0	14.63	14.63	31.71	39.02
Q16	0	14.63	7.32	26.83	51.22
Q17	0	12.2	7.32	31.71	48.78
Q18	0	14.63	14.63	26.83	43.9
Q22	0	12.2	9.76	31.71	46.34

5.5. Feedback Results and Analysis

The students' overall user experience (UX) presented a positive picture. Their responses to the questions that form the Q24 (attitude towards MedChemVR) index described above, were of particular interest for the study, since they were revealing valuable information regarding the acceptance and the usability of the proposed VR application.

The analysis has shown that the students were in favor of the proposed system since they found it easy to memorize the chemical structures with positive responses of 78% in Q5. The system flexibility for training has also received positive outcomes with 68% for Q6, as presented in Figure 5. However, six users did not find the system flexible enough to present and accommodate the course information, since they could not operate the system due to the technical difficulties encountered. These difficulties were mainly due to hand and eye coordination as the operation of the HMD controllers is not visible when the user is immersed in the VR environment. Further work will be required to streamline these issues and potentially offer preset VR HMDs and mobile-phone devices in order to maintain a uniform distribution and usability of the system. Cost-efficient options will have to be considered to also maintain socioeconomic inclusivity.

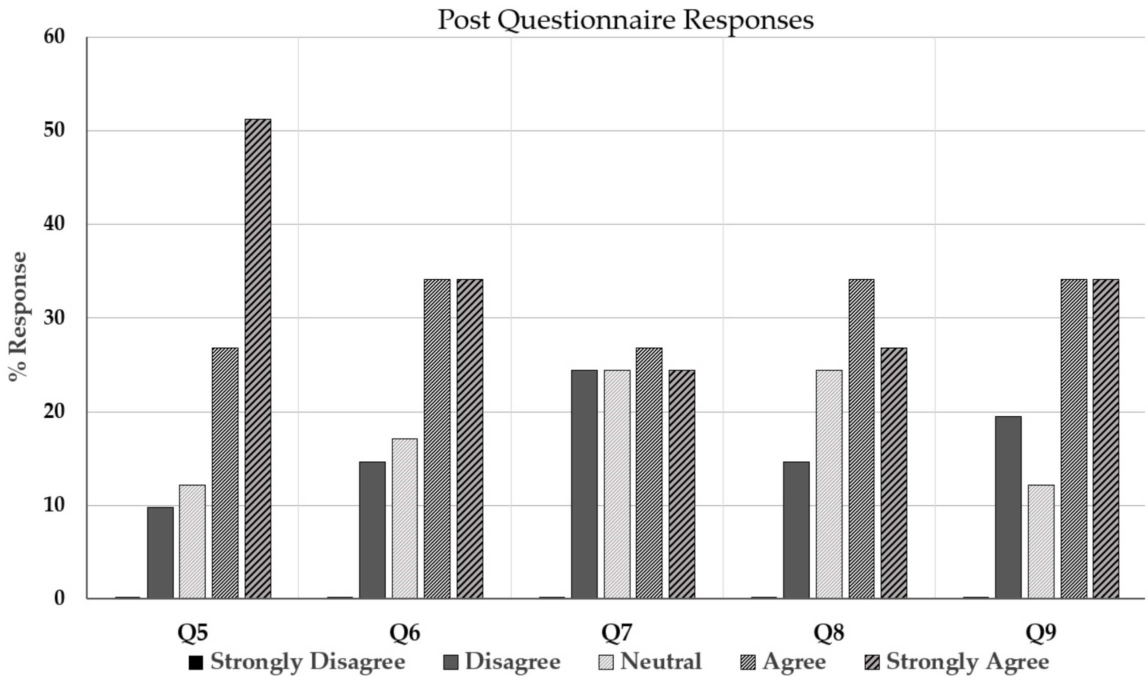

Figure 5. Student responses to questions Q5: Drug chemical structures are easy to understand and memorize using the MedChem VR game; Q6: I think the MedChemVR learning tool is flexible enough for training; Q7: Understanding the structure-activity relationship (SAR) from the drug chemical the structure is easy; Q8: Visualizing and deriving conclusions from a drug's structure is easy; Q9: I can easily recognize and navigate through the 3D structure of drugs from different perspectives.

The Q7 and Q8 questions presented positive results but also some concerns regarding the students' understanding of the structure-activity relationship of the chemical structures, as illustrated in Figure 5. Although the students understood the chemical structures as presented by the responses in Q5, the interaction between the structures and molecular activities was not fully comprehensible as 48.8% of the Q7 results suggested. Since this is a prototype VR application focused primarily on teaching the molecular structures' development, further work should focus on the activities and interactions between the molecules and the chemical reactions produced by the development of specific molecular structures.

The responses regarding Q8 were 61% in favor of the application, which supports the students to visualize a drug's structure and derive crucial information regarding the drug's type and abilities.

A 68% of positive responses in Q9 further supported the hypothesis of this study, since the students were able to recognize and navigate through the 3D drug structures helping them to create a 3D mental map of chemical compounds and the connections between different types of molecules.

The results of the second set of questions included Q13, Q16, Q17, Q18, and Q22, which formed the index Q23 (MedChemVR as a learning tool), as shown in Figure 6.

Q13 received 71% of positive responses from the students regarding the time efficiency provided by the VR application since the students felt that it accelerates the knowledge acquisition process and reduces the learning curve, as illustrated in Figure 6. This positive outcome is attributed to visualize the structures in a 3D immersive environment where different combinations could be explored and viewed from any possible angle.

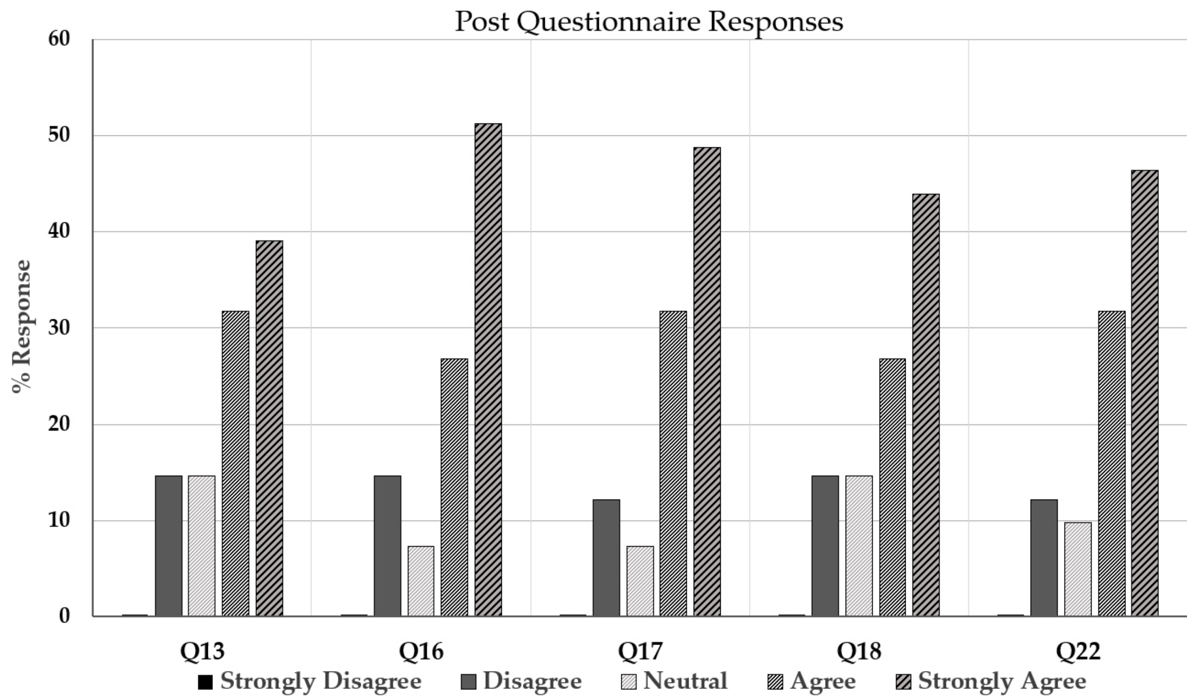

Figure 6. Student responses to question Q13: Using virtual reality saves the time required to learn the chemical structures in medicinal chemistry; Q16: Using the application of 3D models would be easier for me than traditional methods for learning chemical structures in medicinal chemistry; Q17: Using virtual models is useful for me because it will increase my knowledge as I can see the 3D structure model of a drug from several viewing positions; Q18: The experiment content helps me better understand and memorize the chemical structure of a drug; Q22: I would consider using virtual reality visual aids to aid my personal studies outside the classroom.

Reinforcing this outcome further, Q16 received 78% of positive responses, which highlights the ease of use of the VR system in contrast to the traditional teaching methods. The improvement in speed and understanding of such complex structures by the students is encouraging and potentially could reverse the negative approach towards this course.

Similarly, the Q17 responses highlighted the ability of 3D/VR environments to visualize the compounds' scaffolding characteristics with 80.5% of the students, providing positive feedback. The provision of the experiment content has also received an equally high score of 71% (Q18) as this part of the VR application supported the understanding and memorizing of the chemical structures.

The results of the last question (Q22) presented in this paper, highlight the students' intention (75% positive responses) to use the particular and other similar VR applications in the university and class environment to practice and improve their knowledge, as presented in Figure 6. Notably, this study took place before the pandemic breakout and was intended solely as a support system to complement the existing teaching methods. However, it is in our future plans to repeat this experiment in order to identify how the pandemic affected the traditional teaching methods and how this VR application assisted the students during the lockdown isolation and exam periods.

6. Discussion

This study has proposed a VR educational game to aid the teaching/learning of MC. However, the game needs further examination to enhance users' experience and benefit of integrating VR technology as a learning medium. Adhering to the survey results and comments related to the proposed application's future usage by the relevant student cohorts, it is evident that the MedChemVR game was considered a very desirable learning system. Using this game, the students felt comfortable to examine chemical virtual models, on their own time, space, and pace. Moreover, they were enabled to immerse themselves into a virtual classroom where they could easily manipulate the 3D drug structure and explore the structures without any physical limitations.

As such, the MedChemVR game has had a positive effect on student engagement, which was manifested through their responses in the survey. Furthermore, the students commented positively on the enjoyable environment that accommodated their learning experience, which was unburdened from complex interfaces and elaborate manuals.

Some of the student feedback on the background, cursor, and skeleton colors was divergent. This was likely affected by the user's personal preference. Therefore, a future improvement could allow the user to select the preferential color-schemes for the settings' menu.

Participants also suggested the need for a "help" button to provide instructions within the game. Improvement of the SAR information presentation was also suggested by most participants, as well as the possibility of including it within the 3D virtual classroom to better relate it to the structure. These suggestions will be considered in the next version of the game.

Notably, the VR game application was designed primarily as a complementary system to increase student participation and knowledge acquisition in a complex and difficult subject such as medicinal chemistry. Yet, due to the unforeseen major incident response as a result of the COVID-19 pandemic, the proposed MedChemVR application became a new paradigm for teaching and engaging students. The simplistic representation of a classroom and the ability to study in a fully immersive VR environment offers a fresh solution to distance learning, which was considered until recently a merely desirable component in the teaching armory. Therefore, the impact of this research transcends beyond the expected outcome that the research team has anticipated. The inability to gather students in traditional large laboratories and lecturing amphitheatres due to social distancing rules and guidelines, suggests that MedChemVR and similar applications on other fields will be the only way to safely teach large cohorts of students.

To satisfy these new expectations, MedChemVR will require gradual improvements both in the system design and context accommodation. As such, the underlying design has to be modified to enable extra content and levels to be added easily in the future. Other concepts that lend themselves to mobile-enabled, game-based learning in chemistry are being explored, including different conformations and resonance.

Improved visualization and VR graphics will be required to further entice the students, while an interactive tutorial feature and a chemical structure drawing scaffold tool will have to be incorporated. Several levels can be introduced in MedChemVR, where users can earn medals for each level and can post scores on social media or track their progress. The game is to be available for free worldwide on both the Apple (iOS) and Android (Google Play) operating systems. These include the increase in the diversity of activities within the game to suit group learning and enhance student interaction. Additional user trials in full-scale cohorts (400 students) are planned to identify potential associations between the use of this game and students' ability to retain information and how the use of the system reflects on the exam performance. Assessment of the game's impact on examination scores will have to be refined for the establishment of the criteria for a competency-based performance assessment. The presented assessment, although provided indicative results, was hindered by the limited number of drugs applied to the game implemented activities. As such, extending the game will be required to cover all the drug classes and include sufficient information for each drug, building a correlation between the structure and its pharmacological behavior and activities. Another element that will be required for such applications to become the standard teaching methods is the availability of personalized equipment. Although the game provides an enjoyable and useful tool for MC learning, the availability of the required hardware needed to embed this game in the teaching-learning process can limit its active utilization at this point. In particular, the availability of VR hardware to students can also be a potential limitation, as a number of students cannot afford smartphones with 3D/VR capabilities and VR HMDs, especially in low-income countries. To address this hardware limitation, the proposed system was developed aiming to enable a middle to low-level capabilities smartphone to execute the application, while a Google cardboard HMD could provide the VR headset shell. In this way, the MedChemVR could be accessed in a relatively inexpensive kit, without the need for significantly more expensive systems, such as typical VR HMDs (i.e., HTC Vive, Oculus Rift, Oculus Quest, etc.). Yet, as the mobile and VR technology is advancing rapidly, low-cost immersive HMDs will emerge and more cost-efficient smartphones will become available from smaller electronics' manufacturers. Provided that the "economy of the scale" will prevail in this market domain, we envisage that this VR application will have a positive impact on students' learning process and knowledge acquisition even in low-income countries.

7. Conclusions

The paper presented the rationale, development, and evaluation of a prototype distance learning application namely MedChemVR, designed exclusively for teaching the complex course of medical chemistry to university pharmacology students.

The game application is effectively a gamified teaching system that employs VR to immerse the students and present the 3D structural elements of the molecules in a virtual classroom or laboratory. The latter further supports the student requirements in the current situation of the COVID-19 pandemic, since it transfers the user to a familiar environment. In particular, the proposed system contributions are as follows:

- Accessibility: The MedChemVR is an easily accessible educational game as it could be downloaded on smartphones and other portable devices, unlike physical ball-and-stick models.
- Cost-effectiveness: The application can be considered more cost-effective than physical models for both students and educational institutes due to the recent development of affordable VR tools.
- Time and place flexibility: The VR game enhances the learning process as it allows students to freely operate learning where there are no time or place restrictions. Thus, it can help complement and reinforce the taught material by promoting students' participation and engagement in an enjoyable and motivational learning environment.
- User friendly and inclusive: The use of VR provides the students with equal opportunities regardless of their capabilities by allowing each student to learn at a pace suitable for them.
- Designed for both students and educators: The implementation of this game on the student's smartphone can enhance the use of educational games by pharmacy educators.
- Usage of mature technology: Smartphone games overcome the common shortcomings shared by different manual games used previously in MC education, including the extensive time invested by faculty members and students in preparing and learning the game, respectively. These games usually lead to frustration due to the slow speed of the game and difficulty in maintaining control in classes with large numbers of students.

In conclusion, the tentative plan of future work will include the expansion of the proposed system, to include more complex molecular scaffolding for advanced training on the field. Furthermore, it is our intention to design a new research design to explore the students' knowledge acquisition and retention pre- and post-game-playing, in contrast to the traditional learning and teaching methods currently used in the university environment. Finally, an analysis of the future introduction of the MedChemVR platform to accommodate different training contexts for other disciplines such as medicine and engineering will be also commenced.

Author Contributions: Conceptualization, A.A., J.F., and M.A.-T.; methodology, A.A., S.F.M.A., and M.A.-T.; software, M.A.-T., J.F., and R.T.T.; validation, A.A., J.F., and S.F.M.A.; formal analysis, A.A., J.F., and S.F.M.A.; investigation, A.A. and M.A.-T.; resources, A.A.; data curation, A.A., J.F., M.A.-T., and R.T.T.; writing—original draft preparation, A.A., J.F., M.A.-T., R.T.T., and V.C.; writing—review and editing, D.D. and V.C.; visualization, M.A.-T., R.T.T., D.D., and V.C.; supervision, A.A. and S.F.M.A.; project administration, A.A. and S.F.M.A.; funding acquisition, A.A. and S.F.M.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors would like to thank Tahsin Tarawneh for his help in statistical analysis.

Conflicts of Interest: The authors declare no conflict of interest.

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