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Molecular Dynamic Simulations of Ocular Tablet Dissolution

Qian Ru,[†,‡] Hala M. Fadda,[†,‡,§] Chung Li,[†] Daniel Paul,[‡] Peng T. Khaw,[‡] Steve Brocchini,[†,‡] and Mire Zloh[†,∥,*]

[†]UCL School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX, United Kingdom

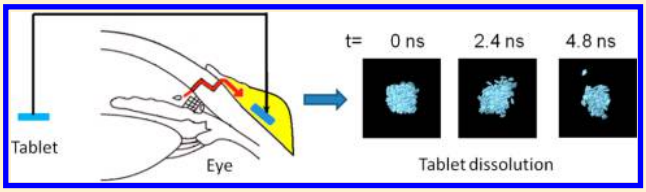
[‡]NIHR Biomedical Research Centre, Moorfields Eye Hospital, UCL Institute of Ophthalmology, 162 City Road, London EC1V 2PD, United Kingdom

[§]Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Butler University, 4600 Sunset Avenue, Indianapolis, Indiana 46208, United States

[∥]Department of Pharmacy, University of Hertfordshire, College Lane, Hatfield AL10 9AB, United Kingdom

Supporting Information

ABSTRACT: Small tablets for implantation into the subconjunctival space in the eye are being developed to inhibit scarring after glaucoma filtration surgery (GFS). There is a need to evaluate drug dissolution at the molecular level to determine how the chemical structure of the active may correlate with dissolution in the nonsink conditions of the conjunctival space. We conducted molecular dynamics simulations to study the dissolution process of tablets derived from two drugs that can inhibit fibrosis after GFS, 5-fluorouracil (5-FU) and the matrix metalloprotease inhibitor (MMPi), ilomastat. The dissolution was simulated in the presence of simple point charge (SPC) water molecules, and the liquid turnover of the aqueous humor in the subconjunctival space was simulated by removal of the dissolved drug molecules at regular intervals and replacement by new water molecules. At the end of the simulation, the total molecular solvent accessible surface area of 5-FU tablets increased by 60 times more than that of ilomastat as a result of tablet swelling and release of molecules into solution. The tablet dissolution pattern shown in our molecular dynamic simulations tends to correlate with experimental release profiles. This work indicates that a series of molecular dynamic simulations can be used to predict the influence of the molecular properties of a drug on its dissolution profile and could be useful during preformulation where sufficient amounts of the drug are not always available to perform dissolution studies.



INTRODUCTION

Glaucoma is the most common cause of irreversible blindness in the world. Reduction of the intraocular pressure (IOP) in the eye is the only proven way to prevent progressive optic nerve damage. Trabeculectomy or glaucoma filtration surgery (GFS) is a procedure that allows the outflow of aqueous humor through a new channel made in the scleral coat. Aqueous outflow then drains under the conjunctival covering of the eye (bleb) (Figure 1A). Allowing sufficient aqueous outflow is important to maintain IOP at a level to stop the progression of the disease. Unfortunately, the formation of scar tissue in the bleb can block aqueous outflow. This causes IOP to increase resulting in progression of disease that can lead to irreversible blindness.

Clinically, the cytotoxic agents 5-fluorouracil (5-FU) and mytomycin C (MMC) are used to control post-surgical fibrosis.[1,2] These agents are used off-label and are potentially toxic and therefore must be carefully administered to the bleb while preventing any exposure to neighboring ocular tissues. The local pharmacokinetics of the subconjunctival area around the bleb are dominated by aqueous outflow through the trabecular meshwork and Schlemm's canal into the vascularized conjunctiva.

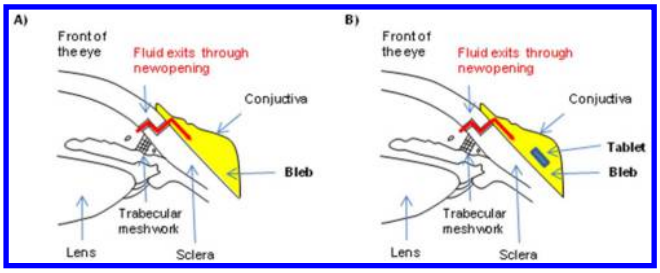


Figure 1. (A) Illustration of the aqueous outflow channel resulting from glaucoma filtration surgery. Aqueous flow from the front chamber of the eye proceeds through the channel and drains into the subconjunctival space to form a bleb. Aqueous fluid quickly absorbs into the conjunctiva. Administration of a drug solution by injection into the bleb is characterized by rapid clearance. (B) Placement of an implantable tablet into the bleb. The tablet is designed to slowly dissolve to provide a prolonged continuous dose at the site of surgery to reduce fibrosis so that aqueous flow can be maintained.

Inhibition of fibrosis at the site of surgery is dependent on both the concentration and the period of exposure to 5-

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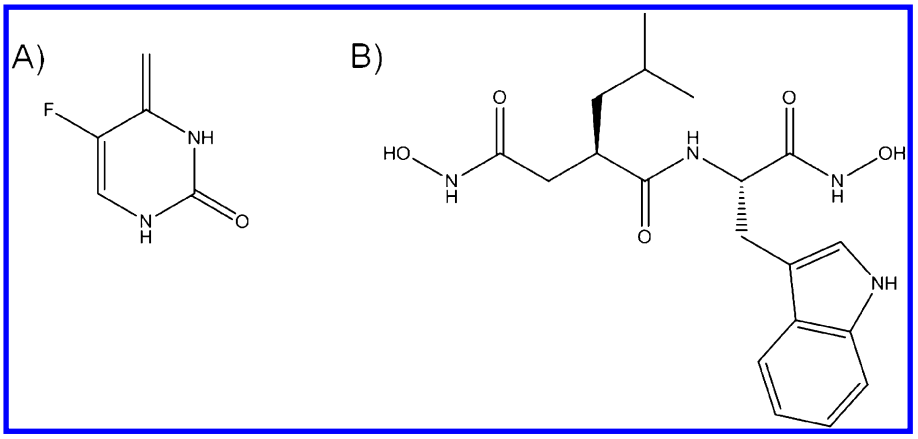

Figure 2. Chemical structures of (A) 5-FU and (B) ilomastat.

fluorouracil (5-FU; Figure 2A).[3] A 5 min single intraoperative application of these cytotoxic agents is widely used by surgeons around the world. This, however, still requires post-surgical treatments to treat localized scarring.[4] To increase local subconjunctival exposure of an antifibrotic agent after GFS, we are developing an implantable dosage form to be left after the surgical procedure in the subconjunctival space within the bleb (Figure 1B). One implantable dosage form that is being examined is a small excipientless tablet that could be placed in the bleb. The tablet must dissolve in a reproducible manner to deliver a prolonged and continuous dose of an active agent to the local ocular tissue where fibrosis tends to occur. To maintain a continuous prolonged therapeutic dose of a drug in the constrained conditions of traumatized inflamed ocular tissue over a prolonged period is challenging. The number of available excipients is limited for intraocular use. If flow characteristics within the bleb remain broadly constant, excipientless tablets will allow drug concentrations in the bleb to be maintained within the therapeutic range for prolonged periods of time.

A matrix metalloproteinase inhibitor (MMPi) known as ilomastat (Figure 2B) has been shown to inhibit fibrosis after GFS in a clinically validated experimental in vivo model.[5] Ilomastat displayed lower toxicity than the currently used cytotoxic agents and multiple injections of ilomastat into the subconjunctival space significantly inhibited fibrosis.

To extend the local tissue exposure time of ilomastat, a small subconjunctival implantable tablet has been fabricated from ilomastat alone.[6] Ilomastat has a solubility of 0.0389 mg/mL in water at room temperature[7] and a solubility of 0.161 mg/mL in phosphate buffer saline at 35.5 °C.[8] Since the bleb volume within the subconjunctival space is in the range of 50−100 μL,[9] a tablet comprised of ilomastat within the bleb will not immediately dissolve. This is known as nonsink dissolution conditions, which is where there is not enough volume of liquid present to dissolve a solid that is placed within the liquid. The flow of the aqueous humor in the bleb occurs at an approximate rate of 2 μL/min.[10] While physical features of the tablet such as its dimension, hardness, density, and wettability will influence dissolution, it is also important to consider the molecular properties of ilomastat in the solid state to determine if the noncovalent interactions of ilomastat may influence dissolution.

While we have determined the release profile of the ilomastat tablet in vitro[6] and characterized the materials properties of ilomastat,[8,11] there is a need to determine how, at the molecular level, intermolecular ilomastat interactions may influence its dissolution rate. We believe that a computational study of the dissolution process can be used to predict the dissolution rates of the subconjunctival tablets when comprised of different active ingredients. Since 5-FU is clinically used off-label to treat post-surgical scarring. we also computationally evaluated its molecular interactions within a solid tablet. 5-FU is significantly more soluble (11.1 mg/mL at 22 °C[12]) than ilomastat.

Molecular dynamics (MD) is a computational method that calculates the behavior of a molecular system over time. The MD used in this work is an "all-atom" simulation. It is widely used to investigate the structure, dynamics, and thermal dynamics of small molecules, proteins, and biomolecules.[13−18] It allows "virtual experiments" to be conducted with high molecular temporal and spatial resolution, which is not always possible to do experimentally. Here, we used MD simulations to predict at the molecular level how tablet dissolution in an excipientless tablet may be influenced by noncovalent molecular interactions such as hydrogen bonds and lipophilicity of the active ingredient. The value of MD to study the molecular properties and dynamics processes of drug dissolution may be useful to supplement other in silico models used in the early stages of drug development, such as predictions of pK_a, intrinsic solubility, logP, and permeability. Of particular importance in this regard would be efforts to correlate dissolution in a range of environments for different crystalline forms of a selected active pharmaceutical ingredient.[19] It is thought that if we can correlate our computations to results of validation experiments for dissolution of an excipientless tablet in nonsink conditions with water turnover, we will then be able to computationally increase the complexity of our system to include components of lachrymal fluid and common excipients used in solid dosage forms. We wish to further develop the MD strategies described in this work to be able to predict dissolution rates in a range of environments while taking into account liquid turnover. Our longer-term goal is to develop more predictive computational strategies for use in formulation studies of new chemical entities, particularly where the quantity of the active ingredient is scarce.

Here, we conducted a series of short molecular dynamic simulations with a procedure to imitate removal of drug molecules due to liquid turnover and evaluate the dissolution of tablets fabricated from ilomastat and 5-FU under such conditions. We describe behavior on a molecular level for two model systems comprised of only the active agent with significantly different solubilities and successfully correlate theoretically predicted dissolution rates with experimentally

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determined. These all-atom simulations may enable early prediction of the influence of tablet composition and physical features, e.g., density and solvent accessible surface area, on its dissolution.

METHODS

Modeling a Tablet. The 3D structures of 5-FU and ilomostat molecules were generated using the 3D builder in Maestro 8.5 directly. Ionization states for 5-FU and ilomastat were generated for pH 7 ± 1 using Ligprep software (Schrodinger LLC), which resulted in single neutral species for both molecules. Resulting structures were optimized using Macromodel 9.11,[20] a MMFFs force field as implemented in Macromodel, and the generalized born/surface area (GB/SA) implicit solvation model.[21] An exhaustive search was carried out on a small number of molecules (25 5-FU, 10 ilomostat) by generating 1000 configurations for each system using the Monte Carlo multiple minimum (MCMM) approach. The number of molecules used in the conformational search was chosen according to the Macromodel limitations for the selected method. The lowest energy conformations were chosen as a starting point for modeling tablets. The final structures of the exhaustive searches were multiplied into a rectangular shape tablet (675 and 110 molecules of 5-FU and ilomastat tablets, respectively). Tablets were then optimized, and final conformations were used to examine the intermolecular packing of drug molecules without the presence of bulk water molecules and their dissolution rates.

Tablet Compression. Molecular dynamics were performed using Desmond v2.2[22] with Maestro 8.5 as a molecular modeling graphical interface. The initial molecular systems that were generated by conformational searchers were then truncated by deleting molecules to form rectangular shapes. Simulation boxes of each tablet containing 672 5-FU and 110 ilomastat molecules were prepared by the Desmond setup. The temperature of simulation of the tablet compression was at 300 K, corresponding to room temperature and the OPLS2005 force field. To imitate the process of tablet compression at increased pressures, the tablet systems were subjected to initial minimization followed by simulation at the initial pressure at 1 bar for 0.6 ns (5-FU) or 4.8 ns (ilomastat). Then, the final structures were further subjected to simulation using constant pressures of 2, 4, 8, and 14 bar without relaxation for 0.48 ns at each pressure. Finally, a production simulation was carried out at 14 bar for 4.8 ns. An additional simulation was conducted at a higher pressure of 100 bar for 4.8 ns to examine if additional interactions are observed at higher pressures. The final result of the simulation at 100 bar was not used as a starting point for further dissolution studies.

Tablet Dissolution. The simulation of tablet dissolution was performed using the final structures of the rectangular-shaped tablets after being compressed at 14 bar. The size of the tablets was reduced to decrease the real CPU time of simulations while the keeping the rectangular shape of the tablets containing 164 5-FU and 90 ilomastat molecules. The initial simulation box systems were formed by solvating the tablets and forming all-atom systems that consisted of a 5-FU or an ilomastat tablet surrounded by simple point charge (SPC) water molecules to generate similar size simulation boxes with the final volume of 2.67e-25 m^3 (Figure 3). These water molecules positioned around tablets are known as "explicit water", and this approach allows solvation effects to be taken into account directly during molecular dynamic simulations. In order to compare the tablet release with or without the turnover of the aqueous humor, two types of simulations were performed. The first type of simulation had a simulation only for 4.8 ns to compare the dissolution rates of the two drugs, 5-FU and ilomastat. The latter simulations were conducted twice at two temperatures (300 and 310 K). The second type was an eight-step simulation with each step lasting for 0.6 ns. The liquid turnover in the bleb was mimicked by manually removing the free drug molecules released from the tablet surfaces into water at the end of each step to reflect the loss of molecules from the system. After each step, a new simulation box consisting of an increased number of water molecules was built, but the size of the box was kept constant to continue the next step of simulation.

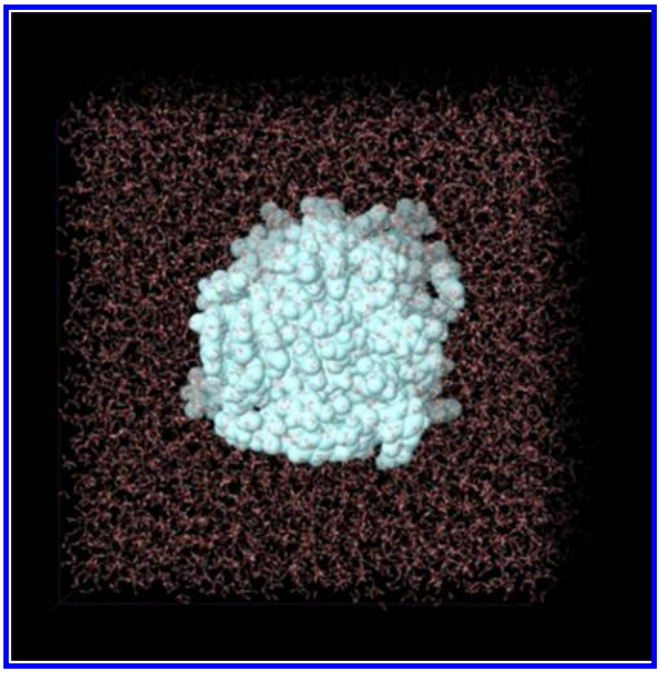

Figure 3. Molecular surface of the system set for a simulation of a tablet in the presence of explicit water.

Analysis of Results. Molecular dynamics trajectories were visualized using Maestro and VMD.[23] The configurations generated during simulation were converted into pdb file formats and sequentially saved for further analysis. The macromolecular properties (solvent accessible surface area, logP, molecular lipophilicity potentials (MLP), lipole) of exported systems were analyzed using Vega ZZ.[24,25]

Tablet Fabrication and in Vitro Release Studies. The dissolution studies were carried using procedures described elsewhere.[8] Briefly, ilomastat and 5-FU tablets were prepared without excipients by direct compression, and initial drug release studies were performed in an in-house-designed 200 μL chamber with an open flow system using water as the dissolution media. The drug concentrations in the liquid collected in the outgoing reservoir were analyzed using HPLC. All drug release studies described in this work were run in triplicate in water and at room temperature.

RESULTS

All-atom MD simulations of the model system tablets were conducted to examine the dissolution of two therapeutically relevant molecules with different solubilities. Dissolution was correlated with molecular properties of the drugs related to the

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number of hydrogen bond donors (HBDs) and acceptors (HBAs) and logP. It is important to emphasize that the size of the system and time needed for a tablet to dissolve (up to 4 weeks) cannot be simulated using current molecular modeling methods. Thus, model systems must be smaller (10^{16} times smaller), and simulation times are shorter (10^{14} times shorter). These implantable tablets would be used in the subconjunctival space, which is characterized by aqueous outflow. Dissolved substrates would flow from the bleb region and be taken up into the vascularized conjunctiva. Once in solution, a substrate would then be expected to clear quickly from the local bleb environment. It was thus assumed that the initial stages of dissolution could be used to predict longer-term correlates.

Conformational Search. Initial 5-FU and ilomastat conformations that were generated by the conformational searches are comparable to the experimentally determined structures available in the Protein Databank and Open Crystallography databases and to those obtained in-house recently[8] (Figures S1 and S2, Supporting Information). The single point energies calculated for various conformations of 5-FU were within 1 kcal/mol range (Table S1, Supporting Information), and the single point energies of ilomastat ranged from −165.6 to −298.7 kcal/mol (Table S2, Supporting Information). These results are not surprising because 5-FU does not have rotatable bonds, while ilomastat has higher conformational flexibility with nine rotatable bonds.

The models of tablets that were generated by the MCMM method suggests that the noncovalent interactions between 5-FU molecules are defined by aromatic and to a lesser extent hydrogen bonding. The observed aromatic−aromatic interactions between ilomastat molecules were mainly face to edge. It is known that the aqueous solubilities of 5-FU and ilomastat are 11.1 and 0.03885 mg/mL respectively. From the chemical structure of the two molecules, 5-FU has three HBAs and two HBDs, while ilomastat has five HBDs and four HBAs. The conformational searches have resulted in the arrangement of these molecules at the molecular level.

To compare the change of lipophilicity of the tablets, we used Vega ZZ[24,25] to predict their log *P* values at pH 7.0. The predicted log *P* values of 5-FU and ilomastat were −1.36 and 0.65, respectively. The experimental log *P* of 5-FU is known to be −0.83 at pH 4.0.[26] Although the difference in log *P* for 5-FU may relate to differences in pH, the predicted log *P* values do provide a relative comparison of both molecules, which is based on the structural differences between these two molecules. The lipole, which represents the sum of lipophilicity of a molecule projected on its surface,[27] was predicted to be 0.56 and 1.27 for single molecules of 5-FU and ilomastat, respectively (Table 1).

Model "Tablet" Compression. We have used the total solvent accessible surface area (SASA) of all molecules to monitor molecular rearrangements in the tablet model systems. The 5-FU and ilomastat tablets were computationally compressed using different pressures. No significant change was observed in the SASA from the beginning to the end of the compression step (Figure 4). Similarly, the SASA for ilomastat was constant, although it can be seen that there was a sudden increase of SASA in ilomastat tablets. This is a result of translational movements of the whole ilomastat tablet that resulted in periodic boundary conditions where it appeared that some molecules came out of the simulation box and re-entered from the other side. These events did not affect the overall conformation of the system, and the resulting molecular arrangement within the ilomastat tablet was suitable for further studies.

Table 1. Molecular Lipophilicity Potential of 5-FU and Ilomastat Molecules and Tablets

drug		simulation time (ns)	lipole	log *P*
5-FU	single molecule		0.56	−1.36
	tablet at 300 K	0	0.17	
		4.8	0.04	
	tablet at 310 K	0	0.14	
		4.8	0.06	
ilomastat	single molecule		1.27	0.652
	tablet at 300 K	0	0.92	
		4.8	0.90	
	tablet at 310 K	0	0.99	
		4.8	0.73	

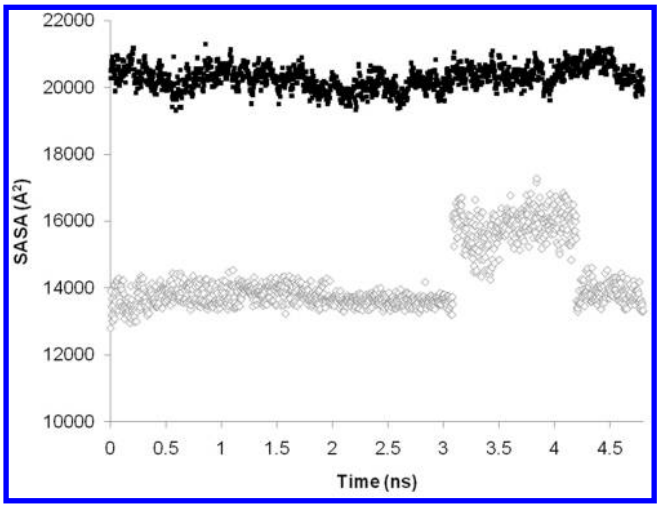

Figure 4. Solvent accessible surface area observed for during the simulation of tablets under 100 bar pressure and 300 K (■ 5-FU; ◇ ilomastat).

It was observed that on average an ilomastat molecule in the tablet during tablet compression in the absence of solvent forms 2.3 H-bonds during simulation at room temperature, while a 5-FU molecule forms 1.15 H-bonds. The average number of H-bonds does not change during the simulations conducted at 14 bar or lower, and the number of H-bonds did not change significantly (data not shown). This higher number of H-bonds formed between ilomastat molecules in the crystal lattice may contribute to its lower solubility in aqueous media because ilomastat does not appear to be too hydrophobic (log *P* = 0.652).

Dissolution. *Simulation without Liquid Turnover (4.8 ns continuous simulation).* Before simulating the liquid turnover, a 4.8 ns continual simulation was conducted in a closed box without liquid turnover at two different temperatures for which the experimental data exists (300 and 310 K). It was found that the number of released molecules from the 5-FU tablet was considerably higher than the number of molecules released from the ilomastat tablet. During this process, only one ilomastat molecule came into the solution (figure not shown), but 5-FU reached its saturated concentration at around 4 ns. Both 5-FU and ilomastat tablets dissolved faster when the temperature was set at 310 K due to the kinetic energy of tablet dissolution at 310 K being higher than at 300 K. The solvent accessible surface area of the tablets increased more rapidly at

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310 K rather than at 300 K (Figure 5), indicating higher solubility of the drug at higher temperatures, which is expected and in general agreement with experimental observations.

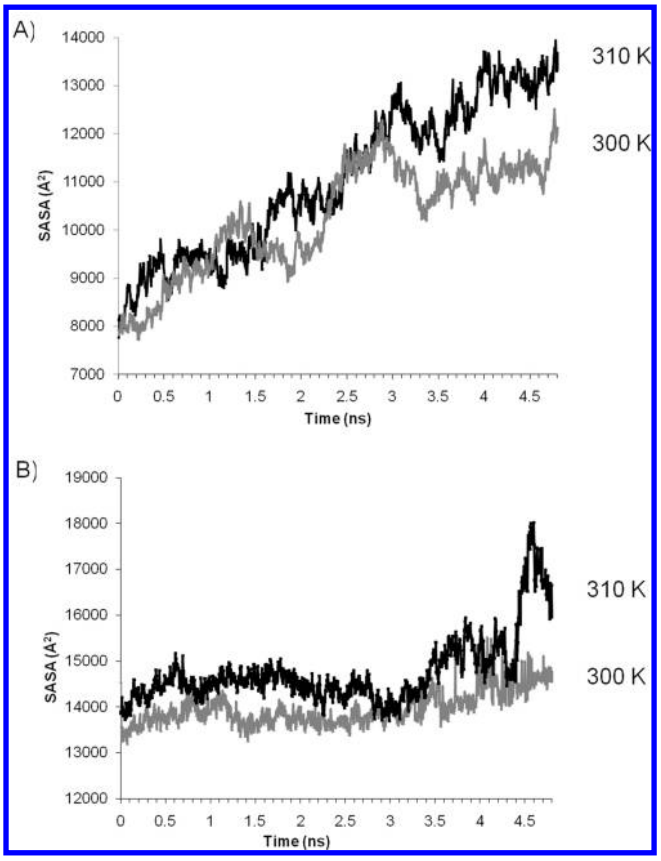

Figure 5. Solvent accessible surface area of 5-FU (A) and ILO (B) tablets during a 4.8 ns simulation of dissolution in a water box at different temperatures (black line represents 310 K; gray line represents 300 K).

The longer simulations of these systems in nonsink conditions indicated that after 5 ns the solution of 5-FU becomes saturated, which prevents further release of 5-FU molecules into solution (Figure S3, Supporting Information). We have conducted simulations of larger systems with different molar ratios of a drug to water content, and the observed patterns of SASA were similar regardless of the size of the system (Figures S4 and S5, Supporting Information). Although, the molecular simulations of larger systems gave comparable results, we decided to validate the minimal systems for simulation in nonsink conditions with liquid turnover to allow for shorter times being required for computational experiments. This aspect would be important in development of higher throughput experiments enabling testing of a wider range of formulations in a pharmaceutical industry setting.

The molecular lipophilicity potentials (MLP) of the single molecules and tablets are shown in Table 1. The estimated lipole values are calculated by projecting lipophilicity on the surface and depend on the conformation of the system. It was observed that lipophilicity of both of the tablets decreased after the 4.8 ns simulation as a result of molecules interacting with water molecules and exposing their polar surface to the external environment. The lipole value of 5-FU decreased significantly, more than that for ilomastat, and that is the result of the higher mobility of 5-FU molecules due to their smaller size and lower number of hydrogen bonds.

Simulation with Liquid Turnover (eight-step simulation). Due to software and computational limitations, liquid flow in the subconjunctival space was not simulated. Hence, the computational experiment was designed to simulate the loss of drug molecules. Once dissolved, the solvated drug would be removed from the subconjunctival space by the aqueous outflow from the anterior chamber into the conjunctiva and then into the systemic circulation. To approximate the continuous dissolution media (water) flow, we designed the molecular dynamics experiment where eight simulation stage steps were used (Figure 6). Each step was simulated for 0.6 ns,

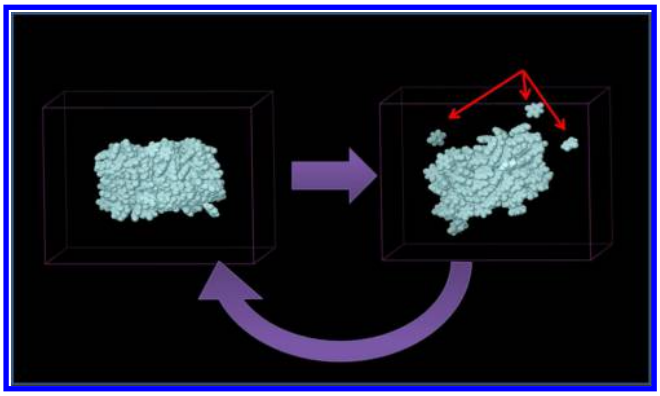

Figure 6. Schematic representation of simulation of dissolution of a 5-FU tablet with liquid turnover. The short arrow represents 0.6 ns of the simulation; the long curved arrow represents the removal of all molecules indicated by thin arrows released from the tablet surface and addition of new molecules of water. Eight cycles of 0.6 ns simulations were conducted for both 5-FU and ilomastat.

where at the end of a stage dissolved molecules (molecules that have detached from a tablet) were removed and replaced manually with dissolution media to keep the constant volume. Because dissolution did not reach saturation concentration in our in vitro experiments,[6] it was thought this approximation would not adversely impact the relative differences in the dissolution profile of these two molecules as calculated from their molecular interactions.

The dissolution was monitored by calculating the molecular SASA of 5-FU in the system at all steps of its trajectory (Figure 7). It was observed that at the beginning of the simulations the SASA of 5-FU that was exposed to water molecules increased initially due to the detachment of molecules from the solid surface to form hydrated molecules at the solid−liquid interface. At the end of the 0.6 ns of simulation, about 10 5-FU molecules were far enough from the tablet surface to be considered in bulk solution and therefore transported away from the solid−liquid interface.

The removal of these molecules and replacing them with water molecules resulted in a decrease in total SASA of all 5-FU molecules remaining in the system. On average, about 10 5-FU molecules were removed at the end of each step. At the beginning of the next step, the SASA decreased due to a smaller number of molecules left in the solution, and then, the SASA of the remaining tablet increased slowly due to further dissolution with more 5-FU molecules being released into the solution and exposing their surface to the solvent (Figure 8). However, in the simulation of the computation experiment with the ilomastat tablets, the observed molecular SASA did not change

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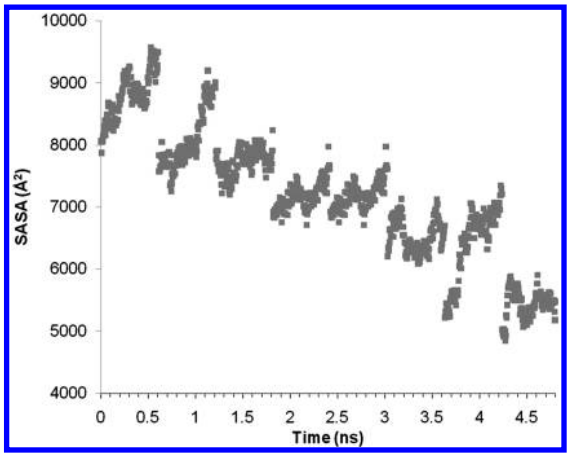

Figure 7. Solvent accessible surface area of a 5-FU tablet observed during eight cycles of 0.6 ns simulations to emulate liquid turnover at 300 K.

significantly because only one or two ilomastat molecules were released at the end of the eighth step (Figure 8). This indicated that the 5-FU tablet dissolved faster than the ilomastat tablet, which was in good qualitative agreement with experimental observation of the in vitro dissolution rates (Figure 9).

The computationally predicted dissolution profiles of 5-FU and ilomostat, constructed by plotting the percent of released drug against time, were similar to their corresponding dissolution profiles determined in vitro using the flow chamber (Figure 9.). The predicted dissolution rates of 5-FU and ilomastat were 11.73% and 0.18% of released drug per ns, respectively, while the experimentally determined dissolution rates were 0.51% and 0.08% of released drug per h. Interestingly, the ratio of predicted dissolution rates of 5-FU and ilomastat (65.2) was in excellent agreement with the corresponding ratio of experimentally determined rates (63.7). This supports our hypothesis that the molecular dynamic simulations can provide valuable insights into dissolution profiles of drugs with different physicochemical properties.

DISCUSSION

Compression. Many pharmaceutical characteristics of dosage forms have been computationally modeled. The compaction of a pharmaceutical powder has been simulated using different computational models in recent years.[28−30] The effects of the speed of compression on the deformation behavior of the powder column, microstructure, and integrity of the formed tablet were investigated.[29,30] Han et al. simulated the stress and density distributions during the tablet-making process.[28] It is known that in real tablet compression, the SASA of the particles or powders decreases after they are compressed. However, in our simulation, no significant SASA change was observed because the initial tablet was built without empty space between molecules. The 5-FU particles do not deform on compression. Ilomastat has increased degrees of freedom that could lead to creating defects in molecular packing to create spaces that need to be taken into consideration in future studies. The surface energy of particles controls the intermolecular bonding, which in turn controls tablet compaction.[7]

The SASA of the tablets would certainly change by the introduction of excipients into the tablet. However, in this application where space is limited and there may be a need to maintain a local dose over 1−4 weeks, we are examining the development of ocular implantable tablets that are comprised primarily of the active compound. Formulating a drug into the amorphous form can improve its compaction properties and therefore reduce the compression force needed to produce a tablet.[31]

Here, we show that tablet properties and dissolution rates depend on the chemical structures of 5-FU and ilomastat. For example, ilomastat has more hydrogen bond acceptors and donors, and consequently, the observed average number of H-bonds per molecule during simulations for the ilomastat tablet (2.3) is higher than those observed in the 5-FU tablets (1.15). However, the changes in the number of H-bonds during simulation are not significant because it was not possible to induce changes of molecular arrangement during the compression. For example, ilomastat is a larger molecule compared to 5-FU, and the lack of space around the 5-FU molecules prevents conformational rearrangement. Therefore, the properties of simulated tablets will be influenced by the molecular structure and initial conformations, as well as on the starting conformation of the system.

It should be noted that the compression force and simulation time used in the computer simulation cannot be directly correlated to real conditions. In some MD simulations of compression, the pressure was set at hundreds or thousands of bars.[32−34] We therefore conducted a 4.8 ns continuous simulation of tablets compressed at 100 bar to reinforce interactions between molecules in a tablet so it could be used for further study of its dissolution.

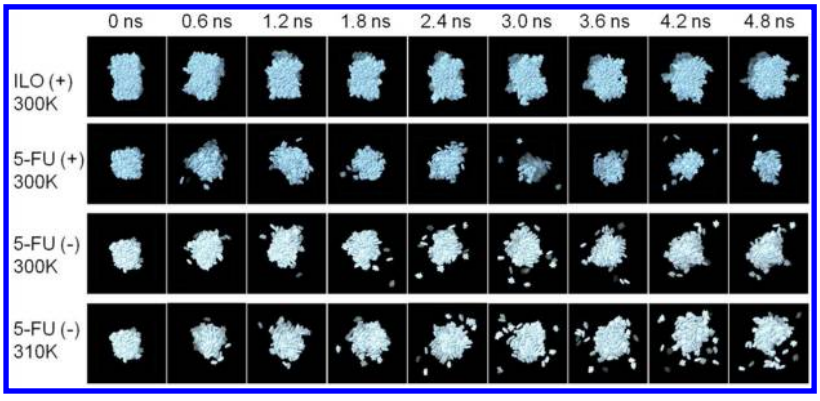

Figure 8. Molecular dynamic simulations of the tablets dissolution at different time points and different temperatures with (+) or without (−) the liquid turnover.

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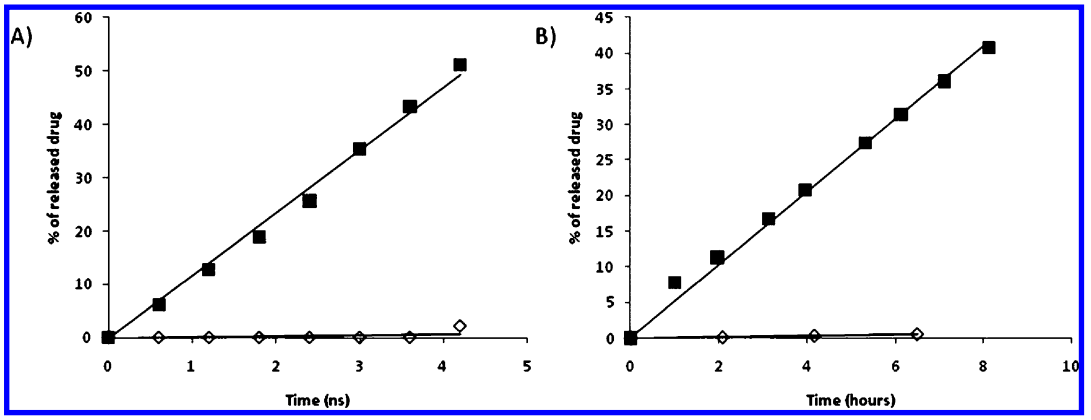

Figure 9. Dissolution profiles of 5-FU (■) and ilomastat (◇) with liquid turnover at 300 K obtained (A) computationally using molecular dynamic simulations and (B) experimentally using flow chamber.

Dissolution. Takehara et al. started a series of numerical simulations on drug release from different formulations in 1970s.[35−41] However, few studies were conducted on tablet dissolution using molecular dynamics. There appears to be a lack of molecular simulation studies that have been conducted on an all-atom level. A few groups have studied the dissolution of NaCl crystals by computational simulation.[42−44] Their studies were focused on the dissolution dynamics and energy interactions between ions, and between ions and water.

We aimed to investigate if it would be possible to study the dissolution of tablets in nonsink conditions that would occur in the subconjunctival space. Our main aim is to correlate experimental data on the dissolution of the two different drugs with liquid turnover conditions with results of simulation by monitoring molecular structural properties of the tablets and how these properties would influence properties related to dissolution such as SASA. Initially, we tested the method by simulating tablets without liquid turnover and by changing the temperature of the system.

When the system for molecular dynamic simulations was built, the proportion of molecules between 5-FU and water was calculated to correspond with the experimental conditions (5 mg 5-FU in 50 μL water, molecular ratio 1:72). The same size of water box was set up for the ilomastat tablet. However, the number of ilomastat molecules (90) was smaller than 5-FU (164) to keep the volume of the water box the same.

It is understood that the reported aqueous solubility of 5-FU (11.1 mg/mL) is more than 280 times higher than the solubility of ilomastat (0.0388 mg/mL), which is qualitatively comparable to our observations based on simulations at room temperature without liquid turnover. It was encouraging that our simulation results showed that both tablets have relatively higher dissolution rates when the temperature was increased. This corresponds to the results of the in vitro experiments. Even more significant was the finding that the ratio of the total number of the released 5-FU molecules to the number of ilomastat molecules correlates to the ratio of their experimental solubilities with liquid turnover, where ratios of dissolution rates were in excellent agreement.

It should be noted that the time scale of simulations do not directly correspond to the time scale of experiments, and further experiments are needed to find relevant correlations for conversion of computationally determined dissolution rates to match values derived from in vitro experiments. Furthermore, it has to be taken into account that a different determination method of the solubility can led to different results.[45] Using 5-FU as an example, the molar ratio between the drug and water is 1:722 when using the reported method (3 mg drug placed in 0.3 mL).[45] In our case, this molar ratio is 10 times smaller (1:72). Therefore, the micro-solubilities of the drugs could not be directly correlated with the values reported in the literature. For example, because of the ionizable nature of ilomastat, it exhibits different solubilities in media of varying ionic composition and pH. We measured the solubility of ilomastat to be 415.6 ± 68 uM in pH 7.6 in balanced salt solution simulating the aqueous humor, which is over 4 times the reported solubility in water. At this stage, molecular dynamic simulations can be used to qualitatively compare solubilities of different molecules by calculating the change in their total molecular SASA during simulations. For example, after the 4 ns simulation at 310 K, the total molecular SASA of 5-FU increased 62.5% (from 8000 to 13000 Å^2), while the total molecular SASA of ilomastat increased only approximately 1% (from 14000 to 15000 Å^2).

The MLP describes the hydrophobic and hydrophilic surface properties molecules. Here, we monitored the hydrophobicity of the tablet surface and assessed if a correlation can be established with the tablet dissolution rate. The 5-FU tablet lipole value decreased significantly because its SASA was decreasing rapidly during the simulation. The ilomastat tablet lipole value was not reduced as significantly as the 5-FU because there was no significant change in its SASA. A consideration of the magnitude of change in the lipole values before and after 4.8 ns of simulation suggests that ilomastat molecules tend to orient their hydrophilic moieties to the bulk aqueous environment. The reduction in the lipole value is greater at 310 K as the molecules have greater kinetic energy for the reorientation.

When comparing the change of the ilomastat tablet lipole value before and after the 4.8 ns simulation, the reduction of the ilomastat lipole value indicates that the ilomastat molecules tend to expose their hydrophilic parts to the water.

Further studies should consider other factors apart from the physical and chemical properties of the tablets, such as the flow properties of the subconjunctival space, temperature, and actual composition of the dissolution media. The temperature and pressure could be examined for different types of simulations. The volume of the dissolution media can also be changed manually. Although the software cannot yet simulate the flow system, the change in the total molecular SASA predicts the time that is required to achieve equilibrium between the released drug and the dissolution media. Hence, the tablet

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release profiles can be predicted by comparing the observed equilibrium times for different systems. This can be correlated with the in vitro release data in the future.

Although our simulations were conducted for two different molecules, these efforts indicate that there may be some value to evaluating dissolution at the molecular level for tablets that might be used for indications that require nonsink conditions. We have also demonstrated that a protocol of short MD simulations can be utilized to reproduce the experimental data for micro-dissolution with liquid turnover. Further experiments are designed to explore dissolution rates of ocular tablets at physiologically relevant temperature, 37 °C. One advantage of computational simulations is that "virtual experiments" can be conducted with a range of different drug molecules. Using additional experimental input to feed into the computation effort will increase the efficiency and predictive ability of these "virtual experiments". In addition to predicting the dissolution rates, molecular dynamic simulations provide the means to monitor the dynamic process and molecular interactions that are occurring during the dissolution process. This could inform the design of pharmaceutical formulations. Further work is underway to explore tablets with excipients to modify the drug release profile. Instead of water, the tablet dissolution media could be changed to reflect more realistic features of biological fluids where ions and proteins are considered. In the subconjunctival space, aqueous flow was taken to be the main mechanism for removal of the drug from the local environment; however, efforts will also need to focus on the permeation of the drug molecules through biological membranes.

CONCLUSIONS

Our computational efforts indicate that the dissolution process of a tablet under nonsink conditions can be modeled using molecular dynamic simulations. Our molecular dynamic simulations were successful at predicting dissolution trends of ocular tablets comprised of different drugs under various conditions. The dissolution process of 5-FU and ilomastat tablets under various conditions was studied at a molecular level. As expected, the release rate of 5-FU molecules from the tablet surface was found to be faster than that of ilomastat. Both 5-FU and ilomastat tablets were found to dissolve faster when the temperature was increased from 300 to 310 K. The observed trends for dissolution of two tablets with liquid turnover of the dissolution medium are in good agreement with experimentally observed in vitro dissolution rates. From these initial studies, we also found the that (1) solubility is not the sole determinant of the dissolution rate of excipient free tablets under nonsink conditions, (2) dissolution rate is related to chemical structural features of the drug as well as environmental temperature, and (3) combined noncovalent interactions between drug molecules contribute to the different solubilities of the compounds as well as the different dissolution rates of tablets. Other factors that may affect tablet dissolution rates include the crystalline state of a drug, volume and composition of the dissolution media, and tablet formulation. The influence of these factors will be studied using molecular dynamic simulations to assess the value of such computational techniques to predict dissolution rates in the absence of experimental data for different drugs or their formulations.

ASSOCIATED CONTENT

Supporting Information

Comparison of the experimentally available and calculated structural data for 5-FU and ilomastat. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: m.zloh@herts.ac.uk. Tel: +441707 284 540.

Notes

The authors declare no competing financial interest.

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