
Interaction of Glucocorticoid Drug with Model Lung Surfactant Monolayers: Molecular Dynamics Simulation Approach

A thesis submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy in Engineering

by

Mohammad Zohurul Islam

B.Sc. (Math.), M.Sc. (Appl. Math.)

University of Technology Sydney
Faculty of Engineering and Information Technology

Sydney, Australia

September 2022

© 2022 by Mohammad Zohurul Islam

All Rights Reserved

Certificate of original authorship

I,

Mohammad Zohurul Islam declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Mechanical and Mechatronic Engineering, Faculty of Engineering and Information Technology at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

Production Note:

Signature removed prior to publication.

Signature:
(Mohammad Zohurul Islam)

Date: 12th September 2022

Place: Sydney, Australia

This page intentionally left blank

Dedication

This thesis is dedicated to my father, Md. Amzad Ali Shikder, who passed away 8 years ago, to the one I loved the most, my mother, Rokeya Khatun with eternal appreciation, my brothers and sisters, and my wife Jesmin Naher, my children Tahsin Shikder, and Tasfia Shikder.

This page intentionally left blank

Acknowledgements

This PhD was an enormous journey of learning, research, innovation, self-understanding, and time management. The journey would have been quite impossible without the significant contribution of my supervisors, team members, fellow students, colleagues, and family members. All of these people played a significant role in the successful progress of this PhD study at UTS, Australia.

First, my supervisor, Dr Suvash Chandra Saha, provided me with generous support and motivation throughout my PhD. I would like to express my gratitude and respect to him for allowing me to work with him as a PhD researcher and helping me to become an independent researcher. In addition, he assisted me to enhance my capabilities in scientific presentation, drafting articles for publication and presenting research outcomes in seminars and conferences. It is quite difficult to mention each and every contribution of a research supervisor, but undoubtedly, he was a major driving force during this study, helping me to focus on the aim of this research project. I still remember when I moved from my previous project on Microfluidics to my current Molecular Dynamics project, and a lot of patience was required to cope with this research field, where my supervisor guided me properly to obtain deep learning in the field. He showed me how to design scientific arguments in steps and to solve them with proper evidence. His interest in this field helped me tremendously to successively reach a deeper area of knowledge.

I am also grateful to my co-supervisor, Dr Evelyne Deplazes, for her patient support, enthusiasm, and constructive discussion. She explained the rational design of this study based on the relevant background literature and future perspective of this research field. A heartfelt thanks is insufficient for the time and effort they (my supervisor and co-

supervisor) provided me during this research course but expressing my thanks now will remind me to be grateful for the rest of my life.

I would also like to express my sincere gratitude to Dr Sheikh Imamul Hossain for his endless support and guidance. I know a mere "thank you" is not enough for him because of the extent of his guidance, inspiration and assistance. However, I will always remember that I am indebted to him. I would like to thank Martyna Krajewska and Krystyna Prochaska for their help in conducting the experimental part of my research, and Dr Michael Lake for supporting and guiding me with the computational facilities provided by the UTS eResearch High-Performance Computer Cluster, UTS iHPC and NCI Australia. I was lucky enough to be allowed into Emeritus Professor Alan Mark's research group, where I received feedback of my work from him and his colleagues. I am grateful to all the group members of our Lung Research team at UTS for their constructive discussion, sharing of ideas and skills from group meetings, as well as their curiosity, which has encouraged me to move forward with those relevant research goals. I am thankful to Dr Saidul Islam, who always inspired and made me confident in my academic life, from my master's degree to this PhD. I am also thankful to Md Mizanur Rahman, Isabella Francis, Dr Tanvir Ahmed, S M Arifuzzaman, Md Bellal Hossain and my other friends at UTS for their continuous support and advice. I want to acknowledge professional editor, Diane Kolomeitz, for the proofreading services according to the guidelines laid out in the university-endorsed national guidelines for editing research theses.

I also want to thank the UTS authority for providing me the UTS FEIT Research Scholarship, and the UTS International Research Scholarship (IRS). My gratitude also goes to Jashore University of Science and Technology (JUST), Bangladesh, to allow study leave to pursue this PhD research.

Finally, it is time to thank my family members - parents, and siblings, especially my elder brothers Md. Sharof Uddin Sikder, A. Rashid Sikder and Md. Faruk Hosen - for their inspiration to continue my study. Without their endless support, sympathy, tolerance, prayers and unconditional love, it would have been impossible to continue this PhD journey. It was also part of their time that I invested in the research progress, and my family members always generously allowed me to do this. I have to give thanks to my wife, who almost single-handedly managed all the matters of our children; her patience and encouragement helped me most of all to concentrate on my work. I left a lot of personal responsibilities to my family. Most of the time, my family members managed to complete all the household tasks, which provided me more intensive time to perform this research. All these reasons inspire me to dedicate and credit my thesis to them.

This page intentionally left blank

Statement indicating the format of the thesis

This thesis is structured according to the format “Thesis by Compilation” comprising chapters and published or publishable works.

Student Signature:
Production Note:
Signature removed prior to publication.
(Mohammad Zohurul Islam)

Date of signature: 12/09/2022

This page intentionally left blank

List of publications

- [1] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Bhowmick, S., Saha, S. C., Molecular dynamics study of prednisolone concentration on cholesterol based lung surfactant monolayer, *AIP Conference Proceedings*, **2324** (1), 060008, 2021. <https://doi.org/10.1063/5.0037471>. (Published)
- [2] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Saha, S. C., The steroid mometasone alters protein containing lung surfactant monolayers in a concentration-dependent manner, *Journal of Molecular Graphics and Modelling*, **111**, 108084, 2021. <https://doi.org/10.1016/j.jmgm.2021.108084>. (Published)
- [3] Hossain, S. I., **Islam, M. Z.**, Saha, S. C., Deplazes, E., Drug Meets Monolayer: Understanding the Interactions of Sterol Drugs with Models of the Lung Surfactant Monolayer Using Molecular Dynamics Simulations, *Membrane Lipids: Methods and Protocols, Methods in Molecular Biology (Clifton, N.J.)* **2402**, 103-121, 2022. https://doi.org/10.1007/978-1-0716-1843-1_9. (Published)
- [4] **Islam, M. Z.**, Krajewska, M., Hossain, S. I., Prochaska, K., Anwar, A., Deplazes, E., and Saha, S. C., Concentration-Dependent Effect of the Steroid Drug Prednisolone on a Lung Surfactant Monolayer, *Langmuir*, **38** (14), 4188-4199, 2022. <https://doi.org/10.1021/acs.langmuir.1c02817>. (Published)
- [5] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., and Saha, S. C., Concentration-dependent cortisone adsorption and interaction with model lung surfactant monolayer, *Molecular Simulation*, **48** (16), 2022. <https://doi.org/10.1080/08927022.2022.2113397>. (Published)
- [6] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Luo Z., and Saha, S. C., The concentration-dependent effect of hydrocortisone on the structure of model lung surfactant monolayer by using an in-silico approach. *RSC Advances*. (Under Review)

List of conferences

[1] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Bhowmick, S., Saha , S. C., Molecular dynamics study of prednisolone concentration on cholesterol-based lung surfactant monolayer, 13th International Conference on Mechanical Engineering, ICME 2019, 18-20 December 2019, BUET, Dhaka, Bangladesh.

[2] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Saha , S. C., Understanding the concentration-dependent Interaction of Sterol Drugs with Model Lung Surfactant Monolayers Using Molecular Dynamics Simulations, 44th Meeting of Australian Society for Biophysics, 02-04 December 2020, Australia, and New Zealand.

[3] **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Saha , S. C., The steroid mometasone alters protein containing lung surfactant monolayers in a concentration-dependent manner, MM2021, 06-08 December 2021, Queensland University of Technology, Locked Bag 3407, Brisbane, QLD 4001, Australia.

Statement of authors' contribution to publications

- Publication 1 **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Bhowmick, S., Saha, S. C., Molecular dynamics study of prednisolone concentration on cholesterol based lung surfactant monolayer, *AIP Conference Proceedings*, **2324** (1), 060008, 2021. <https://doi.org/10.1063/5.0037471>. **(Published)**
- Authors' contributions M.Z.I. performed the simulations, data analysis and drafted the original manuscript. S.I.H. edited the manuscript. E.D. help to data analysis, supervised M.Z.I. and edited the manuscript, and S.C.S. developed the concept, supervised M.Z.I. edited the manuscript.
- Publication 2 **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Saha, S. C., The steroid mometasone alters protein containing lung surfactant monolayers in a concentration-dependent manner, *Journal of Molecular Graphics and Modelling*, **111**, 108084, 2021. <https://doi.org/10.1016/j.jmgm.2021.108084>. **(Published)**
- Authors' contributions M.Z.I. participated in the design of the study, performed simulations, data analysis, and drafted the original manuscript. S.I.H. edited the manuscript. E.D. supervised M.Z.I., helped in concept clarification and revised the manuscript, and S.C.S. developed the concept, supervised M.Z.I. revised the manuscript.
- Publication 3 Hossain, S. I., **Islam, M. Z.**, Saha, S. C., Deplazes, E., Drug Meets Monolayer: Understanding the Interactions of Sterol Drugs with Models of the Lung Surfactant Monolayer Using Molecular Dynamics Simulations, Membrane Lipids: Methods and Protocols, *Methods in Molecular Biology (Clifton, N.J.)* **2402**, 103-121, 2022. https://doi.org/10.1007/978-1-0716-1843-1_9. **(Published)**
- Authors' contributions S.I.H. wrote the introduction part of this book chapter, M.Z.I. participated in writing the technical part of the book chapter, S.C.S. supervised M.Z.I. revised the manuscript and E.D. supervised M.Z.I., helped in concept clarification and revised the manuscript.
- Publication 4 **Islam, M. Z.**, Krajewska, M., Hossain, S. I., Prochaska, K., Anwar, A., Deplazes, E., and Saha, S. C., Concentration-Dependent Effect of

the Steroid Drug Prednisolone on a Lung Surfactant Monolayer, *Langmuir*, **38** (14), 4188-4199, 2022.

<https://doi.org/10.1021/acs.langmuir.1c02817>. (**Published**)

Authors' contributions M.Z.I. performed the simulations, analysed data and drafted the original manuscript. M.K. conducted the experimental part of the study. S.I.H. helps to analyse data and edit the manuscript. K. P. developed the concept of the experimental part and supervised M.K. A. A. edited the manuscript. E.D. help to design the simulations and analysis, supervised M.Z.I. and edited the manuscript, and S.C.S. developed the concept, supervised M.Z.I. and edited the manuscript.

Publication 5 **Islam, M. Z.**, Hossain, S. I., Deplazes, E., and Saha, S. C., Concentration-dependent cortisone adsorption and interaction with model lung surfactant monolayer, *Molecular Simulation*, **48** (16), 2022. <https://doi.org/10.1080/08927022.2022.2113397>. (**Published**)

Authors' contributions M.Z.I. performed the simulations, data analysis, participated in the design of the study and drafted the original manuscript. S.I.H. edited the manuscript. E.D. analysed data, supervised M.Z.I. and critically revised the manuscript, and S.C.S. developed the concept, supervised M.Z.I. and edited the manuscript.

Publication 6 **Islam, M. Z.**, Hossain, S. I., Deplazes, E., Luo Z., and Saha, S. C., The concentration-dependent effect of hydrocortisone on the structure of lung surfactant monolayer, *RSC Advances*. (**Under Review**)

Authors' contributions M.Z.I. participated in the design of the study, performed simulations, data analysis, and drafted the original manuscript. S.I.H. edited the manuscript. E.D. supervised M.Z.I., helped in concept clarification and revised the manuscript. Z.L., edited the manuscript and S.C.S. coordinated the study, supervised M.Z.I. revised the manuscript.

Production Note:

Signature removed prior to publication.

Student Signature:
(Mohammad Zohurul Islam)

Date of signature: 12/09/2022

Confirmation of the authorship from principal supervisor (corresponding/co-corresponding author of the publications)

As the corresponding or co-corresponding author of each publication listed above, I am confirming the contributions of all co-authors and their authorship.

Principal supervisor Signature:
Production Note:
Signature removed prior to publication.
(Dr Suvash C. Saha)
(Corresponding/co-corresponding author and Principal supervisor)
Date of signature: 12/09/2022

This page intentionally left blank

Table of contents

Serial No.	Name of the topics	Page
Front matters	Certificate of original authorship	I
	Dedication	III
	Acknowledgements	V
	Statement indicating the format of the thesis	IX
	List of publications	XI
	List of conferences	XII
	Statement of authors' contribution to publications	XIII
	Table of contents	XVII
	List of figures	XXI
	List of tables	XLVII
	List of abbreviation and symbols	LI
	Abstract	LIII
Chapter 1	Introduction	1-16
	Introduction	1
1.1	Background	3
1.2	Motivation and significance	6
1.3	Research aims and objectives	7
1.4	Thesis outline and layout of the chapters	9
	References	12
Chapter 2	Literature Review	17-102
	The respiratory system and steroid drug	
2.1	The respiratory system	17
2.1.1	Anatomy and function of the respiratory system	17
2.1.2	Composition of lung surfactants	22
2.1.3	Function of the lung surfactant monolayer	27
2.1.4	Relationship between surface tension and pressure at lung surfactant monolayer	32
2.1.5	Structure and phase of the lung surfactant monolayer	35
2.2	Effect of corticosteroid drug on lung surfactant	39
2.2.1	Structure and function of corticosteroid	39
2.2.2	Inhaled glucocorticoid interaction with lung surfactant	42
2.2.3	Glucocorticoid delivery using exogenous lung surfactant	43
2.3	Physiology related to pulmonary drug adsorption	47

2.4	Studies on the interaction of lung surfactant with small molecules	49
2.4.1	Experimental studies	50
2.4.2	Computational studies	65
2.5	Summary of literature review	80
	References	83
Chapter 3	Methodologies	103-142
	Computational Methodologies	
3.1	Molecular dynamics simulation overview	103
3.1.1	Mathematical formulation of classical molecular dynamics	107
3.1.2	Force field in molecular dynamics	113
3.1.3	Martini coarse-grained force field	113
3.1.4	Algorithms that implement molecular dynamics simulation	116
3.1.5	Periodic boundary condition	118
3.1.6	Molecular dynamics simulation ensemble	119
3.1.6.1	NVE micro-canonical ensemble	119
3.1.6.2	NVT canonical ensemble	120
3.1.6.3	NPT Isothermal–isobaric ensemble	120
3.2	Overview of simulation approach	120
3.2.1	Parameterisation of corticosteroid molecules	123
3.2.1.1	Umbrella sampling	127
3.2.2	Set up of simulation system	129
3.2.3	Simulation protocol	130
	References	133
Chapter 4	Concentration-dependent effect of the steroid drug prednisolone on a lung surfactant monolayer	143-210
4.1	Abstract	145
4.1.1	Graphical abstract	146
4.2	Introduction	147
4.3	Materials and Methods	150
4.3.1	Langmuir Trough Experiments	150
4.3.2	Molecular dynamics simulation	151
4.3.3	Simulation systems for fixed area per lipid	152
4.3.4	Simulation systems for fixed surface tension	153
4.4	Results and Discussion	154
4.4.1	Langmuir trough experiment results	154
4.4.2	Fixed area per lipid simulation results	158
4.4.3	Fixed surface tension simulation results	160
4.4.4	Aggregation and spreading of prednisolone	168

4.5	Conclusions	173
Appendix 1	Supplementary Information (Chapter 4)	174
	References	202
Chapter 5	The steroid mometasone alters protein containing lung surfactant monolayers in a concentration-dependent manner	211-274
5.1	Abstract	213
5.1.1	Graphical abstract	214
5.2	Introduction	215
5.3	Methods	219
5.3.1	System setup	219
5.3.2	Simulation parameters	220
5.3.3	Drug concentration and conditions for the different simulation systems	222
5.3.4	Analysis	222
5.4	Results and Discussion	224
5.4.1	Effect mometasone on the structure and dynamics of LSM	224
5.4.1.1	Effect of mometasone on the LSM surface tension	224
5.4.1.2	Effect of mometasone on the compressibility of the LSM	226
5.4.1.3	Density profile	228
5.4.1.4	Effect of mometasone on lipid order parameter	231
5.4.2	Effect of mometasone on the diffusion of LSM components	232
5.4.3	Clustering and monolayer stability	235
5.4.3.1	Surfactant protein clustering	235
5.4.3.2	Mometasone clustering	239
5.5	Summary and conclusion	241
Appendix 2	Supplementary Information (Chapter 5)	242
	References	262
Chapter 6	Concentration-dependent cortisone adsorption and interaction with model lung surfactant monolayer	275-324
6.1	Abstract	278
6.2	Introduction	279
6.3	Methods	283
6.3.1	Simulation parameter and simulation system setup	283
6.3.2	Simulation details	286
6.4	Results and discussions	287
6.4.1	Effect of cortisone on the compressibility of the monolayer	287

6.4.2	The effect of cortisone on monolayer thickness	292
6.4.3	MSD and Diffusion coefficient calculation	293
6.4.4	The effect of cortisone adsorption on monolayer stability	296
6.5	Implication and limitation	300
6.6	Summary and conclusion	301
Appendix 3	Supplementary Information (Chapter 6)	303
	References	313
 Chapter 7	 The concentration-dependent effect of hydrocortisone on the structure of model lung surfactant monolayer by using an in-silico approach	 325-380
7.1	Abstract	326
7.2	Introduction	328
7.3	Methodology	334
7.3.1	Simulation parameter and simulation model setup	334
7.3.2	Molecular dynamics simulation	337
7.3.2.1	Simulation systems for fixed surface tension and fixed APL	337
7.3.2.2	Data Analysis and visualisation	339
7.4	Results and discussion	339
7.4.1	Monolayer compressibility and stability analysis	340
7.4.1.1	Effect of surface tension on monolayer stability	340
7.4.1.2	Effect of hydrocortisone concentration on the pressure-area isotherm	345
7.4.2	Structural and dynamical properties of monolayer at conditions mimicking exhalation and inhalation breathing	347
7.4.2.1	Structural properties	347
7.4.2.2	Dynamical properties	352
7.5	Implications	356
7.6	Conclusion	357
Appendix 4	Supplementary Information (Chapter 7)	359
	References	369
 Chapter 8	 General conclusions and future directions	 381-392
8.1	General conclusions	382
8.2	Future directions	389

List of figures

Figure no.	Title	Page
Figure 2.1	Diagram of the human respiratory system.	18
Figure 2.2	Cell types in the respiratory system. Goblet cells, basal cells, Clara cells, and ciliated cells found in the upper airway (trachea and bronchi), whereas PNEC, Clara cells, ciliated cells, type I and type II cells found in the lower airway.	19
Figure 2.3	Cellular structure and pathways of inhaled air and particles. (a) The pathway of inhaled aerosolised particles in the respiratory system. (b) Once crossing bronchial, particles first make contact with lung surfactant lining fluid then interact with lung surfactants and mucus before penetrating to the lung cell epithelium. (c) Aerosolised particles interact with lung surfactants in the alveoli.	20
Figure 2.4	The schematic structure of the alveolus and procedure of lung surfactant extraction from alveolar Type II pneumocytes cells. Surfactant adsorption and surface monolayer formation at the air-water interface from alveolar Type II cells. Direct adsorption of the lamellar bodies (LBs) and LBs are then transformed into tubular myelin (TM), and finally adsorbed through a continuous process from alveolar cells to the interface.	23
Figure 2.5	The average composition of lipids and surfactant proteins in mammalian lung surfactant monolayers. The fractions of lipids and proteins components 1, 2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC); 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC); 1-	25

palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol (POPG); other phospholipids (PLs); Neutral lipids (NLs); Surfactant proteins (SPs).

- Figure 2.6 Schematic of lipid lung surfactant components at the air-water interface: (a) Zwitterionic (+/-) and negatively charged (-) surfactant molecules at the air-liquid interface, (b) saturated, zwitterionic (+/-) phospholipid DPPC, (c) unsaturated, zwitterionic (+/-) phospholipid lipid POPC, (d) negatively charged (-), unsaturated phospholipid POPG and (e) uncharged sterol cholesterol. 28
- Figure 2.7 Lung surfactant components and their organisation during the compressed and expanded state and the reversible processes of monolayer formation from the bilayer reservoir. (a) Compressed state (end of exhalation): Lung surfactant organises in multilayer structures characterised by the presence of phospholipids (DPPC, POPC, POPG), cholesterol and surfactant proteins at the air-liquid interface characterised by a low surface tension ($\gamma = \sim 0 \text{ mNm}^{-1}$). (b) Expanded state (inhalation): Re-adsorption of phospholipids (DPPC, POPC, POPG), cholesterol and surfactant proteins containing lung surfactant membrane at the air-liquid interface reaching an equilibrium surface tension of $\gamma = \sim 20\text{-}25 \text{ mNm}^{-1}$. 30
- Figure 2.8 Surface pressure and surface tension regulation at alveolar air-water interface in the absence and presence of lung surfactants. Schematic representation of the interfacial behaviour of phospholipids and reduction of surface tension (i.e., increase of surface pressure). 33
- Figure 2.9 Lung surfactant monolayer compression (a) and expansion (b) at the air-water interface. During monolayer compression (exhalation), there is a re-arrangement of the surfactant 34

molecules in the interfacial region: less surface-active molecules (POPC and POPG) are removed from the monolayer interface, so that the monolayer is enriched with molecules that are more surface-active (*e.g.*, DPPC). The reservoirs underneath the monolayer are stabilised by surfactant proteins B and C (SP-B and SP-C). During expansion (inhalation), the POPC and POPG placed beneath the monolayer are redistributed to the monolayer interface. DPPC is shown in green, POPC in blue, POPG in cyan, cholesterol in red, SP-B in dark-green and SP-C in dark red and water in light blue-orange.

Figure 2.10	Pressure-area isotherm of a phospholipid (DPPC) monolayer at temperatures 297.15 K and 310.15 K. The data has been plotted from an experimental study by Crane <i>et al.</i> , [55]. The schematic compression/expansion driven lateral transitions in the surfactant monolayer and their corresponding phase transition has been shown. The distribution of surfactant components over the monolayer surface and corresponding interfacial orientation of the phospholipids at the different surface pressures has also been depicted (I, II, III, IV and V). LC: liquid-condensed phase, LC-LE: liquid-condensed-liquid-expanded coexistence, LE: liquid-expanded phase and G: gas phase.	36
Figure 2.11	The ring structure of steroid core and the carbon number denoted by C1 to C17.	39
Figure 2.12	The chemical structure of common glucocorticoids.	41
Figure 2.13	Experimental method to study pulmonary surfactant monolayer, membrane structure and molecular reorganisation: (a) An illustration of schematic diagram of Langmuir trough experiment subjected to lateral compression and concurrent transfer of surfactant components in the	52

interfacial monolayer. Langmuir trough comprise a frame with a trough that holds a pressure sensor from top into the water sub-phase of the monolayer. A set of software control movable barriers are used for making monolayer compression and expansion to measure the compressibility, monolayer packing density of the monolayer. (b) Monolayer pressure-area isotherm curve from Langmuir experiment and various phases of the monolayer. The interfacial orientation of the phospholipids at varying surface pressures corresponds to lateral shifts in the surfactant monolayer as variations in surfactant component redistribution over the monolayer surface. LC: liquid-condensed phase, LC-LE: liquid-condensed-liquid-expanded coexistence, LE: liquid-expanded phase and G: gas phase.

Figure 2.14 Experimental and simulated pressure-area isotherm curves obtained from different studies for two pure phospholipids monolayer (DPPC and POPC) and their mixture (DPPC-POPC) in the absence and presence of pollutants. In all the panels, the experimental isotherms are indicated by solid lines and simulated isotherms are specified by points. (b) The vibrational wavenumbers of the monolayer system composed of binary phospholipids (DPPC-POPC) in the pollutant-free and in the presence of two pollutants (dibenzodioxin and 2-chlorodibenzodioxin) at surface tension 30 mNm^{-1} from PM-IRRAS experiment. (c) Order parameters of lipids chain-2 ($sn-2$) of the monolayers in the presence of two environmental pollutants (dibenzodioxin and 2-chlorodibenzodioxin).

Figure 2.15 Effect of the corticosteroid drugs budesonide and beclomethasone dipropionate at different concentrations on the monolayer compressibility and stability of commercially available surfactant Infasurf. (a) The pressure area isotherm

curves and (b) AFM topography images at different surface pressure for three different corticosteroid drug concentrations.

- Figure 2.16 (a) Time evolution of bovine lipid extract surfactant and Survanta adsorption before and after addition of low and high concentration of two corticosteroids (salbutamol and budesonide). (b) Lowest stable surface tension of exogenous surfactant lipid extract surfactant and Survanta in the presence of low and high concentration of budesonide and salbutamol. (c) Quasi-static surface tension as a function of relative surface area of budesonide at low and high concentration of budesonide for Survanta. 61
- Figure 2.17 (a) Fraction of glucocorticoids Beclomethasone, Budesonide and Fluticasone) or cholesterol added in the exogenous pulmonary surfactant (EPS). (b) The experimental lipids order parameter of the phospholipids presents in the exogenous surfactant for different glucocorticoids and cholesterol concentrations. Surface tension and surfactant monolayer compression of the exogenous surfactant for different corticoid drug at various concentration. The asterisk “*” in Fig. 2.17b represent the statistically significant results compared to the control system. 63
- Figure 2.18 Polymer grafting nanoparticles translocation into the LSM: (a) MD simulation setup with phospholipids, cholesterol and surfactant proteins. (b) Effect of surfactant proteins on translocation of the nanoparticles through the LSM. (c) Effect of surface tension on nanoparticle translocation into the LSM. 67
- Figure 2.19 Interaction of different nanoparticles with LSM (DPPC-POPG-SP-B₁₋₂₅-SP-C). (a) Injection of nanoparticles from air space into the simulated LSM system separated by water box between two monolayers. Comparison of pressure-area 68

isotherms from simulation (MD) with experimental (Langmuir) results of LSM. The lateral patterns of the LSM monolayer are shown in the insets (top image: AFM and bottom image: MD simulation) across the plateau area of the compression isotherms. (c) Three different types of hydrophobic and hydrophilic nanoparticles (neutral, cationic, and anionic) translocation into the LSM in three compressed stage of monolayers (60.0, 51.4 and 44.1 Å²).

Figure 2.20 Interaction of different nanoparticles with LSM (DPPC-POPG-SP-B₁₋₂₅-SP-C). (a) The initial final configuration of the DPPC phospholipid monolayers (a, c) Naringin and (b, d) Naringenin. (e) Gibbs free energy profiles of translocation of the Naringin (top) and Naringenin (bottom) for octano-water and water-octanol phase. (f) the intensity curves of GIXOS scattering patterns pure monolayer (blue curve), Naringin containing monolayer (green) and Naringenin containing monolayer (red) at 28 mNm⁻¹ surface tension. 71

Figure 2.21 (a) The antibiotic levofloxacin containing LSM (DPPC-POPC) system. The levofloxacin is first incorporated into the lipid-air interface. (b) The density profile of DPPC (green), POPC (red), amphoteric levofloxacin (yellow), and water (blue) in the system at surface pressures of 55 (top) and 43 (bottom) mNm⁻¹. (c) Experimental surface pressure-area isotherms as a function of the trough area in the absence of drug (black) as well as in the presence of 0.1% w/w (red), and 10% w/w (blue) drug concentration. (d) BAM images of drug-free LSM, and 0.1% and 10% w/w of levofloxacin at different surface pressure of 0, 10, 20, 30, ad 40 mNm⁻¹. 73

Figure 2.22 (a) Pressure-area isotherms for DPPC-DPPG LSM at drug free (black) and a range of drug concentration at the air-water interface. (b) Compression modulus-pressure curves of the 77

	same monolayer obtained from Langmuir experiment. (c) Simulated tension-area curves for drug-free and presence of drug. (d) Experimental tension-area curves in the absence and presence of drug.	
Figure 2.23	Simulation system of CG model with (a) 10 prednisolone molecules in the vacuum space, (b) the LSM states including monolayer collapsing at two different surface tensions and (c) the order parameter of phospholipids at three different surface tension and various drug content.	79
Figure 3.1	(a) Atomistic to CG mapping strategy of DPPC lipid, the image has been reproduced from Molecular Physics (Song <i>et al.</i> [57], copyright 2022 with permission from Taylor & Francis. with permission from Taylor & Francis, Molecular Physics). (b) CG model for Benzene, DPPC and Cholesterol, (c) CG water, (d) CG butane, (e) CG octanol and (f) CG hexadecane.	115
Figure 3.2	The schematic of periodic boundary conditions for MD simulation are represented in two-dimensional graph. The simulation cell is infinitely reproduced in three dimensions. When a particle 'leaves' a simulation cell, it returns from the other side, ensuring that the total number of particles in each cell remains constant.	118
Figure 3.3	Flow chart for overall simulation protocols used in this investigation.	122
Figure 3.4	(a) Chemical and (b) schematic of coarse-grained structure of prednisolone, mometasone, cortisone and hydrocortisone. The collor represent the corresponding bead types (SNa: lime; SC4: black; SC3: purple; SP1: red; SNda: dark red; SC2: light black; SC1: green; C3: blue; P2: pink). See also Table 3.1.	124

Figure 3.5	Flow chart for drug parameterisation by partition coefficient calculation procedure.	126
Figure 3.6	Simulation system for potential mean force calculation of steroid drug transferred from octanol phase to water phase. Schematic of octanol-water model to calculate potential mean force of drug molecule from octanol phase to water phase.	128
Figure 3.7	Schematic of system to generate a LSM simulation model comprised of lipids, surfactant proteins. (a) Bilayer, (b) Drug-free monolayer and (c) Drug containing monolayer. The lipid head groups are shown in ochre. Lipid tails for DPPC, POPC, POPG are shown in green, blue and cyan respectively. Cholesterol, SP-B and SP-C, water and corticosteroid drug are shown in red, orange, yellow and silver, respectively.	130
Figure 3.8	Simulation overview for this thesis to investigate the effect of drugs on the LSM. (a) The drug-free LSM is used as a reference system with two extreme cases of breathing (expanded and compressed states). The drug-LSM simulation systems were prepared from equilibrated reference systems. (b) n number of drug-LSM systems were used to investigate the concentration-dependent effect of the drug on the LSM. Each of the drug-LSM system was simulated in the expanded and compressed state as reference systems.	132
Figure 4.1	Inhaled prednisolone interaction with LSM at different time.	146
Figure 4.2	Simulation system. (a) Schematic representation of the simulation system with lipid-containing surfactant monolayer separated by 6 nm water layer and 40 nm vacuum above and below. The LSM system is composed of DPPC, POPC and cholesterol. (b) LSM in the absence of prednisolone molecules. (c) Top view of LSM with 11.2% w/w prednisolone molecules. DPPC is shown in green, POPC in blue, cholesterol in red and prednisolone in purple. (d)	152

Topology and bead types for DPPC, POPC, cholesterol and prednisolone (SNa: yellow; SC4: black; SC1: grey; SNda: blue; P2: light blue). Parameters for prednisolone and cholesterol can be found in Table 4.2A1.

- Figure 4.3 Surface pressure-area per lipid (π -APL) isotherms for the mixture of DPPC-POPC-CHOL (7:3:1 mol %) with increasing concentrations of prednisolone (310 K, water subphase); inset: (a)-(d) BAM images taken during the experiment for the system without prednisolone and (e)-(h) for the system with 11.2% w/w of prednisolone. 156
- Figure 4.4 Compression modulus (C_s^{-1}) as a function of surface pressure (π) for the mixture of DPPC-POPC-CHOL (7:3:1 mol %) with different content of prednisolone. 157
- Figure 4.5 The simulated pressure-area per lipid (π -APL) isotherm of mixed monolayer composed of DPPC-POPC-CHOL (7:3:1) at different drug concentrations (0-5.9% w/w). The inset table shows the calculated effective surface tension and collapsing surface area of the simulated systems at different drug concentrations. The errors bars indicate the standard deviation of the data from two independent runs of the simulation. 159
- Figure 4.6 The order parameter of DPPC *sn*-1 and *sn*-2 tail groups (a, b) and POPC *sn*-1 and *sn*-2 tail groups (c, d) at 20 mNm⁻¹ in the presence of increasing concentrations of prednisolone. Order parameters were calculated from the last 1 μ s of the 2 μ s production simulations of DPPC-POPC-CHOL (3:7:1) monolayers. The calculated order parameters were adjusted considering one-fourth of the second-ranked order parameter to account for the coarse-graining of the lipids. The lines for 0%, 0.5% and 1.0% w/w prednisolone are in some cases not 167

distinguishable. The error bars represent standard deviation across at least two repeated runs of the simulation.

Figure 4.7 Snapshots from the simulation of DPPC-POPC-CHOL 169
monolayers in the presence of 5.9% w/w prednisolone as the representative for all drug concentrations, simulated at 20 mNm⁻¹ surface tension. (a) Initial configuration of the system with 60 prednisolone drug molecules (equivalent to 5.9% w/w) in the vacuum space outside each monolayer, (b) at 10 ns NVT equilibration, (c) at 10 ns NPγT equilibration, and (d) at 1500 ns production run. Prednisolone molecules are shown in purple. DPPC and POPC lipids are shown in green and blue, respectively, while cholesterol is shown in red. Water between the monolayers is shown in silver colour.

Figure 4.8 Aggregation of drug molecules (a) at 50 ns (b) 400 ns. The 171
subsequent buckling followed by the complete collapse of the monolayer in simulations of the DPPC-POPC-CHOL model at surface tension $\gamma = 0$ mNm⁻¹ with drug concentration 5.9% w/w as the representative case of other drug concentrations. Drug molecules are shown in purple surface representation. The lipids head region (NC3 and PO4 beads) is shown in ochre surface representation. The hydrophobic lipid tails (DPPC-green; POPC-blue) and cholesterol (red) are shown as sticks. The water molecules are shown in silver colour.

Figure 4.9A1 The area per lipids at two different surface tensions (0 and 20 184
mNm⁻¹) in the presence and absence of cholesterol with simulations of DPPC-POPC (7:3) and DPPC-POPC-CHOL (7:3:1) monolayer model at 0 and 20 mNm⁻¹ surface tensions. Error bar represents the error calculation by using the standard deviation.

Figure 4.10A1 Effect of cholesterol on the order parameter (S_z) of DPPC and 186
POPC lipids in a LSM composed of DPPC-POPC-CHOL,

7:3:1 (solid lines), and DPPC-POPC, 7:3 (dashed lines) at surface tension 0 mNm^{-1} (a, b) and 20 mNm^{-1} (c, d) in the absence of drug molecules. Order parameters were calculated from the last $1 \mu\text{s}$ of the $2 \mu\text{s}$ simulations of a given system. The calculated order parameters were adjusted considering one-fourth of the second-ranked order parameter to account for the coarse-graining of the lipids. The error bars represent standard deviation across at least two repeat runs of the simulation.

Figure 4.11A1 Effects of cholesterol on the density profiles of monolayer components DPPC, POPC and water from simulations of lung surfactant monolayers composed of DPPC-POPC-CHOL, 7:3:1 (solid lines), and DPPC-POPC, 7:3 (dashed lines) at surface tension 0 and 20 mNm^{-1} . Both the figures (a, b) are the density profiles from simulations in the absence of prednisolone. 187

Figure 4.12A1 The effects of drug (PRED) concentrations on phospholipids (DPPC and POPC) order parameters. The order parameters of DPPC *sn*-1 and *sn*-2 tail groups (a, b) and POPC *sn*-1 and *sn*-2 tail groups (c, d) were calculated from the last $1 \mu\text{s}$ of the $2 \mu\text{s}$ production simulations of DPPC-POPC-CHOL (7:3:1) monolayers at 0 mNm^{-1} in the presence of increasing concentrations of drug molecules. The calculated order parameters were adjusted considering one-fourth of the second-ranked order parameter to account for the coarse-graining of the lipids. The low level of drug concentrations ($\leq 1.0 \text{ \% w/w}$) in the monolayer showed negligible effect on phospholipids order parameters, meaning the overlapping of the phospholipids order parameters curves at these low-level concentrations. The error bars represent standard deviation across at least two repeat runs of the simulation. 189

- Figure 4.13A1 Order parameter (sz) calculation for both chains (*sn*-1 and *sn*-2) of POPC and POPG lipids in a LSM composed of DPPC-POPC-CHOL, 7:3:1 and DPPC-POPG-CHOL, 7:3:1. (a, b) at surface tensions 0 and 20 mNm⁻¹ in the absence of drug molecules, respectively. Order parameters were calculated from the last 1 μs of the 2 μs simulations of a given system. The calculated order parameters were adjusted considering one-fourth of the second-ranked order parameter to account for the coarse-graining of the lipids. The error bars represent standard deviation across at least two repeated runs of the simulation. 190
- Figure 4.14A1 The density profile of DPPC, POPC, water and cholesterol from simulations of DPPC-POPC-CHOL (7:3:1) at surface tension 20 mNm⁻¹ and with increasing prednisolone drug concentrations, calculated from the last 1 μs of the 2 μs production runs. The density profiles are plotted at the half of the monolayer normal due to the symmetry of the profile. Note that the profiles for 0%, 0.5%, 1.0 % and 3.0% w/w are overlapped. The lines for 0%, 0.5%, 1.0% and 3.0% w/w prednisolone are not distinguishable. 192
- Figure 4.15A1 The density profile of DPPC, POPC, water and cholesterol from simulations of DPPC-POPC-CHOL (7:3:1) at surface tension 0 mNm⁻¹ and with increasing prednisolone drug concentrations, calculated from the last 1 μs of the 2 μs production runs. The density profile is plotted at the half of the monolayer normal due to the symmetry of the profile. Note that the profiles for 0%, 0.5% and 1.0% w/w are overlapped. The lines for 0%, 0.5% and 1.0% w/w prednisolone are not distinguishable. 193
- Figure 4.16A1 Mean square displacement (MSD) of phospholipids (DPPC and POPC combined), calculated from the simulation of a 194

DPPC-POPC-CHOL (7:3:1) monolayer in the presence of the different drug concentrations, at surface tension 20 mNm^{-1} . The curves were fitted from 500 ns to 1500 ns of total $2 \mu\text{s}$ MSD calculation.

- Figure 4.17A1 Two-dimensional lateral diffusion coefficient (D) of the phospholipids (DPPC and POPC combined) and prednisolone calculated from simulations of a DPPC-POPC-CHOL (7:3:1) LSM model at 0 and 20 mNm^{-1} . Diffusion coefficients were calculated at surface tensions, 0 and 20 mNm^{-1} using the Einstein diffusion equation. Error bars correspond to the standard deviation of the data, and it is calculated using the block averaging method. 198
- Figure 4.18A1 Clustering analysis of drug molecules at 3.0% w/w drug concentration of DPPC-POPC-CHOL model. The x -axis represents the simulation time, and y -axis indicates the number of clusters and the number of drug molecules in the largest cluster. The number of clusters (top two panels) and the number of drug molecules in the largest cluster (bottom two panels) at 0 mNm^{-1} surface tension (a, c) and at 20 mNm^{-1} surface tension (b, d). Color bar represents the number of drug molecules. 199
- Figure 4.19A1 Clustering analysis of drug molecules at 5.9% w/w drug concentration of DPPC- POPC-CHOL (7:3:1) model at 20 mNm^{-1} surface tension. The x -axis represents the simulation time, and y -axis indicates the number of clusters of drug molecules (a) and the number of drug molecules in the largest cluster (b). Color bar represents the number of drug clusters (a) and drug molecules in the largest cluster (b) in the monolayer. The data was prepared using $2.5 \mu\text{s}$ simulation time: including equilibration with NP γ T (first 500 ns) equilibration. 200

Figure 4.20A1	Aggregation of drug molecules at 1000 ns (a) 1200 ns (b). The subsequent buckling followed by the complete collapse of the monolayer in simulations of the DPPC-POPC-CHOL (7:3:1) model at surface tension $\gamma = 0 \text{ mNm}^{-1}$ with drug concentration 11.2% w/w. Drug molecules are shown in purple surface representation. The hydrophobic lipid tails (DPPC-green; POPC-blue) and Cholesterol (red) are shown as sticks. The water molecules are shown by silver colour.	201
Figure 5.1	Inhaled mometasone interaction with LSM at inhalation and exhalation breathing condition for different drug concentration.	214
Figure 5.2	Schematic of the simulation system consisting of two monolayers composed of DPPC-POPC-POPG-CHOL with surfactant proteins SP-B ₁₋₂₅ , SP-C. (a) Lateral view of the simulation system at drug concentration 3.51% w/w. DPPC is shown in green, POPC in blue, POPG in cyan, cholesterol in red, mometasone in purple, SP-B ₁₋₂₅ in light yellow, SP-C in orange, positive ions in light blue and negative ions in light yellow. (b) Coarse-grained structure of surfactant proteins (SP-B ₁₋₂₅ , SP-C) and mometasone.	220
Figure 5.3	The effect of drug concentrations on the surface tension of an LSM calculated from fixed-APL simulations at APL 0.48, 0.52, 0.56 and 0.60 nm ² . Simulations were carried out in the absence and presence of mometasone at concentrations 1.78 and 3.51% w/w.	226
Figure 5.4	Mass density profiles of phospholipid molecules in the monolayer. Comparison of density profiles from simulations of DPPC-POPC-POPG-CHOL model at surface tension, $\gamma = 0$ (green), 20 (purple) and 25 (red) mNm ⁻¹ , in the absence (solid lines) and in the presence (dotted lines) of surfactant proteins. (a) Drug free monolayer and (b) at a drug concentration of	230

6.78% w/w. The monolayer normal is the z-axis of the simulation system, and $z = 0$ denotes the center of mass of the monolayer.

Figure 5.5 The effect of drug concentrations on order parameter of DPPC (solid lines) and POPC (dashed lines) for lipid chain-1 (*sn*-1) (a, c) and lipid chain-2 (*sn*-2) (b, d) of the monolayer at surface tensions 20 mNm^{-1} (a, b) and 25 mNm^{-1} (c, d). Drug concentrations in % w/w are 0 (black), 0.60 (green), 1.78 (purple), 3.58 (blue), 6.78 (red) and 12.69 (orange). Order parameters were calculated from the last $1 \mu\text{s}$ of the $2 \mu\text{s}$ production simulations of DPPC-POPC-POPG-CHOL (60:20:10:10) monolayers with surfactant proteins SP-B₁₋₂₅ and SP-C (1:1). The error bars represent standard deviation across at least two repeat runs of the simulation. 232

Figure 5.6 Mean square displacement (MSD) of phospholipids (DPPC, POPC and POPG) at different surface tensions (0, 20 and 25 mNm^{-1}) in the absence of drug (solid lines) and the presence of mometasone (12.69% w/w drug concentration, dashed lines). Data was calculated from simulation of a DPPC-POPC-POPG-CHOL (60:20:10:10) monolayer with surfactant proteins (SP-B₁₋₂₅ and SP-C=1:1) The MSD curves were fitted for entire $2 \mu\text{s}$ simulation. The MSD for 0 mNm^{-1} surface tension at drug concentration 12.69% w/w is not consider due to the collapse of the monolayer. 233

Figure 5.7 Cluster size analysis of surfactant proteins in the (a) absence and (b) presence of drugs on the monolayer composed of DPPC-POPC-POPG-CHOL (60:20:10:10) with surfactant proteins at surface tensions 0 mNm^{-1} (red), 20 mNm^{-1} (purple) and 25 mNm^{-1} (green). The x-axis represents the simulation time, and y-axis indicates the number of clusters. The analyses have been performed over $2 \mu\text{s}$ simulations. The 235

clustering analysis at 0 mNm⁻¹ surface tension in the presence of drug was not estimated due to collapse of the monolayer.

- Figure 5.8 Snapshot of the monolayer at different simulation time in the presence of two extreme drug content (a) 0.60% and (b) 12.69% w/w at surface tensions 0 mNm⁻¹. The system contains DPPC-POPC-POPG-CHOL (60:20:10:10) with surfactant proteins, SP-B₁₋₂₅ and SP-C (1:1). DPPC is shown in green, POPC in blue, POPG in cyan, cholesterol in red, mometasone in purple, SP-B₁₋₂₅ in light yellow, SP-C in orange and water in grey. 237
- Figure 5.9 Proteins cluster size analysis in the presence of mometasone (1.78% w/w). Data was obtained from a fixed-APL simulations of a monolayer composed of DPPC-POPC-POPG-CHOL (60:20:10:10) with surfactant proteins, SP-B₁₋₂₅:SP-C (1:1) system. (a) APL = 0.48 nm² and (b) APL= 0.60 nm². Density map of peptides at APL= 0.48 nm² (c) and APL= 0.60 nm² (d). The colour scale bar represents the probability of low (0) and high (1) density of the surfactant proteins. 238
- Figure 5.10A2 Chemical, schematic, and coarse-grained structure of (a) Prednisolone and (b) Mometasone. The color represent the corresponding bead types (SNa: lime; SC4: black; SC3: purple; SP1: red; SNda: dark red; SC2: light black; SC1: green; C3: blue; P2: pink). 244
- Figure 5.11A2 Schematic representation of octanol-water model to calculate potential mean force of mometasone drug from octanol phase to water phase. 247
- Figure 5.12A2 The weighted histogram analysis of the overlap between umbrellas windows from 0 to 8 nm in the reaction coordinate 247

(along, z-axis). The color has no meaning unless a better visualisation of the overlapping between windows.

- Figure 5.13A2 Potential mean force (PMF) at various simulation time as the function of reaction coordinate of the steroid drug (mometasone) to get the well converged potential mean force curve. 248
- Figure 5.14A2 Free energy profile (PMF) of mometasone transferred from octanol phase to water phase. 249
- Figure 5.15A2 Comparison of partition coefficient (logP values) of different sterols/steroids between experimental and predicted results from cheminformatics tools (ChemAxon and Alog P). 250
- Figure 5.16A2 The effect of drug on phospholipids density profiles of the monolayer in the absence (dotted lines) and in the presence of 6.78% w/w drug concentration (solid lines) from the simulations of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C (60:20:10:10:1:1) at surface tension, $\gamma = 20 \text{ mNm}^{-1}$. The monolayer normal, $z = 0$ denotes the center of mass of the monolayer. 253
- Figure 5.17A2 The density profiles of monolayer components (DPPC, POPC, POPG, CHOL, proteins and water) from the simulations of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C (60:20:10:10:1:1) at surface tensions, (a) $\gamma = 20 \text{ mNm}^{-1}$ and (b) $\gamma = 25 \text{ mNm}^{-1}$. The solid lines indicate low drug concentrations (0.60% w/w) and the dotted lines denotes drug concentration (12.69% w/w). The inset figure represents POPC, POPG, CHOL and surfactant proteins density for clarity. 254
- Figure 5.18A2 The effect of drug concentrations on order parameter of POPC (dashed lines) and POPG (dotted lines) for lipid chain-1 ($sn-1$) and chain-2 ($sn-1$) at surface tensions (a, b) $\gamma = 20 \text{ mNm}^{-1}$ and (c, d) $\gamma = 25 \text{ mNm}^{-1}$. Drug concentrations in % w/w 256

are 0 (black), 0.60 (green), 1.78 (purple), 3.58 (blue), 6.78 (red) and 12.69 (orange). Order parameters were calculated from the last 1 μ s of the 2 μ s production simulations of DPPC-POPC-POPG-CHOL (60:20:10:10) monolayers with surfactant proteins SP-B₁₋₂₅ and SP-C (1:1). The error represent standard deviation across at least two repeat runs of the simulation.

Figure 5.19A2 The effect of surfactant proteins on order parameter of DPPC (black lines), POPC (dark red lines) and POPG (purple lines) for lipid chain-1, *sn*-1 (a, c) and chain-2, *sn*-2 (b, d) of the monolayer at surface tension, $\gamma=20$ mNm⁻¹ (a, b) and $\gamma=25$ mNm⁻¹ (c, d). The solid lines indicate the monolayer without surfactant proteins and the dashed lines refers to the monolayers with surfactant proteins (SP-B₁₋₂₅ and SP-C). Order parameters were calculated from the last 1 μ s of the 2 μ s production run simulations of DPPC-POPC-POPG-CHOL (60:20:10:10) monolayers with and without surfactant proteins (SP-B₁₋₂₅ and SP-C, 1:1) at drug concentration 6.78% w/w. The error bars have been calculated using the standard deviation across at least two repeat runs of the simulation. 257

Figure 5.20A2 Mean square displacement (MSD) of phospholipids (DPPC, POPC and POPG), calculated from the simulation of surfactant proteins (SP- B₁₋₂₅ and SP-C=1:1) containing DPPC-POPC-POPG-CHOL (60:20:10:10) monolayer in the presence of the different drug concentrations, at surface tension (a) 20 mNm⁻¹ and (b) 25 mNm⁻¹. The curves were fitted for entire 2 μ s simulation. 259

Figure 5.21A2 Snapshot of protein clustering at different simulation time for three different surface tensions in the absence of drugs on the monolayer composed of DPPC-POPC-POPG-CHOL 260

(60:20:10:10) with surfactant proteins, SP-B₁₋₂₅ (yellow) and SP-C (orange).

- Figure 5.22A2 Snapshot of the monolayer at different surface tension in the 261
absence and presence of three different drug content. The
system contains DPPC-POPC-POPG-CHOL (60:20:10:10)
with surfactant proteins, SP-B₁₋₂₅ and SP-C (1:1). DPPC is
shown in green, POPC in blue, POPG in cyan, cholesterol in
red, mometasone in purple, SP-B₁₋₂₅ in light yellow, SP-C in
orange and water in gray.
- Figure 5.23A2 Protein cluster size analysis in the presence of mometasone 262
(1.78% w/w). Data was obtained from a fixed-APL
simulations of a monolayer composed of DPPC-POPC-
POPG-CHOL (60:20:10:10) with surfactant proteins, SP-B₁₋₂₅:SP-C (1:1) system. (a) APL = 0.52 nm² and (b) APL= 0.56
nm². Density map of proteins at APL= 0.52 nm² (c) and APL= 0.56 nm² (d). The colour scale bar represents the probability
of low (0) and high (1) density of the surfactant proteins.
- Figure 6.1 Illustration of the simulation system and its components for 284
(a) the drug-free system and (b) for a system with drugs. The
system consists of two surfactant monolayers separated by a
12 nm water box, and 21 nm vacuum on either end of the two
monolayers. The monolayer system is comprised of DPPC,
POPC, POPG and cholesterol with surfactant proteins B and
C (SP-B and SP-C). The system components are indicated by
DPPC (green), POPC (blue), POPG (cyan), cholesterol (red)
and cortisone (purple), SP-B₁₋₂₅ (light yellow), SP-C (orange)
and water (silver). (c-e) Schematic representation of the CG
topology of phospholipids DPPC, POPC and POPG,
cholesterol, the surfactant proteins SP-B₁₋₂₅ and SP-C, and the
corticosteroid drug cortisone.

- Figure 6.2 Area per lipids (APL) as a function cortisone content from the 289
system simulation of DPPC-POPC-POPG-CHOL
(60:20:10:10) in the absence and presence of surfactant
proteins SP-B₁₋₂₅ and SP-C at surface tension, $\gamma=20 \text{ mNm}^{-1}$.
The APL data were calculated over the last 1 μs of the
simulation. The errors represent standard deviations of the
APL data from two independent simulations.
- Figure 6.3 Order parameters of phospholipids from simulations of drug- 290
free monolayers in the presence and absence surfactant
proteins (SP-B₁₋₂₅, SP-C) of DPPC (a, b), POPC (c, d) and
POPG (e, f) for lipid chain-1 (*sn*-1, solid lines) and lipid
chain-2 (*sn*-2, dotted lines) at surface tensions $\gamma=0 \text{ mNm}^{-1}$ (a,
c, e) and $\gamma= 20 \text{ mNm}^{-1}$ (b, d, f). Order parameters were
measured for last one microsecond of the two microsecond
simulations in the absence and presence of surfactant proteins
for drug-free system. The error bars denote standard
deviations of two independent simulations.
- Figure 6.4 Order parameter of (a) DPPC, (b) POPC and (c) POPG for 291
sn-1 (solid lines) and *sn*-2 (dotted lines) chains as a function
of drug concentration at surface tension 20 mNm^{-1} . Order
parameters were measured for last one microsecond of the
two microsecond simulations in the presence of surfactant
proteins. The error bars denote standard deviations of two
independent simulations. The corresponding data from the
protein-free monolayer is shown in supplementary Fig.
6.13A3.
- Figure 6.5 Density profiles for the phospholipids (DPPC, POPC, 292
POPG), cholesterol, protein and water from the simulations
of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C at surface
tension $\gamma=20 \text{ mNm}^{-1}$. The solid and dotted lines indicate drug
concentrations 0.48% w/w and 5.49% w/w, respectively. The

inset figure shows enlarged density profiles for cholesterol and surfactant protein.

- Figure 6.6 Normalized density profiles of cortisone at different drug 293
content (0.48-5.49% w/w) from the simulations of DPPC-
POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C at surface tensions $\gamma=20$
mNm⁻¹.
- Figure 6.7 Mean squared displacement (MSD) of protein (light blue), 294
cortisone (red), cholesterol (green) and phospholipids
(black), calculated from the simulation of surfactant proteins
containing monolayer at the lowest (0.48% w/w) and highest
(5.49% w/w) drug concentration at surface tension 20 mNm⁻¹.
Data from two drug concentrations are indicated by dotted
(0.48% w/w) and solid lines (5.49% w/w). Curves were fitted
to the entire 2 μ s production simulation.
- Figure 6.8 Normalised drug cluster analysis at a range of drug 297
concentrations (0.48-5.49% w/w) in the surfactant protein-
containing LSM at surface tensions $\gamma=20$ mNm⁻¹. (a) The time
evaluation of the total number of drug clusters formed over
the simulation time. (b) A histogram of the average number
of clusters and the number of drug molecules in the largest
cluster. (c) The corresponding 2D density map of the drug
cluster at various drug concentrations. The data was
normalised using the number of drugs in the corresponding
drug concentration.
- Figure 6.9 Snapshots of simulation systems for monolayers at surface 299
tension 20 mNm⁻¹ are shown in the absence and presence of
five different cortisone concentrations of 0.48, 1.42, 2.82,
5.49 and 10.41% w/w for the protein containing LSM.
Components are shown as DPPC (green), POPC (blue),
POPG (cyan), CHOL (red), SP-B₁₋₂₅(orange), SP-C (yellow),

cortisone (purple), water (silver), and phospholipids head groups (ochre).

Figure 6.10A3 Bead mapping of cortisone: (a) chemical structure with CG 304
bead selection, (b) schematic structure of CG beads and (c)
coarse-grained structure of cortisone.

Figure 6.11A3 Simulation system for potential mean force calculation of 305
cortisone transferred from octanol phase to water phase. (a)
Schematic of octanol-water model to calculate potential mean
force of cortisone drug from octanol phase to water phase. (b)
The umbrella windows from 0 to 8 nm along the reaction
coordinate (*z*-axis) obtained using weighted histogram
analysis.

Figure 6.12A3 Free energy profile of cortisone shifted from octanol to water 307
phase. (a) Potential mean force (PMF) at various simulation
times. (b) PMF curve of cortisone transferred from octanol
phase to water phase with uncertainties calculated using
Bootstrapping analysis.

Figure 6.13A3 Order parameter of DPPC (a, b), POPC (c, d) and POPG (e, 310
f) for *sn*-1 (solid lines) and *sn*-2 (dotted lines) chains as a
function of drug concentration at surface tensions $\gamma=0$ mNm⁻¹
(a, c, e) and 20 mNm⁻¹ (b, d, f) for surfactant protein-free
monolayers. For 0 mNm⁻¹ surface tension, the order
parameter at concentration (>1.42% w/w) is not calculated
due to monolayer collapse. Order parameters were measured
for last one microsecond of the two microsecond simulations
in the absence of surfactant protein. The error bars have been
calculated using the standard deviations of two independent
simulations.

Figure 6.14A3 The density profiles of monolayer components (DPPC, 311
POPC, POPG, CHOL, proteins and water) from the
simulations of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C

(60:20:10:10:1:1) as the function of cortisone concentrations ranging from 0.48% to 5.49% w/w at surface tensions 20 mNm⁻¹.

- Figure 6.15A3 Snapshots of simulation systems for monolayers at surface 312
tension $\gamma=0$ mNm⁻¹ in the absence and presence of four
different cortisone concentrations of 0.48, 1.42, 2.82 and
5.49% w/w for the LSM monolayer composed of
DPPC:POPC:POPG:CHOL with surfactant proteins SP-B₁₋₂₅
and SP-C. DPPC (green), POPC (blue), POPG (cyan), CHOL
(red), SP-B₁₋₂₅(orange), SP-C (yellow), cortisone (purple),
water (silver), and phospholipids head groups (ochre) are
shown in respectively colour.
- Figure 6.16A3 The time dependent clustering analysis of proteins in the 313
presence of different cortisone concentrations (0-10.41%
w/w) at surface tensions 20 mNm⁻¹. Cluster calculation was
conducted for whole two microsecond simulation.
- Figure 7.1 (a) The representation of the simulation system with LSM 336
components in the presence of hydrocortisone. The system
consists of two surfactant layers separated by a 12 nm water
box, and 21 nm vacuum on each side of the layer. The
monolayer system is comprised of DPPC, POPC, POPG and
cholesterol with surfactant proteins B and C (SP-B and SP-C)
and the coarse-grained structure of these molecules can be
found in the supplementary Fig. 7.10A4. The system
components are indicated by DPPC (green), POPC (blue),
POPG (cyan), cholesterol (red) and hydrocortisone (purple),
SP-B₁₋₂₅ (yellow), SP-C (orange) and water (silver). (b)
Chemical structure of hydrocortisone and (c) Coarse grained
bead representation of hydrocortisone.
- Figure 7.2 The compressibility of the lung surfactant monolayer as a 341
function of surface tension in the absence and presence of

5.52% w/w of glucocorticoid drug hydrocortisone for the monolayer composed of DPPC-POPC-POPG-CHOL with surfactant protein SP-B₁₋₂₅ and SP-C. The error bars indicate standard deviations of the time evolution of APL data across the frames of the trajectories.

Figure 7.3 Snapshots of simulation system at surface tension 0 mNm⁻¹ 343

are shown in the absence and presence of increasing hydrocortisone concentrations of 0.49, 1.44, 2.84% w/w. Components are shown as DPPC (green), POPC (blue), POPG (cyan), CHOL (red), SP-B₁₋₂₅(orange), SP-C (yellow), cortisone (purple), water (silver), and phospholipids head groups (ochre).

Figure 7.4 Order parameter of DPPC (a, b), POPC (c, d) and POPG (e, 345

f) for *sn*-1 (a, c, e) and *sn*-2 (b, d, f) chains at different surface tension (0, 10, 20, 30, 40 and 50 mNm⁻¹) of drug-free monolayers composed of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C. Order parameters were estimated for last one microsecond of the two microsecond simulations. The error bars denote standard deviations across the frames of the trajectories.

Figure 7.5 Mass density profiles of phospholipid (left pannels) and 347

surfactant protein (right pannels) in the monolayer. Comparison of density profiles from simulations of LSM model at different surface tension in the absence (a, c) and presence (b, d) of 5.52% w/w hydrocortisone concentration. The monolayer normal is the z-axis of the simulation system, and $z = 0$ refers to the center of mass of the monolayer.

Figure 7.6 The effect of monolayer compression on the organisation of 348

the lateral structure of LSM for increasing hydrocortisone concentrations by pressure-area (π -APL) isotherms calculation of the LSM composed of DPPC-POPC-POPG-

CHOL-SP-B₁₋₂₅-SP-C in the absence and presence of increasing hydrocortisone concentrations.

Figure 7.7 The effect of hydrocortisone concentration on the area per lipid (APL) from the simulation of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C at 20 mNm⁻¹. The data were calculated over the last 1 μs of the 2 μs simulation. The error bar refers to standard deviations of the APL data across the frames. 349

Figure 7.8 Effect of hydrocortisone concentration on the order parameter of (a, b) DPPC, (c, d) POPC, and POPG (e, f) for *sn*-1 (a, c, e) and *sn*-2 (b, d, f) chains at surface tension 20 mNm⁻¹. Order parameters were estimated for last one microsecond of the two microsecond simulations. The error bars were calculated across the frames of the simulation. 351

Figure 7.9 Normalised hydrocortisone cluster analysis for four concentrations (0.49, 1.44, 2.84, 5.52% w/w) in the LSM at surface tension $\gamma=20$ mNm⁻¹. (a) Number of hydrocortisone cluster formation over the time. (b) Number of normalised hydrocortisone cluster and the number of hydrocortisone molecules in the largest cluster are shown for different hydrocortisone concentrations. (c) The two-dimensional (2D) density map of the hydrocortisone to show the cluster formation on the monolayer at different hydrocortisone concentrations. The data was normalised using the number of drugs in the corresponding drug concentration with respect to the 0.49% w/w hydrocortisone concentration. 355

Figure 7.10A4 Schematic representation of the CG structure of (a) DPPC, (b) POPC, (c) POPG, (d) cholesterol, (e) surfactant protein B (SP-B₁₋₂₅) and (f) surfactant protein C (SP-C). 361

Figure 7.11A4 Free energy profile of hydrocortisone shifted from octanol to water phase. (a) Potential mean force (PMF) calculation at various simulation times for convergency test of the 362

calculation to get the reliable partition coefficient. (b) PMF curve of hydrocortisone transferred from octanol phase to water phase with uncertainties calculated using Bootstrapping analysis.

- Figure 7.12A4 Order parameter of DPPC (a, b), POPC (c, d) and POPG (e, 366
f) for *sn*-1 (a, c, e) and *sn*-2 (b, d, f) chains at different surface
tension (0, 10, 20, 30, 40 and 50 mNm⁻¹) in the presence of
5.52% w/w drug containing monolayers composed of DPPC-
POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C. Order parameters were
estimated for last one microsecond of the two microsecond
simulations. The error bars denote standard deviations across
the frames of the trajectories.
- Figure 7.13A4 Snapshots of simulation system at (a) APL=0.47 nm² (highly 367
compressed monolayer), (b) APL=0.55 nm² (intermediate
state, i.e., compressed-expanded monolayer) and (c)
APL=0.63 nm² (expanded monolayer) in the absence
hydrocortisone. Components are shown as DPPC (green),
POPC (blue), POPG (cyan), CHOL (red), SP-B₁₋₂₅(orange),
SP-C (yellow).
- Figure 7.14A4 Snapshots of simulation systems for monolayers at surface 368
tension $\gamma=20$ mNm⁻¹ in the presence of 10.46% w/w
hydrocortisone concentrations for the LSM monolayer
composed of DPPC-POPC-POPG-CHOL-SP-B₁₋₂₅-SP-C.
DPPC (green), POPC (blue), POPG (cyan), CHOL (red), SP-
B₁₋₂₅(orange), SP-C (yellow), hydrocortisone (purple), water
(silver), and phospholipids head groups (ochre).
-

List of tables

Table No.	Title	Page
Table 2.1	Various commercially available exogenous lung surfactant with their sources and composition.	45
Table 3.1	Representation of CG parameter for different sterol/corticosteroid drugs.	123
Table 4.1	Summary of the simulation system and APL of all the systems composed of DPPC-POPC (7:3) and DPPC-POPC-CHOL (7:3:1), with and without prednisolone drug molecules at surface tension 0 mNm^{-1} (exhalation), 10 mNm^{-1} (intermediate) and 20 mNm^{-1} (inhalation). APL values were calculated from the last $1 \mu\text{s}$ of the $2 \mu\text{s}$ production run of a given system. Uncertainties represent standard deviations of the APL data from two independent simulations for each case. The “*” sign refers to a statistically significant difference in APL compared to the cholesterol free monolayers at the same surface tension.	162
Table 4.2A1	Details information about the parameterisation of cholesterol and prednisolone CG model.	175
Table 4.3A1	Summary of the 54 simulation systems for LSM models composed of DPPC-POPC (7:3), DPPC-POPC-CHOL (7:3:1), DPPC-POPG-CHOL (7:3:1) and DPPC-POPC-POPG-CHOL (7:3:3:1) in the absence (System I, System II, System V and System VI) and presence of prednisolone (PRED) drug molecules (System III-a to III-e, System IV-a to IV-e, System V-a to V-b and System VI-a to VI-b). Each System is simulated at surface tension 0 and 20 mNm^{-1} . Systems III-a to III-e have also been simulated at surface tension of 10 mNm^{-1} . The systems at constant APL were carried out at NVT ensemble in the absence and presence of prednisolone (PRED) drug	178

molecules. Every simulation was carried out at least two repeated runs.

Table 4.4A1	Control system composition of monolayer simulation in the current study. Summary of the 2 simulation systems for LSM models composed of DPPC-POPC-CHOL (7:3:1) in the presence of CHOL instead of PRED (control system). Each System is simulated at surface tension 0 and 20 mNm ⁻¹ .	179
Table 4.5A1	Area per lipid (APL) of LSM components composed of DPPC-POPC-CHOL (7:3:1), DPPC-POPG-CHOL (7:3:1) and DPPC-POPC-POPG-CHOL (7:3:3:1) with a range of drug (prednisolone molecules) concentrations, at two different surface tensions referring to the exhalation and inhalation breathing cycles. APL values for the present study are calculated from the last 1 μs of the 2 μs simulations of a given system. Uncertainties represent the error calculation by using the standard deviation of at least two repeated runs of the simulation.	188
Table 4.6A1	Two-dimensional lateral diffusion coefficient of the cholesterol (D_{CHOL}) calculated from simulations of a DPPC-POPC-CHOL (7:3:1) LSM model at 0 mNm ⁻¹ and 20 mNm ⁻¹ . Diffusion coefficients were calculated using the Einstein diffusion equation. Errors are given as standard deviation calculated by using the block averaging method.	195
Table 5.1	Summary of the 94 simulation systems for LSM models composed of DPPC-POPC-POPG-CHOL (60:20:10:10) in the presence of surfactant proteins (SP-B and SP-C, 1:1) with a range of mometasone concentrations (0-12.69% w/w). Each system was simulated at different constant surface tensions (NPγT) and different fixed-APL (NVT). $N_{\text{mometasone}}$ denotes the number of mometasone molecules per monolayer. Each system was run in duplicate.	223

Table 5.2	Summary of the system (612 DPPC, 204 POPC, 100 POPG, 100 Cholesterol and 8 peptides (4 SP-B ₁₋₂₅ and 4 SP-C) per monolayer. The uncertainties were calculated using the standard deviation of the data. ‘*’ Indicates a statistically significant difference in APL compared to the absence of drug, at the same surface tension.	228
Table 5.3	Two-dimensional lateral diffusion coefficient (in units of D , $10^{-7} \text{ cm}^2\text{s}^{-1}$) of the monolayer components calculated from simulations of surfactant proteins (SP-B ₁₋₂₅ -SP-C=1:1) containing DPPC-POPC-POPG-CHOL (60:20:10:10) LSM monolayer model at 20 and 25 mNm ⁻¹ surface tension. Diffusion coefficients were calculated using the Einstein diffusion equation. Errors are calculated by using block averaging of the data.	234
Table 5.4	The number of drug cluster and the number of drug molecules in the largest cluster at various drug concentrations (0.60-12.69% w/w). The data was obtained from simulations of a monolayer composed of DPPC-POPC-POPG-CHOL-SP-B ₁₋₂₅ -SP-C (60:20:10:10:1:1). The uncertainties represent standard deviations. The data was calculated using the full 2 μs of the production run.	239
Table 5.5A2	Bead types of mometasone and prednisolone [43] MARTINI CG model.	243
Table 6.1	List of 48 simulation systems composed of DPPC-POPC-POPG-CHOL (60:20:10:10) in the absence and presence of surfactant proteins (SP-B ₁₋₂₅ and SP-C, 1:1) with a range of cortisone (CORT) concentrations (0 to ~10.5% w/w). Each system is simulated at surface tension 0 and 20 mNm ⁻¹ . $N_{\text{cortisone}}$ denotes the number of cortisone molecule. All systems were simulated for 2 μs production run in duplicate.	287

Table 6.2	Diffusion coefficient (D , 10^{-7} cm ² s ⁻¹) of the monolayer components calculated from simulations of surfactant protein containing LSM model at 20 mNm ⁻¹ . Diffusion coefficients were evaluated from the Einstein diffusion equation [67]. The diffusion coefficients were calculated from entire 2 μ s production run simulation. Errors represent standard deviations obtained from block averaging of the data.	295
Table 6.3A3	Detail information about the CG model of Cortisone.	304
Table 6.4A3	Partition coefficient (logP value) of different steroids drug molecules calculated from different ways.	308
Table 7.1	List of 136 simulation systems composed of DPPC-POPC-POPG-CHOL (60:20:10:10) in the presence of surfactant proteins (SP-B ₁₋₂₅ and SP-C, 1:1) with a range of hydrocortisone concentrations (0 to ~10.5% w/w). Each system is simulated at various constant surface tensions (NP γ T) and different fixed APL (NVT). $N_{\text{hydrocortisone}}$ denotes the number of cortisone molecule per leaflet of the monolayer. Each of all systems were simulated in two repeated runs.	338
Table 7.2	Diffusion coefficient (D , 10^{-7} cm ² s ⁻¹) of the LSM components estimated from LSM model at 20 mNm ⁻¹ . Diffusion coefficients were calculated from the Einstein diffusion equation. The diffusion coefficient was measured from entire 2 μ s production run simulation. Errors represent standard deviations obtained from block averaging of the data from 20 fs time step.	354
Table 7.3A4	Detailed information about the CG model for Hydrocortisone.	361
Table 7.4A4	Partition coefficient (logP value) of various corticosteroid drug molecules.	364

List of abbreviation and symbols

Abbreviation and symbols	Definition
AFM	Atomic Force Microscopy
APL	Area per Lipid
BAM	Brewster angle microscopy
BaP	Benzo[a]pyrene
BLES	Bovine lipid extract surfactant
CG	Coarse-Grained
CGMD	Coarse-Grained Molecular Dynamics
CHOL	Cholesterol
DPPC	Dipalmitoylphosphatidylcholine
DPPG	Dipalmitoylphosphatidylglycerol
DOPC	Dioleoylphosphatidylcholine
EPS	Exogenous pulmonary surfactant
FA	Fatty acids
HBD3	Human beta-defensin-3
LC	Liquid-Condensed
LE	Liquid-Expanded
LPC	Lysophosphatidylcholine
LS	Lung Surfactant
LSM	Lung Surfactant Monolayer
NP/NPs	Nanoparticle/Nanoparticles
NR	Neutron reflectometry
PC	Phosphatidylcholine
PE	Phosphatidyl-ethanolamine
PG	Phosphatidylglycerol
PL/PLs	Phospholipid/Phospholipids
PMF	Potential mean force
PM-IRRAS	Polarisation modulation-infrared reflection-absorption
POPC	Palmitoyl-oleoyl-phosphatidylcholine

POPE	Palmitoyl-oleoyl-glycero-phosphoethanolamine
POPG	Palmitoyl-oleoyl-phosphatidylglycerol
PI	Phosphatidylinositol
SM	Sphingomyelin
SP-A, SP-B, SP-C, SP-D	Surfactant Protein - A, B, C, D
SP-B ₁₋₂₅	Surfactant Peptide B residues (1-25)
SPH	Sphingomyelin
US	Umbrella sampling
VMD	Visual molecular dynamics
WHAM	Weighted histogram analysis method

Abstract

Glucocorticoids are used to treat a wide range of inflammatory conditions, including lung diseases such as asthma, respiratory allergies, chronic obstructive pulmonary disease, bronchitis, and emphysema. The use of glucocorticoids via oral, intravenous, or topical administration causes side effects by systemic pathway i.e., the drug enters the bloodstream. The lung airways are the most effective routes for corticosteroid drug administration by inhalation or nebulisation, both for the upper airways and the peripheral airways at alveoli, especially for drugs with low solubility in aqueous media and poor bioavailability by avoiding systemic side effects. The benefits of corticosteroid administration by inhalation over other modes of drug administration are corticosteroid delivery to the target area with relatively low systemic adsorption, avoiding side effects of the drug, and reducing drug wastage.

The lung surfactant monolayer (LSM) is the main barrier to drugs entering the lung. Understanding the molecular interaction of corticosteroid drugs with the LSM is critical for the effective dosing and delivery of existing drugs. The rational design of new corticosteroid drugs is to avoid damage to the LSM by the adsorption. However, the molecular-level mechanism of how drugs interact with the LSM is poorly understood. Part of that is a lack of a molecular-level model that mimics the physicochemical properties of the LSM. This study carried out biomolecular simulations to investigate the molecular interactions between LSM and several clinically relevant glucocorticoid drugs (prednisolone, mometasone, cortisone and hydrocortisone). Specifically, coarse-grained (CG) molecular dynamics (MD) simulations were carried out to understand the concentration-dependent interaction of the different corticosteroids under different

breathing conditions (inhalation and exhalation). The major components of the LSM, namely phospholipids, cholesterol, and the surfactant proteins B and C (SP-B and SP-C), were used to mimic the structural and dynamical properties of the LSM at the air/water interface. Based on these simulations, the effect of drug concentrations on the structural and dynamical properties and phase behaviour of the LSM were characterised. In addition to these, the role of individual components of lung surfactants on the diffusion of corticosteroid drugs over the LSM was studied. The effect of cholesterol and LSM associated surfactant proteins will also be examined. The outcomes from this study demonstrate that corticosteroid drug has a concentration-dependent effect on the structural and dynamical properties of LSM for a critical drug concentration ($\sim 5\text{-}6\%$ w/w), and structural damage of the LSM has been seen once the drug exceeds the critical concentration. The structural damage of LSM can also be found in the time exhalation breathing condition, i.e., at low surface tension ($< 5 \text{ mNm}^{-1}$). Surfactant protein and drug concentration both contribute to influence the LSM instability. Cholesterol has a major impact on controlling the LSM fluidity. Precise spreading of the drug over the LSM is found at higher surface tension. The findings will provide a better understanding of the interaction mechanism between corticosteroid drugs and lung surfactants, particularly how altering the spreading mechanism might be used to prevent monolayer collapse. The current PhD project will also provide guidelines for the future design of effective corticosteroid dosing to treat various lung diseases.