UTS UNIVERSITY OF TECHNOLOGY SYDNEY

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

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Certificate of original authorship

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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.

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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.

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Statement indicating the format of the thesis

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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.

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

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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
$SP\text{-}B_{1\text{-}25}$	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 (~5-6% 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 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.