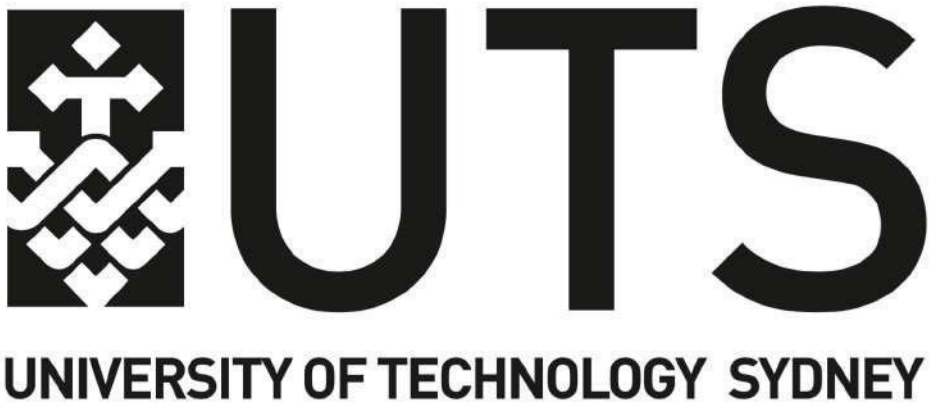

Drug delivery to the nose: formulation, deposition and permeation of poorly soluble drugs

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Pharmacy

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as part of the collaborative doctoral degree and/or fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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“I was just guessing at numbers and figures
“Pulling your puzzles apart
Questions of science; science and progress
Do not speak as loud as my heart”
-The Scientist by Coldplay-

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I dedicate this thesis to the past and to the future

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GLOSSARY AND ABBREVIATIONS

ABS	Acrylonitrile butadiene styrene
API	Active Pharmaceutical Ingredient
ALI	Air Liquid Interface
ATCC	American Type Culture Collection
Papp	Apparent permeability
BMP	Beclomethasone Monopropionate
BDP	Beclomethasone Dipropionate
BSA	Bovine Serum Albumin
BET	Brunauer–Emmett–Teller
Bud	Budesonide
$CaCO_3$	Calcium Carbonate
CI	Cascade Impactor
R2	Coefficient of determination
f1	Difference factor
DSC	Differential Scanning Calorimetry
DMSO	dimethyl sulfoxide
DVS	Dynamic Vapor Sorption
EC	Expansion Chamber - Glass Chamber
FBS	Foetal Bovine Serum
Tag	Glass Transition Temperature
HBSS	Hank's Buffer Salt Solution

HPLC	High Performances Liquid Chromatography
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropylmethyl cellulose
LCC	Liquid Cover Culture
Lyo	Lyophilized/ Freeze-dried
MEM	Minimum Essential Media
MC	Modified Chamber - Developed Apparatus
NGI	Next Generation Impactor/ Apparatus E
P-gap	P-Glycoprotein
PSD	Particle Size Distribution
PBS	Phosphate Buffer Saline
RGB	Red Green Blue
RH	Relative Humidity
SEM	Scanning Electron Microscopy
f2	Similarity factor
Flu-Na	Sodium Fluorescein
StDev	Standard Deviation
TGA	Thermogravimetric Analysis
TEER	Trans Epithelial Electric Resistance
FDA	United States of America Food and Drug Administration
Dv(X)	Volumetric diameter (percentage of population related to)
XRPD	X-Ray Powder Diffractometry
ZO-1	Zonula occludens-1

THESIS ABSTRACT

The nose, is a promising site to deliver drugs with low oral bioavailability and for treatment of conditions that require a rapid onset of action. It is the first option to treat localized diseases such as rhinitis but also it can be used as site to deliver drug systemically. In the future, the number of product administered through the nose it is expected to increase, as more drugs will require an effective route for drug absorption. Hence, while the current characterization of nasal product focus mainly on the physicochemical properties of spray formulations, the biopharmaceutical evaluation of new nasal drug delivery products and formulations will require robust and reliable pre-clinical *in vitro* models.

The first aim of this study was to develop an apparatus able to perform deposition and permeation of nasal formulation at the same time, mimicking so the *in vivo* process of drug administration.

The second aim was the application of this model to the characterization of commercial products and the development of novel formulations.

In particular, to provide a physiologically relevant surface and barrier for the deposition and permeation studies, the cell line RPMI 2650 was chosen in order to establish a model of the nasal mucosa. The model was obtained using the air-liquid interface culturing method, in which the upper surface of the cell is exposed to air after the seeding on cell culture insert. The model developed showed production of

mucus, expression of xenobiotic transporters similar to primary nasal cells and barrier properties matching those reported in literature for excised human nasal mucosa.

The deposition apparatus was produced via 3D printing starting from an expansion chamber proposed by FDA for the determination the aerodynamic particle size of nasal sprays with cascade impactors. The apparatus developed consists of a plastic chamber able to accommodate cell culture inserts on its internal surface. This allows the deposition of aerosolised particles directly onto the surface of the RPMI 2650 cells previously cultured on inserts. The apparatus was validated against FDA glass expansion chamber using three different commercial products: two suspensions and one powder. The powder has shown faster permeation rate across RPMI 2650 cells nasal mucosa model.

In conclusion, this work has developed, validated and tested an *in vitro* method to assess particles deposition and drug permeation in conditions similar to those occurring *in vivo* and which will be useful for the characterization and development of future nasal products.