

UNIVERSITI TEKNOLOGI MARA

**PULMONARY INHALATION PERFORMANCE
OF CHITOSAN NANOPARTICLES ADMIXED
WITH LACTOSE-POLY ETHYLENE GLYCOL
MICROPARTICLES**

NASSER AHMED MOHAMMED AL HAJJ

Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science

Faculty of Pharmacy

August 2016

ABSTRACT

Nanoparticles are characterized by poor pulmonary inhalation performance as they are exhalation prone, in addition to their tendency to form agglomeration due to large surface area to volume ratio thereby hindering their deep lung deposition. Coarse carriers commonly used in dry powder inhaler cannot be used to deliver nanoparticles to the lung. The nanoparticles will be attach strongly to them and deposit in the throat, or they will detach, enter the lung and be exhaled. This study aimed to develop a platform where the nanoparticles were distributed over the microparticles for pulmonary delivery of nanoparticulate system. The chitosan nanoparticles of varying size, size distribution, zeta potential, crystallinity, shape and surface roughness were prepared by spray drying technique through employing chitosan of different molecular weight, surfactants, and changing the parameters of processing conditions. The lactose-polyethylene glycol microparticles of different geometric size, aerodynamic size, size distribution, specific surface area, density, crystallinity, shape and surface roughness were prepared using the same technique with polyethylene glycol of varying molecular weights and the introduction of ethanol. The inhalation performance of chitosan nanoparticles was assessed by mean of andersen cascade impactor method as a function of the physicochemical properties of nanoparticles and microparticles using a blend of nano-to-microparticles weight ratio of 1:9. The inhaled fine particle fraction of the chitosan nanoparticles was dictated by their shape and z-potential. An increase in the sphericity and z-potential of the chitosan nanoparticles decreased their tendency to agglomerate and improved their dispersion and inhalation performance. The specific surface area of the lactose-polyethylene glycol microparticles had a significant influence on the aerosolization performance of the chitosan nanoparticles. An increase in the specific surface area of lactose-polyethylene glycol microparticles increased their capacity to accommodate more nanoparticles and decreased the chances of nanoparticles being deposited at deep lung as a result of increasing the mass of nanoparticles-loaded microparticles. The analysis of FTIR spectra of powder collected at each stage of the cascade impactor suggested that the attachment force between chitosan nanoparticles and lactose-polyethylene glycol microparticles was strong enough to survive for deep lung deposition. The chitosan nanoparticles were successfully delivered to the deep lung utilizing the lactose-polyethylene glycol microparticles in a coarse carrier-free dry powder system.

ACKNOWLEDGMENT

I would like to express my sincere gratitude to my supervisor Assoc. Prof. Dr. Wong Tin Wui who selflessly dedicates his time and knowledge to build his students' confidence, broaden their horizons, and shape their futures. I also would like to thank my co-supervisor Assoc. Prof. Dr. Fakhrol Ahsan, Texas Tech University Health Sciences Center, who provided invaluable outsiders perspectives on my research when most needed.

I thank my fellow laboratory mates in Non-Destructive Biomedical and Pharmaceutical Research Centre, iPROMISE and Faculty of Pharmacy, UiTM for the stimulating discussions and knowledge sharing. My thank goes to all staff and technicians at the Faculty of Pharmacy, UiTM whom precious supports are essential to succeed this research study.

TABLE OF CONTENTS

	Page
CONFIRMATION BY PANEL OF EXAMINERS	ii
AUTHOR'S DECLARATION	iii
ABSTRACT	iv
ACKNOWLEDGEMENT	v
TABLE OF CONTENTS	vi
LIST OF TABLES	x
LIST OF FIGURES	xi
LIST OF SYMBOLS	xiii
LIST OF ABBREVIATIONS	xvi
CHAPTER ONE: INTRODUCTION	1
1.1 Overview	1
1.2 Problem Statement	2
1.3 Objectives of Study	3
1.3.1 General Objective	3
1.3.2 Specific Objectives	3
1.4 Scope of Study	3
1.5 Significance of Study	4
CHAPTER TWO: LITERATURE REVIEW	5
2.1 Lung Morphology and Function	5
2.1.1 Conducting Zone	5
2.1.2 Respiratory Zone	7
2.1.3 Breathing Pattern	7
2.1.4 Lung Physiology	8
2.2 Pulmonary Drug Delivery Devices	9
2.2.1 Metered Dose Inhalers	9
2.2.2 Nebulizers	10
2.2.3 Dry Powder Inhalers	10

2.3	Dry Powder Inter-Particle Forces	12
2.3.1	Lifshitz - van der Waals Forces	12
2.3.2	Electrostatic Forces	13
2.3.3	Capillary Forces	14
2.3.4	Mechanical Interlocking	15
2.4	Factors Influencing Inter-Particle Forces	15
2.4.1	Size	15
2.4.2	Shape	16
2.4.3	Surface Roughness	17
2.4.4	Crystallinity	17
2.4.5	Surface Free Energy	17
2.4.6	Relative Humidity	18
2.5	Coating Microparticles by Nanoparticles	18
2.6	Powder Fluidization	19
2.6.1	Single Particle Fluidization	20
2.6.2	Bulk Powder Fluidization	20
2.7	Agglomeration and Deagglomeration	21
2.8	Deposition Mechanism of Inhaled Particles	22
2.8.1	Inertial Impaction	23
2.8.2	Sedimentation	23
2.8.3	Diffusion	24
2.8.4	Interception	25
2.8.5	Electrostatic Precipitation	25
2.9	Spray Drying	25
2.9.1	Feeding Liquid	26
2.9.2	Spray Drying Procedure	28
2.10	Lactose	29
2.10.1	Chemical Structure	29
2.10.2	Lactose as Dry Powder Inhaler Carrier	29
2.11	Chitosan	31
2.11.1	Physicochemical Properties	31
2.11.2	Biological Activity	32
2.11.3	Chitosan in Pulmonary Drug Delivery System	34
2.12	Nanoparticles as Drug Delivery System	34