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Candidate's declaration

I, **Mr. Sanjay Kumar Singh**, declare that I have pursued my research work under the supervision of **Prof. Sanjay Singh** from March 2011 to December 2016. I hereby supplicate my thesis entitled "**Asenapine Loaded Nanostructured Lipid Carriers for Intranasal Delivery**" for the award of Ph.D. degree.

Date: 31/12/2016

Place: IIT(BHU), Varanasi


(**Mr. Sanjay Kumar Singh**)



ANNEXURE - E

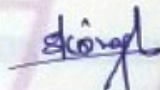
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I, **Sanjay Kumar Singh**, certify that the work embodied in this Ph.D. thesis is my own bonafide work carried out by me under the supervision of **Prof. Sanjay Singh** for a period of **5 years and 10 months** from **March 2011** to **December 2016** at **Department of Pharmaceutics, Indian Institute of Technology (Banaras Hindu University)**. The matter embodied in this Ph.D. thesis has not been submitted for the award of any other degree/diploma.

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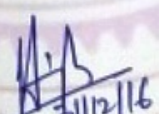
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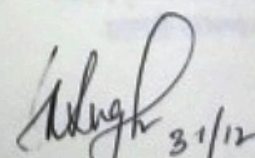
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Certificate from the Supervisor

This is to certify that the above statement made by the candidate is correct to the best of our knowledge.


Supervisor Signature
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Department of Pharmaceutics
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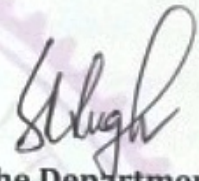
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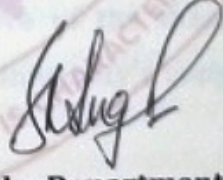
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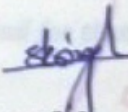
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ACKNOWLEDGEMENTS

First of all, I bow with reverence to thank 'Baba Vishwanath' who enriched me with such golden opportunity and infused the power in my mind to fulfill the task assigned to me.

At the outset, I would like to pay my tribute to the father and founder of the Banaras Hindu University, respected **Mahamana Pandit Madan Mohan Malaviya ji**, because of whom thousands of students put their step towards bright and prosperous future and receive a warm gesture wherever they go by the spirit of Bharat, BHU and Mahamana.

I welcome this opportunity to express my heartfelt gratitude and thankfulness to my admired supervisor, **Prof. Sanjay Singh (Guru ji)**. His inspiration and kind support helped me throughout the period of my research. I always remain indebted for his diligent efforts and professional competencies, which contributed for me to get matured towards the completion of the research work methodically. I feel very much honored and it has been a real privilege for me to get an opportunity to work under his guidance.

I am grateful to **Prof. S. K. Singh**, Head, **Prof. B. Mishra**, Former-Head, and **Prof. R. S. Srivastava**, Ex-Head, Department of Pharmaceutics, IIT (BHU) for allowing me to access the facilities in the Department for carrying out my research work and for their kind help during the course of my study.

I acknowledge my respected **Research Progress Committee (RPC)** members, **Mr. A. K. Srivastava**, DPGC Nomine, Department of Pharmaceutics, IIT (BHU), **Prof. B. Mishra**, Expert in the field from the Department and **Dr. Pradeep Srivastava**, External Subject Expert, School of Biochemical Engineering, IIT (BHU) Varanasi. It is my pleasure to thank all other teachers of the Department of Pharmaceutics, **Prof. S. K. Srivastava**, **Dr. (Mrs.) Hema Latha**, **Dr. Sairam Krishnanmurthy**, **Dr. A. Senthil Raja**, **Dr. Alakh N. Sahu**, **Dr. Ashok Kumar**, **Dr. S. K. Mishra**, **Dr. (Mrs.) Ruchi Chawla**, **Dr. M.S. Muthu**, **Dr. Prasanta Kumar Nayak** and **Dr. Gyan Prakash Modi** for their valuable suggestion and guidance throughout the course of my research.

I pay my sincere thanks to **Mr. Ram Jiyawan**, **Mr. Sanjeev Kumar Singh**, **Mr. Yaswant Singh**, **Ms. Shyamali Ghosal**, **Mr. Chhote Lal**, **Mr. Virendra Kumar**, **Mr. Nand Lal**, **Mr. Madan Lal**, **Mr. Ram Hriday Pathak**, **Mr. Akhila Nand Upadhyay**, **Mr. Arun Kumar**, **Ms. Archana Singh**, **Mr. Mohd. Jameel**, **Mr. Kapil Dev Rai**, **Mr. Prakhar Mishra**,

Mr. Sunil Kumar Singh, Mr. Gopal Prasad and all other non-teaching staff of the department who had provided me all the requirements that I needed for my research.

My heartfelt thanks to **Prof. Sitaram Velaga**, for his kind invitation to visit his lab at the Department of Health Sciences, Lulea University of Technology, Lulea, Sweden under STINT project which broadened my perspective of solid state pharmaceuticals and DSC/XRD study of my formulations.

I would like to convey my regards and thanks to **Dr. Shio Kumar Singh**, Ex-Head, Pharmacokinetics & Metabolism Division, CSIR-Central Drug Research Institute, Lucknow, for providing LC-MSMS facilities to carry out pharmacokinetic studies. I express my sincere thanks to **Dr. Krishna Pal Singh**, Associate Professor, Department of Zoology, University of Allahabad for assistance in protocol designing and guidance in embryo fetal toxicity studies.

I record my thanks to Department of Science and Technology (DST) and IIT (BHU) Varanasi for extending my financial support to attend International Conferences at San Francisco, United State of America.

Most importantly, I would like to put my heartiest warm regards and eminent indebtedness to my **Parents, Shri Krishna Kumar Singh and Smt. Urmila Singh** for their love, encouragement, moral support and blessings to reach this height in my journey of present existence. I would like to convey my gratitude to my respected elder brother **Mr. Arun Kumar Singh** who has been a constant source of inspiration. I owe him for showing great confidence on my abilities and encouraging me time to time. I am also very much grateful to **all my family members** for their constant inspiration, encouragement and love. This journey cannot be possible without their support. I have no words to express my innermost feelings for my loving wife **Vibha**, for her unconditional support and love. God has blessed me with a son, **Anshuman**, who missed me the first 6 months from his birth. I just forgot my worries while seeing his face after my busy academic and professional schedule.

I would like to express my special thanks and indebtedness to my most supportive seniors and lab mates, **Dr. Manoj Rawat, Dr. Achint Jain, Dr. Parameshwara Rao Vuddanda, Dr. Subhashis Chakraborty, Dr. Amit Mishra, Dr. Anuj Garg, Mr. Ramoji Kisuru, Hitesh, Krishna Kumar Patel, Laxmi, Meraj, Uddipak, Swati, Dr. Awaneesh Singh, Dr. Jyoti Wadhwa and Dr. Amritha Srivastava** who always helped me whenever I was in need. I express my hearty thanks to my batch mate **Vijaykumar M.R.** for being with me in entire duration of Ph.D., helped me a lot and provided moral support.

Contents

I extend my heartfelt gratitude and indebtedness to my beloved seniors from Department Dr. Rahul Thripati, Dr. Parbhat Shrivasta, Dr. Gireesh Kumar Singh, Dr. Satyendra K. Prasad, Dr. Saurabh Sinha, Dr. Damiki Laloo, Dr. Dileep Kumar, Mr. Anupam Banerjee, Mr. Piyush Sharma, Dr. Manish Kumar and all Research scholars of this department for their affection, love and help.

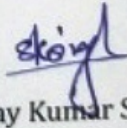
I would also like to thank my lab Master Degree students **Anand Kumar Kushwaha, Bhupender Singh, Patel Chitrang Girishbhai, Upadhyay Gayaprasad, Prabhjot Singh, Sarvesh Khoshla, Sandeep Kumar Mishra, Preethi Agrawal, Parth Dadhania, Yuraj Singh, Mahender Hidau, Babu Nageswararao, Santhosh Kumar Puttrevu, Durgesh Kumar, Priyadharshan Jain, Vijayakumar E, Raju Prasad Sharma, Ruchi Kumari Gupta, Ashit Kumar Sharma, Jagdeep Gaur Sandhu, Faruq Mohammed, Surbhi Soni, Nitin Verma, Tushar Batra, Nancy Kapoor and Neha Singh** for their support and help in lab hours.

Special thanks to my friends from IIT (BHU), **Gopal Kumar Rai, Nagendra Kumar, Anshul Shakya, Sandeep Chaurasia and juniors Gayasuddin Khan, Ravi Patel, Gufran** and many others for their moral support and encouragement during my Ph.D tenure.

I pray to almighty for the 'Moksha' of my experimental animals, whose sacrifices proved the truth of my thesis work done for the betterment of the ailing humanity.

Date: 31/12/2016

Place: Varanasi



(Sanjay Kumar Singh)

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List of Abbreviations and Symbols

ACN	:	Acetonitrile
AEs	:	Adverse Effects
AFM	:	Atomic Force Microscopy
ANOVA	:	Analysis of Variance
ANLC	:	Asenapine Loaded Nanostructured Lipid Carriers
ASM	:	Asenapine Maleate
AUC	:	Area Under Curve
BBB	:	Blood Brain Barrier
BBD	:	Box-Behnken Design
BCS	:	Biopharmaceutical Classification System
BR	:	Bromocriptine
CDSCO	:	Central Drugs Standard Control Organization
CNS	:	Central Nervous System
CSF	:	Cerebro Spinal Fluid
CF	:	Charles Foster
CH-NLC	:	Chitosan Coated Nanostructured Lipid Carrier
CH-NPs	:	Chitosan Nanoparticles
CE	:	Collision Energies
CLSM	:	Confocal Laser Scanning Microscopy
CMA	:	Critical Material Attribute
CPP	:	Critical Process Parameters

CQA	:	Critical Quality Attribute
C _{max}	:	Maximum Concentration
DP	:	Declustering Potential
DSC	:	Differential Scanning Calorimetry
DTE	:	Drug Targeting Efficiency
DMEM	:	Dulbecco's Modified Eagle Medium
DLS	:	Dynamic Light Scattering
EP	:	Entrance Potential
EE	:	Entrapment Efficiency
EPS	:	Extrapyramidal Side Effects
FBS	:	Fetal Bovine Serum
FDA	:	Food And Drug Administration
FRT	:	Forelimb Retraction Time
FT-IR	:	Fourier Transform Infrared Spectroscopy
GC	:	Glycol Chitosan
GC-NLC	:	Glycol Chitosan Coated Asenapine Loaded Nanostructured Lipid Carriers
GMS	:	Glyceryl Monostearate
HDL	:	High-Density Lipoprotein
HPLC	:	High Performance Liquid Chromatography
HRT	:	Hindlimb Retraction Time
HS	:	Homogenization Speed
IS	:	Internal Standard

i.n	:	Intra Nasal
i.v	:	Intra Venous
LOD	:	Limit Of Detection
LOQ	:	Limit Of Quantification
LC-MS/MS	:	Liquid Chromatography-Mass Spectroscopy
LDL	:	Low-Density Lipoprotein
MRHD	:	Maximum Recommended Human Dose
MRT	:	Mean Residence Time
NLC	:	Nanostructutred Lipid Carrier
OA	:	Oleic Acid
P-gp	:	P-glycoprotein
PS	:	Particle Size
%CV	:	Percent Coefficient of Variation
PBS	:	Phosphate Buffer Saline
PDA	:	Photodiode Array
PCS	:	Photon Correlation Spectroscopy
PDI	:	Poly Dispersity Index
QBD	:	Quality by Design
QC	:	Quality Control
QTTP	:	Quality Target Product Profile
RSD	:	Relative Standard Deviation
RSM	:	Response Surface Methodology
RT	:	Retention Time

SEM	:	Scanning Electron Microscopy
SGA	:	Second Generation Antipsychotic
S/N	:	Signal to Noise
SLN	:	Solid Lipid Nanoparticle
ST	:	Sonication Time
SD	:	Standard Deviation
TEM	:	Transmission Electron Microscopy
UV	:	Ultra Violet
US-FDA	:	United States Food and Drug Administration
WHO	:	World Health Organization
XRD	:	X-Ray Diffraction

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	±	: Plus minus	
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	µM	: Micromolar	
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	R ²	: Correlation Coefficient	
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Preface

In recent decade, central nervous system (CNS) disorders have been increasing enormously. In CNS disorders, schizophrenia is severe chronic debilitating psychological disease affecting approximately 1-2% of the world population. Asenapine maleate (ASM) is a newer antipsychotic drug. It is slightly soluble in water and classified as BCS class II drug. It is the first antipsychotic drug to be administered through a sublingual route of administration. The bioavailability of ASM is around 35% by sublingual route while it is <2% via oral route due to its high gastro-hepatic metabolism. The limiting factors with current dosage forms of ASM such as low bioavailability, drinking and eating restriction, twice a day dosing regimen and extra pyramidal side effect are still a very challenging task for pharmaceutical researchers. In the present work, nanostructured lipid carriers formulations with and without glycol chitosan coated were prepared which have improved brain availability and sustainability. The intranasal route for the delivery of nanocarriers was explored here for better targetability to brain. Formulations were prepared by quality by design (QbD) approach using Box-Behnken design. Both uncoated and coated formulations were characterized by *in-vitro* and *in-vivo* methods. The coated nanostructured lipid carriers (GC-ANLC) clearly demonstrated the superior pharmacokinetic and safety profile for better treatment of schizophrenia in rats. Data suggest that GC-ANLC via intranasal route is an efficient delivery route for targeting the brain with increase in bioavailability with corresponding decrease in dose and dosage frequency.
