Dedicated to my Beloved Family

CERTIFICATE

It is certified that the work contained in the thesis titled **"CONTROL DRUG DELIVERY USING CYCLODEXTRIN GRAFT FOR EFFECTIVE TUMOR TREATMENT"** by ***"APARNA SHUKLA"*** has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive, Candidacy and SOTA for the award of Ph.D. degree.

Date:

Place: Varanasi

Prof. Pralay. Maiti
(Supervisor)

DECLARATION BY THE CANDIDATE

I, ***APARNA SHUKLA***, certify that the work embodied in this Ph.D. thesis is my own bonafide work carried out by me under the supervision of **Prof. PRALAY MAITI** for a period from **July 2014** to **June 2019** at the **SCHOOL OF MATERIALS SCIENCE AND TECHNOLOGY**, Indian Institute of Technology (Banaras Hindu University), Varanasi, India. The matter embodied in this Ph.D. thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, *etc*., reported in journals, books, magazines, reports dissertations, thesis, *etc*., or available at websites and have not included them in this thesis and have not cited as my own work.

Date……

Place: Varanasi (Aparna Shukla)

CERTIFICATE BY THE SUPERVISOR

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

Prof. Pralay Maiti

Supervisor **Coordinator**

COPYRIGHT TRANSFER CERTIFICATE

Title of the Thesis: "Control Drug Delivery Using Cyclodextrin Graft for Effective Tumor Treatment"

Candidate's Name: Ms. Aparna Shukla

Copyright Transfer

The undersigned hereby assigns to the Indian Institute of Technology (Banaras Hindu University), Varanasi all rights under copyright that may exist in and for the above thesis submitted for the award of the *Doctor of Philosophy*.

Date:

Place: Varanasi (Aparna Shukla)

Note: However, the author may reproduce or authorize others to reproduce materials extracted verbatim from the thesis or derivative of the thesis for author's personal use provided that the source and the Institute's copyright notice is indicated.

Acknowledgements

At this moment of retrospection, it gives me immense pleasure to acknowledge the persons who have me directly or indirectly during the course of my work and stay in IIT (BHU) To express my heartfelt gratitude is not only my moral duty but I consider it an act of pleasure and humility as well.

First and Foremost, I wish to express my sincere gratitude to my supervisor, **Prof. Pralay Maiti,** for his trust, nice guidance, faithful support and valuable suggestions throughout my Ph.D. work. His constant monitoring and interest in my work will always remain as a happy memory. His patient and enthusiastic approach for my training can not be expressed in words and I will always remain thankful to him.

I have spent almost five years in the School of Materials Science and Technology, IIT (BHU), Varanasi. During this period, I have experienced lot of things which will not only help me in further research carrier but also in real life. I feel proud to be a part of this school. I would like to thank all the respected teachers of the school, Prof. Dhananjay Pandey, Prof. Rajiv Prakash, Dr. Chandanan Rath, Dr. Akhilesh Kr. Singh, Dr. Chandan Upadhyay, Dr. Bholanath Pal, Dr. Ashish Kumar Mishra, Dr. Shrawan Mishra, Dr. Sanjay Singh for their valuable suggestions and encouragement during research work.

I would like to thank Prof. Nira Misra, School of Biomedical Engineering, IIT (BHU) for providing different instrumental facility. I would like to acknowledge Prof. Biswajit Ray, Institute of Science, BHU for GPC and DSC measurement. I am thankful to Dr. Vinod K Aswal, BARC, Mumbai for Small Angle Neutron Scattering measurement.

Finally, I wish to thank all the labmates like Dr. Dinesh kumar Patel, Dr. Akhand Pratap Singh, Mr. Arun Kumar Mahanta, Dr. Sudipta Senapati, Dr. Arpan Biwas, Ms. Anupama Gaur, Ms. Dipti Saxena, Mr. Sunil Kumar, Mr. Om Prakash, Mr.

Ravi Prakash, Mr. Shivam Tiwari, Mr. Pravesh Kumar Yadav, Manisha Karelia and Mr. Sulob Roy Chowdhury for nice cooperation and enjoyable company. I am also thankful to Mr. Balavigneswaran Karthikeyan for their valuable suggestions during the work.

I am extremely thankful to my friend and family members Anand Sharma, Shivendra Shukla and Richa Shukla for their support, cooperation and sincere help in many ways as well as for making my stay here enjoyable and for their time to time encouragement during my bad situations.

It fills me with a deep sense of reverence when I think about my family. Their constant encouragement, moral support and cooperation at every step of my life can't be expressed in words. I am thankful for their love and blessings.

Finally, I bow with reverence and gratitude to thank the Almighty **MAHADEV** who has enriched me with such an excellent opportunity and infused the power in my mind to fulfill the work assigned to me.

Date:

Place: Varanasi (Aparna Shukla)

Contents

Table of Figure

List of Table

List of Schemes

Abbreviations

CRS	Control release systems
3D	Three dimensional
PEG	Poly ethylene glycol
PTX	Paclitaxel
DOX	Doxorubicin
i.v	Intravenous
HEMA	Hydroxyl ethyl-meth acrylate
MBA	N,N′-methylene bis(acrylamide)
HA	Hyaluronan
CD	Cyclodextrin
CPT	Camptothecin
ATRP	Atom transfer radical polymerisation
RAFT	Reversible addition fragmentation transfer
CMC	Carboxymethyl cellulose
HEC	Hydroxyl ethyl cellulose
HCPT	Hydroxycamptothecin
TP	Tea polyphenols
G	Guanine
C	Cytosine
h	Hour
t	Time
T	Temperature

^{o}C	Degree Celcius
σ	Stress
ε	Strain

Preface

Chemotherapy is the conventional mode of cancer treatment where the repeated doses of drugs are given to the patient, which impose severe side effects like nausea, hair fall, loss of appetite and liver damage. For most of the times the concentration of drug is either above the therapeutic level or below the required level. Fluctuations in drug concentration in blood stream results in adverse effects and treatment becomes expensive. To address these challenges controlled drug delivery devices came into existence where, there is efficient utilization of drug, desired extended duration, with very low chances of toxicity, facilitating enhanced complication of patient, leading to better management of therapeutics. The efficacious use of drug influences cost factor and economy of therapy too. In general the control drug release system is an entity that delivers the drug at specific site at predetermined rate for prolonged period of time. Polymers are widely used as drug carriers due to their versatile range of hydrophilic and hydrophobic components and their polymer-polymer, polymer-drug, and polymer solvent interactions. Their fabrication is done in such a way that they regulate the entry of drug within body and release them continuously in planned pattern for a particular duration of time, either systematically or to a targeted site. Materials required for control release system (CRS) must be biomaterial, among these are biocompatibility, processibility and sufficient mechanical strength. Polymer based drug delivery systems has enormous impact in therapies, where the drug is entrapped in the polymer matrix and then can be injected or implanted in the body. Both naturally occurring and synthetic polymers have been explored to design drug delivery systems, however naturally occurring biopolymers are preferred due to their inherent non toxic, biodegradable and biocompatiblility and low cost.

Here in we have focused on the preparation of Cyclodextrin based drug delivery systems. Cyclodextrins are a group of cyclic oligosaccharides, containing six (α–CD), seven (β–CD), eight (γ–CD), or more (α-1,4-)-linked D-glucopyranose units, consist of a relatively hydrophobic inner cavity and a hydrophilic outer face. Functionalization of exterior hydroxyl groups with hydrophobic components yielding different functionalized polymers. This thesis presents synthesis of different architectures with varying graft density and chain length through chemical modification of cyclodextrin/dextrin with polyurethanes, characterization and their application in controlled drug delivery. In this thesis graft copolymers with different degree of substitution and graft length have been prepared to obtain polymers with better thermal and mechanical properties as compared to pristine polymers. Due to grafting controlled drug release has been observed along with improved biocompatibility in developed copolymers. Further these polymeric architectures have been utilized in different formulation for cancer treatment.

This thesis has been bind up with following outlines: introduction and literature review, results and discussion, and conclusion. List of journals used to bind up this thesis has been given at the end of the thesis as references.