

Radiation Synthesis and Characterization of Some Functionalized Polymers for Possible Uses

Thesis submitted by **Nehad Ahmed Ahmed Mohmmed Ahmed**

Assistant Lecture
National Center for Radiation Research and Technology
Atomic Energy Authority, Cairo, Egypt

For The Degree of Doctor of Philosophy in Chemistry (Organic Chemistry)

Thesis supervisors

Prof. Dr. Al-Sayed A. Soliman

Prof. of Organic Chemistry Faculty of Science, Ain Shams Univesity Prof. Dr. El-Sayed A. Hegazy

Prof. of Radiation Chemistry, National Center for Radiation Research and Technology

Prof. Dr. Hassan A. Abd El Rehim

Prof. of Radiation Chemistry, National Center for Radiation Research and Technology Prof. Dr. Amr El-Hag Ali Sayed

Prof. of Radiation Chemistry, National Center for Radiation Research and Technology



Acknowledgment

I would like to express my deep gratitude and thanks to *Prof. Dr. Al-Sayed A. Soliman*, Faculty of Science, Ain Shams University, for his interest, and deep concern in this work.

Deepest thanks and sincere gratitude to *Prof. Dr. El-Sayed A. Hegazy*, Prof. of Radiation Chemistry, ex-Chairman, National Center for Radiation Research and Technology (NCRRT), for suggesting, planning the point of research, his eminent supervision and valuable discussions. Also, for his encouragement and support throughout this work.

Great thanks and gratitude due to *Prof. Dr. Hassan A. Abd El-Rehim*, Prof. of Radiation Chemistry, Vice Chairman, Egyptian Atomic Energy Authority, for his eminent supervision, discussions and guidance.

I offer my sincerest gratitude to my supervisor, *Prof. Dr. Amr El-Hag Ali Sayed*, National Center for Radiation Research and Technology, who for his continuous guidance, honest assistance interest, wise guidance, kind supervision and continuous encouragement throughout this work.

I would like to offer my deep thanks to *Assoc. Prof. Dr. Amany Ismail Arafat* Assoc. Prof. of Radiation Chemistry, National Center for Radiation Research and Technology for her supervision encouragement and support throughout this work. Also for her honest assistance to have this work done.

Many thanks are due to all colleagues and staff members of Polymer Chemistry Department, National Center for Radiation Research and Technology (NCRRT) for their help and facilities provided throughout this work.

"I would like to give big thanks for my mother, dear husband my life partner, my sisters and all my family members for their endless support and care

Special thanks to my sons.

There is no enough words to express my gratitude to all of you"

Thank you.....

Table of content

List of Figures List of Tables Aim of work

Chapter I Introduction

| Biomaterials | 1 |
|---|-----|
| Ceramics | 1 |
| Metals | 1 |
| Polymers | 2 3 |
| Hydrogels | 3 |
| Classification of hydrogels | 3 |
| Synthesis of Hydrogels | 4 |
| A-Hydrogel Synthesis by Physical Crosslinking | 4 |
| B- Hydrogel synthesis by chemical crosslinking | 5 |
| Radiation synthesis of hydrogels | 6 |
| Characteristic properties of polymeric hydrogel | 8 |
| Swelling properties | 8 |
| Mechanical properties | 8 |
| Biocompatible properties | 9 |
| Applications of hydrogels | 9 |
| Hydrogel as drug delivery system | 10 |
| Mucoadhesive drug delivery system | 10 |
| Mucoadhesion | 11 |
| Mucus layer | 11 |
| Oral mucosa | 12 |
| Polymeric materials to be used as mucoadhesives | 14 |
| Mechanism of mucoadhesion | 15 |
| Sites for Mucoadhesive Drug Delivery Systems | 16 |
| Buccal Drug Delivery System | 16 |
| Biomaterials in Tissue Engineering | 18 |
| Roles of Biomaterials in Tissue Engineering | 19 |
| Characteristics of successful scaffold | |
| Types of scaffold | 19 |
| Hydrogel Scaffold | 22 |
| Chapter II | |
| Literature Review | |
| Biomaterials | 23 |
| Hydrogel smart materials for drug delivery | 43 |
| Mucoadhesive Copolymer Hydrogel for Buccal Delivery | 51 |

Ĺ

| Chapter III | |
|--|-----|
| Materials and Experimental Techniques | |
| Materials | 79 |
| Experimental Techniques | |
| Preparation of Dextran/PAAc hydrogels | 79 |
| Preparation of NOCMCs /PVA/ PHEMA terpolymer hydrogels | 79 |
| Synthesis of N,O-Carboxymethyl Chitosan | 79 |
| Determination of degree of substitution | 81 |
| Preparation of NOCMCs /PVA/ PHEMA terpolymer hydrogels | 82 |
| Determination of Gelation | 82 |
| Determination of Swelling | 83 |
| FT-IR spectroscopy measurement | 83 |
| Ultraviolet (UV) measurements | 83 |
| Preparation of drug-Loaded Hydrogels and drug release | 84 |
| Microscopic Observation | 84 |
| Thermogravimetric Analysis (TGA) | 84 |
| Evaluation of (Dextran/PAAc) copolymer hydrogels as a | 84 |
| mucoadhesive for drug release | |
| In vitro evaluation of mucoadhesion Strength | 84 |
| Surface pH determination | 86 |
| Residence time determination | 86 |
| Sterilization of scaffold | 87 |
| Propagation of CaCo cell line by enzyme treatment and MTT test | 87 |
| Chapter IV | |
| Results and Discussion | |
| Radiation synthesis of Dextran/Acrylic acid copolymer hydrogel | 89 |
| | 0) |
| as mucoadhesive drug carrier for buccal delivery system. Radiation Synthesis of (Dextran/PAAc) Copolymer Hydrogel | 90 |
| using Gamma irradiation. | 90 |
| | 02 |
| Optimizing the preparation conditions of (Dextran/PAAc) | 92 |
| copolymer hydrogels. | 0.2 |
| Effect of total Feed solution concentration and composition and | 93 |
| irradiation does on gelation. | 0.5 |
| Fourier Transforms Infrared Spectroscopy. | 95 |
| Swelling behavior of (Dextran/PAAc) copolymer hydrogels. | 97 |
| 1-Time dependent swelling. | 97 |
| 2- Effect of ionic strength on the equilibrium swelling of | 99 |
| Dextran/PAAc). | |

| 3- pH dependent swelling of (Dextran/PAAc) copolymer hydrogels. | 100 |
|---|------------|
| Thermogravimetric Analysis (TGA). | 102 |
| Surface Topography of Dextran/PAAc Copolymer hydrogel. | 102 |
| Evaluation of the potential applicability of the prepared | 104 |
| (Dextran/PAAc) copolymer hydrogel as mucoadhesive carrier for | 100 |
| buccal drug delivery. | |
| Mucoadhesion Strength. | 106 |
| Residence time evaluation. | 108 |
| Surface pH evaluation. | 108 |
| Swelling in Saliva. | 1109 |
| Swelling kinetics. | 110 |
| Buccal drug delivery Evaluation. | 116 |
| B. Radiation synthesis of (N, O-carboxymethyl chitosan/poly | 121 |
| vinylalcohol/2-hydroxyethyl methacrylate) terpolymer | 121 |
| hydrogels for possible use in the field of tissue engineering. | |
| Synthesis of N, O-carboxymethylchitosan. | 122 |
| Characterization of the prepared N, O-carboxymethyl-chitosan. | 124 |
| Quantitative determination of carboxymethylation degree. | 124 |
| Structural characterization of the prepared N, O- carboxymethyl | 124 |
| chitosan. | 123 |
| FTIR. | 125 |
| XRD. | 126 |
| Thermal stability analysis. | 127 |
| Synthesis of (N, O-carboxymethylchitosan/poly vinyl alcohol/2- | 127 |
| hydroxyethyl methacrylate) terpolymer hydrogels. | 129 |
| Optimization of the preparation conditions: | 129 |
| Degree of gelation. | 129 |
| Characterization of NOCMCs /PVA/HEMA terpolymer | 131 |
| Hydrogels. | 131 |
| Investigating the swelling characteristic. | 131 |
| pH dependent swelling of (NOCMCs /PVA/PHEMA) Terpolymer | 134 |
| Hydrogels of Different Compositions. | 134 |
| Structure Topographical study of NOCMCs/PVA/PHEMA | 137 |
| terpolymer hydrogel. | 137 |
| Uses of NOCMCs /PVA/PHEMA prepared hydrogel as scaffold | 139 |
| | 139 |
| for tissue engineer. Call culture of the Prepared NOCMCs/DVA/DHEMA Hydrogal | 1.40 |
| Cell culture of the Prepared NOCMCs/PVA/PHEMA Hydrogel. MTT determination of results. | 140 140 |
| Microscopic observation of cell morphology. | 140 |
| References. | 141 |
| References. | 1+3 |

| Summery | and conclusion. |
|---------|-----------------|
| Summery | in Arabic. |

159

List of Figures

| Figure (1): | The oral cavity structure. | 13 |
|--------------|--|-----|
| Figure (2): | Schematic diagram of buccal mucosa. | 14 |
| Figure (3): | Mechanistic approach of mucoadhesion. | 16 |
| Figure (4): | 11 | 18 |
| | engineering approach based on the introduction of a | |
| | scaffold. | |
| Figure (5): | | 21 |
| rigare (3). | engineering. | 21 |
| Figure (6): | | 85 |
| Figure (7): | ± • • | 91 |
| 1 15010 (7). | reactant. | 71 |
| Figure (8): | Schematic diagram represents the possibilities of free | 92 |
| | radical combination and hydrogel formation. | |
| Figure (9): | • • | 94 |
| 8 | on their gelation degree. | |
| Figure (10 | | 95 |
| 8 | gelation degree of (Dextran/PAAc) prepared at different | |
| | at different AAc content. | |
| Figure (11 | | 96 |
| 1 -50-10 (11 | hydrogel and (c) polyacylic. | , 0 |
| Figure (12 | | 98 |
| • | copolymers hydrogels of different AAc content. | |
| Figure (13 | | 100 |
| υ . | (Dextran/PAAc) copolymer hydrogel of different PAAc | |
| | content. | |
| Figure (14 |): pH dependent swelling of (Dextran/PAAc) copolymer | 101 |
| 8 (| hydrogels of different PAAc content. | |
| Figure (15 | • • | 103 |
| 1 18010 (10 | of different PAAc content. | 100 |
| Figure (16 | | 104 |
| 6 (| copolymer hydrogels of different acrylic acid content. | |
| Figure (17 | | 105 |
| 1 18010 (17 | swollen in artificial saliva solution, prepared at different | 100 |
| | PAAc content. | |
| Figure (18 | | 107 |
| 1 15010 (10 | prepared copolymer hydrogel to mucos membrane. | 107 |
| Figure (19 | · · · · · | 110 |
| 115000 (1) | hydrogel in saliva solution at different PAAc content in | 110 |
| | artificial. | |
| | ur une rat. | |

| Figure (20): | Kinetic curve of (Dextran/PAAc) hydrogels in artificial saliva at different PAAc contents. | 113 |
|--------------|---|-----|
| Figure (21) | t ^{1/2} vs swelling kinetic curves of (a) (Dextran/PAAc) hydrogels in artificial saliva at different PAAc contents. | 114 |
| Figure (22): | Time dependent swelling of Dextran/PAAc copolymers hydrogel placed on richly saliva wet sponge at different PAAc content. | 116 |
| Figure (23): | Time dependent release profile of Propranolol HCl from Dextran/PAAc copolymer hydrogels of different PAAc content. | 117 |
| Figure (24): | Time dependent release profile of Cefadroxil from Dextran/PAAc copolymer hydrogels of different PAAc content. | 118 |
| Figure (25): | Time dependent release profile of Trifluoperazine from Dextran/PAAc copolymer hydrogels of different PAAc content. | 119 |
| Figure (26): | Effect of PAAc content on the cumulative release profile of (Dextran/PAAc) copolymer hydrogels in saliva using different therapeutic agents. | 120 |
| Figure (27): | Schematic diagram represents the chemical conversion of chitosan into N, O- carboxymethylchitosan. | 123 |
| Figure (28): | Potentiometric determination of the carboxymethylation degree of the prepared carboxymethyl chitosan. | 124 |
| Figure (29): | FTIR spectrum of (a) pure chitosan, (b) NOCMCs. | 125 |
| Figure (30): | X-ray diffraction patterns of (a) chitosan and (b) carboxymethylchitosan. | 127 |
| Figure (31): | TGA traces of (a) Chitosan and (b) N, O-Carboxymethyl chitosan. | 128 |
| Figure (32): | Effect of total exposure dose on produced gel fraction of the (NOCMCs /PVA/PHEMA) terpolymer hydrogels prepared at different total feed solution concentration. | 130 |
| Figure (33): | Effect of NOCMCs content on the gel fraction of (NOCMCs/PVA/PHEMA) terpolymer hydrogel. | 131 |
| Figure (34): | Time dependent swelling of NOCMCs/PVA/PHEMA terpolymer as a function of total feed solution concentration. | 132 |
| Figure (35): | Time dependent swelling of NOCMCs /PVA/PHEMA terpolymer of prepared at different NOCMCs concentration. | 133 |
| Figure (36): | | 135 |
| Figure (37): | | 136 |

| | content in aqueous HCl/NaOH solutions. | |
|--------------|--|-----|
| Figure (38): | SEM micrograph of NOCMCs/PVA/PHEMA terpolymer | 138 |
| | hydrogel swollen at different pHs. | |
| Figure (39): | SEM micrograph of NOCMCs/PVA/PHEMA terpolymer | 139 |
| | hydrogel swollen at pH 7.2 and prepare using different | |
| | irradiations doses. | |
| Figure (40): | Effect of irradiation dose used in the preparation of | 141 |
| | NOCMCs/PVA/PHEMA terpolymer on the viability of | |
| | CaCo cells as a function of time. | |
| Figure (41): | Optical microscopic observation of the control sample; | 142 |
| | cultured in a glass surface without scaffold. | |
| Figure (42): | Optical microscopic observation of the 3day cultured | 142 |
| | CaCo cells in NOCMCs/PVA/PHEMA terpolymer | |
| | prepared at 20 kGy; (a) on the hydrogel, (b) under the | |
| | hydrogel. | |
| Figure (43): | Optical microscopic observation of the 3day cultured | 143 |
| | CaCo cells in NOCMCs/PVA/PHEMA terpolymer | |
| | prepared at 30 kGy; (a) on the hydrogel, (b) under the | |
| | hydrogel. | |
| Figure (44): | Optical microscopic observation of the 3day cultured | 143 |
| | CaCo cells in NOCMCs/PVA/PHEMA terpolymer | |
| | prepared at (a) 40 kGy and (b) 50 kGy | |

List of Tables

| Table (1): | Chemical structure of the employed materials. | 80 |
|------------|--|-----|
| Table (2): | Chemical constituents and formulation of saliva | 81 |
| | solution. | |
| Table (3): | Effect of PAAc content on the residence time of the | 108 |
| | prepared Dextran/PAAc copolymer hydrogel to | |
| | mucos membrane. The hydrogels prepare at total | |
| | concentration 40%. Irradiation does; 30 kGy using | |
| | distilled water as a solvent. | |
| Table (4): | Effect of PAAc content on the surface pH of the | 109 |
| | prepared copolymer hydrogel in artificial saliva | |
| | solution. The hydrogels prepare at total concentration | |
| | 40%. Irradiation does; 30 kGy. | |
| Table(5): | Diffusion parameters of (Dextran/PAAc) copolymer | 115 |
| | hydrogel of different compositions in artificial saliva. | |