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PREPARATION, CHARACTERIZATION AND *IN-VITRO* EVALUATION OF CHITOSAN-BASED SMART HYDROGELS FOR CONTROLLED DRUG RELEASE

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Abstract

Controlled drug release enhances the safety, efficacy and reliability of drug therapy. Regulation of the drug release rate results in a reduction in the frequency of drug administration and should encourage patients to comply with dosing instructions.

Hydrogels are crosslinked, three-dimensional hydrophilic polymers, which swell without dissolving when brought into contact with water or other biological fluids. The number of polymers suitable for the controlled release of viable therapeutics is quite limited because of inherent toxicity or lack of certain properties such as biodegradability. In this thesis, chitosan was chosen as the base polymer for the development of new hydrogels that can be tailored for use in the site-specific delivery of drugs to the gastrointestinal tract. Chitosan is a non-toxic and biodegradable polymer obtained through the alkaline deacetylation of natural chitin. The interesting characteristics of chitosan make it an ideal candidate for use in controlled drug release formulations. However, chitosan exhibits some shortcomings such as hydrophobicity and a high pH-dependency for its physical properties. Hence, it is very difficult to control drug release with chitosan itself because of the various pH values of the internal organs of the human body. This may negatively affect the human body because of drug under- or over-release.

In a structured programme, some new chitosan-based hydrogels have been prepared for controlled drug release investigations by applying three main approaches to overcome the shortcomings of chitosan. The first approach was the incorporation of chitosan into interpenetrating polymer network hydrogels with either a hydrophilic polymer or with hydrophilic monomers treated to bring about in situ copolymerization in the presence of chitosan and a suitable crosslinking agent. The second approach was the chemical modification of chitosan by grafting of a suitable vinyl macromer such as poly(ethylene glycol)-diacrylate, then crosslinking this modified chitosan. The equilibrium swelling studies were carried out for the hydrogels prepared using these two approaches at 37 °C at pH 2.1 (simulated gastric fluid, ***SGF***) and at pH 7.4 (simulated intestinal fluid, ***SIF***). The swelling results showed a pH-responsive nature of these hydrogels. They attained higher swelling values in ***SGF*** than in ***SIF***. 5-Fluorouracil (***5-FU***), an anti cancer drug,

was entrapped as a model drug in all the hydrogels prepared using these two approaches. The *in-vitro* drug release studies were carried out at 37 °C in ***SGF*** and ***SIF***. From the preliminary investigations of the prepared hydrogels, they may be customized and used to expand the utilization of these systems in drug delivery applications.

In the third approach, chitosan was modified in such a fashion that the hydrogels produced were also pH-responsive but attained limited swelling in ***SGF*** and higher swelling in ***SIF***. Hence, the resulting hydrogels could be tailored for utilization for intestine–targeted delivery of peptide and protein drugs with a potential protection of the drugs from the harsh acidity of the stomach. In this third approach the ionotropic gelation was used for the preparation of the hydrogels based on the modified chitosan with another natural polymer (sodium alginate) in the presence of a divalent ion. Bovine serum albumin (***BSA***) was entrapped as a model protein drug and the *in-vitro* drug release profiles were established at 37 °C in ***SGF*** and ***SIF***. The results showed promising release profiles of ***BSA***. However, this hydrogel study requires more effort to limit the swelling and consequently the loss of drug in the ***SGF***, to act as an excellent candidate for intestine-specific delivery of peptide and protein drugs.

Dedicated to Amal (my wife)
and the spirit of my Dad

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Table of Contents

Abstract....ii
Acknowledgement....v
Table of Contents....vii
List of Abbreviations....xiii
List of Tables....xv
List of Figures....xvii
List of Schemes....xxi

CHAPTER 1....1
INTRODUCTION....2
1.1. Controlled drug release technology....2
1.2. Hydrogels and their applications in controlled drug release....5
1.2.1. Hydrogels as compared to gels....7
1.2.2. Classifications of hydrogels....9
1.2.2.1. According to the hydrogel origin....9
1.2.2.2. According to the hydrogel durability....11
1.2.2.3. According to the hydrogel response to the environmental factors...11
1.2.3. Methods of preparation of hydrogels....15
1.2.3.1. Free radical polymerization....15
1.2.3.2. Irradiation crosslinking of polymers....16
1.2.3.3. Chemical crosslinking of polymers....17
1.2.3.4. Physical crosslinking of polymers....18
1.2.4. Applications of hydrogels in controlled drug release....21
1.2.4.1. Ch and Ch-based hydrogels for controlled drug release....22
Production of Ch....23
Properties of Ch....24
(A) Physical properties....24
(B) Chemical properties....25
(C) Biological properties....29
General applications of Ch....29
Ch-based hydrogels and IPN hydrogels (films and beads)....35
THESIS OUTLINE....40

REFERENCES.....41

CHAPTER 2.....**60**

pH-RESPONSIVE SEMI-INTERPENETRATING POLYMERIC HYDROGELS BASED ON CHITOSAN AND POLY(VINYL ALCOHOL) FOR IN-VITRO CONTROLLED RELEASE STUDY

ABSTRACT.....61

2.1. INTRODUCTION.....62

2.2. MATERIALS AND METHODS.....63

2.2.1. MATERIALS.....63

2.2.2 METHODS.....63

2.2.2.1 Characterization of Ch.....63

2.2.2.2 Film preparation (Casting technique).....65

(A) Preparation of Ch and Ch/PVA films.....65

(B) Preparation of Ch/PVA IPN hydrogel films.....65

2.2.2.3 Determination of the gel fraction of the irradiated Ch/PVA films....66

2.2.2.4 Characterizations.....66

2.2.2.5 Entrapment of a model drug.....68

2.2.2.6 Determination of the amount of drug entrapped.....68

2.2.2.7 Equilibrium swelling studies.....68

2.2.2.8 In-vitro cumulative release studies.....69

2.3. RESULTS AND DISCUSSION.....69

2.3.1. Structure investigations.....69

2.3.1.1. Degree of N-deacetylation of Ch.....69

2.3.1.2. Average molecular weight of Ch.....70

2.3.1.3. FTIR investigation.....71

2.3.1.4. The SEM investigation.....78

2.3.1.5. The X-ray diffraction patterns.....80

2.3.2. Equilibrium swelling studies.....82

2.3.2.1. Effect of PVA content.....82

2.3.2.2. Effect of glutaraldehyde content.....84

2.3.2.3. Effect of irradiation dose.....86

2.3.3. Cumulative release measurements.....90

2.3.3.1. Effect of PVA content.....90

2.3.3.2. Effect of glutaraldehyde content.....91
2.3.3.3. Effect of irradiation dose.....93
CONCLUSIONS.....100
REFERENCES.....101

CHAPTER 3.....105
pH AND THERMALLY RESPONSIVE SEMI-INTERPENETRATING POLYMERIC HYDROGELS BASED ON CHITOSAN AND POLY(N-ACRYLOYL GLYCINE) FOR IN-VITRO CONTROLLED RELEASE STUDY
ABSTRACT.....106
3.1. INTRODUCTION.....107
3.2. MATERIALS AND METHODS.....108
3.2.1. MATERIALS.....108
3.2.2. METHODS.....108
3.2.2.1. Synthesis of NAGly.....108
3.2.2.2. Preparation of the Ch/Poly(NAGly) semi-IPN hydrogel.....109
3.2.2.3. Characterizations.....109
3.2.2.4. Entrapment of a model drug.....110
3.2.2.5. Determination of the amount of drug entrapped.....110
3.2.2.6. Equilibrium swelling studies.....110
3.2.2.7. In-vitro cumulative release studies.....110
3.3. RESULTS AND DISCUSSION.....111
3.3.1. Synthesis and characterization of NAGly.....111
3.3.2. Preparation and characterization of the semi-IPN hydrogel.....112
3.3.3. The SEM investigation.....114
3.3.4. Equilibrium swelling studies.....116
3.3.5. Amount of drug entrapped.....119
3.3.6. In-vitro cumulative release studies.....119
CONCLUSIONS.....122
REFERENCES.....123

CHAPTER 4.....**126**

pH RESPONSIVE INTERPENETRATING POLYMERIC HYDROGELS BASED ON CHITOSAN, POLY(N-ACRYLOYL GLYCINE) AND POLY(ETHYLENE GLYCOL) FOR IN-VITRO CONTROLLED RELEASE STUDY.

ABSTRACT.....127

4.1. INTRODUCTION.....128

4.2. MATERIALS AND METHODS.....129

4.2.1. MATERIALS.....129

4.2.2. METHODS.....129

4.2.2.1 Characterization of Ch.....129

4.2.2.2. Synthesis of (NAGly) monomer.....130

4.2.2.3. Preparation of the IPN hydrogel.....130

4.2.2.4. Characterizations.....131

4.2.2.5. Entrapment of a model drug.....131

4.2.2.6. Determination of the amount of 5-FU entrapped.....131

4.2.2.7. Equilibrium swelling measurements.....131

4.2.2.8. In-vitro cumulative release studies.....132

4.3. RESULTS AND DISCUSSION.....132

4.3.1. Synthesis and characterization of NAGly.....132

4.3.2. Preparation and characterization of the IPN hydrogel.....132

4.3.3. The SEM investigation.....135

4.3.4. Equilibrium swelling measurements.....137

4.3.5. In-vitro cumulative release studies.....142

CONCLUSIONS.....143

REFERENCES.....144

CHAPTER 5.....**147**

pH AND THERMALLY RESPONSIVE HYDROGELS BASED ON CHITOSAN-g-POLY(ETHYLENE GLYCOL) FOR IN-VITRO CONTROLLED RELEASE STUDY.

ABSTRACT.....148

5.1. INTRODUCTION.....149

5.2. MATERIALS AND METHODS.....150

5.2.1. MATERIALS.....150

5.2.2. METHODS.....150

5.2.2.1 Characterization of Ch.....150
5.2.2.2. Preparation of Ch-g-PEGDA.....150
5.2.2.3. Preparation of (Ch-g-PEGDA) hydrogels.....151
5.2.2.4. Characterizations.....154
5.2.2.5. Entrapment of anticancer drug.....154
5.2.2.6. Determination of the amount of drug entrapped.....154
5.2.2.7. Equilibrium swelling studies.....154
5.2.2.8. In-vitro cumulative release studies.....155
5.3. RESULTS AND DISCUSSION.....155
5.3.1. Preparation and characterization of Ch-g-PEGDA and its hydrogels....155
5.3.2. Equilibrium swelling studies.....159
5.3.3. In-vitro cumulative release studies.....169
CONCLUSION.....171
REFERENCES.....173

CHAPTER 6.....177
PREPARATION AND IN-VITRO EVALUATION OF NEW pH-SENSITIVE GEL BEADS BASED ON CHEMICALLY MODIFIED CHITOSAN FOR ORAL DELIVERY OF PROTEIN DRUGS.
ABSTRACT.....178
6.1. INTRODUCTION.....179
6.2. MATERIALS AND METHODS.....180
6.2.1. MATERIALS.....180
6.2.2. METHODS.....181
6.2.2.1. Characterization of Ch.....181
6.2.2.2. Preparation of CMCh.....181
6.2.2.3. Characterization of CMCh.....182
6.2.2.4. Graft copolymerization 182
6.2.2.5. Preparation of CMCh-g-MAA/sodium alginate hydrogel beads....183
6.2.2.6. Characterizations.....186
6.2.2.7. Entrapment of a model protein drug.....186
6.2.2.8. Determination of the entrapment efficiency of BSA.....186
6.2.2.9. Swelling studies.....187
6.2.2.10. In-vitro cumulative release studies.....187

6.2.2.11. Statistical analysis.....188
6.3. RESULTS AND DISCUSSION.....188
6.3.1. Preparation of CMCh and CMCh-g-MAA copolymer.....188
6.3.2. Preparation of CMCh-g-MAA/sodium alginate hydrogel beads.....193
6.3.3. Bead size measurements.....196
6.3.4. Swelling characteristics.....200
6.3.5. Entrapment efficiency.....205
6.3.6. In-vitro cumulative release studies.....205
CONCLUSIONS.....206
REFERENCES.....207

CHAPTER 7.....212
SUMMARY AND FUTURE WORK

APPENDICIES.....218
Copy of the reported and published work from the thesis

List of Abbreviations

AA	Acrylic acid
AO	Amine oxide
APS	Ammonium persulfate
BIS	Methylene bisacrylamide
BMA	Butyl methacrylate
BSA	Bovine serum albumin
Ch	Chitosan
CMCh	Carboxymethyl chitosan
CAN	Ceric ammonium nitrate
Da	Dalton
2D-XRD	Two dimensional X-ray diffraction
DSC	Differential scanning calorimetry
EG	Ethylene glycol
EO	Ethylene oxide
E	Ethylene
FTIR	Fourier transform infrared
5-FU	5-Fluorouracil
-g-	Grafted copolymer
HPLC	High performance liquid chromatography
IPN	Interpenetrating polymer network
MAA	Methacrylic acid
MVE	Methyl vinyl ether
MMA	Methyl methacrylate
Mw	Average molecular weight
MPa	Mega Pascal
NIPA	N-isopropyl acrylamide
NVP	N-vinyl pyrrolidone
NAGly	N-acryloylglycine
^{1}H-NMR	^{1}H-Nuclear magnetic resonance
^{13}C-NMR	^{13}C-Nuclear magnetic resonance
PHEMA	Poly(2-hydroxyethyl methacrylate)

PEG	Poly(ethylene glycol)
PHB	Poly(hydroxy butyrate)
PBCPP	Poly(bis-carboxy-phenoxy-phosphazene)
PET	Poly(ethylene terephthalate)
PVA	Poly(vinyl alcohol)
PEO	Poly(ethylene oxide)
PAAm	Poly(acrylamide)
P(…..)	Poly(.....)
PAA	Poly(acrylic acid)
PMAA	Poly(methacrylic acid)
PNVP	Poly(N-vinyl pyrrolidone)
P(NIPA)	Poly(N-isopropyl acrylamide)
PDEAEMA	Poly(diethyl-aminoethyl methacrylate)
PAS	Positron annihilation lifetime spectroscopy
PEGDA	Poly(ethylene glycol diacrylate)
PEt	Polyether
Semi-IPN	Semi-interpenetrating polymer network
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
SEM	Scanning electron microscope
SD	Standard deviation
TPP	Sodium tripolyphosphate
VAc	Vinyl acetate
VA	Vinyl alcohol
η_r	Relative viscosity
η_{sp}	Specific viscosity
η_{red}	Reduced viscosity
$[\eta]$	Intrinsic viscosity
p	Probability

List of Tables

CHAPTER 1

Table 1.1. Some examples of the techniques used for characterization of hydrogels.....7

Table 1.2. Some examples of different classes of polymers used in the preparation of hydrogels.....10

Table 1.3. Examples of utilization of some stimuli-responsive hydrogels in controlled drug release.....13

Table 1.4. ***Ch*** derivatives and their proposed uses.....27

CHAPTER 2

Table 2.1. Compositions of ***Ch*** and ***Ch/PVA*** blend films.....67

Table 2.2. The 2D-XR diffraction data for ***Ch***, ***PVA***, drug-free and drug-loaded ChVA1.....82

Table 2.3. The cumulative release % of ***5-FU*** from γ-irradiated ***Ch/PVA*** films with different ***PVA*** contents at pH 7.4 and 37°C.....95

Table 2.4. The cumulative release data from ***Ch*** and ***Ch/PVA*** films loaded with different concentrations of ***5-FU*** at pH 7.4 and 37°C.....97

Table 2.5. The cumulative release data from chemically crosslinked ***Ch*** films loaded with different concentrations of ***5-FU*** at pH 2.1 and 7.4 at 37°C.....98

Table 2.6. The cumulative release data from chemically crosslinked ***Ch/PVA*** hydrogel films loaded with different concentrations of ***5-FU*** at pH 2.1 and 7.4 at 37°C.....99

CHAPTER 3

Table 3.1.Composition of the prepared semi-***IPNs***.....109

CHAPTER 4

Table 4.1. Composition of the prepared poly[***NAGly-PEGDA***]-***Ch IPN*** hydrogels..130

Table 4.2. Swelling values of poly[***NAGly-PEGDA***]-***Ch IPN*** hydrogels (GEC 3-4) at pH 7.4 at 37 °C as compared to crosslinked ***Ch*** (GEC 1-2).....137

CHAPTER 5

Table 5.1. Preparation details of the ***Ch***-g-***PEGDA*** copolymers and their hydrogels..152

CHAPTER 6

Table 6.1. Different compositions of the prepared ***CMCh***-g-***MAA***/alginate hydrogel beads and their characteristics.....184

Table 6.2. The 2D-XRD data of ***Ch***, ***CMCh*** and ***CMCh***-g-***MAA*** copolymer.....191

List of Figures

CHAPTER 1

Figure 1.1. Graphical representations showing the typical pharmacokinetic profiles in case of (a) conventional and (b) controlled drug release formulations.....3

Figure 1.2. Some of the main advantages of controlled drug release technology.....5

Figure 1.3. The distinct behaviors of gels and hydrogels in aqueous environment.....8

Figure 1.4. Stimuli-responsive swelling of hydrogels.....12

Figure 1.5. Schematic representation of pH-dependent swelling of a smart hydrogel...14

Figure 1.6. General examples of hydrogels prepared by chemical crosslinking of an amino-bearing polymer using (a) formaldehyde and (b) dialdehyde crosslinking agents.....18

Figure 1.7. Examples of hydrogels prepared from the polyelectrolyte complexation of (a) sodium alginate with ***Ch*** acidic solution and (b) poly(sodium styrene sulfonate) with poly(4-vinylbenzyltrimethylammonium chloride).....19

Figure 1.8. Recent example of a hydrogel resulting from the hydrogen bond formation between ***PAA*** and ***PNVP***.....20

Figure 1.9. General example of a hydrogel in which polymeric chains are held together via crosslinking with divinyl benzene in addition to the hydrophobic association.....21

Figure 1.10. Structure of ***Ch*** as compared with that of chitin and cellulose.....23

Figure 1.11. The alkaline deacetylation of chitin to ***Ch***.....24

Figure 1.12. Schematic representation for the role of ***Ch*** as a fat trapper.....31

Figure 1.13. Schematic representation of ***IPN*** and Semi-***IPN*** hydrogels.....34

CHAPTER 2

Figure 2.1. Determination of $[\eta]$ and M_w of ***Ch***.....71

Figure 2.2. FTIR spectrum of ***Ch***.....72

Figure 2.3. FTIR spectra of chemically crosslinked films (**A**) ***Ch***: a) Ch, b) CCh1 and c) CCh3; (**B**) ***Ch/PVA***: a) ChVA1, b) CVA1 and c) CVA3.....73

Figure 2.4. FTIR spectrum of a) ***Ch***, b) ***PVA*** and c) ChVA1 films.....75

Figure 2.5. FTIR spectrum of ChVA1 films a) non-irradiated b) irradiated (10KGy) and c) irradiated (20KGy).....76

Figure 2.6. Scanning electron micrograph of the surface of (a) ChVA1 film, (b) ChVA1 film loaded with ***5-FU*** (24 mg/g matrix) and (c) ChVA1 film after 24 h of ***5-FU*** release at pH 7.4 at 37 °C.....79

Figure 2.7. The 2D-XR diffraction patterns of (a) ***Ch*** (b) ***PVA*** (c) ChVA1 (d) ChVA1 loaded with 5% of ***5-FU*** (feathery part of the film) (e) ChVA1 loaded with 5% of ***5-FU*** (non-feathery part of the film).....81

Figure 2.8. The swelling behavior of (A) non-crosslinked and (B) crosslinked ***Ch*** and ***Ch/PVA*** films with different blend ratios at pH 7.4 and 37°C.....83

Figure 2.9. The swelling behavior of crosslinked (A) ***Ch*** and (B) 1:1 ***Ch/PVA*** films at pH 2.1 and pH 7.4 at 37 °C.....85

Figure 2.10. Influence of glutaraldehyde content on the swelling % of ***Ch*** and ***Ch/PVA*** films after 24 h at pH 2.1 and 7.4 at 37 °C.....86

Figure 2.11. The swelling behavior of (A) 10 KGy and (B) 20 KGy γ-irradiated ***Ch/PVA*** films of different blend ratios in pH 2.1 and 7.4 at 37 °C.....87

Figure 2.12. The swelling behavior of γ-irradiated 1:1.5 ***Ch/PVA*** films at pH 2.1 and 7.4 at 37 °C.....88

Figure 2.13. The effect of irradiation dose and the ***PVA*** content on the gel % of the crosslinked ***Ch/PVA*** films.....89

Figure 2.14. The cumulative release of ***5-FU*** from (A) non-crosslinked (pH 7.4) and (B) crosslinked ***Ch*** and ***Ch/PVA*** films of different blend ratio at pH 2.1 and 7.4 at 37 °C.....91

Figure 2.15. The cumulative release behavior of ***5-FU*** from (A) ***Ch*** and (B) 1:1 ***Ch/PVA*** crosslinked films with varying amounts of glutaraldehyde at pH 2.1 and 7.4 at 37 °C.....92

Figure 2.16. The cumulative release of ***5-FU*** from γ-irradiated ***Ch/PVA*** films of different ***PVA*** contents at pH 2.1 and 37 °C.....94

CHAPTER 3

Figure 3.1. FTIR spectra for ***Ch*** (upper trace) and ***Ch***/Poly(***NAGly***) semi-***IPN*** hydrogels (lower trace).....114

Figure 3.2. Scanning electron micrograph of the surface of ***Ch***/poly(***NAGly***) hydrogel film (a) drug-free, (b) drug-loaded, and (c,d) after 24 h of ***5-FU*** release at pH 7.4 at 37 °C.....115

Figure 3.3. Swelling behaviour of ***Ch***/Poly(***NAGly***) semi-***IPN*** hydrogels at pH 2.1 and pH 7.4 at 37 °C.....116

Figure 3.4. Swelling behaviour of AGC-2 hydrogel at pH 2.1 and pH 7.4 at 25 °C, 37 °C and 45 °C.....118

Figure 3.5. Swelling behaviour of AGC-2 and AGC-2FU at pH 2.1 and pH 7.4 at 37 °C.....119

Figure 3.6. *In-vitro* cumulative release measurements of ***5-FU*** loaded ***Ch***/Poly(***NAGly***) semi-***IPN*** hydrogels at pH 2.1 and 7.4 at 37 °C.....121

CHAPTER 4

Figure 4.1. FTIR spectra for ***Ch*** (upper trace) and the poly[***NAGly-PEGDA***]-***Ch IPN*** hydrogel (lower trace).....134

Figure 4.2. Scanning electron micrograph of the surface of poly[***NAGly-PEGDA***]-***Ch IPN*** hydrogel film (a) drug-free, (b) drug-loaded, and (c,d) after 24 h of ***5-FU*** release at pH 7.4 at 37 °C.....136

Figure 4.3. Swelling behavior of poly[***NAGly-PEGDA***]-***Ch IPN*** hydrogels at pH 2.1 and 7.4 at 37 °C.....138

Figure 4.4. Swelling behavior of GEC-4 and GEC-4FU at pH 2.1 and 7.4 at 37°C...140

Figure 4.5. The cyclic swelling for (A) GEC-4 and (B) GEC-4FU at pH 7.4 at 37°C.141

Figure 4.6. *In-vitro* cumulative release measurements of ***5-FU*** loaded poly[***NAGly-PEGDA***]-***Ch IPN*** hydrogels at pH 2.1 and 37 °C.....142

CHAPTER 5

Figure 5.1. Effect of the amount of the macromer, ***PEGDA*** on the grafting parameters (***Ch***, 1.5 g; CAN, 0.12 g; time, 6 h; temperature, 80 °C).....158

Figure 5.2. FTIR spectra for; ***Ch*** (upper trace) and ***Ch***-g-***PEGDA*** (lower trace).....159

Figure 5.3. Swelling behavior of hydrogels prepared from ***Ch***-g-***PEGDA*** with different G % at 37 °C at pH 2.1 and 7.4, (A) 5% glutaraldehyde and (B) 10% glutaraldehyde.....160

Figure 5.4. Swelling behavior of hydrogels prepared with varying amounts of glutaraldehyde (5% and 10%) at 37 °C at pH 2.1 and 7.4.....162

Figure 5.5. Swelling behavior of CB-3 and CB-3FU at 37 °C at pH 2.1 and 7.4.....164

Figure 5.6. Cyclic swelling profile of CB-3 and CB-3FU at 37 °C and pH 7.4.....165

Figure 5.7. Swelling behavior of CB-3 at 25 °C, 37 °C and 45 °C at pH 2.1 and 7.4.166

Figure 5.8. Scanning electron micrographs of (a) the freeze-dried ***Ch***-g-***PEGDA*** copolymer, (b) the freeze-dried hydrogel before the drug release, and (c) the freeze-dried hydrogel after 24 h of drug release at 37 °C at pH 2.1...168

Figure 5.9. *In-vitro* cumulative release measurements for ***5-FU*** loaded CA-3, CB-3 and CC-3 hydrogels at 37 °C and pH 7.4.....169

Figure 5.10. *In-vitro* cumulative release measurements of ***5-FU***-loaded CB-1–CB-3 hydrogels at 37 °C at pHs 2.1 and 7.4.....170

CHAPTER 6

Figure 6.1. FTIR spectra of (a) ***Ch***, (b) ***CMCh*** and (c) ***CMCh***-g-***MAA*** (G %=1930%).....189

Figure 6.2 . 2D-XRD patterns of (a) ***Ch***, (b) ***CMCh*** and (c) ***CMCh***-g-***MAA***.....192

Figure 6.3. Structure of sodium alginate.....193

Figure 6.4. Photographs illustrate the differences in size of some dry drug-free ***CMCh***-g-***MAA***/alginate beads.....197

Figure 6.5. Microscopic photographs of ***CMCh***-g-***MAA***/alginate hydrogel beads, : 1 mm scale).....199

Figure 6.6. Swelling behaviour of some formulations of ***CMCh***-g-***MAA***/alginate beads in ***SGF*** for 3 h, followed by 8 h in ***SIF***.....201

Figure 6.7. Swelling % of some ***CMCh***-g-***MAA*** (G%= 1930)/alginate hydrogel beads in ***SGF*** for 3 h followed by 8 h in ***SIF***.....203

Figure 6.8. Illustrations of the difference in size between the dry and the swollen states of some drug-free ***CMCh***-g-***MAA***/alginate beads, a) dry b) after 3 h in ***SGF*** c) after 8 h in ***SIF***.....204

Figure 6.9. Cumulative release profiles of ***BSA*** from the ***CMCh***-g-***MAA***/alginate hydrogel beads at 37 °C for 3 h in ***SGF*** followed by 8 h in ***SIF***.....206

List of Schemes

CHAPTER 2

Scheme 2.1. Mechanism of formation of the Schiff's base (C=N) between the amino groups of ***Ch*** and the aldehyde groups of glutaraldehyde.....74

Scheme 2.2. The decay products of the alkoxy radicals resulted from γ-irradiation of ***PVA***.....76

Scheme 2.3. Schematic representation of possible crosslinking reactions occurring for ***PVA*** polymer upon γ-irradiation.....77

Scheme 2.4. Schematic representation of ***Ch***/***PVA*** semi-***IPN*** hydrogels resulting from (a) chemical crosslinking and (b) γ-irradiation.....78

Scheme 2.5. Schematic representation of the proposed structure of ***Ch***/***PVA*** blend.....84

CHAPTER 3

Scheme 3.1. Preparation of ***NAGly***.....111

Scheme 3.2. Preparation of ***Ch***/Poly(***NAGly***) semi-***IPN*** hydrogels.....113

CHAPTER 4

Scheme 4.1. Preparation of ***NAGly***.....132

Scheme 4.2. Preparation of poly[***NAGly***-***PEGDA***]-***Ch IPN*** hydrogels.....133

CHAPTER 5

Scheme 5.1. Preparation of (***Ch***-g-***PEGDA***) hydrogel.....153

Scheme 5.2. The role of Ce^{4+} in the initiation of graft copolymerization onto ***Ch***.....156

CHAPTER 6

Scheme 6.1. The preparation of ***CMCh*** and ***CMCh***-g-***MAA*** from ***Ch***.....190

Scheme 6.2. A schematic representation of the structure of ***CMCh***-g-***MAA***/alginate hydrogel beads at both pH 2.1(***SGF***) and pH 7.4 (***SIF***).....195