

CONTENTS

<i>Foreword</i>	(v)
<i>Preface</i>	(vii)

CHAPTER 1

INTRODUCTION TO BIOADHESIVE DRUG DELIVERY

1.1 Bioadhesion and Mucoadhesion.....	3
1.2 History of Bioadhesion.....	4
1.3 Merits of Bioadhesion/Mucoadhesion	5
1.4 Demerits of Bioadhesion/Mucoadhesion	6
1.5 Recent Developments in Bioadhesive Drug Delivery Systems	6
1.5.1 Developments in Bioadhesive Nanoparticulate Drug Delivery Systems	7

CHAPTER 2

BASIC CONCEPTS OF BIOADHESION

2.1 The Bioadhesive/Mucosa Interactions	9
2.1.1 Ionic Bonds.....	9
2.1.2 Covalent Bonds.....	10
2.1.3 Hydrogen Bonds	10
2.1.4 Van-der-Waals Bonds.....	10
2.1.5 Hydrophobic Bonds	10
2.2 Mucus Structure, Function and Composition.....	10
2.3 Theories of Bioadhesion.....	11
2.3.1 Wetting Hypothesis.....	11
2.3.2 Diffusion Hypothesis	13
2.3.3 Electronic Hypothesis	14
2.3.4 Adsorption Hypothesis	14
2.3.5 Fracture Hypothesis	15
2.3.6 Mechanical Hypothesis.....	17
2.3.7 Cohesion Hypothesis	17
2.4 Mechanism of Bioadhesion.....	19

(x) *Contents*

2.5 Factors Affecting Bioadhesion.....	21
2.5.1 Polymer Related Factors.....	21
2.5.1.1 Molecular weight of polymer.....	21
2.5.1.2 Chain length of polymer	22
2.5.1.3 Spatial arrangement	22
2.5.1.4 Polymer chains flexibility	23
2.5.1.5 Hydration of polymer.....	23
2.5.1.6 Hydrogen bonding	24
2.5.1.7 Functional group contribution	24
2.5.1.8 Polymer surface charge and degree of ionization	24
2.5.1.9 Active polymer concentration.....	24
2.5.2 Environmental Factors.....	25
2.5.2.1 pH	25
2.5.2.2 Applied strength.....	25
2.5.2.3 Interaction time	25
2.5.2.4 Swelling	25
2.5.2.5 Selection of the model substrate surface.....	26
2.5.3 Physiological Factors.....	26
2.5.3.1 Mucin turnover	26
2.5.3.2 Diseased state.....	26
2.6 Bioadhesion and Drug Absorption.....	26
2.6.1 Passive Diffusion	26
2.6.2 Facilitated Passive Diffusion	27
2.6.3 Active Transport	28
2.6.4 Pinocytosis	28

CHAPTER 3

BIOADHESIVE POLYMERS

3.1 Categorization of Bioadhesive Polymers	30
3.1.1 Based on Origin	30
3.1.1.1 Synthetic mucoadhesive polymers.....	30
3.1.1.2 Natural mucoadhesive polymers.....	31

3.1.2 Based on Nature.....	31
3.1.2.1 Hydrophilic polymers	31
3.1.2.2 Polysaccharides and its derivatives.....	32
3.1.2.3 Hydrogels.....	32
3.2 Novel Bioadhesive Polymers	33
3.2.1 Lectins.....	33
3.2.2 Thiolated Polymers	34
3.2.2.1 Cationic thiomers	36
3.2.2.2 Anionic thiomers.....	37
3.2.2.3 Explanations for the superior bioadhesion property of thiomers formation of disulfide bonds	38
3.2.3 Bioadhesive Nanopolymers as Drug Carriers.....	39
3.2.4 Alginate-Polyethylene Glycol Acrylate (Alginate-PEGAc)	40
3.2.5 Poloxamers	40
3.2.6 Pluronics and Combination.....	41
3.2.7 Other Novel Bioadhesive Polymers.....	41
3.2.7.1 Bacterial bioadhesion.....	42
3.2.7.2 Amino acid sequences for bioadhesion.....	43
3.2.7.3 Antibodies for bioadhesions	43
3.3 Selection of Bioadhesive Polymer	43
3.4 Characteristics of Ideal Bioadhesive Polymer to be used in Drug Delivery System.....	44
3.5 Some of the Important and Frequently used Bioadhesive Polymers	45
3.5.1 Chitosan	45
3.5.2 Gelatin.....	49
3.5.3 Sodium Alginate	53
3.5.4 Albumin	57

CHAPTER 4

BIOADHESIVE DRUG DELIVERY SYSTEM

4.1 Targets for Bioadhesive Formulations	62
4.1.1 Ocular Bioadhesive Delivery.....	63
4.1.2 Nasal Bioadhesive Delivery.....	66

(xii) *Contents*

4.1.3 Oral Bioadhesive Delivery.....	71
4.1.3.1 Sublingual bioadhesive delivery.....	72
4.1.3.2 Buccal bioadhesive delivery	72
4.1.4 Dermal and Transdermal Bioadhesive Delivery	73
4.1.5 Vaginal Bioadhesive Delivery	76
4.1.6 Rectal Bioadhesive Delivery	81
4.2 Types of Bioadhesive Formulations.....	85
4.2.1 Solid Bioadhesive Formulations.....	85
4.2.1.1 Mucoadhesive tablets.....	85
4.2.1.2 Inserts.....	87
4.2.1.3 Lozenges	87
4.2.2 Semi-Solid Bioadhesive Formulations	87
4.2.2.1 Gels	87
4.2.3 Liquid Bioadhesive Formulations.....	87
4.2.3.1 Viscous liquids.....	87
4.2.3.2 Gel-forming liquids.....	88
4.2.4 Novel Bioadhesive Drug Delivery Systems	88
4.2.4.1 Bioadhesive films/patches	88
4.2.4.2 Bioadhesive micro/nanopatches.....	88
4.2.4.3 Mucoadhesive nanogels and microgels	90
4.2.4.4 Self-assembled nano-carriers.....	93

CHAPTER 5

EVALUATION OF BIOADHESIVE FORMULATIONS

5.1 Evaluation of Bioadhesive Properties	97
5.1.1 Tensile Strength Measurement	98
5.1.2 Shear Strength Measurement.....	99
5.1.3 Rheological Measurements.....	100
5.1.4 Florescence Probes	101
5.1.5 Refractive Index BIACORE® System.....	102
5.1.6 Detachment Force Measurement	102
5.1.7 Wilhelmly Plate Technique	103

Contents (xiii)

5.1.8 Other <i>In-vitro</i> Tests.....	103
5.1.8.1 Thumb test	103
5.1.8.2 Adhesion number.....	103
5.1.8.3 Falling liquid film method	104
5.1.8.4 Electrical conductance	104
5.1.8.5 Novel electromagnetic force transducer technique.....	104
5.1.9 <i>In-vivo</i> Evaluation of Bioadhesive Properties.....	104
5.1.9.1 Radioisotopic method	104
5.2 Evaluation of Bioadhesive Properties of Multiparticulate Systems	105
5.2.1 <i>In-vitro</i> Characterization of Cellular Interaction	105
5.2.1.1 Flow cytometry	105
5.2.1.2 Laser scanning cytometry	106
5.2.1.3 High content screening assays	107
5.2.1.4 Confocal laser scanning microscopy	107
5.2.1.5 Fluorescence confocal microscopy	108
5.2.1.6 Laser capture micro-dissection	108
5.2.1.7 Pharmacoscintigraphy.....	109
5.3 Factors Affecting Evaluation of Bioadhesive Properties	109
5.3.1 Surface Cleanliness.....	109
5.3.2 Externally Applied Load.....	110
5.3.3 Probe Size	111
5.3.4 Topography.....	112
5.3.5 Contact Time	112
5.3.6 pH	112

CHAPTER 6

BIOADHESIVE NANOPARTICLES

6.1 Nanoparticles.....	115
6.1.1 Advantages of Bioadhesive Nanoparticles	116
6.1.2 Factors Influencing Characteristics of Bioadhesive Nanoparticles	116
6.1.1.1 Composition of bioadhesive polymer	116
6.1.1.2 Polymer solubility.....	117

(xiv) *Contents*

6.1.1.3 Surface properties	117
6.1.1.4 Drug properties	118
6.2 Methods of Preparation	119
6.2.1 Polymerization based Methods for the Preparation of Nanoparticles	120
6.2.1.1 Emulsion polymerization	120
6.2.1.2 Mini-emulsion polymerization.....	120
6.2.1.3 Microemulsion polymerization.....	120
6.2.1.4 Interfacial polymerization.....	121
6.2.1.5 Controlled/living radical polymerization (C/LRP)	121
6.2.2 Dispersion based Methods for the Preparation of Nanoparticles.....	122
6.2.2.1 Solvent evaporation	122
6.2.2.2 Nanoprecipitation.....	122
6.2.2.3 Emulsification/solvent diffusion (ESD).....	123
6.2.2.4 Salting out.....	124
6.2.2.5 Dialysis	125
6.2.2.6 Supercritical fluid technology (SCF)	125
6.2.3 Ionic Gelation or Coacervation of Hydrophilic Polymers	127
6.3 Protein Stabilized Nanoparticles	128
6.3.1 Biological Characteristics of Protein Nanoparticles	129
6.3.1.1 Biocompatibility	129
6.3.1.2 Biodegradation.....	130
6.3.2 Biodistribution and Applications	130
6.4 Drug Loading	132
6.5 Drug Release	132
6.6 Characterization of Bioadhesive Nanoparticles	133
6.6.1 Size and Surface Morphology.....	133
6.6.2 Surface Charge and Electrophoretic Mobility	134
6.6.3 Specific Surface Area	135
6.6.4 Surface Hydrophobicity	135
6.6.5 Density	135
6.6.6 Entrapment Efficiency and Nanoparticle Recovery.....	136
6.6.7 <i>In-vitro</i> Release.....	136

6.7 Applications	136
6.7.1 Cancer Therapy.....	137
6.7.2 Antibody Targeting.....	137
6.7.3 Vaccine Delivery	137
6.7.4 Drug Delivery	138
6.7.5 Improvement in the Gastrointestinal Tract Absorption	138
6.7.6 Diagnostic Medicine	138

CHAPTER 7

BIOADHESIVE MICROSPHERES

7.1 Advantages of Bioadhesive Microsphere.....	140
7.2 Mechanism of Drug Release	140
7.3 Polymers for Bioadhesive Microspheres.....	141
7.3.1 Synthetic Polymers	141
7.3.1.1 Non-biodegradable polymers.....	142
7.3.1.2 Biodegradable polymers	142
7.3.2 Natural Polymers	142
7.3.2.1 Proteins	142
7.3.2.2 Carbohydrates	143
7.3.2.3 Chemically modified carbohydrates	143
7.4 Preparation of Bioadhesive Microspheres.....	144
7.4.1 Single Emulsion Technique	144
7.4.2 Double Emulsion Technique	145
7.4.3 Polymerization Techniques.....	145
7.4.3.1 Normal polymerization	145
7.4.3.2 Interfacial polymerization.....	146
7.4.4 Phase Separation Coacervation Technique.....	146
7.4.5 Spray Drying and Spray Conealing	147
7.4.6 Solvent Extraction Technique.....	147
7.5 Drug Loading	147
7.6 Evaluation of Bioadhesive Microspheres.....	148
7.6.1 Particle Size and Shape	148
7.6.2 Electron Spectroscopy for Chemical Analysis	149

(xvi) Contents

7.6.3 Attenuated Total Reflectance Fourier Transform-Infrared Spectroscopy	149
7.6.4 Density Determination.....	149
7.6.5 Isoelectric Point	149
7.6.6 Surface Carboxylic Acid Residue.....	150
7.6.7 Surface Amino Acid Residue	150
7.6.8 Entrapment Efficiency	150
7.6.9 Angle of Contact.....	150
7.6.10 Release Studies	151
7.6.10.1 <i>In-vitro</i> methods.....	151
7.6.10.2 <i>In-vivo</i> methods.....	152
7.6.11 <i>In-vitro-In-vivo</i> Correlations.....	153
7.6.11.1 Percent of drug dissolved <i>in-vitro</i> v/s peak plasma concentration	154
7.6.11.2 Percent of drug dissolved v/s percent of drug absorbed ...	154
7.6.11.3 Dissolution rate v/s absorption rate.....	154
7.6.11.4 Percent of drug dissolved v/s serum drug concentration ..	154
7.6.11.5 Percent of drug dissolved v/s percent of the dose excreted in urine	154
7.6.12 Evaluation of Bioadhesive Properties.....	155
7.7 Applications	155
7.7.1 In Vaccine Delivery	155
7.7.2 Targeting using Bioadhesive Microspheres as Carriers.....	156
7.7.3 Monoclonal Antibodies Mediated Microspheres Targeting	156
7.7.4 Chemoembolization	157
7.7.5 Imaging	157
7.7.6 Topical Porous Microspheres	157
7.7.7 Surface Modified Microspheres.....	157

CHAPTER 8**BIOADHESIVE NANOGELS**

8.1 Materials for NGs.....	161
8.2 Properties of NGs.....	161

Contents (xvii)

8.3 Methods of Preparation	162
8.3.1 Photolithographic Techniques	162
8.3.2 Micro-Molding Methods.....	164
8.3.3 Microfluidic Preparation	165
8.3.4 Preparation of NGs using Biopolymers	167
8.3.4.1 Water-in-oil (w/o) heterogeneous emulsion methods.....	167
8.3.4.2 Aqueous homogeneous gelation method	169
8.3.4.3 Spray drying method.....	170
8.3.4.4 Chemical cross-linking method	170
8.3.5 Heterogeneous Free Radical Polymerization.....	171
8.3.5.1 Dispersion polymerization.....	171
8.3.5.2 Precipitation polymerization (PP).....	171
8.3.5.3 Inverse (Mini) emulsion polymerization	172
8.3.5.4 Inverse microemulsion polymerization.....	173
8.3.6 Heterogeneous Controlled Radical Polymerization (HCRP).....	173
8.4 Drug Loading in NGs.....	174
8.4.1 Covalent Conjugation	175
8.4.2 Self-Assembly.....	175
8.4.3 Physical Entrapment	175
8.5 Drug Release	175
8.5.1 Diffusion Controlled Release Systems	176
8.5.2 Chemically Controlled Systems.....	176
8.5.3 Swelling Controlled Release System	176
8.5.4 Environmentally Responsive Systems.....	176
8.6 Characterization of NGs.....	177
8.6.1 Dynamic Light Scattering (DLS).....	177
8.6.2 Surface Charge Studies.....	177
8.6.3 Scanning Electron Microscopy (SEM)	177
8.6.4 Fluorescence Analysis	178
8.6.5 Atomic Force Microscopy (AFM).....	178
8.6.6 Nuclear Magnetic Resonance (NMR).....	178
8.6.7 Circular Dichroism (CD)	178
8.6.8 Size Exclusion Chromatography (SEC).....	179

(xviii) Contents

8.6.9 Force Spectroscopy.....	179
8.6.10 Swelling Studies	179
8.7 Stability Studies of NGs.....	179
8.8 Applications	180
8.8.1 NGs as Potential Gene and Antisense Delivery Agents	180
8.8.2 Toxic Scavengers.....	181
8.8.3 Bone Medicine.....	181
8.8.4 NGs in Alzheimer's Disease.....	181
8.8.5 Encapsulation of Enzyme in NGs to Enhance Bio-Catalytic Activity and Stability	181
8.8.6 Insulin Delivery by NGs.....	182
8.8.7 NGs for Treatment of Neurodegenerative Disorders.....	182
8.8.8 Antiviral Therapy.....	182
8.8.9 Small Molecular Weight Drug Delivery.....	182
8.8.10 Protein, Peptide and Oligosaccharide Delivery	183
8.8.11 Vaccine Delivery	183
8.8.12 Targeting.....	183

CHAPTER 9**BIOADHESIVE PATCHES/FILMS**

9.1 Types of Bioadhesive Patches.....	186
9.1.1 Matrix Type	186
9.1.2 Reservoir Type.....	186
9.2 Components of Bioadhesive Patches	186
9.2.1 Drug Substance	187
9.2.2 Bioadhesive Polymers.....	187
9.2.2.1 Semi-natural/natural bioadhesive polymers.....	188
9.2.2.2 Synthetic bioadhesive polymers cellulose derivatives.....	188
9.2.2.3 Water-soluble bioadhesive polymers.....	188
9.2.2.4 Water-insoluble bioadhesive polymers.....	188
9.2.2.5 Cationic bioadhesive polymers.....	188
9.2.2.6 Anionic bioadhesive polymers.....	188
9.2.2.7 Non-ionic bioadhesive polymers	188

Contents (xix)

9.2.2.8 Covalently bonding bioadhesive polymers.....	189
9.2.2.9 Hydrogen bonding bioadhesive polymers	189
9.2.2.10 Bioadhesive polymers with electrostatic interaction	189
9.2.3 Backing Membrane.....	189
9.2.4 Permeation Enhancers.....	189
9.2.4.1 Mechanisms of action of permeation enhancers	190
9.3 Methods of Preparations.....	190
9.3.1 Solvent-Film Casting	191
9.3.2 Hot-Melt Extrusion	192
9.3.2.1 Ram extrusion.....	193
9.3.2.2 Screw extrusion.....	193
9.4 Characterization of Bioadhesive Patches/Films	196
9.4.1 Film Weight and Thickness	196
9.4.2 Surface pH of Films	196
9.4.3 Percent Swelling	196
9.4.4 Folding Endurance	196
9.4.5 <i>In-vitro</i> Residence Time	196
9.4.6 Drug Content Uniformity.....	197
9.4.7 Vapor Transmission Test.....	197
9.4.8 <i>In-vitro</i> Release Study	197
9.4.9 <i>Ex-vivo</i> Permeation Studies	197
9.4.10 Measurement of Mechanical Properties.....	198
9.4.11 Stability Studies	198
9.5 Bioadhesive Patches for Transdermal Delivery	198
9.5.1 Types of Transdermal Patches	199
9.5.1.1 Membrane permeation controlled systems	199
9.5.1.2 Matrix diffusion-controlled systems	200
9.5.1.3 Adhesive dispersion-type systems	200
9.5.1.4 Micro-reservoir type or micro-sealed dissolution controlled systems	201
9.5.2 Mechanism of Permeation	201
9.6 Bioadhesive Patches/Films for Buccal Delivery	202
9.6.1 Advantages of Buccal Patches	203
9.6.2 Mechanism of Buccal Absorption	204

(xx) *Contents*

9.6.3 Factors Affecting Buccal Absorption	204
9.6.3.1 Membrane factors	204
9.6.3.2 Environmental factors.....	204
9.7 Bioadhesive Patches for Local Delivery and Wound Dressings.....	205
9.7.1 Classification of Dressings	206
9.7.2 Modern Wound Dressings	207
9.7.2.1 Hydrocolloid dressings	207
9.7.2.2 Alginate dressings.....	208
9.7.2.3 Hydrogel dressings	209
9.7.2.4 Semi-permeable adhesive film dressings.....	209
9.8 Current Research in the Field of Bioadhesive Patches.....	209
9.8.1 Testosterone Transdermal Patch	209
9.8.2 Oxybutynin Transdermal Patch for Over Active Bladder (OAB)	210
9.8.3 Transdermal Patch for Menstrual Problems	210
9.8.4 Transdermal Patches for Parkinson's Disease	210
9.8.5 Bioadhesive Buccal Films	210
9.8.6 Sustained Release Bioadhesive Buccal Patches	210
Bibliography	211
Index	251