Contents

Preface		v
Exp	panded contents	ix
SE	CTION I: GENERAL CONSIDERATIONS AND BIOCHEMICAL CONCEPTS	
1.	Introduction to parenteral drug delivery	3
2.	Molecular basis of targeted drug delivery	38
3.	Bioconjugates	81
4.	Chemical drug delivery	122
SE	CTION II : CARRIER CONCEPTS IN DRUG DELIVERY	
5.	Liposomes	173
6.	Niosomes	249
7.	Submicron emulsions	280
8.	Multiple emulsions	303
9.	Nanoparticles	331
10.	Resealed erythrocytes	387
11.	Microspheres	417
12.	Magnetically modulated drug delivery	458
SE	CTION III : SITE-SPECIFIC DRUG DELIVERY	
13.	Drug delivery to brain	487
14.	Drug delivery to tumour	512
15.	Drug delivery to bone marrow	562
Index		587

SECTION I General Considerations & Biochemical Concepts

1. Introduction to Parenteral Drug Delivery	3-37
Introduction	3
Liposomes	7
Liposomes in intracellular infections	9
Liposomes in tumour therapy	11
Other liposome applications	12
Niosomes	12
Nanoparticles and microspheres	13
Nanoparticles in chemotherapy	14
Avoidance of multidrug resistance	14
Adjuvant effect for vaccines	15
Solid lipid nanoparticles	15
Hydrogel nanoparticles	16
Nanocrystals and nano-suspensions	16
Microparticles	17
Long circulating microparticles	17
Specialized emulsions	18
Multiple emulsions	18
Emulsome™	19
Long circulatory emulsions	19
Resealed erythrocytes	20
Supramolecular biovectors	21
Orientation, organization and function	22
Chylomicrons	22
Lipoproteins	23
Extravasation of lipoproteins for cellular interaction	23
Cyclodextrins	23
Prodrúgs	24
Antibody directed enzyme prodrug therapy (ADEPT)	25
Polymeric prodrugs (polymer-drug conjugates)	26
Biotin-avidin conjugates	27
Polymeric micelles	27
Aquasomes ·	28
Dendrimers	_28
Implant systems	30
Systems for non-invasive systemic administration	33

	Conclusion References	33 34
2.	Molecular Basis of Targeted Drug Delivery	38-80
	Introduction	38
	The concepts of targeting	39
	Rationale of drug targeting	39
	Carriers	40
	Levels of drug targeting	42
	Cellular biochemistry and molecular events in drug targeting	47
	Cell surface biochemistry and molecular targets	47
	Molecular targets for cellular targeting	47
	Receptor as delivery ports Ligands as delivery and targeting tools	49 50
	Ligand driven receptor mediated drug delivery	51
	Cellular machinery that drive receptor mediated bioevents	51
	Intracellular processing and disposition of drug-carrier composites	55
	Receptor mediated drug delivery using biochemical and molecular ligands	60
	Carbohydrate specific (lectin) receptors	61
	Asialo-glycoprotein receptor	62
	Mannose, mannosyl-fucosyl (MF) receptors	64
	Lymphocyte homing receptors	66
	Cell surface receptor expressed for immunoregulatory molecules	66
	Fc receptors Complement receptors	66 67
	Interleukin receptors	68
	Interferons	70
	MHC and CD glycoproteins	70
	Receptors for endogenous proteins and macromolecules	70
	Tumour/viral cell surface biochemistry and ligand mediated targeting strategies	75
	Altered/over expression of cell specific receptors	76
	Expression of vasoactive and angiogenic epitopes on tumour vascular endotheliur	
	Future perspectives	79
	References	79
3.	Bioconjugates	81-121
	Introduction	81
	Bioconjugation techniques	81
	Covalent conjugation	82
	Non-covalent conjugation	85
	Classes of bioconjugates	87
	Characterization of bioconjugates	88
	Applications of bioconjugates	89
	Bioconjugates in drug delivery and targeting	89
	Antibody conjugates (immunoconjugates)	89
	Antibody conjugated delivery systems	90
	Antibody enzyme conjugates Bispecific antibodies	91 92

122-169

Antibody conjugated liposomes (Immunoliposomes)	93
Haptenated conjugates of liposomes	96
Antibodies conjugates developed against angiogenic peptides	96
Bioconjugates of immunotoxins/ chimeric proteins	98
CD4 bioconjugates	99
Recombinant CD4 toxin conjugates	100
Liposome conjugated CD4 fragments	100
Transferrin based bioconjugates	100
Transferrin-drug conjugates	102
Transferrin-liposome conjugates	102
Anti-transferrin antibody-conjugates	103
Folic acid (folate) based bioconjugates	105
Insulin based bioconjugates	107
Bioconjugates with cytokines	108
Glycoconjugates	110
Neoglycoprotein-drug conjugates	110
Neoglycoprotein-liposome conjugates	112
Poly ethylene glycol (PEG) conjugates	114
PEG conjugates with peptides and proteins (mainly enzymes)	114
PEG conjugates with low molecular weight drugs	115
PEG conjugates with lipids	115
PEG conjugates with biological macromolecules	116
Poly-L-lysine conjugates	116
Future perspectives	118
References	118

4. Chemical Drug Delivery

Introduction	122
Prodrug and chemical delivery systems	123
Eye as a target organ	123
Chemical delivery systems for eye	124
Skin	125
CDS for kidney	127
Lung as a target organ	127
Colon targeting	128
CDS for liver targeting	129
Lymphatic targeting	129
Brain as a target organ for CDS	137
Tumour targeting by CDS	154
Antibody and enzyme based tumour targeting	157
Soft drug approach	160
Membrane transporters as targeting site	163
Peptide transporter associated prodrug therapy	164
Conclusion	164
References	165

SECTION II Carrier Concepts in Drug Delivery

5.	Liposomes	173-248
	Introduction	173
	Mechanism(s) of liposome formation	174
	Rigidization of fluid phase vesicles with cholesterol	176
	Molecular geometry and liposome formation (Israelachvili hypothesis)	180
	Vesicle formation in living cells	180
	Classification of liposomes	181
	Methods of liposome preparation and drug loading	181
	Passive loading techniques	182
	Mechanical dispersion methods of passive loading	182
	Thin film hydration using hand shaking (MLVs) and non-shaking methods (ULVs)	182
	Pro-liposomes	183
	Mechanical treatment of MLVs	183
	Dried-reconstituted vesicles (DRVs)	186
	Freeze thaw sonication (FTS) method	187
	Liposomes from preformed vesicles	188
	Solvent dispersion methods of passive loading	188
	Ethanol injection	189
	Ether injection	189
	Rapid solvent exchange vesicles (RSEVs)	190
	De-emulsification methods	190
	Detergent depletion (removal) methods of passive loading	191
	Dialysis	193
	Column chromatography	193
	Detergent adsorption using bio-beads	193
	Remote (active) loading	193
	Microencapsulation or locus of drugs in liposomes	195
	Lipophilic transformation of drugs: Pharmacosomes	196
	Removal of unentrapped drug from liposomes	196
	Characterization of liposomes	196
	Vesicle shape and lamellarity	197
	Vesicle size and size distribution	198
	Surface charge	201
	Encapsulation efficiency and trapped volume	201
	Phase response and transitional behaviour	203
	Vesicle fusion measurements	203
	Chemical characterization of liposomes	204
	Stability of liposomes	205
	Stability <i>in vitro</i>	205
	Long term and accelerated stability	207
	Stability after systemic administration	208
	Stability in vivo after oral administration	209
	Interactions of liposomal drug delivery systems with cells	209
	Liposomal pharmacokinetics	210
	Pharmacokinetics of liposomes after intravenous administration	210
	Pharmacokinetics of release of liposomal contents in tissues	213
	Pharmacokinetics of long-circulatory liposomes for tumour targeting/localization	213

Commercial development and scale up	215
Freeze-drying and cryoprotection/ lyoprotection of liposomal products	215
Commercial manufacturing of liposomal drugs	216
Therapeutic applications of liposomes	217
Liposomes as drug delivery vehicle	217
Liposomes in anti-microbial, anti-fungal (lung therapeutics) anti-viral (anti-HIV) therapy	221
Liposomes in tumour therapy	224
Liposomes in gene therapy	228
Liposomes in antisense oligonucleotide therapy	234
Immunological applications of liposomes	235
Liposomes in dermatology and cosmetology	239
Liposomes as radiopharmaceutical and radiodiagnostic carriers	241
Liposomes as red cell substitutes and artificial RBCs	242
Miscellaneous applications	242
Conclusion	243
References	

6. Niosomes

249-279

Introduction	249
Physicochemical aspects of non-ionic surfactant vesicles	251
Structural components and niosomes bilayer	251
Other structural components	253
Methods of preparation	258
Ether injection	259
Hand shaking method	259
Sonication	259
Reverse phase evaporation	259
Aqueous dispersion	259
Extrusion	259
Separation of free drug	260
Characterization of niosomes	260
Size, shape and morphology	260
Entrapment efficiency	261
Encapsulation efficiency and solute release rates	262
Vesicle surface charge	264
Stability of niosomes	265
Stability in buffer	265
Stability in hypertonic media	265
Stability in hypotonic media	265
Stability <i>in vivo</i>	265
Rheological properties of niosomal dispersion	266
Solute release profile form niosomal formulations	266
Colloidal properties of niosomal dispersion	267
Discomes	267
NSVs reversed vesicles	269
Non-ionic surfactant vesicle-in-water-in-oil (V/W/O) systems	269
Non-ionic surfactant based organogels	270
Polymer coated non-ionic surfactant vesicles	270
Proniosomes	270
FIONOSONES	210

Non-ionic surfactant vesicles and their therapeutic potential Niosomes for the treatment of leishmaniasis Niosomes in oncology	271 271 272
Niosomes as immunological adjuvant	274
Nonionic surfactants and oral drug delivery	274
Niosomes for transdermal drug delivery	275
Niosomes and diagnostic imaging	276
References	277
7. Submicron Emulsions	280-302
Introduction	280
Submicron lipid emulsions	281
Microemulsions	282
Basic aspects of microemulsions	282
Microemulsion formation and phase behaviour	284
Phase behaviour	285
Theoretical aspects of the preparation of microemulsions	286
Single surfactant systems	288
Temperature-insensitive microemulsions	289
Characterization of microemulsions	291
Phase behaviour studies	292
Scattering techniques for microemulsions characterization	292
Nuclear magnetic resonance studies	293
Electron microscopic studies	293
Interfacial tension, electrical conductivity and viscosity measurements	293
Advantages of microemulsion-based systems	294
Applications of microemulsions	294
Oral drug delivery	295
Topical drug delivery	295
Ocular and pulmonary delivery	297
Solubilization of drugs in microemulsions	297
Parenteral administration	297
Perflouro microemulsions	298
Microemulsions in biotechnology	298
Solid colloildal systems prepared from microemulsions	299
From W/O microemulsions	299
From O/W microemulsions	300
Self emulsifying drug delivery systems (SEDDs)	300
References	300
8. Multiple Emulsion	303-330

Introduction	303
Principles of liquid surfactant membrane emulsion	304
Preparation aspects of multiple emulsion	304
A static aspect of multiple emulsion formation	304
Methods of preparation	306
Two step emulsification (double emulsification)	306
Phase inversion technique (one step technique)	306
Phase inversion technique (one step technique)	30

	Membrane emulsification technique	307
	In vitro characterization	308
	Average globule size and size distribution	308
	Area of interfaces	308
	Number of globules	309
	Rheological evaluation	309
	Zeta potential	309
	Percent drug entrapment	309
	In vitro drug release	309
	In vitro stability studies	309
	Stability of multiple emulsions	310
	Breakdown pathways	316
	Factors affecting stability	311
	Methods to stabilize multiple emulsion	312
	Drug release mechanisms and models	314
	Fusion of unionized drug (hydrophobic species) through	
	-the oil layer (diffusion rate model)	314
	Planer sheet model	315
	Micelle formation model/oil thining or rupture model	316
	Carrier oriented transport	316
	Carrier oriented transport	316
	In vivo fate of multiple emulsions	317
	Applications in therapeutics and cosmetics	319
	Controlled and sustained drug delivery	319
	Targeting of bioactives	322
	Vaccine adjuvant	322
	Multiple emulsion for local immunosuppression	323
	Absorption enhancement through gastrointestinal tract	323
	Delivery of proteins and peptides	323
	Haemoglobin multiple emulsion as an oxygen delivery system	324
	Enzyme immobilization	324
	Microencapsulation technology using multiple emulsion as an intermediate step	325
	Cosmetics and health care	327
	Miscellaneous applications	328
	Future perspectives	328
	References	328
9.	Nanoparticles	331-386

Introduction	331
Natural hydrophilic polymers	332
Synthetic hydrophobic polymers	332
Preparation techniques of nanoparticles	332
Nanoparticle preparation by cross linking of amphiphilic macromolecule	333
Nanoparticle preparation using polymerization based methods	336
Nanoparticle preparation using polymer precipitation methods	342
Novel nanoparticulate systems	346
Solid lipid nanoparticles	346
SLN vs other colloidal drug carriers	347
Synthetic nanoparticles using microemulsions as nano-size reactors	348
Copolymerized peptide nanoparticles (CPP)	350

.

10.

Hydrogel nanoparticles	350
Nanocrystals and Nanosuspensions	351
Drug loading and <i>in vitro</i> release process	351
In vitro release profile of lipophilic drugs	352
In vitro release profile of hydrophilic drugs	353
Pharmaceutical aspects of nanoparticles	353
Purification of nanoparticles	353
Freeze drying of nanoparticles	355
Sterilization of nanoparticles	355
Characterization of nanoparticles	356
Size and morphology	356
Specific surface	357
Surface charge and electrophoretic mobility	357
Surface hydrophobicity	358
Density	358
Molecular weight measurements of nanoparticles	358
Nanoparticle recovery and drug incorporation efficiency	358
In vitro release	359
In vivo fate and biodistribution of nanoparticles	359
Surface engineering of nanoparticles	361
Steric stabilized (stealth) nanoparticles	361
Nanoparticles for bioadhesion	365
Biomimetic nanoparticles	366
Magnetic nanoparticles	366
Nanoparticles coated with antibodies	367
Therapeutic applications of nanoparticles	368
Intracullular targeting	368
Nanoparticle in chemotherapy	371
Adjuvant effect for vaccine	372
Nanoparticles for peroral administration of protein and peptides	373
Nanoparticles in intraarterial applications	374
Nanoparticles for ocular delivery	374
Nanoparticles for brain delivery	375
Nanoparticles for DNA delivery	376
Nanoparticles for oligonucleotide delivery	377
Nanoparticle in lymph targeting	379
Fuctionalized nanoparticles: a new dimension in innovative research	379
Conclusion	381
References	381
Resealed Erythrocytes	387-416
Introduction	387
Drug carrying potential of erythrocytes	387

Basic features of erythrocytes	388
Composition of erythrocytes	388
Electrolyte composition of erythrocytes	388
Haematocrit value and erythrocyte sedimentation rate	389
Source, fractionation and isolation of erythrocytes	389
Methods of drug loading	390
Hypotonic haemolysis and isotonic resealing methods	390

423

424

424

425

425

426

426

427

	Electro-insertion or electroencapsulation	394
	Loading by electric cell fusion	394
	Entrapment by endocytosis	396
	Loading by chemical perturbation of membrane (drug mediated loading)	396
	Loading by lipid fusion	397
	In vitro characterization	397
	Drug content	397
	In vitro drug and haemoglobin release	397
	Osmotic fragility	398
	Osmotic shock	398
	Turbulence shock	399
	Morphology and percent cellular recovery	399
	Different forms of drug loaded red blood cells	399 400
	Shelf and storage stability of resealed erythrocytes	
	<i>In vivo</i> survival and immunological consequences	400
	Influence of membranolytic and membranotropic substrates	401
	Biomedical applications of resealed erythrocytes	401 401
	Erythrocytes as drug/enzyme carriers Drug targeting	401
	Targeting to sites other than RES rich organs	405
	Erythrocytes as circulating bioreactors	407
	Macrophage activation Thrombolytic therapy	409 409
	Delivery of interleukins	409
	Oxygen deficiency therapy	410
	Resealed erythrocytes in cell biological applications	411
	Cell biological applications	411
	Novel systems	413
	Nanoerythrosomes	413
	Erythrosomes	413
	Future prospectives	413
	References	413
11.	Microspheres	417-457
	Introduction	417
	Material(s) used	418
	Prerequisites for ideal microparticulate carriers	418
	General methods of preparation	419
	Single emulsion technique	419
	Double emulsion techniques	420
	Polymerization techniques	420

Spray drying and spray congealing Solvent extraction Loading of drug Drug release kinetics

Phase separation coacervation technique

Reservoir type system Matrix type system Polymeric microspheres

12.

Albumin microspheres	427
Gelatin microspheres	428
Starch microspheres	429
Dextran microspheres	430
Poly lactide and poly glycolide microspheres	431
Polyanhydride microspheres	432
Polyphosphazene microspheres	433
Chitosan microspheres	434
Carrageenan microspheres	436
Alginate microspheres	436
Poly(alkyl cyanoacrylate) microspheres	438
Poly acrolein microspheres	439
Fate of microspheres in body	439
Characterization	441
Particle size and shape	442
Electron spectroscopy for chemical analysis	442
Attenuated total reflectance fourier transform-infrared spectroscopy	442
Density determination	442
Isoelectric point	442
Surface carboxylic acid residue	442
Surface amino acid residue	443
Capture efficiency	443
Release studies	443
Angle of contact	444
Applications	444
Microspheres in vaccine delivery	444
Microspheres and immune system	447
Targeting using microparticulate carriers	447
Magnetic microspheres	449
Monoclonal antibodies mediated microspheres targeting-immunomicrospheres	450
Chemoembolization	451
Imaging	453
Microsponges: Topical porous microspheres	453
Surface modified microspheres	453
Future perspective	454
References	454
	404
Magnetically Modulated Drug Delivery	458-483
Introduction	458
History of magnetic guidance	459
Magnatically modulated microcarriers	459
Magnetic microspheres	460
Magnetite (Fe_3O_4)	463
Biodistribution and tissue concentration of microspheres	465
Carrier localization	465
Biomodulators	466
Magnetic nanoparticles	467
Magnetic liposomes	471
Magnetic resealed erythrocytes	476
Magnetic emulsions	478

Magnetic carriers in protein immobilization	478
Magnetically modulated systems and devices	478
System parameters	479
Mechanism	479
In vivo experiments	480
Magnetically modulated, implantable, hemispheric drug delivery device	480
Magnetic systems in contraceptive drug delivery	480
Magnetically programmable infusion pumps	480
Conclusion	481
References	482

SECTION III Site-Specific Drug Delivery

13.	Drug Delivery to Brain	487-511
	Introduction	487
	The fluid-brain barrier	488
	Cell biology and anatomy of BBB	488
	Multiple function of BBB	491
	The BBB as an active pump	491
	The BBB as a metabolic barrier	494
	Regulation of BBB function	494
	Limitation in brain uptake of drugs	494
	Transport through BBB	494
	Carrier mediated transport system	495
	Receptor mediated transcytosis (RMT)	495
	Absorptive mediated transcytosis (AMT)	498
	Factors affecting drug permeation through BBB	499
	Brain drug delivery strategies	500
	Neurosurgical or invasive strategies	500
	Physiologic based strategies	501
	Pharmacologic strategies	503
	Small colloidal particles for brain targeting	507
	Nanoparticles for brain targeting	507
	Liposomes for brain targeting	508
	Monocytes for brain targeting	508
	Future prospects	508
	References	509
14.	Drug Delivery to Tumour	512-561

Introduction	512
Tumour vasculature vs normal vasculature	512
How tumour develops	513
Vascularization and localization of drug carriers in tumours	515
Barriers offered by tumour vasculature	516
Molecular targets for tumour therapy	518
Surface determinants on the tumour sites	519
Folate, transferrin, fucose and lipoproteins as over-expressed tumour receptors	519
Epitopes on tumour vascular endothelium for selective drug delivery	520

	Angiogenesis as a target	520
	Immunotherapy of tumour	521
	Antibodies as targeting tools	521
	Recombinant antibodies	521
	Antibody enzyme conjugates	522
	Bispecific antibodies	523
	Bioconjugates of immunotoxins/chimeric proteins	524
	Problems of delivery of monoclonal antibodies	、 525
	Tumour antigens and vaccines	526
	Cytokines	527
	Interleukins	527
	Molecular approaches in tumour therapy	528
	Vasoactive and angiogenic peptides	528
	Fas receptor-Fas ligand systems	529
	Cell adhesion molecules	530
	Altered/over expression of cell specific receptors	535
	Gene therapy	538
	Molecular targets (defective genes) for tumour therapy	539
	Non-viral gene delivery for p53	540
	Targeted, non-viral gene delivery for tumour gene therapy	541
	Suicide gene therapy	541
	Targeting delivery of genes using Mabs; immunogene approach	542
	Antisense oligonucleotides as genetic medicines	542
	Tumour targeting and drug delivery systems	542
	Site specific drug delivery	543
	Multi drug resistance	544
	Role of drug carriers in overcoming multi-drug resistance	545
	Problems associated with tumour targeted delivery systems	546
	Liposomes in tumour therapy	547
	Micro/nanoparticles in chemotherapy	554
	Future perspectives	556
	Vascular targeting with phage peptide libraries	556
	Application of peptide nucleic acid in tumour therapy	556
	Polyethylene glycol modifications in tumour targeting	556
	Local delivery of anti-neoplastic agents using biodegradable polymers	557
	Others	557
	References	557
15.	Drug Delivery to Bone Marrow	562-585
	Introduction	562
	Stem cells and progenitor cells of bone marrow	562
	Anatomy and physiology of bone marrow	563
	Bone marrow transplantation	565

Bone marrow transplantation

Types of Transplants Bone marrow targeting Reduction in the haemopoietic damage during chemo or radiotherapy Hereditary and congenital disorders Bone marrow related diseases Drugs that have catastrophic and unpredicted action on haematopoiesis Distinct physiological functions of the components of the bone marrow

566

566

567

567

567

568

568

Bone marrow targets for drug delivery	568
Reticuloendothelial system (RES) of bone marrow for passive	
-and intravascular targeting	568
Sinusoidal capillaries for extravascular targeting	569
Haemopoietic cytokines as homing molecules	570
Carbohydrate determinants as possible homing ligands	570
Adhesion molecules as possible homing ligands	571
Colloidal carriers for bone marrow targeting	571
Colloidal particles	572
Liposomes	575
Purging of bone marrow with liposomes	578
Monoclonal antibodies and immunoconjugates for ex vivo drug delivery	580
Diagnostic imaging of bone marrow using radiolabelled particulate	581
Bone marrow transplantation using cytostatic drug loaded carriers	583
Antigen presentation to bone marrow	583
Future trends	584
References	

Index

586