Introduction to Novel Drug Delivery Systems

SP Vyas Roop K Khar Sonal Vyas

EBS Dedicated to Education CBS Publishers & Distributors Pvt Ltd

4111

Introduction to Novel Drug Delivery Systems

Introduction to Novel Drug Delivery Systems

SP Vyas PhD Postdoc

Department of Pharmaceutical Sciences Dr H S Gour University, Sagar (MP) 470003

Roop K Khar PhD

BS Anangpuria Institute of Pharmacy, Faridabad (Pt B D Sharma University of Health Sciences) Faridabad District, Alampur, Haryana 121004

Sonal Vyas MBBS MD

Practicing Pathologist Department of Pharmaceutical Sciences Dr HS Gour University, Sagar (MP) 470003



CBS Publishers & Distributors Pvt Ltd

New Delhi • Bengaluru • Chennai • Kochi • Kolkata • Mumbai Bhopal • Bhubaneswar • Hyderabad • Jharkhand • Nagpur • Patna • Pune Uttarakhand • Dhaka (Bangladesh) • Kathmandu (Nepal)

Disclaimer

Science and technology are constantly changing fields. New research and experience broaden the scope of information and knowledge. The authors have tried their best in giving information available to them while preparing the material for this book. Although, all efforts have been made to ensure optimum accuracy of the material, yet it is quite possible some errors might have been left uncorrected. The publisher, the printer and the authors will not be held responsible for any inadvertent errors, omissions or inaccuracies.

eISBN: 978-93-546-6378-9

Copyright © Authors and Publisher

First eBook Edition: 2020

All rights reserved. No part of this eBook may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system without permission, in writing, from the authors and the publisher.

Published by Satish Kumar Jain and produced by Varun Jain for CBS Publishers & Distributors Pvt. Ltd.

Corporate Office: 204 FIE, Industrial Area, Patparganj, New Delhi-110092 Ph: +91-11-49344934; Fax: +91-11-49344935; Website: www.cbspd.com; www.eduport-global.com; E-mail: eresources@cbspd.com; marketing@eduport-global.com

Head Office: CBS PLAZA, 4819/XI Prahlad Street, 24 Ansari Road, Daryaganj, New Delhi-110002, India. Ph: +91-11-23289259, 23266861, 23266867; Fax: 011-23243014; Website: www.cbspd.com; E-mail: publishing@cbspd.com; eduportglobal@gmail.com.

Branches

- Bengaluru: Seema House 2975, 17th Cross, K.R. Road, Banasankari 2nd Stage, Bengaluru 560070, Karnataka Ph: +91-80-26771678/79; Fax: +91-80-26771680; E-mail: bangalore@cbspd.com
- Chennai: No.7, Subbaraya Street Shenoy Nagar Chennai 600030, Tamil Nadu
 Ph: +91-44-26680620, 26681266; E-mail: chennai@cbspd.com
- Kochi: 36/14 Kalluvilakam, Lissie Hospital Road, Kochi 682018, Kerala
 Ph: +91-484-4059061-65; Fax: +91-484-4059065; E-mail: kochi@cbspd.com
- Mumbai: 83-C, 1st floor, Dr. E. Moses Road, Worli, Mumbai 400018, Maharashtra Ph: +91-22-24902340 - 41; Fax: +91-22-24902342; E-mail: mumbai@cbspd.com
- Kolkata: No. 6/B, Ground Floor, Rameswar Shaw Road, Kolkata 700014
 Ph: +91-33-22891126 28; E-mail: kolkata@cbspd.com

Representatives

- Hyderabad
- Pune
- Nagpur
- Manipal
- Vijayawada
- Patna

Preface

Novel Drug Delivery System refers to strategy, technology, formulation based approaches and customized system(s) developed for safe administration and within body transportation of drugs as needed for optimum therapeutic benefits while ensuring minimum to nil toxic effects.

Multidisciplinary approaches and cutting edge technology have been used to develop the carrier modules to deliver the contained drug to the target tissues in a pre-programmed manner. The process desirably modifies the drug distribution and accumulation thereby producing optimum therapeutic effects.

Carrier-mediated drug delivery has emerged as a powerful technology for the treatment of various difficult pathologies.

The therapeutic index of conventional and novel drug is enhanced owing to specificity due to targeting of drug to the particular tissue.

There has been a persistent need of a book which introduces the concept, carrier(s), material, design, novelty, present status and future prospects of various novel drug delivery systems/ carriers. The present book shall be a useful source for the undergraduates and also to all those interested in the working concepts of a system and its performance. The book contains 23 chapters including introduction to novel drug delivery, oral osmotic pumps, bioadhesive and mucoadhesive systems, multiple emulsions, colon-specific drug delivery systems, transdermal drug delivery systems, spherical crystallization, microemulsion, implants and inserts, micellar systems, liposomes, microspheres and microcapsules, nanoparticles, nanospheres and nanocapsules, resealed erythrocytes, transfersomes and ethosomes, organogels, dendrimers, niosomes, solid lipid nanoparticles, drug conjugates, cyclodextrin complexes, multifunctional nanomedicines, and floating drug delivery system(s). Each chapter attempts to discuss introduction, concept, progress, status and future prospects of the concerned novel drug delivery system. Hope the book shall be a useful compilation to the undergraduate, postgraduate, pharmacy students and researchers working in drug delivery research, research and development and National Research Institutes.

I am thankful to my research team that includes Madhu Gupta, Udita Agrawal, Devyani Dubey, Nishi Mody, Surbhi Dubey, Neeraj Mishra and Rajeev Sharma. The inputs and support from them helped enormously in bringing out the book to the presentable and printable shape. I thankfully acknowledge the support of my family who assisted me to their fullest by sparing me from family responsibilities. I place on record the motivation/inspiration of my wife Mrs Vasundhara Vyas during the preparation of this book. My sincere thanks are due to my daughter Dr Sonal, son Himanshu and daughter-in-law Akanksha who have ever been supporting. I am also thankful to CBS Publishers & Distributors Pvt. Ltd., New Delhi for their interest and support in quality printing of the book. I realize that feedback, suggestions and inputs from teachers in pharmacy, researchers and students shall help improving the next edition of the book.

Contents

Pre	face	υ
1.	Introduction to Novel Drug Delivery	1-30
	Drug Delivery 1	
	Physicochemical Properties 11	
	Biological Factors 13	
	Potential Applications of Nanocarriers in Targeted Drug Delivery 23	
	Future Opportunities and Challenges 29	
2.	Oral Osmotic Pumps	31-51
	Introduction 31	
	Osmosis: An Overview 31	
	Classification 33	
	Rose–Nelson Pump 35	
	Higuchi–Leeper Osmotic Pump 36	
	Higuchi–Theeuwes Osmotic Pump 37	
	Elementary Osmotic Pump 37	
	General Considerations and Materials Used 41	
	Modified Multichamber Elementary Osmotic Pump 44	
	Advantages 47	
	Disadvantages and Limitations 48	
3.	Bioadhesive and Mucoadhesive Systems	52-81
	Introduction 52	
	Fundamentals of Bioadhesion 53	
	Mechanism of Bioadhesion 55	
	Bioadhesion at Exposed Epithelial Surface 59	
	Naturally Occurring Bioadhesives 59	
	Factors Affecting Bioadhesion 60	
	Modulation of Mucoadhesion 63	
	Adhesion Promoters 63	
	Mucoadhesive Polymers Used in the Oral Cavity 64	
	Evaluation of Bioadhesive Drug Delivery Systems 66	
	Evaluation of Various Bloadhesion Properties 66	
	A-ray Studies for Monitoring Gi Transit /1 Recovariability Studies of Radialabalad Managartialas 72	
	Bioavailability Studies of Drug Engangulated Bioadhesiya Microscheres 72	
	Challenges 78	
	Chanenges 70	

vii	Introduction to Novel Drug Delivery Systems	
4.	Multiple Emulsions	82-91
	Introduction 82 Formulation Aspects of Multiple Emulsions 83 General Methods of Preparation 83 Applications 88	
5.	Colon-specific Drug Delivery Systems	92-130
	Introduction 92 Anatomic and Physiological Considerations 93 Factors Governing the Colon Drug Delivery 95 Targeting Approaches to Colon 101 Formulations for Colon-specific Drug Delivery 116 Conclusion 126	
6.	Transdermal Drug Delivery Systems	131-156
	Introduction 131 Skin: A Biological Barrier to Drug Transport 133 Mechanistic Aspects of Drug Delivery in TDDS 134 Factors affecting percutaneous absorption 136 Characterization of Transdermal Drug Delivery Systems 142	
7.	Spherical Crystallization	157-171
	Introduction 157 Methods of Spherical Crystallization 157 Applications of Spherical Crystallization in Pharmaceuticals 169	
8.	Microemulsion	172-195
	Introduction 172 Methods of Preparation 172 Structure of Microemulsion 174 Formulation of Microemulsion 175 Preparation of Microemulsions 180 Characterization of Lipid Microemulsion 180	
9.	Implants and Inserts	196-214
	Introduction 196 Classification 196 Classification-based on Mechanisms of Drug Release from Implants 197 Implantable Infusion Pump 199 Implantable Mini-osmotic Pump (ALZET) 201 Ophthalmic Inserts 202 Evaluation of Implantable Polymeric Materials 205 Therapeutic Applications of Implants and Inserts 207 Intra-arterial Catheter Infusion Drug Delivery System 211	
	Present Status and Future Prospects 213	

Cor	ntents	ix
10. Micellar Systems		-233
Introduction 215 Formation of Micelles 217 Critical Micellar Concentration (CMC) 218 Stability of Polymer Micelle 219 Application of Micelles in Pharmaceutical Science 225 Conclusion 231		
11. Liposomes	234	-260
Introduction 234 Mechanism(s) of Liposomes Formation 234 Classification of Liposomes 238 Characterization of Liposomes 251 Therapeutic Applications of Liposomes 252		
12. Microspheres and Microcapsules	261	-288
Introduction 261 Material(s) Used 261 Prerequisites for Ideal Microparticulate Carriers 262 Methods of Preparation 262 Loading of Drug 267 Drug Release Kinetics 268 Characterization of Microparticles 270 Various Types of Polymeric Microspheres 271 Fate of Microspheres in Body 278 Applications of Microspheres 279 Chemoembolization 284		
13. Nanoparticles	289	-317
Introduction 289 Preparation Techniques of Nanoparticles 290 Characterization of Nanoparticles 302 Therapeutic Applications of Nanoparticles 304 Magnetic Nanoparticles 312		
14. Resealed Erythrocytes	318	-341
Introduction 318 Composition of Erythrocytes 318 Erythrocytes Morphology 319 In Vitro Characterization 323 In Vivo Survival and Immunological Consequences 325 Pharmacokinetics of Drugs or Peptides Administered in Loaded Erythrocytes Applications of Carrier Red Cells 327 Other Applications 338	326	

x	Introduction to Novel Drug Delivery Systems	
15. T	iransfersomes and Ethosomes	342-358
I S	Introduction 342 Bkin 343	
] H	Transfersomes 344 Ethosomes 351	
16. (Organogels	359-377
	Introduction 359 Organogelators 360 Properties of Organogelators 365 Low Molecular Weight Organogelators 367 Organogels as Drug Delivery Vehicles 370	
17. [Dendrimers	378-392
I C I I I I C S S Z Z I	Introduction 378 Origin of Dendrimers 379 Dendrimers and Polymers: A Comparison 380 Properties of Dendrimers 381 Featured Advantages of Dendrimers as Drug Carrier 381 Classification of Dendrimers 381 Synthesis and Designing of Dendrimers 382 Analytical Methods for Structure Validation of Dendrimers 384 Dendrimer Toxicity 385	
18. 1	Niosomes	393-415
I F C S T	Introduction 393 Formulation Aspects 394 Methods of Preparation 399 Characterization of Niosomes 401 Stability of Niosomes 404 Types of Niosomes 405 Applications of Niosomes 409	
19. 5	Solid Lipid Nanoparticles	416-439
I S I N I	Introduction 416 Advantages of SLNs as Alternative Particulate Carrier 416 SLNs versus Other Colloidal Drug Carriers 417 Ingredients and Formulation Processes 418 Microemulsion-based SLNs Preparations 420 Influence of Ingredient Composition on Product Quality 424	_

Characterization of SLNs 425

Toxicity Aspects and In Vivo Fate of SLNs 434

Applications of SLNs in Drug Delivery 434

	Contents	xi
20. Drug Conjugates	440	-469
Introduction 440		
Bioconjugate Techniques 440		
Glutaraldehyde-based Hapten-carrier Conjugation 447		
Carbodiimide-based Conjugation to Phosphatidylethanolami	ine Lipid Derivatives 4	147
Glutaraldehyde-based Conjugation to Phosphatidylethanolar	mine Lipid Derivative	447
Avidin-biotin System 448		
Preparation of Colloidal Gold-labeled Proteins 449		
Radiolabeled Antibodies 450		
Antibody-toxin Conjugates 451		
Protein Conjugates of Fungal Toxins 452		
Poly-L-lysine Conjugates 453		
Dextran and Inulin Conjugates as Drug Carriers 456		
Lectin as Carrier 456		
Glycoproteins as Drug Carriers 457		
Galactose Terminated Fetuin as Carriers for Pepstatin 457		
Bioconjugates with Protein Drugs 458		
Polymer-drug Conjugates 459		
Advantages in the Preparation of Bioconjugates with Low Meight Drugs 461	olecular	
Limitations in the Conjugation of Polymers to Low Molecula	r Weight Drugs 462	
Polyglutamic Acid (PGA)-E-[c(RGDfk)2]-paclitaxel Conjugat	e 463	
N-(2-hydroxypropyl) Methacrylamide (HPMA)-based Polym	ieric	
Drug Conjugates 465		
Polyethylene Glycol (PEG)-based Polymeric Drug Conjugates	s 467	

21. Cyclodextrin Complexes

470-488

Introduction 470 Cyclodextrin-based Products 471 Advantages 472 Limitations 473 Mechanism of Drug Cyclodextrin Complexation 473 Inclusion and Noninclusion Complexes 475 Methods to Enhance the Complexation Efficiency 476 Toxicological Aspects 476 Drug Availability from CD-containing Products 477 Regulatory Status 477 Patents 478 Pharmaceutical Applications of Drug-CD Complexes 479 CD Used in the Design of Delivery Systems 483

xii	Introduction to Novel Drug Delivery Systems	
22.	Multifunctional Nanomedicines	489-509
	Introduction 489	
	Designing of Multifunctional Nanomedicines 490	
	Applications 493	
23.	Floating Drug Delivery System(s)	510-527
	Introduction 510	
	Low Density System or Floating Drug Delivery System 511	
	Classification of FDDS: Classification of Single Unit FDDS 512	
	Classification of Multiple Unit FDDS 513	
	Raft Forming Systems 515	
	Ingredients Used in Preparation of FDDS 515	
•	List of Drugs Explored for Various Floating Dosage Forms 515	
	Approaches to Design FDDS 516	
	Formulation Development and Mechanism of FDDS 519	
	In Vitro and In Vivo Evaluation 520	
	Advantages of FDDS 521	
	Disadvantages of FDDS 522	
	Marketed Products of FDDS 522	
	Applications of FDDS 523	
	Pharmaceutical Aspects 525	
	Future Perspectives in FDDS 525	

Index

.

529