This book presents new approaches for the management of skin aging and photocarcinogenesis and topical formulations based on nanocarrier systems for skin disorders. It discusses cosmeceuticals, laser, photodynamic therapy, and melatonin-based treatments as important strategies for photoaging management. The book covers topical formulations, including emulsions (conventional formulations and emulsions stabilized by solid particles), nail films, and nanocarriers used for the delivery of actives in various skin and nail diseases such as acne, psoriasis, atopic dermatitis, fungal diseases, leishmaniasis, and skin cancer. Finally, it introduces several nanocarriers, such as lipid vesicles (ranging from the first-generation conventional liposomes to the more recent deformable vesicles), liquid crystalline nanodispersions, gelatin, and solid lipid nanoparticles. It elaborates their composition, formulation, characterization, and topical applications. The book also presents the most important (nano)pharmaceutical formulations, although it is a broad topic.

Andreia Ascenso is professor of pharmaceutical technology in the Faculty of Pharmacy, University of Lisbon, Portugal. She manages the Nanomedicine and Drug Delivery Systems group of the Research Institute for Medicines (iMed.ULisboa) and collaborates with other research teams from the University of Aveiro, Portugal, and Universidade de São Paulo, Brazil. Her research focuses on the study of antioxidants and new drugs incorporated into nanocarriers topically delivered for the management of skin disorders.

Sandra Simões is a researcher at iMed.ULisboa. Her research work focuses on the design, development, and biological evaluation of drug delivery systems for topical application and dermal and transdermal delivery, with special application on the topical delivery of antioxidants and on the chemoprevention of skin photocarcinogenesis.

Helena Ribeiro is associate professor in the Faculty of Pharmacy, University of Lisbon, and a researcher at iMed.ULisboa. She brings over 30 years of experience as a formulating pharmacist to her role as a personal care, pharmaceutical, and cosmetic research and industry expert. Dr. Ribeiro was a fellow at L’Oreal, Université Libre de Bruxelles, Belgium, and Strathclyde University, UK. She has been involved in the development of a number of products and has 40 papers, more than 100 communications, and 1 patent to her credit.
Carrier-Mediated Dermal Delivery
Carrier-Mediated Dermal Delivery

Applications in the Prevention and Treatment of Skin Disorders

edited by
Andreia Ascenso
Sandra Simões
Helena Ribeiro
## Contents

*Preface*  
vii

### PART 1: NEW APPROACHES FOR MANAGEMENT OF SKIN AGING AND PHOTOCARCINOGENESIS

1. **New Trends in Anti-Aging Skin Care**  
   *Joice Lana and Andreia Ascenso*
   
   1.1 Introduction  
   1.2 Skin  
      1.2.1 Structure  
         1.2.1.1 Epidermis  
         1.2.1.2 Dermis  
      1.2.2 Innervation  
         1.2.2.1 Sensory receptors  
         1.2.2.2 Non-sensory receptors  
         1.2.2.3 Neuropeptides  
      1.2.3 Skin Changes with Aging  
   1.3 Rejuvenation Procedures  
      1.3.1 Injectable Techniques  
         1.3.1.1 Skin resurfacing techniques: Chemical peelings and dermabrasion  
         1.3.1.2 Skin resurfacing techniques: Laser and light therapy  
      1.3.2 Cosmeceuticals  
      1.3.3 Procedures Comparison  
   1.4 Conclusions and Future Perspectives

2. **Melatonin: A “Guardian” of the Genome and Cellular Integrity for Prevention of Photocarcinogenesis**  
   *Patrícia Manteigas and Andreia Ascenso*
   
   2.1 Introduction
2.2 What Is Melatonin? 4
2.3 Melatoninergic System 4
  2.3.1 Synthesis of Melatonin in the Skin 4
  2.3.2 Melatonin and Its Metabolites 4
  2.3.3 Melatonin Receptors in the Skin 5
  2.3.4 Mechanism of Action 5
2.4 Photocarcinogenesis 5
  2.4.1 Genomic Instability and Its Impact on Photocarcinogenesis 6
  2.4.2 Circadian Cycle Connection between Cell Physiology and Photocarcinogenesis 6
2.5 Melatonin as a “Guardian” for Prevention of Photocarcinogenesis 6
  2.5.1 Endogenous and Exogenous Anti-Oxidant as Skin Defenders 6
  2.5.2 Melatonin Protects against Skin Photodamage 6
  2.5.3 Cosmetic and Therapeutic Perspectives 7
2.6 Conclusion 7

3. Safety and Efficacy of Sunscreen Formulations Containing Carrier or Non-Carrier-Based UV-Filters 91
   Carolina Gomes Benevenuto and Lorena Rigo Gaspar
   3.1 UV Radiation and the Skin 92
   3.2 UV-Filters and Photoprotection 94
   3.3 Chemical UV-Filters 95
     3.3.1 Nanocarrier-Based Chemical UV-Filters 98
   3.4 Physical UV-Filters 98
     3.4.1 Nanocarrier-Based Physical UV-Filters 99
     3.4.2 Side Effects of Carrier- and Non-Carrier-Based Physical UV-Filters 100
   3.5 Assessment of Sunscreen Performance 102
     3.5.1 Efficacy of Carrier- and Non-Carrier-Based UV-Filters 102
3.5.1.1 Efficacy-characterization of carrier-based UV-filters 105
3.5.2 Safety of Carrier- and Non-Carrier-Based UV-Filters 105
3.5.3 Stability and Photostability of Carrier- and Non-Carrier-Based UV-Filters 108
3.6 Conclusions 109

Fabíola Silva Garcia Praça, Patrícia Mazureki Campos, Josimar O. Eloy, Raquel Petrilli, Maria Vitória Lopes Badra Bentley, and Wanessa Silva Garcia Medina

4.1 Introduction 123
4.2 Photodynamic Therapy and Mechanism of Photosensitization 124
4.3 Most Commonly Used Photosensitizers for Dermatological Diseases 126
4.3.1 Topical Photodynamic Therapy with Aminolevulinic Acid and Methyl Aminolevulinic 126
4.3.2 Topical Photodynamic Therapy with Phthalocyanines Class and Chlorine Derivatives 128
4.4 PDT Applied to Skin Diseases 131
4.4.1 Skin Cancer Treatment 133
4.4.1.1 Actinic keratosis and squamous cell carcinoma in situ 133
4.4.1.2 Non-melanoma carcinoma 135
4.4.2 Other Skin Disease Treatments 139
4.4.2.1 Viral lesions treated with PDT 139
4.4.2.2 Bacterial lesion treated with PDT 140
## Contents

4.4.2.3 Fungal skin lesions treated with PDT 141
4.4.2.4 Other microbiological lesions treated with PDT 142
4.4.2.5 Other inflammatory lesions treated with PDT 143
4.4.2.6 Other dermatological applications of PDT 144

4.5 Nanocarriers and Physical Methods for Improved Dermal Skin Delivery of Photosensitizers in PDT 146
  4.5.1 Nanocarriers used in Topical PDT 147
    4.5.1.1 Polymeric carriers 148
    4.5.1.2 Lipid-based carriers 149
    4.5.1.3 Inorganic nanoparticles 151
  4.5.2 Physical Methods Applied for PDT 152

4.6 Potentials and Limitations of Topical PDT 154

### PART 2: DELIVERY SYSTEMS AND NANOCARRIERS FOR TOPICAL ROUTE: EXAMPLES AND ILLUSTRATION OF SOME THERAPEUTIC AND COSMETIC APPLICATIONS

5. Novel Starch-Derived Topical Delivery Systems 175
   Joana Marto, Inês Jorge, António José de Almeida, and Helena Margarida Ribeiro

5.1 Introduction 175
   5.1.1 Starch: Functional Characteristics and Relevance 175
     5.1.1.1 Modified Starch: A Strategy to Prepare High Performance Starch 179
     5.1.1.2 Starches: From Granules to Novel Applications 180

5.2 Topical Delivery Systems 186
   5.2.1 Conventional Topical Delivery Systems 186
     5.2.1.1 Emulsions 186
     5.2.1.2 Gels 191
5.2.1.3 Starch in Personal Care: A Multifunctional Ingredient 198

5.2.2 Non-Conventional Topical Delivery Systems 201
5.2.2.1 Polymeric Nanoparticles 201

5.3 Conclusions 208

6. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers as Topical Delivery Systems for Antioxidants 217

Carla Vitorino and António J. Almeida

6.1 Introduction 217
6.2 Antioxidants 226
   6.2.1 Vitamins 235
      6.2.1.1 Vitamin A and derivatives 235
      6.2.1.2 Ascorbic acid derivatives 236
      6.2.1.3 Vitamin E derivatives 238
   6.2.2 Carotenoids 238
      6.2.2.1 Beta-carotene 239
      6.2.2.2 Lutein 240
   6.2.3 Co-factors 241
      6.2.3.1 Coenzyme Q10 241
      6.2.3.2 Idebenone 243
      6.2.3.3 Alpha-lipoic acid 243
   6.2.4 Polyphenols 244
      6.2.4.1 Flavonoids 244
      6.2.4.2 Phenolic acid derivatives 247
      6.2.4.3 Other polyphenols 248

6.3 Conclusions 250

7. Manufacture and Applications of Gelatin Nanoparticles: A Practical Approach 265

Diogo Pineda Rivelli and Silvia Berlanga de Moraes Barros

7.1 Introduction 265
7.2 Preparation methods 266
7.2.1 Desolvation 266
7.2.2 Emulsification-Solvent Evaporation 269
7.2.3 Reverse-Phase Microemulsion 269
7.2.4 Nanoprecipitation 270
7.2.5 Self-Assembly 270
7.2.6 Layer-by-Layer Coating 271
7.3 Uses 271
7.3.1 Ilex paraguariensis Extract Gelatin Encapsulation 272

8. Lipid Vesicles for Skin Delivery: Evolution from First Generation 281
Tiago Mendes, Maria Manuela Gaspar, Sandra Simões, and Andreia Ascenso

8.1 Introduction 281
8.2 Vesicles Composition 283
8.3 Preparation Methods 286
8.4 Vesicles Characterization 290
8.5 Pharmacokinetics 293
8.6 Toxicology 297
8.7 Evolution from First Generation 298
8.8 Therapeutic, Diagnostic, and Cosmetic Applications 304
8.9 Regulatory Considerations 306
8.10 Conclusion and Future Perspectives 307

9. Archaeosomes for Skin Injuries 323
Monica Vazzana, Joana F. Fangueiro, Caterina Faggio, Antonello Santini, and Eliana B. Souto

9.1 Introduction 323
9.2 Archaeosomes: Definitions and Properties 328
9.2.1 Biotechnological Applications of Archaeosomes 332
9.2.2 Preparation and Physicochemical Characterization of Archaeosomes 335
9.3 Other Ultradeformable Liposomes 342
9.4 Applications for Skin Injuries 342
9.5 Conclusions 350

10. Ethosomes: A Novel Carrier for Dermal or Transdermal Drug Delivery 357

Dinesh Kumar Mishra, Neelam Balekar, Vinod Dhote, and Pradyumna Kumar Mishra

10.1 Introduction 357
10.2 Novel Carriers as Tools for Modulation of Skin Permeability 360
  10.2.1 Microparticles/Nanoparticles 361
  10.2.2 Liposomes 361
  10.2.3 Elastic Liposomes 362
  10.2.4 Niosomes 362
  10.2.5 Ethosomes 363
    10.2.5.1 Ethosomes composition 364
    10.2.5.2 Mechanism of skin penetration 365
    10.2.5.3 Advantages and limitations 367
    10.2.5.4 Methods of preparation 368
    10.2.5.5 Characterization of ethosomes 370
    10.2.5.6 Stability of ethosomes 372
10.3 Applications 373
  10.3.1 Pilosebaceous Targeting 373
  10.3.2 Hormones Delivery 374
  10.3.3 Antimicrobial Delivery 374
  10.3.4 DNA Delivery 374
  10.3.5 Macromolecules Delivery 374
  10.3.6 Vaccines Delivery 375
  10.3.7 Cosmeceuticals 375
10.4 Marketed Products Based on Ethosomes 376
10.5 Translational Perspective 377
11. Lipid-Based Nanocarriers for the Treatment of Infected Skin Lesions 385

*Sandra Simões, Manuela Carvalheiro, and Maria Manuela Gaspar*

11.1 Skin Infections 385
   11.1.1 Mycobacterial Skin Infections 386
      11.1.1.1 Buruli ulcer 387
   11.1.2 Parasitic Skin Infections 389
      11.1.2.1 Cutaneous leishmaniasis 390
   11.1.3 Current Therapies 393
      11.1.3.1 Buruli ulcer 394
      11.1.3.2 Cutaneous leishmaniasis 396

11.2 Advanced Drug Delivery Systems in Topical Therapy 399
   11.2.1 The Skin Barrier 400
   11.2.2 Overcoming the Skin Barrier 402
      11.2.2.1 Strategies for intact skin 403
      11.2.2.2 Permeation in infected skin 404
   11.2.3 Lipid-Based Nanocarriers Applied in the Treatment of Buruli Ulcer and Cutaneous Leishmaniasis 406
      11.2.3.1 Liposomes 407
      11.2.3.2 Transfersomes 412
      11.2.3.3 Ethosomes 413
      11.2.3.4 Other 414

11.3 Conclusions 415

12. Liquid Crystals as Drug Delivery Systems for Skin Applications 431

*Marilisa Guimarães Lara*

12.1 Liquid Crystals 431
12.2 Liquid Crystal-Forming Lipids 433
12.3 Liquid Crystalline Macroscopic Forms 434
12.4 Liquid Crystalline Mesophases 436
12.5 Identification of Mesophases 438
12.6 Factors That Affect the Formation of Liquid Crystals 439
12.7 Liquid Crystals as Drug Release Systems 442
12.8 Liquid Crystals and Skin Permeation 446

13. Cyclodextrins and Skin Disorders: Therapeutic and Cosmetic Applications 463

Oluwatomiide Adeoye, Ana Figueiredo, and Helena Cabral Marques

13.1 Introduction 463
13.2 Cyclodextrins: Historical Background and Description 464
13.3 Cyclodextrin-Guest Molecule Complexes 469
13.4 Skin Safety and Toxicity Considerations of Cyclodextrins 471
13.5 Cyclodextrins and Dermal Drug Delivery 471
   13.5.1 Enhancement of Dermal Drug Absorption and/or Penetration 473
   13.5.2 Enhancement of Drug Tolerability 475
   13.5.3 Enhancement of Drug Stability in Dermal Formulations 475
      13.5.3.1 Encapsulation and controlled delivery of volatile compounds 476
13.6 Application of Cyclodextrin in Dermatologic Products 477
   13.6.1 Anti-Acne 478
   13.6.2 Psoriasis 479
   13.6.3 Dermatitis 480
   13.6.4 Microbial Skin Diseases 481
   13.6.5 Wound Healing 482
13.7 Application of Cyclodextrins in Cosmetics 483
   13.7.1 Deodorants and Formulations for Odour Control 484
   13.7.2 Fragrances 485
   13.7.3 Sunscreens 485
13.7.4 Skin Cleansers and Scrubs 486
13.8 Conclusions and Prospects for the Future 487

14. Topical Formulations for Onychomycosis: A Review 503

Barbara S. Gregori Valdes, Carolina de Carvalho Moore Vilela, Andreia Ascenso, João Moura Bordado, and Helena M. Ribeiro

14.1 Introduction 503
14.2 Onychomycosis 504
  14.2.1 Epidemiology 504
  14.2.2 Risk Factors 505
  14.2.3 Clinical Classification 506
    14.2.3.1 Distal and lateral subungual onychomycosis 506
    14.2.3.2 Proximal subungual onychomycosis 507
    14.2.3.3 Superficial white onychomycosis 507
    14.2.3.4 Endonyx onychomycosis 507
    14.2.3.5 Total dystrophic onychomycosis 508
14.3 Transungual Delivery 508
  14.3.1 Nail Structure and Transungual Permeation 508
    14.3.1.1 Mathematical description of nail permeability 511
14.4 Onychomycosis Topical Therapy 512
  14.4.1 Drug Delivery Enhancers 513
    14.4.1.1 Disulfide bond cleaving by reducing agents 514
    14.4.1.2 Disulfide bond cleaving by oxidizing agents 514
    14.4.1.3 Enhancement by solvents 514
    14.4.1.4 Keratolytic agents 515
    14.4.1.5 Enzymes 515
    14.4.1.6 Other enhancers 516
  14.4.2 Examples of Antifungal Drugs 518
14.4.3 Examples of Topical Pharmaceutical Forms
  14.4.3.1 Cream 525
  14.4.3.2 Solution 525
  14.4.3.3 Gel 527
  14.4.3.4 Nail lacquer 528

14.4.4 Nail Lacquer Formulations for Onychomycosis Treatment 529

14.4.5 Advances in Nail Formulations 538
  14.4.5.1 Colloidal carriers 538

14.5 Conclusion 541

Index 555
Preface

We are honored to present to the readers the book entitled *Carrier-Mediated Dermal Delivery: Applications in the Prevention and Treatment of Skin Disorders*, which is based on the systematic revision of the most recent findings. This book contains several contributions on new approaches for the management of skin aging and photocarcinogenesis and topical formulations based on nanocarrier systems for skin disorders. These chapters discuss the structure and skin morphology in detail. Cosmeceuticals, laser and photodynamic therapy, and melatonin-based treatments are presented as important strategies for photoaging management. Photodynamic therapy and melatonin can be also used in the context of photocarcinogenesis. Therefore, the inclusion of this strong antioxidant in sunscreen products could be a promising approach. The book discusses the safety and efficacy of sunscreen products as well.

Topical formulations, including emulsions (conventional formulations and emulsions stabilized by solid particles), nail films, and nanocarriers used for different actives delivery, are reviewed concerning certain skin and nail diseases context (e.g., acne, psoriasis, atopic dermatitis, fungal diseases, leishmaniasis, skin cancer). Finally, several nanocarriers are introduced, such as lipid vesicles (from the first generation of conventional liposomes until the more recent deformable vesicles), liquid crystalline nanodispersions, and gelatin and solid lipid nanoparticles. Their composition, formulation process, characterization, and examples of topical applications are discussed in detail for each system. In fact, these nanocarrier systems can be useful as topical and/or transdermal delivery systems attending to a higher skin penetration and permeation profiles, besides contributing to improving technological drawbacks (e.g., formulation stability) and increasing the therapeutic index.
Although this is a quite broad topic, the most important (nano)pharmaceutical formulations are presented in the book. Future perspectives are also discussed in some chapters. This book will be a useful reference for researchers and professionals interested in nanotechnology in the skin delivery context.