ISSN 2041-5990

Therapeutic Delivery

newlands press

Future Science

Therapeutic Delivery – Editorial Advisory Board

Senior Editors

Banga AK, Mercer University, Atlanta, GA, USA

Dr. Ajay K. Banga is a Professor in the Department of Pharmaceutical Sciences at the College of Pharmacy, Mercer University (Atlanta, GA). He serves as Department Chair and as Endowed Chair in transdermal delivery systems. He has served as a consultant to over 25 companies in the area of his research expertise, which is skin delivery systems. Such systems include traditional transdermal patches, dermatologicals, and non-traditional delivery approaches, such as microneedles and iontophoresis, for the delivery of small conventional drugs, macromolecules, and cosmetic actives. Dr. Banga has a Ph.D. in Pharmaceutics from Rutgers University (NJ, USA). He has mentored 40 Ph.D. students as their major advisor, and his laboratory has been funded by over 90 grants/contracts from leading pharmaceutical and cosmetic companies, and by federal funds. Dr. Banga currently serves on the Editorial Board of 10 journals and has served as the Editor-in-Chief for a drug delivery journal. He has written three books in the areas of proteins and transdermal delivery, and published 140 manuscripts, 12 book chapters, and 200 conference abstracts. He has given over 80 invited lectures, and served on over 60 thesis/dissertation advisory committees and as a referee for over 40

journals. He is a Fellow of the American Association of Pharmaceutical Scientists (AAPS).

Associate Editors

Brayden D, University College Dublin, Republic of Ireland

Prof. David Brayden is Full Professor of Advanced Drug Delivery at the School of Veterinary Medicine, University College Dublin (UCD) and also a Fellow of the UCD Conway Institute. Following a Ph.D. in Pharmacology at the University of Cambridge, UK (1989), and a post-doctoral research fellowship at Stanford University (CA, USA), he set up Elan Biotechnology Research's in vitro pharmacology laboratory in Dublin (1991). At Elan, he became a senior scientist and project manager of several of Elan's Joint-Venture drug delivery research collaborations with US biotech companies. In 2001, he joined UCD as a lecturer in veterinary pharmacology and was appointed Associate Professor in 2006 and Full Professor in 2014. He was Director of the Science Foundation Ireland (SFI) Research Cluster (The Irish Drug Delivery Research Network) from 2007-2013, is Deputy Coordinator of an FP7 Consortium on oral peptides in nanoparticles ("TRANS-INT", 2012-2017), and is a Co-Principal Investigator in "CURAM", SFI's Centre for Medical Devices (2014-2020). He was made a Fellow of the Controlled Release Society in 2012. He is the author or co-author of more than 200 research publications and patents. Professor Brayden serves on the Editorial Advisory Boards of Drug Discovery Today, European Journal of Pharmaceutical Sciences, Advanced Drug Delivery Reviews, the Journal of Veterinary Pharmacology and Therapeutics, and Frontiers in Drug Delivery.

Professor Brayden works as an independent consultant for drug delivery companies.

Chow MSS, Western University of Health Sciences, CA, USA

Moses is currently Professor of Pharmacy Practice and Director of the Center for Advancement of Drug Research and Evaluation at the College of Pharmacy, Western University of Health Sciences., in Pomona, California. He was a graduate of the University of California San Francisco. His previous appointments included Professor of Clinical Pharmacy at the University of Connecticut (UCONN), and Professor of Pharmacy and Director of the School of Pharmacy at the Chinese University of Hong Kong (CUHK). At UCONN, his research efforts were devoted primarily to pharmacokinetics and cardiovascular pharmacology and at CUHK, his research team concentrated in pharmacogenetics, drug development of herbal products and sublingual drug delivery. His current research efforts are in translational research and drug development, especially herbal product for cancer. He has supervised/co-supervised over 40 Masters and Ph.D. degree students and post-doctoral fellows. He has authored/co-authored over 300 hundred articles, book chapters, and monographs. His has served as consultant to the Clinical Trial Committee of NHLBI, NIH and USP. He has also served as Advisory Editorial Board number of several pharmaceutical journals including section editor of Journal of Clinical Pharmacology. In addition he has served as Secretary and Board member of the American College of Clinical Pharmacology, President of the American Chinese Pharmaceutical Association, and Founding President and Board member of the Asian Association of Schools of Pharmacy. He is a

fellow of the American College of Clinical Pharmacy as well as American College of Clinical Pharmacology.

Dinh S, CutisPharma, Wilmington, MA, USA

Steve is currently Executive Vice President and Chief Scientific Officer at CutisPharma. During his tenure in the pharma/biotech industry, he has been involved in building and leading multinational organizations to develop and commercialize small molecule and biologics drug products by applying innovative drug delivery technologies. His work in drug delivery technology innovations and pharmaceutical product development have resulted in over 60 US patent publications, and numerous NDA and ANDA approvals. He also serves on the Board of Advisors in the College of Arts and Sciences at FIU, and provides guidance to entrepreneurship and innovation. He is a Fellow of the American Association of Pharmaceutical Scientists, and a Fellow of the American Institute for Medical and Biological Engineering. Steve received his doctoral degree from the Massachusetts Institute of Technology.

French E, Pfizer Ltd, UK

Lennernäs H, Uppsala University, Sweden

Dr. Hans Lennernäs is a full professor of Biopharmaceutics at Uppsala University since 1 July 2000, Sweden and he also holds an adjunct professor of Biopharmaceutics at Royal Danish School of Pharmacy in Copenhagen, Denmark since 2000. Since 2004 he is also the chief Scinetific Office of LIDDS AB (www.liddspharma.com) and the scientific adviser to Duocort AB (www.duocort.com). His research interest is focused on clinical significance of mechanisms and regulation of membrane transport and metabolism of drugs/metabolites in the gastrointestinal tract, hepatobiliary system and cancer tissues. This work is performed in vivo with clinical models in humans and in various tissue and cell culture models. His research aims to develop novel strategies of tissue drug targeting and delivery that aims to improve the clinical use and efficacy of drugs in various disease states, such as metabolic and cancer diseases. Hans Lennernäs has together with gastroenterologists developed and validated two new clinical intestinal perfusion techniques for investigations of intestinal transport and metabolism of drugs and nutrients. He has been the Principal Investigator in an extensive collaboration with Food Drug & Administration, USA, University of Michigan, USA, and Medical Product Agency, Sweden during several years to develop a new guideline for the Biopharmaceutics Classification System. He has established an extensive human permeability database (45 compounds) that today is widely used in academia and pharmaceutical industry. Dr. Lennernäs has been the chairman for numerous international conferences. He serves as reviewer for several scientific journals in clinical pharmacology and pharmaceutical science. His work had led to more 140 publications, 190 invited lectures and more than 300 submitted presentations at scientific meetings. He has supervised 16 doctorial theses and acted as co-supervisor for two neurologists. He has obtained several national and international research grants. Dr. Lennernäs has received Glaxo Wellcome Achievement Award 1997 and Annual Award from the Industrial Pharmacy Section 1998, Fédération Internationale Pharmaceutique (FIP), a Honourable Mentions at EURAND AWARD 2000, been elected the

AAPS Fellow 2004, the AAPS Meritorious Manuscript Award 2004 and the EUFEPS New Safe Medicines Faster Award In Drug Development Science 2008. He is on the board of the non-profit Drug Delivery Foundation, which promotes research and education in this area all around the world. He is also one of the innovators to a novel sublingual drug delivery system for the treatment of various acute pain conditions (Rapinyl®). He has invented seven patent/patent applications, which have resulted in drug products in clinical phase (I, II and III clinical trials). These two start-up companies are focused of a novel oral replacement therapy (www.duocort.com) and focal drug treatment of prostate cancer (www.liddspharma.com). His research team is currently composed of 6 Ph.D. students, and has an extensive national and international interdisciplinary collaboration with both universities and national and international pharmaceutical companies.

Ogris M, Ludwig-Maximilians Universitat München, Germany

Manfred is a Biotechnologist with a tenured position as a group leader at the Department of Pharmacy, Center for Drug Research. Within his research group, macromolecular carrier systems with a focus on nucleic acid delivery are developed for tumor therapy. Several projects are pursued in the field of targeted gene delivery ex vivo and after systemic administration in tumor models in vivo. Bioimaging methods based on near infrared fluorescence and bioluminescence are applied in rodents to optimize tumor targeted nucleic acid carriers. Therapeutic approaches include cancer gene therapy in combination with chemotherapy or radiation, but also tumor targeted delivery of immune-stimulatory and pro-apoptotic RNA. Several projects are carried out within national and international research cooperation with academic groups and the pharmaceutical industry. As a lecturer Manfred teaches Pharmaceutical

Biology and Biochemistry at the Faculty for Chemistry and Pharmacy. Before starting as a group leader in Munich in 2001, Manfred was a post-doctoral research fellow at the CRC Institute for Cancer Research in Birmingham/UK and was granted a Marie Curie Fellowship from the European Union. Manfred obtained his PhD in Biotechnology in 1999 at the University of Natural Resources and Applied Life Sciences in Vienna/Austria.

Patton JS, Dance Pharmaceuticals, San Francisco, CA, USA

John is a biotechnologist and entrepreneur in the field of drug delivery, particularly peptide and protein delivery. Prior to founding Dance this year, he was co-founder of Inhale Therapeutics (now Nektar), where he served as a Director, Head of Research and Chief Scientific Officer from 1990-2008. Before that he led the drug delivery group at Genentech (l985-1990), where he demonstrated the feasibility of systemic delivery of large molecules through the lungs. Prior to joining Genentech, Dr. Patton was a tenured professor at the University of Georgia. Dr. Patton received his Ph.D. in marine biology from the University of California, San Diego, and held post-doctoral positions in biomedicine at Harvard Medical School and the University of Lund, Sweden. He serves on scientific advisory boards for Penn State University, Scripps Institution of Oceanography and Aridis Pharmaceuticals as well as the executive boards of Halozyme, Pikamab and Pleiades Cardiotherapeutics. He is author or co-author of >100 publications and inventor or co-inventor of >30 patents.

Prud'homme RK, Princeton University, NJ, USA

Tendler S, University of York, UK

Saul is Deputy Vice-Chancellor and Provost at the University of York. He attended the University of Manchester, where he graduated with First Class Honours in Pharmacy in 1982. He subsequently qualified as a pharmacist in 1983. His doctoral studies were undertaken at the University of Aston where he was awarded his PhD in Pharmaceutical Sciences in 1986. Following a personal MRC Fellowship at the National Institute for Medical Research, Mill Hill, Saul was appointed in 1988 to the academic staff of the University of Nottingham's School of Pharmaceutical Sciences. He was promoted to a personal Chair of Biophysical Chemistry in1998. From 1999-2003 Professor Tendler was the Dean of the Graduate School, from 2009-2015 he was a Pro-Vice-Chancellor of the University of Nottingham.

Professor Tendler's research is directed towards the biophysical investigation of biomolecular systems and their interactions. He has over two hundred peer reviewed publications in this field. These studies have been recognized through a number of international prizes including the 1998 Pfizer Prize. He was the recipient of the Royal Society of Chemistry Theophilus Redwood 2003 Lectureship and his laboratory was awarded the 2003 GlaxoSmithKline International Achievement Award by the Royal Pharmaceutical Society of Great Britain.In 2007 Professor Tendler was awarded his DSc by the University of Nottingham.

Wang G, China Pharmaceutical University, China

Dr Guangji Wang is Professor and director in the Key Lab of Drug Metabolism and Pharmacokinetics, China Pharmaceutical University, Nanjing, Jiangsu, China. Prof. Wang obtained Ph.D at University of Otago under supervision of Prof. Michael Stephen Roberts, and then worked as a postdoctoral Fellow at the University of Otago. His research is major in evaluation and investigation system of preclinical pharmacokinetic, including drug absorption, transport, and metabolism in vivo and in vitro. His laboratory is currently devoted to the research of pharmacokinetics of traditional Chinese medicine, cell pharmacokinetics etc. Prof. Wang has been elected as the president of Application Pharmacological Committee under Chinese Pharmacy Society, Vice-president of Drug Metabolism and Pharmacokinetics Committee under Chinese Pharmacological Society, President of China Pharmacy Engineering Pharmacological Society. Prof. Wang is a Member of the International Society of the Study of Xenobiotics (ISSX). His laboratory is funded by many national key research projects and pharmaceutical companies. Prof. Wang is an associate editor and editorial member of 5 journals and a referee for over 12 journals. He is an editor-in-chief of two books in the areas of pharmacokinetics.

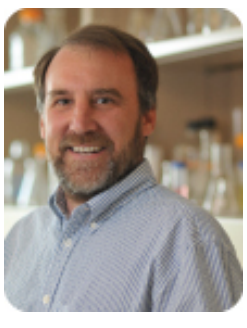
International Editorial Advisory Board

Al-Salami H,Curtin University, Perth, Australia

Professor Hani Al-Salami is an AHPRA registered Australian and New Zealand pharmacist, a clinician, an academic, and a Program Lead in Biotechnology and Pharmaceutical Sciences at Curtin Medical School and Curtin Health Innovation Research Institute. In November 2020, Dr Al-Salami's team was declared the overall winner at the Curtin Innovation Program for most innovative inner-ear drug delivery for treating hearing loss. In May 2021, Dr Al-Salami took a new jointly created role as the Head of Hearing Therapeutics Department at Ear Science Institute Australia. The new role focuses on development of novel and commerciable therapeutics to reduce burden associated with disorders which compromise hearing. Dr Al-Salami, originally from New Zealand, was trained at the School of Pharmacy, Otago University, and owned a Dunedin-based pharmacy prior to commencing a doctorate supported by the pharmaceutical industry. He moved to Montreal (Canada) for postdoctoral training at the Artificial Cell and Organs Research Centre at McGill University andthe drug company Micropharma Ltd, under Prof Thomas Chang and Prof Satya Prakash (nano/microencapsulation pioneers and nominated Nobel Prize Laureate in medicine). Dr Al-Salami moved to Curtin University where he founded his lab, the Biotechnology and Drug Development Research Lab (2014). He has published > 150 publications and conference presentations, including books, book chapters and research papers. Dr Al-Salami research is currently supported by the Australian Medical Health Research Council, the European Horizon 2020, Cures Within Reach (USA), and the pharmaceutical industry nationally and internationally (Australia, China, and the EU).

Arora M, University of Alamaba, AL, USA

Dr. Arora is an Associate Professor in the Bioscience and Medicine stream at the College of Community Health Sciences (CCHS) and holds a joint appointment in the Department of Biological Sciences, The University of Alabama. Following a Ph.D. (2001) in Chemistry at the Indian Institute of Technology Roorkee, India and a few research appointments at a) University of Kentucky Medical Center, Lexington, USA, b) Saarland University, Saarbruecken, Germany, c) University of Strathclyde, Glasgow, and d) Texas A&M University, College Station, USA, she joined The University of Alabama in Jan 2021. Her current interests include custom polymers for modular drug delivery applications and has expertise in bioanalytical methods. Her recent research is funded through grants as a CO-PI from the National Institutes of Health.



Anchordoquy T, University of Colorado, CO, USA

Dr. Anchordoquy is an associate professor of pharmaceutical biotechnology in the University of Colorado Denver School of Pharmacy on the Anschutz Medical Campus in Aurora, Colorado. His research expertise is in the area of formulation and drug delivery, with a particular emphasis in lipid-based delivery systems. He received his Ph.D. in 1989 from the University of California Davis in Zoology for his work on stabilizing liposomes during freezing and drying. He moved to the University of Colorado in 1990, and has been on the faculty in the School of Pharmacy since 1998. His research has focused on the development of nonviral gene delivery systems and their stability both in vitro and in vivo. His most recent work has exploited cholesterol nanodomains to enhance tumor targeting in xenograft mouse models. He teaches pharmaceutics and membrane/liposome courses at the professional and graduate levels, and currently serves on three editorial boards. In addition to traditional academic publications, Dr. Anchordoquy has seven patent applications and has founded two small biotechnology companies.

Bakshi P,GlaxoSmithKline, VA, USA

Bhattacharjee H, The University of Tennessee Health Science Center, TN, USA

With a background in drug discovery, Dr. Bhattacharjee brings a new direction in conducting pre-formulation studies to design novel delivery systems for parenteral administration. He is actively involved in research, design and development of nanoparticulate drug delivery systems for small molecules as well as high molecular weight bio-molecules. His current research efforts are to develop clinically relevant, efficacious and safe drug delivery systems for the treatment and prevention of metastasis observed in high mortality diseases like pancreatic, ovarian, lung, and brain cancers. Most of Dr. Bhattacharjee's previous research efforts have yielded valuable insights for therapies that show potential especially in the field of hemorrhagic shock, sepsis, cancer, and inflammation that are currently involved in licensing agreements with pharmaceutical industry. He has extensive experience in teaching aspects of quality control and sterility testing of parenteral dosage forms to academic as well as industry professionals. Additionally, he offers and instructs graduate level courses based on pre-formulation, drug development, and dispersed systems. Dr. Bhattacharjee is currently appointed as a steering committee member for the Sterile Processing Focus Group (SPGF) from AAPS. He is a member of American Chemical Society (ACS), American Association of Pharmaceutical Scientists (AAPS),Parenteral Drug Association (PDA), and International Society of Pharmaceutical Engineers (ISPE).

Curmi P,Université d'Evry-Val d'Essonne, France

Das S, Bulter University, College of Pharmacy & Health Sciences, IN, USA

Dr. Sudip K. Das is the Director of the Graduate Program and an Associate Professor of Pharmaceutics at Butler University, College of Pharmacy & Health Sciences, Indianapolis, IN. He has served as the chair of the Department of Pharmaceutical Sciences at Butler University from 2004-09. Dr. Das obtained his bachelor's and master's degrees in pharmacy and Ph.D. in pharmaceutical sciences from Jadapur University, India. He pursued postgraduate training in pharmaceutical technology at the State University of Ghent, Belgium as a UNIDO scholar. His postdoctoral training was at the University of Queensland, Australia, following which he joined Memorial University of Newfoundland, Canada, as an Assistant Professor of Pharmaceutics. Thereafter, he held a faculty position at Nova Southeastern University in Florida and most recently at Idaho State University as an Associate Professor of Pharmaceutics.

Dr. Das has over twenty years of teaching experience in the professional pharmacy and graduate programs in USA and Canada. He has supervised a number of undergraduate and graduate research students and postdoctoral trainees. His current research involves delivery of siRNA for neurodegenerative diseases, delivery of vaccines and targeting of anticancer drugs. Dr. Das has obtained a number of extramural research grants, including NIH funding. He has over 150 research publications, review articles, conference presentations, and book chapters. He is a recipient of a number of awards and honors.

As an active member of the AAPS (American Association of Pharmaceutical Scientists) since 1991, Dr. Das has served on many committees of the PDD and BIOTEC sections. He is also a member of the Board of Directors of the American Association of Colleges of Pharmacy (AACP) and was the chair of the pharmaceutics section of AACP in 2007-08. He continues to serve on several study sections for the NIH - Center for Scientific Review since 2004.

Dash AK, Creighton University, NE, USA

Dr. Alekha K. Dash received his bachelor's and master's degrees in pharmacy from Jadavpur University, India, and a Ph.D. from the University of Minnesota in 1990. He is professor and chair of the Department of Pharmacy Sciences. He holds the Gilbert F. Taffe Jr. Endowed Chair of Pharmacy at the School and serves as the associate dean for research. Dr. Dash's research interests include design and evaluation of novel drug delivery systems, preformulation studies, solid-state characterization of drugs and dosage forms, pharmaceutical analysis, and evaluation and design of dosage forms for nutraceuticals. Dr. Dash has more than 65 peer-reviewed publications. He has four patents and member of six professional societies. He serves on numerous editorial boards, and is a reviewer for 20 peer-reviewed journals. Dr. Dash has authored chapters in a number of texts, and has been invited to present at the international, national, and local levels. Dr. Dash is an Academic Leadership Fellow of American Association of Colleges of Pharmacy, and a Fellow of American Association of Pharmaceutical Scientists.

Destache C, Creighton University, NE, USA

Exner A, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Agata is an Assistant Professor of Radiology and Biomedical Engineering at Case Western Reserve University School of Medicine in Cleveland, OH. She oversees an interdisciplinary research laboratory in the Case Center for Imaging Research, exploring new synergies between drug delivery and image-guided interventions. The Exner lab is currently engineering several innovative technologies including drug-eluting polymer implants for intratumoral chemotherapy, multifunctional nanoparticles for ultrasound-mediated detection and treatment and targeted thermosensitizers for improved hyperthermia treatment of cancer. Research from her laboratory is supported by the National Cancer Institute of the NIH, and has been documented in numerous peer-reviewed publications, abstracts and conference proceedings. In continuing service to the academic community, she has held an active role in providing biomedical research training opportunities for students of all ages from high school to postdoctoral and beyond. Dr. Exner received her B.S. and Ph.D. in Biomedical Engineering from Case Western Reserve University.

Gabathuler R, Cydweli Consultants Inc., Quebec, Canada

Dr. Reinhard Gabathuler obtained his Ph.D. at the University of Lausanne, Switzerland, in 1982, and completed postdoctoral studies at the University of Washington, Seattle. Over the years, he held various research positions, namely at the Swiss Institute for Cancer Research, in Lausanne, the Ludwig Institute for Cancer Research at the Karolinska Institutet, Stockholm, and the Biotechnology Laboratory of the University of British Columbia in Vancouver, Canada. Dr. Gabathuler's discovery of a new vector for delivery of therapeutics to the brain led to the creation of Synapse Technologies Inc., where he began as Director, Blood Brain Barrier Research, ultimately rising to the position of Vice-President, Research. The company was later acquired by BioMarin Pharmaceutical Inc. where Dr. Gabathuler assumed the position of Vice-President, Brain Research. Dr. Gabathuler joined Angiochem Inc. in 2004 as its CSO and has applied his extensive knowledge in biochemistry, cell biology and immunology in directing the R&D programs thus advancing the Company's products to IND application and clinic. He has been a recognized expert in the biology of blood-brain barrier (BBB) for 15 years and used his expertise in the development of a new peptide vector Angiopep for the physiologic transport of therapeutic compounds across the BBB.

Greish K,Arabian Gulf University, Kingdom of Bahrain

Dr. Khaled Greish is associate professor of Molecular Medicine, and head of the Nano-research unit, at Princes Al-Jawhara Center, Arabian Gulf University,

Kingdom of Bahrain. His previous appointments included senior lecturer of Pharmacology at the University of Otago, New Zealand, and assistant professor of Pharmaceutical Chemistry at University of Utah (UT, USA). He has had published over 70 peer reviewed papers, and 10 book chapters in the field of targeted anticancer drug delivery. Controlled Release Society (CRS) awarded him the CRS Postdoctoral Achievement award in 2008 and in 2010; he was elected as member of the CRC College of Fellows. In recognition of his research, University of Otago awarded him “Early Career Awards for Distinction in Research” in 2014. His research focuses on Nanomedicine, tumor vascular biology, and anticancer drug discovery/development.

Goswami T, Senior Manager, Amneal Pharmaceuticals, NJ, USA

Tarun Goswami obtained his BS in 2003 from Delhi University and his PhD inPharmaceutical Sciences in 2008 from University of the Pacific (CA, USA). He currently works at Amneal Pharmaceuticals as a Formulation Scientist in the Transdermal Drug Delivery Group. He has published multiple abstracts andarticles in the area of transdermal and oral mucosal drug delivery. He isinterested in the development of drug products which are administered via alternate route of drug delivery such as skin and oral mucosa

Heng P, National University of Singapore, Singapore

Dr. Paul W S Heng has a basic degree in pharmacy and obtained his PhD from the National University of Singapore in 1985. He has since joined the National University of Singapore as a faculty member, currently an associate professor with the Department of Pharmacy. He is the Principal Investigator for GEA-NUS Pharmaceutical Processing Research Laboratory, a research laboratory for studying the science of process and product manufacturing technologies. Dr Heng is currently the Chairman of Quality Control Advisory Committee, Ministry of Health, Singapore; Vice-Chairperson of the Specialty Committee of TCM Pharmaceutics of World Federation of Chinese Medicine Societies, Advisory Board member of the Asian Association of Schools of Pharmacy, among others. His research interest is in pharmaceutics, studying the manufacturing science of solids, drug delivery systems - oral and inhalable - and semi-solid dosage forms. He has authored or co-authored over 170 international refereed research journal articles, 7 book chapters and several patents. He is the editor-in-chief of the Asian J Pharm Sci. and is in the editorial boards of several other research journals.

Ho P, National University of Singapore, Singapore

Dr Paul C. Ho is an associate professor and deputy head of the Department of Pharmacy, National University of Singapore. He received his B. Pharm. and Ph.D. degrees in pharmacy from the University of Queensland. After his post-doctoral attachment at the Upjohn Center for Clinical Pharmacology,

University of Michigan, USA and Queensland Institute of Medical Research, Australia, Dr Ho was appointed in 1993 as the faculty member in the Department of Pharmacy, National University of Singapore. The current research focuses and interests of Dr Ho include the pharmacokinetics and biopharmaceutics of chemotherapeutic agents, submicron- and nano-particulate drug delivery systems. Dr Ho has published over 90 scientific research articles, 60 abstracts and 4 chapters in books in his field of study. He is currently the editorial board member and reviewer of a number of international refereed journals. He has been the consultant to some international pharmaceutical companies; and external reviewer for the regulatory authority of government.

Ho RJY, University of Washington, USA

Dr Ho is the Milo Gibaldi Endowed Professor of Pharmaceutics and Director of the DNA Sequencing and Gene Analysis Center at University of Washington, Seattle. He also holds appointments at Clinical Pharmacology, Fred Hutchinson Cancer Research Center, the Center for AIDS and STD Research, the Center for Human Development and Disability, the Center for Ecogenetics at University of Washington, and the Washington National Primate Research Center. He is an elected fellow of the American Association for the Advancement of Science; and was an elected chair of the American Association for the Advancement of Sciences. He is also an elected fellow of the American Association of Pharmaceutical Scientists. In 2008, he was named as one of the top 25 entrepreneurs in the Pacific Northwest. He is a recipient of the prestigious Paul R. Dawson Biotechnology Award in 2009, cited for his teaching and scholarship in biotechnology. Dr Ho received his undergraduate degree from the University of California, Davis in 1983, and

received his master and Ph.D. in 1985 and 1987, from the University of Tennessee focusing on biochemistry and drug targeting. His post-doctoral fellowship focused on infectious diseases at the Division of Infectious Diseases, Stanford University School of Medicine, before joining the University of Washington, School of Pharmacy as an Assistant Professor in December 1990. Dr. Ho was promoted to associate professor with tenure in 1996 and full professor rank in 2002. In 2003, he founded the DNA Sequence and Gene Analysis Center and serves as the Director for the Center. Dr Ho's accomplishments include 6 patents and numerous patent disclosures, over 90 original research publications, 20 book chapters; and two edited books. He was honored to receive funding notice from the National Institutes of Health (NIH) within 3 months of his arrival at UW. As a principal investigator, he leads multiple interdisciplinary biomedical research programs in HIV/AIDS and cancer focusing on novel strategies to improve drug effectiveness and safety. He enjoys continuous support from NIH totaling over $15 M as a PI. His creativity and accomplishments are also recognized by peers at the national level, as he is invited to serve on expert NIH panels chartered to review grant proposals submitted to the National Institute of General Medical Sciences, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases.

Jia L, National Institutes of Health (NIH), Bethesda, USA

Dr. Lee Jia is currently Senior Pharmacologist and Project Officer with the Developmental Therapeutics Program at the National Cancer Institute/ NIH. In this position, he is responsible for directing, managing, evaluating and budgeting collaborative contract- and grant-supported projects to conduct preclinical and clinical pharmacology, pharmacokinetics, biomarker, and

toxicology studies for developing anticancer, anti-AIDS/HIV, antituberculosis and cardiovascular drugs. Dr. Jia has contributed 70 original papers, review articles, and book chapters to high-impact journals including Science, Nature, PNAS, JPET, Br. J. Pharmacol., and many others in addition to 70 abstracts. His research interests and publications cover the areas of nitric oxide drug development, drug physicochemical characterization, biomedical analysis, phytomedicine, pharmacology, ADME, toxicology, nanotechnology, cancer metastasis mechanism and prevention, angiogenesis, proteomics, and drug regulation policy. Dr. Jia currently serves on the Editorial Board of 5 journals and as the Associate Editors for Current Drug Metabolism and Drug Metabolism Letter, respectively. He has been invited as reviewers for over 24 peer-reviewed journals. Within the American Association of Pharmaceutical Scientists (AAPS), Dr. Jia is holding positions of the vice-Chair of the section of Drug Design & Development, the Steering Committee Member of Nanotechnology, and the AAPS annual meeting programming committee.

Jelvehgari M, University of Tabriz, Tabriz, Iran

Jones DS, The Queen's University of Belfast, Medical Biology Centre, School of Pharmacy, Northern Ireland, UK

Khan Ghilzai N, School of Pharmacy, West Coast University, CA, USA

Khang G, Chonbuk National University, Korea

Lee BJ, Ajou University, Republic of Korea

Beom-Jin Lee is a professor and dean of College of Pharmacy, Ajou University. He received his BS and MS in College of Pharmacy, Seoul National University and Ph.D. from College of Pharmacy, Oregon State University. He had served as a professor in Kangwon National University (KNU) for 1993-2011 and moved to Ajou University in 2012. He had served as a dean of KNU Pharmacy from 2005-2007. He is an internationally well-known scientist in the area of Pharmacy and Pharmaceutical Sciences. His research areas are mainly focused on "controlled bioavailability of poorly soluble and poorly absorbable drugs, solubilizations, formulation and drug delivery, and recently development of nanobiomaterials for drug targeting". He is an author/co-author of more than 110 journal articles, patents, book chapters and abstracts. He has also invited many international oral presentations. He has received more than 20 achievement awards from government, academia and organizations. He is serving as an editorial Board member for several peer-reviewed journals. He is currently serving as a Head, Pharmaceutical Research and Development Agency (PRADA), Korean Pharmaceutical Manufacturing Associations and as a vice president in three Korean Pharmaceutical Societies. He is an active member and a delegate of FIP.

Li S,Queen's University Belfast, Northern Ireland, UK

Matsumura Y, National Cancer Center Hospital East, Japan

Dr. Yasuhiro Matsumura is the Director of the Investigative Treatment Division at the National Cancer Center Hospital East, Japan. He has been involved in basic research on drug delivery systems (DDS) and in the clinical development of drugs used in DDS. After graduating from Kumamoto University Medical School in 1981, he received training in the Department of Surgery at the Medical School. During this period, he administered arterial injection therapy using styrene maleic acid neocarzinostatin (SMANCS)/Lipiodol to patients with hepatocellular carcinoma. He also discovered the enhanced permeability and retention (EPR) effect under the supervision of Prof. H Maeda during his work in the Department of Microbiology, Kumamoto University. He then accepted a postdoctoral position with Dr. D Tarin at the Nuffield Department of Pathology, University of Oxford; his work was on the molecular pathology of cancer, and it was during this period that he discovered the abnormal splicing of CD44 mRNA in various cancers. In 1994, he commenced his career as an oncologist at the National Cancer Center Hospital, Japan. From 1999, as the Head of the Special Therapy Division, he introduced clinical trials on DDS and conducted translational study of DDS. In 2002, he was appointed as the Director of the Investigative Treatment Division of National Cancer Center Hospital East. His current research focuses on delivering cytotoxic immunoconjugates to cancer stroma and clinical trials of anticancer agents that are transported using micelle carriers.

Mandal S, University of Nebraska-Lincoln, NE, USA

McCartney F, University College Dublin, Republic of Ireland

Medintz I, U.S. Naval Research Laboratory Code 6900, USA

Igor L Medintz initially studied chemistry and forensic science at John Jay College of Criminal Justice, City University of New York (CUNY). After subsequently working for 3 years as an analytical toxicologist in New York, he pursued his Ph.D. in molecular, cellular and developmental biology at Queens College (also CUNY). His graduate research studies focused on understanding the molecular genetics of sugar metabolism in the model organism Saccharomyces. He carried out further postdoctoral research on the development of FRET-based assays using microfabricated devices for genetic analysis at the College of Chemistry, University of California Berkeley with Prof. Richard Mathies. Since 2002 he has been at the Center for Bio/Molecular Science and Engineering at the U.S. Naval Research Laboratory in Washington D.C. where he is a Research Biologist. He is currently focusing on developing chemistries for biofunctionalizing nanoparticles, delivering them to cells and

utilizing them as sensors. He is an author/co-author of more than 100 publications as well as several book chapters and patents.

Miller AD, Imperial College Genetic Therapies Centre, UK

Mitragotri S, University of California, Santa Barbara, CA, USA

Mohammed AR, Aston University, UK

Moridani M, Medical College of Wisconsin, USA

Dr. Moridani is Professor and the Director of Chemistry and Toxicology at Froedtert & Medical College of Wisconsin, Milwaukee, Wisconsin, USA. He has obtained his pharmacy degree from Tehran Medical University, his PhD in medicinal chemistry from King's College London, and postdoctoral fellowship in clinical chemistry from University of Toronto. His research interest is in the following areas of: 1) drug metabolism, toxicology, drug discovery, organ targeted drug delivery and prodrug design; 2) pharmacogenetics of drug metabolizing enzymes; 3) pain management and therapeutic drug monitoring; 4) personalized medicine, translational and clinical research.

Müllertz A, University of Copenhagen, Denmark

Dr. Anette Müllertz is associate professor and head of the Bioneer:FARMA, Danish Drug Development Center, at the Faculty of Pharmaceutical Sciences, University of Copenhagen (FARMA). She received her PhD degree in lipid nutrition at the Technical University of Denmark in 1991. She spent 8 years as a research scientist at Novo Nordisk A/S, Denmark, working on the development of structured lipids, digestive lipases and digestion models, among other projects. In 1998 she joined the Royal Danish School of Pharmacy, Copenhagen, Denmark, as an associate professor. She is heading the research group for poorly soluble drugs at the Department of Pharmaceutics and Analytical Chemistry, at what is now FARMA. Her area of research is biopharmaceutics and oral delivery of poorly soluble drugs, including development of oral lipid based drug delivery systems, in vitro lipolysis models, simulated intestinal fluids, physiologically relevant absorption models and lymphatic transport. She has published more than 45 papers in international peer reviewed journals, most of them during the last 5 years, as

well as 6 book chapters. She has been supervising 18 PhD students and numerous Masters students. She was the winner of the 2005 AAPS Lipid Based Drug Delivery Award. Presently she is leading the Predicting Drug Absorption Consortium, sponsored by the Danish government and involving 5 pharmaceutical companies.

Nadia Passerini,University of Bologna, Italy

Nadia Passerini is Associate Professor of Pharmaceutical Technology at the University of Bologna (Italy). She obtained the Degree in Pharmaceutical Chemistry and Technology at the University of Bologna in 1992 and the PhD in Pharmaceutical Science in 1997. In 1997 she spent four months as visiting scientist at the School of Pharmacy, University of London (UK) working in the group of Prof. D. Craig. In 1998 she won a one-year post-doctoral fellowship sponsored by the European Union (Marie Curie Grant) at The School of Pharmacy, The Queen's University of Belfast (UK) where she worked again in the research group of Prof. D. Craig. From1999 to 2014 she was lecturer in Pharmaceutical Technology at the University of Bologna. Her research focus on the study of drug delivery systems, developing new technologies and new apparatus for the production of solid dosage forms (microparticles, granules and tablets) which can optimize the biovailability of drugs according to the specific needs of the therapy. Furthermore, she is interested in the solid state characterization of the produced delivery systems in order to correlate their physicochemical properties to the in vitro release of the drugs. Currently her research focuses in particular on the production and characterization of microparticles produced by the spray congealing technology. She is author of over 50 international peer reviewed publications and over 50 contributions (poster and oral presentations) to national and international conferences.

Rautio J, University of Eastern Finland, Finland

Jarkko Rautio is Professor of Pharmaceutical Chemistry at the University of Eastern Finland, Finland. He is the head of the multidisciplinary Pharmaceutical and Medicinal Chemistry (PMC) research group and his research focuses on the chemistry-based methods, especially prodrug technology, to overcome liabilities of drugs. Professor Rautio co-founded the American Association of Pharmaceutical Scientists (AAPS) Prodrug Focus Group in 2005.

Rees G, Genesis Oral, UK

Dr Rees has spent over 25 years working at the interface between industry and academia both as a senior researcher at the University of East Anglia and King's College London and as Principal Scientist/Associate Director in one of the world's largest oral healthcare companies working across the full range of

indications and pertinent scientific disciplines. Dr Rees is an Honorary Senior Lecturer at the School of Pharmacy & Biomolecular Sciences at the University of Brighton, and has published over 65 peer-reviewed articles and over 100 conference papers. Dr Rees is Director of Genesis Oral Bioscience, a company specialising in scientific writing and consultancy in the field of oral bioscience and dental research, with a focus on local and transmucosal drug delivery within the oral cavity.

Reis C, Universidade Lusófona de Humanidades e Tecnologias, Portugal

Catarina Pinto Reis is currently Professor of Pharmaceutical Technology and Drug Delivery in the Department of Health Sciences at the Universidade Lusófona de Humanidades e Tecnologias (Lisbon, Portugal) and a consultant for the National Authority of Medicines and Health Products (INFARMED). She attended the University of Coimbra (Coimbra, Portugal) and graduated with First Class Honors in Pharmaceutical Sciences in 2003. Her doctoral studies were also undertaken at the University of Coimbra with several important international collaborations where she developed an interest in advanced drug delivery systems. Those studies have been recognized through a number of national prizes including the BES National Award for Innovation 2006 and the Bluepharma/University of Coimbra Award 2009 for the best PhD thesis in Health Sciences. She finished her PhD in Pharmacy in 2008 as Distinguished Honor Graduate. Since then, she has continued to work in the design and evaluation of nanoparticles and microparticles for peptide drug and gene delivery. She is author or co-author of several articles, book chapters and inventor of 2 patents

Rosenmayr-Templeton L, Tower Pharma Consulting, Austria

Louise Rosenmayr-Templeton is a pharmacist with over 15 years' experience in pharmaceutical product development and project management. In 2002 she set up her consultancy business, Tower Pharma Consulting (http://www.towerpharmacon.com). Based in Vienna, Austria, it provides a variety of scientific and project management services to pharmaceutical and biotech companies, as well as government agencies, in the fields of pharmaceutical product development and drug delivery research. These include technical due diligence, service provider evaluation and the provision of formulation expertise to companies, particularly those managing their development efforts virtually.Before setting up her consultancy, Louise worked in various capacities for major pharmaceutical companies such as Abbott (UK, USA), the Élan Corporation (Ireland) and Boehringer Ingelheim (Austria). Her experience spans the whole spectrum of product development from managing pre-clinical research projects, to the successful scale-up and technology transfer of products to manufacturing sites, and the preparation and review of regulatory documents. During her career she led teams developing formulations and delivery technologies for NCEs, proteins, peptides and antigens. In addition, she has provided scientific expertise on a variety of different projects. These include the development of solid, colloidal and liquid dosage forms, the delivery of oligonucleotides and the handling of very potent compounds.Louise graduated from Strathclyde University with first class honours and obtained her PhD in the field of novel drug delivery from Nottingham University. She also holds a postgraduate Diploma in Management Studies from Canterbury Christ Church University.Louise is a member of the Royal Pharmaceutical Society of Great Britain. She sits on the Drug Delivery Focus Group of the International Association for Pharmaceutical

Technology (APV) and is editor of its newsletter. She is also co-chair of the Young Scientist Committee of the Controlled Release Society.

Shameem M, Regeneron Pharmaceuticals, Tarrytown, NY, USA

Mohammed Shameem is a Vice President and Head of Drug Product Formulation, Process and New Technology at Regeneron Pharmaceuticals, USA. He received his Ph.D. from Kumamoto University, Japan in Pharmaceutical Sciences and postdoctoral training from National Institute of Health Sciences, Tokyo, University of Kentucky and University of Southern California. Dr. Shameem has been actively involved over 20 years in innovating and developing drug products across a wide range of therapeutic modalities, route of administrations and dosage forms. Dr. Shameem contributed to the successful development and registration of several marketed products (Eylea®, Dupixent®, Libtayo®, Keytruda® PegIntron®, Sylatron®, Temodar IV®) in the US, EU and Japan and holds numerous patents and publications including edited book. He was a recipient of Schering Plough's 2004 President Award for development of Pegylated Interferon (Redipen) and the ACS 2015 Biotechnology award for CMC development of the Keytruda IV Product. His research interest focuses on the development of high-concentration formulations for monoclonal antibodies and sustained release technologies of intra-vitreal administration.

Stinchcomb AL, University of Kentucky and AllTranz Inc, Lexington, KY, USA

Audra Stinchcomb is Associate Professor of Pharmaceutical Sciences at the College of Phar macy, University of Kentucky, Lexington, KY. Her basic science and translational research involves the design and testing of novel prodrugs for transdermal delivery, as well as intranasal delivery, testing of novel nanomaterials for programmable transdermal patches, microneedle drug delivery and cannabinoid drug delivery optimization. She is the founder and Chief Scientific Officer of the specialty pharmaceutical company AllTranz Inc. She obtained her Ph.D. in Pharmaceutics from The University of Michigan College of Pharmacy and completed a postdoctoral fellowship at the University of California, San Francisco. She serves as a reviewer for over twenty-five pharmaceutical and drug delivery journals, and is on the editorial advisory board of five of these journals. Audra has mentored 7 PhD students and 10 postdoctoral fellows. Her laboratory has been continuously funded since 1996 by the National Institutes of Health, the American Cancer Society, the Food and Drug Administration, and numerous pharmaceutical companies. She has served as a member of the United States Pharmacopeia, an Institutional Review Board for clinical research, and as a scientific advisor for the EPA.

Sun D, The University of Michigan, MI, USA

Tambuwala M, Ulster University, Northern Ireland, UK

Dr. Murtaza Tambuwala is a Molecular and Pharmaceutical scientist, who holds a Masters in Pharmaceutical Technology from the School of Pharmacy, Trinity College Dublin and has completed his doctoral research at the School of Medicine and Medical Sciences, University College Dublin. Dr. Tambuwala joined Ulster University as a Lecturer in 2013 to establish his independent research in the field of inflammation and cancer targeted drug delivery and has published over 115 peer-reviewed manuscripts. The over-arching aims of his research lab are to understand the mechanisms by which hypoxia regulates transcriptional events in inflammation and the development of cancer. In particular, he is interested in the regulation of global gene expression in response to the hypoxic environment of inflamed adipose tissue/tumour, and the modification of transcriptional regulators which underlies the induction of inflammation, development, and progression of cancer. His research is focused on translating this understanding of hypoxia-sensitive pathways to developing new therapeutics in chronic inflammatory diseases such as IBD, intestinal fibrosis, cardiovascular diseases, and colon & breast cancer.

Tiwary AK, Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, India

Dr. Tiwary is an alumnus of the Department of Pharmaceutical Sciences, Birla Institute of Technology, Ranchi, India. He obtained his Ph. D. degree in Pharmaceutics from Birla Institute of Technology, Ranchi, India and is currently working as Professor of Pharmaceutics and Head of the Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, India. Dr. Tiwary has supervised many M. Pharm. students and five Ph. D. students. The trust areas of his research include investigating the mechanisms of percutaneous permeation enhancers, using natural polymers for formulating mouth dissolving tablets and colon drug delivery systems. He is also working on contraception with an aim of exploring the possibility of using approved drugs as contact spermicides. Dr. Tiwary has authored fifty and co-authored eleven research papers / articles in international peer reviewed journals and books. He is a reviewer for many journals including AAPS PharmSci Tech, Drug Delivery and Formulation, Drug Delivery and Industrial Pharmacy, International Journal of Pharmaceutics etc. His laboratory is funded by CSIR, New Delhi, ICMR, New Delhi, DST, New Delhi and UGC, New Delhi, India through various research and consultancy grants.

Uchegbu IF, University of London, UK

Ijeoma Uchegbu holds a Chair in Pharmaceutical Nanoscience at the School of Pharmacy, University of London. Ijeoma obtained her PhD from the School of Pharmacy, University of London in 1994, was appointed to a lectureship within the Department of Pharmaceutical Sciences, Strathclyde University in 1997 and a Chair in Drug Delivery at Strathclyde University in 2002. In 2006 Ijeoma was appointed to the Chair in Pharmaceutical Nanoscience at the School of Pharmacy, University of London. Ijeoma's research in pharmaceutical nanoscience has provided insights into nanoparticle design for drug delivery, producing nanosystems (nanomedicines) that promote oral drug absorption and drug transport to the brain for example. Ijeoma and Andreas Schätzlein have also designed an anti-cancer gene medicine that is currently in pre-clinical development. Ijeoma is the Scientific Secretary of the Controlled Release Society (CRS), a US based learned society with over 2,000 members and with interests in the delivery of pharmaceuticals, former Chair of the Academy of Pharmaceutical Sciences of Great Britain and is the Academia Expert on the Department for Business Innovation and Skills' Science Engineering and Technology Strategy for Women Expert Group. Ijeoma has been awarded various prizes for her work, the latest of which is the Department for Innovation University and Skills' Women of Outstanding Achievement in Science Engineering and Technology award. Ijeoma along with five other awardees took part in a national photographic exhibition in 2007 at various venues including the Science Museum and the British Museum. Ijeoma is the editor of two books and over 80 patents, patent applications, peer reviewed journal articles and book chapters.

Vig B, Bristol-Myers Squibb, USA

Dr Vig is the head of the Integrated Technical Strategy group within the Manufacturing Science & Technology Department at Bristol-Myers Squibb Company. In his current role, Dr. Vig's team is accountable for the CMC strategy for the BMS Commercial portfolio of Biologics and Pharma products. Dr. Vig has led several groups within BMS and is responsible for preformulation, formulation and process development, materials selection, solid state analytical chemistry, biopharmaceutics, and drug delivery. Dr. Vig has been extensively involved in development of in vitro, in silico and in vivo models to understand the effects of physiological and formulation variables on drug absorption, and application of biopharmaceutical and drug delivery approaches to understand and improve developability of drugs. Dr. Vig received his Ph.D in Pharmaceutical Sciences from University of Maryland, Baltimore. Following his Ph.D., Dr. Vig pursued a postdoctoral research fellowship in the laboratory of Dr. Gordon Amidon at the University of Michigan, Ann Arbor. As a Research Fellow, he utilized transporter- and enzyme-based prodrug strategies and drug delivery approaches to improve oral absorption, stability, and targeting of anticancer and antiviral drugs. Dr. Vig has presented extensively at national and international meetings and has over 30 publications in peer reviewed journals and 30 abstracts.

Younes HM, Qatar University, Qatar

Dr. Husam Younes is an Associate Professor and the Founding Chair of Pharmaceutical Sciences at the College of Pharmacy, Qatar University, Doha, Qatar. He is also an Adjunct Professor at the School of Pharmacy, Memorial University of Newfoundland, St. John's, Canada. He previously worked in the pharmaceutical industry and also as a senior consultant to Newfoundland Health Department in Canada. His main research is in the areas of controlled drug release, biomaterials, tissue engineering and synthesis of novel biodegradable polymers designed for localized and targeted delivery of therapeutic proteins in cancer therapy. In addition, he has conducted studies on the effect of inflammation onthe pharmacokinetic and pharmacodynamic

parameters of antihypertensive drugs. Research from his Pharmaceutics and Polymeric Drug Research laboratory is supported by the National Sciences and Engineering Research Council in Canadaand numerous grants from Qatar Foundation in Qatar and has been documented innumerous patents, peer-reviewed publications, books chapters, abstracts and conference proceedings. He supervised graduate students and postdoctoral fellows in his lab and acted as a reviewer for many pharmaceutical and drug delivery journals. He also served on the Pharmacy Examining Board of Canada. Dr. Younes received his PhD in Pharmaceutical Sciences from University of Alberta, Edmonton, Canada.

Zinzalla G, Karolinska Institute, Sweden

Giovanna Zinzalla is Assistant Professor of Chemical Biology at the Microbiology, Cell and Tumor Biology (MTC) department, and a group leader at the Advanced Cancer Therapy (ACT) centre of the Karolinska Institutet (Stockholm, Sweden). Her research focuses on dissecting how transcription factors control cell differentiation, growth, metabolic activities and apoptosis. This involves the use of chemical probes to modulate protein-protein interactions, with the ultimate goal of developing therapeutics. To this aim she leads an interdisciplinary team of scientists whose efforts encompass biochemistry, biophysics, chemistry and structural biology.

Future Science Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK
+44 (0)20 8371 6090

Therapeutic Delivery

ISSN (print): 2041-5990 | ISSN (online): 2041-6008
Frequency: 12 issues per year

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Therapeutic Delivery

Ultradeformable vesicles: concepts and applications relating to the delivery of skin cosmetics

Andang Miatmoko*,[1], Qurrota Ayunin[2,3] & Widji Soeratri[1]

[1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Nanizar Zaman Joenoes Building, Campus C Mulyorejo, Surabaya, 60115, Indonesia

[2]Master Program of Pharmaceutical Sciences, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga Nanizar Zaman Joenoes Building, Campus C Mulyorejo, Surabaya, 60115, Indonesia

[3]Study Program of Pharmacy, Faculty of Pharmacy, Hospital Administration, Public Health, and Radiology (FAKAR), Institut Ilmu Kesehatan STRADA, Jl. Manila 37, Kediri, 64133, Indonesia

*Author for correspondence: andang-m@ff.unair.ac.id

Skin aging is a phenomenon resulting in reduced self-confidence, thus becoming a major factor in social determinants of health. The use of active cosmetic ingredients can help prevent skin aging. Transfersomes are well known to be capable of deeply penetrating the dermis. This scoping review provides an insight into transfersomes and their prospective use in anti-aging cosmetics. Numerous reports exist highlighting the successful skin delivery of therapeutic agents such as high-molecular-weight, poorly water soluble and poorly permeable active ingredients by means of transfersomes. Moreover, *in vitro* and *in vivo* studies have indicated that transfersomes increase the deposition, penetration and efficacy of active ingredients. However, the use of transfersomes in the delivery of active cosmetic ingredients is limited. Considering their similar physicochemical properties, transfersomes should possess considerable potential as a delivery system for anti-aging cosmetics.

First draft submitted: 14 June 2021; Accepted for publication: 24 August 2021; Published online: 14 September 2021

Keywords: cosmetic • scoping review • social determinants of health • transfersome • ultradeformable vesicle

Skin aging is a process of changing physical appearance that can reduce an individual's self-confidence. These skin changes are closely related to ones in the balance of the production and decomposition of collagen, elastin and glycosaminoglycans, which constitute quality parameters of the dermis layer [1,2]. There are several triggers, which can be internal physical factors (e.g., DNA damage due to reactive oxygen species, the development of chronic diseases, and metabolic disorders connected with aging) or external factors, including exposure to sunlight and oxidant materials which result in the skin losing elasticity and firmness and the appearance of wrinkles [1–3]. Wrinkles are a sign of aging skin caused by collagen degradation, and these visible skin folds can have an impact on quality of life and physical appearance [4].

Anti-aging strategies that have been implemented include protection against UV rays, invasive procedures and skincare products or cosmetics (e.g., sunblocks). Meanwhile, the use of cosmetics in improving skin biological function and skin care has involved the addition of local biologically active cosmetic ingredients. Anti-aging ingredients have become a popular means of improving intrinsic skin biological function. Therefore such compounds must be able to penetrate the barrier of the stratum corneum (SC) in order to reach the dermis layer and rejuvenate and repair skin wrinkles.

Active anti-aging cosmetic ingredients include coenzyme Q10, which demonstrates low water solubility [5,6], growth factors such as EGF and TGF-β contained in amniotic membrane stem cell metabolite products (AMSC-MPs) that have a significant molecular weight [7,8], vitamins and other herbal and biological products [9]. These compounds should possess different physicochemical characteristics. However, only small molecules less than 500 Da in size and lipophilic molecules with logP values between -1 and 4 can penetrate the SC, which constitutes

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the skin barrier [10,11]. Therefore the use of nanoparticulate carriers in skin delivery has the potential for anti-aging cosmetics to improve the decreased quality of the dermis layer in aged skin. The presence of active cosmetic ingredients within a nanocarrier system in the epidermis and dermis layers indicates that they can promote collagen and elastin repair activity which enhances skin firmness [12].

Certain nanocarriers (e.g., liposomes, transfersomes, glycerosomes, ufosomes and hybrid vesicles) have been developed to improve skin drug delivery. Liposomes are a lipid-based vesicular carrier consisting of an inner water phase surrounded by lipid bilayer membranes [13]. The addition of softening bilayers such as surfactants to liposomes can produce a transfersome [14], while the use of glycerol as the edge activator (EA) of the liposomal bilayer membrane generates glycerosomes [15].

Transfersomes represent the first generation of elastic liposomes which demonstrate liposome-like characteristics with the ability to deform and reform their shapes. Liposomes are known to provide three different environments for substances entrapped inside them: the lipid–water interface, the hydrophobic nucleus and the aqueous interior. Thus, liposomes can entrap hydrophobic, hydrophilic or amphiphilic active ingredients within their structures, in addition to improving their stability. With the presence of EAs, the vesicles can become elastic, resulting in their ability to enhance the penetration by active cosmetic ingredients, thus enabling them to reach deeper skin layers [16]. Under the mechanical stress resulting from transepidermal osmotic gradient force, EAs will be transferred to areas of higher curvature or pressure in the lipid bilayer. This process causes changes in the shape and volume of transfersome vesicles with minimal energy requirements. Moreover, the addition of EAs can disrupt the ordered arrangement of phospholipid molecules within spaces in the lipid bilayers, significantly reducing the transition temperature of the transfersome bilayer membrane [17].

Transfersomes can shrink, thereby facilitating penetration of the skin via intercellular routes and pores of the SC that are much smaller than their own vesicles' diameters. These vesicles are ten-times more deformable than conventional liposomes [18]. However, because the transfersome vesicle has limited entrapment capacity, and content leakage of active ingredients still tends to occur due to water diffusion from dispersing media, a provesicular carrier has been developed, namely protransfersomes. Protransfersomes are lipid provesicles in the form of crystalline liquid which will turn into very flexible transfersome vesicles *in situ* by absorbing water from the skin [19]. These characteristics enable the protransfersomes to protect the encapsulated materials as well as vesicular lipids from any unwanted chemical reactions, such as hydrolysis and oxidation associated with degradation, and physical reactions such as sedimentation, aggregation, fusion or leakage of trapped substances or hydrolysis of encapsulated active ingredients [20–22]. They extend shelf life and are capable of targeting materials encapsulated in the deeper layers of the skin [23–25].

Transfersomes are widely employed in the topical and transdermal delivery of various active pharmaceutical ingredients. However, their applications to cosmetic delivery are limited. Moreover, the recent development of cosmetics is largely intended to improve the appearance of skin by having local biological effects on its tissues. The similar physicochemical properties of the active ingredients provides direct analogies for successful skin delivery using transfersomes, thereby also rendering them prospective active cosmetic ingredients. This review will demonstrate the potential use of transfersomes in enhancing active ingredient penetration, which promotes optimal anti-aging activity within cosmetic delivery systems. This, in turn, increases their effectiveness in impeding skin aging.

This review analyzes the potential use of transfersomes as a carrier in the delivery of anti-aging cosmetics. The existing research into the use of transfersomes in cosmetics is limited. Consideration of the similar physicochemical properties of active pharmaceutical ingredients, such as insulin and hormones, is intended to identify analogies of these substances' successful delivery through ultradeformable vesicles which could also be applied to active cosmetic ingredients.

The method employed in writing this review consisted of an electronic literature study involving the accessing of national and international journal search sites related to the keywords 'ultradeformable vesicles', 'transfersomes', 'protransfersomes', 'anti-aging active compound', 'protein for anti-aging', 'topical delivery', 'skin delivery', 'deformability', 'skin penetration' and 'topical drug classification system'.

The eligibility criteria applied when selecting journal articles comprised original research, short case studies, experimental research design and the year of publication falling within the period 1992–2020. The sites accessed for the purposes of conducting the search included PubMed (Scopus & Scimago) and Google Scholar articles which contained search keywords. Articles published by predatory journals or publishers which include review articles were excluded from the study. Identification, data correlation analysis and paper selection were conducted on the basis of the CONSORT diagram shown in Figure 1.

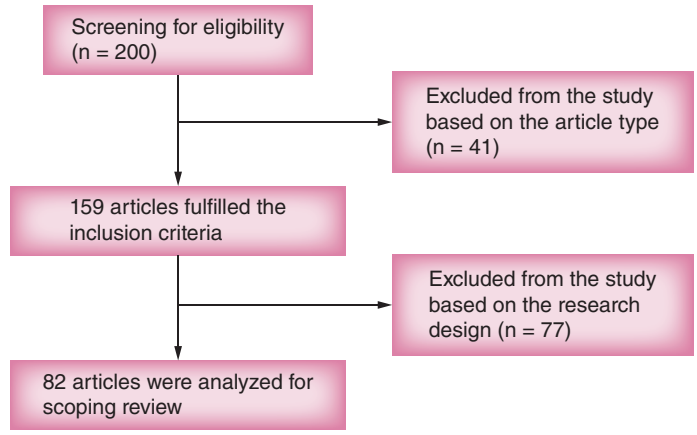

Figure 1. CONSORT diagram of article screening and selection.

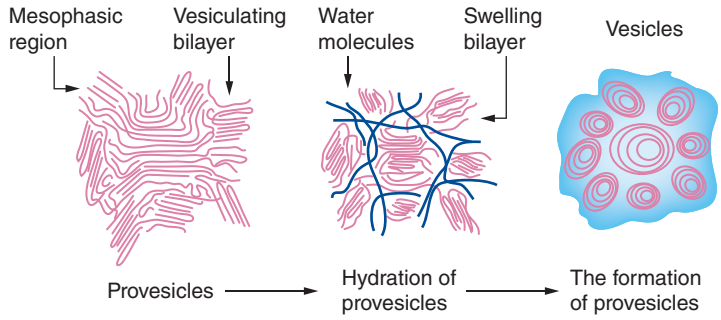

Figure 2. The physical formation of transfersomes from protransfersome gel.

Characteristics of protransfersomes & transfersomes as vesicular carriers for skin delivery

For topical delivery, transfersomes have many advantages relating to their high membrane elasticity and deformability. These can be achieved by combining two lipophilic or amphiphilic components, namely phospholipids and biosurfactants, at the appropriate ratio or formula to form bilayer vesicles [23]. In transfersomes, the surfactant as the EA is in the form of a single-chain surfactant capable of destabilizing the lipid bilayer and causing an increase in the fluidity and elasticity of the vesicular membrane, with the result that the vesicles can change shape and pass through the pore intact by shrinking in size to five- to ten-times smaller than the original, thus increasing the penetration of the active cosmetic ingredients [26]. Protransfersomes, extremely flexible liquid lipid provesicles, provide benefits for improving the stability of transfersomes [19].

During application, the active ingredient interacts with the skin, which is both attached and adheres to the SC. Due to the osmotic gradient resulting from the difference in water content of skin tissue, the active ingredient will be transported to the deeper layers of the skin by passing through the SC. Under light microscopy, the protransfersome, which is originally crystalline and lamellar-shaped, will turn into transfersome vesicles after hydration. This is due to the difference in the degree of hydration of the surfactant and phospholipid molecules, together with the change in shape of the hydrated molecules. Because of its limited solvent content, the resulting protransfersome will form a compact palisade and vesiculation lamellae. The addition of water will cause further swelling of the bilayer and vesicles due to the interaction of the air with the surfactant head groups and will tend to produce random spherical vesicles of transfersomes, as presented in Figure 2 [27].

The deformability of the vesicles is influenced by the chemical structure of the surfactants, with surfactants that have a low hydrophilic–lipophilic balance value generally forming smaller vesicles. The surfactant concentration must also be proper, otherwise the vesicles will harden and be damaged [27]. Another role of surfactants is to increase the hydration properties of transfersome vesicles, with the result that they tend to seek moisture in deeper skin layers after application to the skin hydrotaxis (i.e., xerophobia) [26].

Transfersomes can penetrate the skin layers by means of different mechanisms depending on their composition (Figure 3): either the vesicles maintain their intact shape (deformability) via the intercellular pathway; or the vesicles fuse and mix with skin lipids (transcellular) due to destabilization of the membrane by surfactants; or the vesicles go directly to deeper skin tissues via appendageal routes. Transfersomes can easily shrink to one-tenth of their original

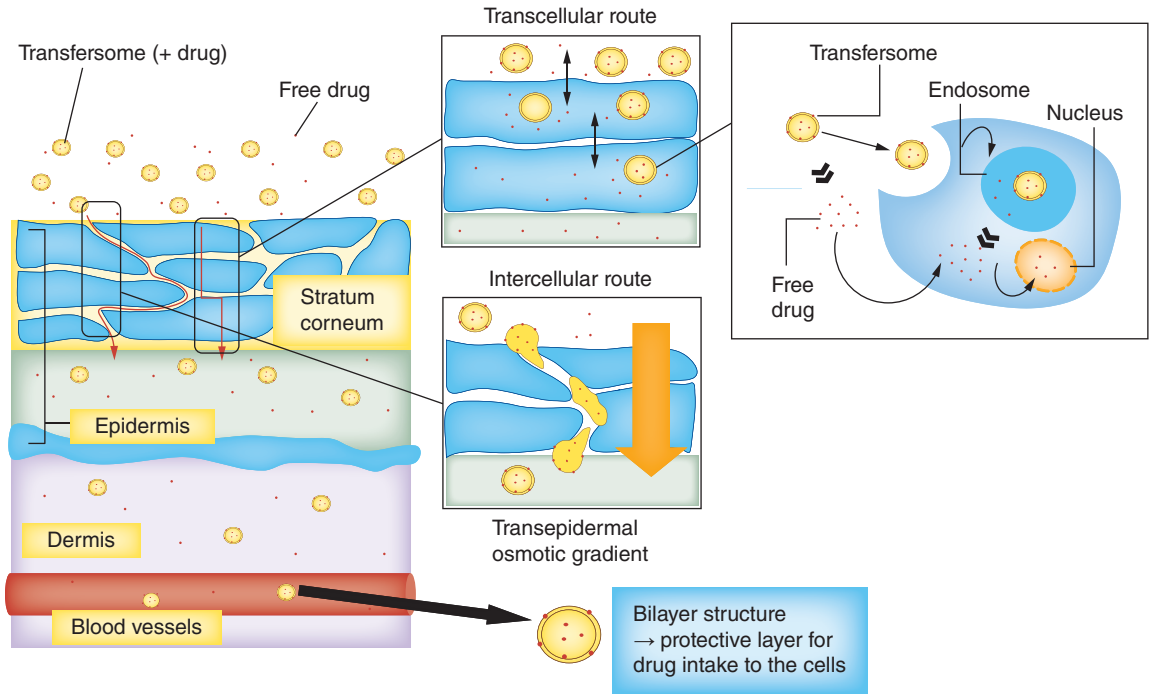

Figure 3. The presence of a transdermal osmotic gradient leads to skin penetration of transfersomes via transcellular and intercellular routes into deeper skin layers.

size in order to pass through the pore by means of a transdermal osmotic gradient due to differences in the water content of the skin surface, which is about 15%, and the dermis, which has a high water content of 75% [28]. This osmotic gradient helps the active ingredients pass through the skin passively via the hydrophilic ducts of the SC [17]. When the transfersomes are applied to skin in non-occlusive conditions, they will dehydrate due to water evaporation, the hydrophilic nature of which causes the vesicles to be attracted to a layer with a high water content, allowing the intact vesicles to penetrate via the intercellular spaces [29,30].

The osmotic gradient is high in the SC and decreases with skin depth to the stratum spinosum layer (0.042 mm) [31]. This osmotic gradient acts as a propulsion for most transfersome vesicles with a total lipid mass of more than 0.1 mg/cm^2 within 1. The occlusive means of application can cause at least 90% of the drug to be retained in the SC due to excess hydration, with the result that only small levels of the drug can enter the bloodstream [21]. The SC is composed of corneocytes embedded in hydrophobic lipids that form a crystalline lamellar phase. The corneocytes are coated with cross-linked soft keratin [23]. The water content in the SC is not evenly distributed according to its thickness. A thin layer of water is in equilibrium with the surrounding water content, while the moisture content of a thicker layer of the epidermis is close to saturation level. Viable skin contains 70–80% water, whereas the surface of the SC is drier than this viable dermis [24]. The electronic diffraction results of biopsy specimens show that the water content regularly drops from 70–80% in the stratum granulosum layer to 15–25% in the upper layer, which means that the water is completely bound, even for fairly high water content values, in these skin layers [25].

Transfersomes act as encapsulating carriers for various active ingredients

Transfersomes as trapping carriers represent the first generation of elastic liposomes that can deliver various active ingredients with different lipophilicities and are able to encapsulate active substances with high molecular weights. Transfersomes are widely reported as being used for topical and transdermal delivery of various active pharmaceutical ingredients. However, the recent development of cosmetics is primarily intended to improve the appearance of the skin through localized biological effects on its tissues. Identifying the similar physicochemical properties of the active ingredients provides direct analogies for successful transfersome-based skin treatment, rendering them prospective active cosmetic ingredients. Active ingredients with hydrophilic properties will be encapsulated in the aqueous core, while lipophilic substances are trapped within the lipid membrane layer. The process of encapsulating

Table 1. The utilization of transfersomes and protransfersomes as delivery carriers for various active cosmeceutical agents.

Therapeutic class	Drug or therapeutic agents	Properties			Type of drug carriers	Ref.
		Water solubility	Permeability	Stability		
Antioxidant	Curcumin	Low	Low (high MW)		Transfersomes	[36,37]
	Resveratrol	Low	High	Low	Transfersomes	[25]
	Psoralen (+ resveratrol)	Low	Low		Transfersomes	[38]
	Epigallocatechin-3-gallate (EGCG)	High	Low	Low	Transfersomes	[39,40]
Antidiabetic agent	Glimepiride	Low	High		Protransfersomes	[41,42]
Anticancer agent	Cisplatin	Low	Low		Protransfersomes	[14,19,43]
	Cisplatin	Low	Low		Transfersomes and protransfersomes	[14]
	Cisplatin + imiquimod	Low	Low		Protransfersomes + carbopol	[44]
	5-Fluorouracil (+ resveratrol)	High	Low		Transfersomes	[10,45]
	Methotrexate	Low	Low		Transfersomes	[46–48]
Analgesic	Ketoprofen	Low	High		Protransfersomes	[23,49,50]
	Ketorolac	High	Low		Protransfersomes	[51]
					Transfersomes	[12,52,53]
	Diclofenac	Low	High		Protransfersomes	[54,55]
	Diflunisal	Low	High		Transfersomes	[56,57]
Hormone and protein	Levonorgestrel	Low	Low		Protransfersomes	[22,58]
	Norgestrel	Low	Low		Protransfersomes	[59]
	Insulin		Low	Low	Transfersomes	[29,35]
	siRNA		Low	Low	Transfersomes	[60]
	Sulforaphane		Low	Low	Transfersomes	[61]
	Phytoestrogen quercetin	Low	High	Low	Transfersomes	[28,62]
Antihypertensive agent	Timolol	Low	Low		Protransfersomes	[24,27,63]
	Nifedipine	Low	High		Protransfersomes	[64,65]
	Minoxidil + caffeine	Low	Low		Transfersomes	[66–68]
Anti-infection	Azaleic acid	Low	Low		Transfersomes and protransfersomes	[20]
	Amphotericin B	Low	Low		Transfersomes	[69–71]
	Rifampicin	Low	High		Transfersomes	[72,73]
Selective estrogen receptor modulator	Raloxifene hydrochloride	Low	High		Transfersomes	[74,75]
Vitamins	Retinoyl palmitate	Low	High	Low	Transfersomes	[76]
	Tocopherol	Low	High	Low	Transfersomes	[77]
Herbal products	Emu oil from *Dromaius novaehollandiae*	Low	Low		Transfersomes	[78]

large molecules for subsequent penetration of deeper skin layers is that of forming a reservoir for slow and sustained release of the encapsulated substances, allowing for a reduction in the frequency of administration [32].

The encapsulation of active cosmetic ingredients with high molecular weights can be based on several studies of transfersome formulation for delivery of proteins, such as growth hormones contained in AMSC-MPs, stem cells and RNAs [7,29,32–34]. The reverse-phase evaporation method for transfersome formulation has been used in the encapsulation of hydrophilic polypeptide molecules (e.g., insulin) by using sodium cholate as the EA, with an entrapment efficiency of up to 81% [35].

Table 1 shows the use of transfersomes for loading various types of active ingredients, which has been proven to improve stability, penetration and effectiveness while reducing the toxicity; this enables their use as references for ultradeformable vesicle formulations of cosmetic active ingredients with similar physicochemical properties. The encapsulation methods of active ingredients in transfersomes depend on the ingredients' solubility and permeability, as discussed in the following sections.

Protein molecules

Proteins are known as active ingredients with a high molecular weight that have been used in skin care. An appropriate delivery system is required to ensure that this active ingredient is stable and can penetrate the skin to produce therapeutic effects. A number of proteins have been formulated into transfersomes, one being insulin, whose particle size can be reduced to 100 nm and which can easily penetrate deeper skin layers, producing a hypoglycemic effect when compared with conventional insulin vesicles via the transdermal route [29]. This is because insulin, which is composed of large molecules and demonstrates high affinity, is distributed in the skin by interstitial fluid flow through the lymphatic system in the skin dermis layer in the presence of lymphatic vessels and capillaries [35]. These anatomical characteristics can be utilized in transdermal delivery of such proteins [79].

Apart from insulin, the progestin hormone used for the purposes of oral birth control or contraception has also been formulated as transfersomes: norgestrel, which is composed of soya phosphatidylcholine and sodium cholate at a weight ratio of 90:10, and levonogestrel, which contains the same elements at a weight ratio of 85:15. Transfersomes have been shown to increase transdermal penetration, double the contraceptive's effectiveness, enhance active ingredient stability, augment entrapment efficiency and facilitate greater reproducibility [22,80].

The current use of siRNA can represent an alternative anti-aging therapy because it is known to be capable of regulating the expression of certain genes that are intimately involved in the skin aging process [81]. This is expected to enhance the ability of skin cells to repair themselves, given that during aging the skin layer tends to become thin and easily damaged due to reduced skin matrix production and lipid synthesis, lower antioxidant capacity and hyperpigmentation [82]. However, several obstacles exist to skin penetration by this oligonucleotide, including its large molecular size, which renders passing through the skin layer difficult, and its negative charge, which hinders internalization by the cells [83,84]. The use of nanocarriers such as transfersomes in encapsulating and modifying the natural properties of siRNA could enhance the biological efficacy and stability of cosmetic delivery.

The use of siRNA and mRNA formulated as transfersomes in the treatment of atopic dermatitis has been shown to increase effectiveness and reduce side effects. RNA which is enzymatically degraded and has low membrane permeability can be delivered to the deeper layers of the skin using a gene carrier with the addition of penetration enhancers containing cysteine, arginine and histidine. Such enhancers work through different mechanisms. The arginine residue forms a complex with siRNA, the histidine portion allows the complex to escape the endosome and the cysteine constituents stabilize and release siRNA in a reducing environment. Peptide modification with stearic acid further stabilizes the complex through hydrophobic interactions. Formulated with the small unilamellar vesicles fusion method, the siRNA particle size can reach 70 nm and is protected from enzymatic degradation. The increased effectiveness of siRNA as a regulator of cytokine production, leading to a reduction in inflammatory cytokines in mice, indicated that transfersomes successfully deliver siRNA transdermally [32]. Phospholipon® 90G and Brij® O20 combined with sponge *Haliclona* sp. *spicula* (SHS) for siRNA delivery, which acts as an enhancer by making many microchannels that are approximately 800 micropores per mm^2, applied at a dose of 10 mg SHS/1.77 cm^2 for 48 h into the SC successfully facilitated protein penetration to the deeper layers of the skin [85].

Cristiano *et al.* [61] have also formulated the enzyme product of sulforaphane (1-isothiocyanate-(4R)-(methylsulfinyl)-butane) encapsulated within transfersomes consisting of Phospholipon 90G and sodium cholate at a weight ratio of 88:12, using the thin-layer evaporation method, for melanoma therapy. The use of transfersomes has been shown to increase penetration into the deeper layers of the skin, thereby increasing the agent's anti-cancer activity.

The new paradigm emphasizes stem cells as an attractive biotechnology product to be formulated as anti-aging cosmetics. The effectiveness of stem cells in regenerating damaged cells due to oxidant-induced shortening of chromosome telomeres has also been studied [86,87]. Stem cells possess the unique characteristic of being unspecialized and, as such, are able to reproduce themselves repeatedly through asymmetric division [88]. As well as those derived from animals, stem cells from plants are also used as cosmetics after being made into standardized stem cell extracts [89]. The characteristics of stem cell products or extracts, which have high molecular weights and are unstable for transdermal preparations, have prompted researchers to utilize nano-sized delivery systems, one of which is elastic liposomes which can reduce particle size to <100 nm as a means of facilitating penetration into deeper skin layers [33].

It has been reported that AMSC-MPs contain numerous cytokines and growth factors, including EGF, TGF-β, bFGF and KGF [7,84,90]. These growth factors and cytokines play important roles in modulating cell behavior in tissues, increasing the proliferation of epidermal keratinocytes and dermal fibroblasts, thereby stimulating the

production of extracellular matrix such as collagen [91]. Recently, microneedle- and laser-assisted drug delivery have been used to deliver AMSC-MPs to the skin dermis layer because these hydrophilic macromolecules have a molecular weight >25 kDa [8], which hinders their penetration of the deep skin layers [7,34]. The ability of transfersomes to encapsulate hydrophilic substances inside the vesicles is dependent on their high deformability, which enables them to pass through intercellular space and enable deep penetration of AMSC-MPs into the dermis.

Active substances with low solubility & high permeability

Transfersomes, which can load active ingredients characterized by low solubility and high permeability, can have an effect by means of several methods, namely: high pressure homogenation, modified coacervation phase separation and conventional thin film hydration. Active ingredients belonging to this group include resveratrol, quercetin, glimepiride, diclofenac, ketoprofen, rifampicin, nifedipine, raloxifene and retinyl palmitate [23,25,28,41,64,72,75,76].

In cosmetics, resveratrol has been shown to promote the proliferation of fibroblasts, in turn increasing the production of collagen matrix, which renders it a potential anti-aging therapy [92]. Moreover, its high antioxidant capacity plays an important role in preventing oxidative damage to skin tissue cells caused by exposure to UV and retarding the photo-aging process [92,93]. Despite demonstrating high levels of permeability in topical delivery [93], resveratrol has low water solubility, and significant issues exist with regard to its stability [94,95]. Resveratrol has been combined with various active ingredients, including psoralen which, in combination with UV-A, can stimulate melanin production and tyrosinase activity in melanocytes. The resulting transfersome vesicles have a homogeneous particle size, are stable and demonstrate high trapping efficiency, with the result that the use of transfersomes both enhances the effect of the combination of active ingredients and is able to inhibit the increase of free radicals for vitiligo therapy [38]. Arora *et al.* [25] prepared transfersomes using central composite design and found that transfersomes comprised of cholesterol hydrochloride, cholesterol and sodium deoxycholate could increase the depot effect on the skin. The addition of a cosmetic base cream and gel has no effect on the physical characteristics of the vesicles; on the contrary, it can increase acceptability during use.

Quercetin, a polyphenol compound, has been reported as having an antifibrotic effect capable of reducing scar formation and accelerating wound healing [96]. The use of Quercetin has also been reported as effective in protecting human skin tissues from photo-aging through inhibition of MMP-1 expression, which prevents collagen degradation [97,98]. However, the use of quercetin is highly restricted by its low water solubility with a partition coefficient value of 1.82 [98,99]. In a previous report, quercetin as a phytoestrogen employed in osteoporosis therapy, had low bioavailability when taken orally [28]. Therefore Pandit *et al.* [28] formulated quercetin in transfersomes using a fractional factorial design optimized by a complete factorial design. The results showed that quercetin loaded in transfersomes, prepared with phosphatidylcholine and Tween® 80 at a weight ratio of 2:1, has a homogeneous and stable particle size and can increase therapeutic effectiveness by topical administration of its transfersomal system, as indicated by femoral thickness, length and density and also by serum biochemical parameters such as calcium, phosphorus, alkaline phosphatase and tartrate-resistant alkaline phosphatase. Thus the use of transfersomes successfully improved topical delivery of quercetin.

Low or reduced levels of retinoids, which affect the maturation of skin epithelial cells, can cause skin disease. Therefore an external supplement in the form of retinyl palmitate can be applied. In the presence of enzymes in the skin, retinyl palmitate will be converted to retinol and oxidized to form tretinoin, which induces thickening of the epidermal layer and collagen production [100]. Retinyl palmitate has low water solubility, therefore in order to improve it for the purposes of dermal delivery, transfersomes were prepared with a weight ratio of phosphatidylcholine:Tween 80 of 18:1. This successfully promoted skin penetration, as evidenced by the discovery of retinyl palmitate in various layers of the skin, suggesting that the transfersomes can be used as carriers for active ingredients with similar characteristics [76].

Interestingly, the topical use of 3% diclofenac sodium with hyaluronic acid repairs, to a great extent, signs of skin damage due to chronic UV exposure, including irregular pigmentation and coarseness. This is probably due to its promotion of cyclooxygenase inhibition, which reduces melanin transfer to the epidermal keratinocytes [101,102]. Diclofenac itself has come to be regarded as a poorly water-soluble substance with good permeability [103]. El Zaafarany *et al.* [104] compared the characteristics of diclofenac topical transfersomes prepared by means of two manufacturing methods, with differing active ingredient contents and phospholipid:EA ratios, and using five variations of surfactants as EAs. The preparation methods used were vortex sonication and rotary evaporator sonication. The manufacturing method has a significant effect, with the transfersome prepared by the rotary evaporator (thin film) and sonication method producing higher trapping efficiency than the vortex and sonication

method due to perfect hydration of the vesicles. In the vortex method, visual observation shows that lipids tend to collect and adhere to the vial walls, rendering difficult hydration of the vesicles. The vortex method is unable to disperse lipids completely, resulting in a clumpy dispersion, difficult homogenization and susceptibility to rapid sedimentation and aggregation [104].

Adding a specific amount of the active substance to the transfersomes affects the loading capacities. Consequently, if it exceeds the optimal capacity of the vesicles, precipitation of active ingredients will occur. The phospholipids:EA ratio also greatly affects transfersome vesicles' characteristics. Optimum deformability is obtained from a phospholipids:EA ratio of 85:15. If the amount of phospholipids is excessive, vesicles will form with low deformability due to a lack of surfactant. A similar phenomenon will occur if too great a quantity of the surfactant is added due to the formation of a rigid micelle mixture [104].

The use of various types of surfactants possessing different chemical structures also results in contrasting vesicle characteristics. Comparing the effect of surfactant types with the optimal phospholipid:surfactant ratio, it was found that the vesicles containing Tween 80 had the highest deformability. This is due to the fact that Tween 80 is composed of flexible, non-bulky hydrocarbon chains. In contrast, the sodium cholate confers lower deformability due to its steroid-like structure, which is larger than the hydrocarbon chain of Tween 80. However, in terms of the entrapment efficiency values, the order is systems containing Span® 85 > Span 80 > Na cholate > Na deoxycholate > Tween 80. The use of Tween 80 in transfersomes loading diclofenac sodium effectively improved deformability of the vesicles, thus increasing skin delivery in non-occlusive topical application [104].

Nifedipine, an antihypertensive drug, has been reported to effectively repair wrinkles as well as promote skin elasticity and hydration when delivered as a 0.5% topical preparation [105]. It blocks muscular contraction and relaxes facial muscular fibers, thus reducing the depth of wrinkles [106]. On the other hand, nifedipine demonstrates very low solubility in water with a high partition coefficient, which limits its use in dermal delivery [107]. Nifedipine constitutes a transdermal protransfersome preparation produced by a coacervation phase separation method. The protransfersome consists of phospholipid and sodium deoxycholate at a weight ratio of 85:15 and produces a bioavailability 6.5-times greater than that of oral administration. This is supported by a high entrapment efficiency of up to 97% and an increase in penetration ability up to three-times greater than the drug suspension, triggering an increase in the drug's antihypertensive effectiveness [64].

Raloxifene hydrochloride is an active therapeutic compound used in the treatment of breast cancer and osteoporosis, but it has low bioavailability. It has been claimed in recent reports that raloxifene is able to improve both collagen synthesis by fibroblasts in human skin tissue and skin elasticity due to its effects on selective estrogen receptor modulators [108,109]. Mahmood *et al.* [26] succeeded in increasing its bioavailability by formulating it into transfersomes for transdermal delivery. The formula was designed with a Box–Behnken design composed of Phospholipon® 90G and sodium deoxycholate at a weight ratio of 300:35, resulting in vesicles with high entrapment efficiency, good stability and high penetration rates.

Transfersomes are also used for delivery of glimepiride, which is an oral antidiabetic drug. The side effects of hypoglycemia, as well as digestive and hepatic disorders that often occur, can be reduced by the ability to release it gradually, thereby increasing patient compliance. The Box–Benkhen design was used in a transdermal transfersome formulation which has a weight ratio of phospholipids:sodium deoxycholate:glimepiride = 200:45:1. Positive vesicle characteristics were obtained, thereby increasing effectiveness due to high penetration into the skin's deeper layers, and showed a higher penetration flux than glimepiride suspension [41]. Increased drug bioavailability, which reduced both the side effects on the gastrointestinal tract and the long-term therapeutic effects due to lower quantities of drugs being used during the therapy, was superior to the oral administration of glimepiride.

The antituberculosis drug rifampicin can be prepared as a transfersome to improve its transdermal bioavailability and patient compliance due to continuous drug release. A comparison of the base of the gel and the suspension confirmed the particle sizes to be similar, but the ζ-potential of the gel was more negative because of the acidity of carbopol as the gelling agent. In addition, the permeation value, depot effect and bioavailability of gel preparations were greater due to the composition of the formula containing Phospholipon 90G and Tween 80 at a weight ratio of 15:7 between ethanol and D-limonene [72].

The capability of transfersomes to encapsulate hydrophobic molecules with physicochemical properties similar to those of glimepiride and rifampicin – such as coenzyme Q10 [110], α-tocopherol [111], idebenone [112], α-lipoic acid [112,113], ferulic acid [114] and tretinoin [115] – within the lipid bilayer would enable modification of physicochemical properties of active ingredients encapsulated in carriers which are nano-sized particles, amphiphilic

self-assembling phospholipids with surfactant presence, thus affecting their dispersibility, solubilization and release into aqueous media at the intended sites, especially dermis, for anti-aging therapy [116].

Active substances with high solubility & low permeability

There are several active substances within this category, including epigallocatechin-3-gallate (EGCG), 5-fluorouracil and methotrexate. The study of the use of transfersomes for delivery of a combination of EGCG and hyaluronic acid as an antioxidant for topical application has been reported. The transfersome was prepared by a combination of thin-layer hydration and high pressure homogenization methods. The formula optimization was performed using a Box–Behnken design prepared with phosphatidylcholine:sodium cholate at a weight ratio of 85:15, resulting in increased UV protection and promoting EGCG's antioxidant and anti-aging effects [39].

It has previously been reported that 5-fluorouracil can be used to manage actinic keratosis and is able to induce collagen synthesis during matrix remodeling and wound healing through a 5% topical administration, reversing photo-aging [117]. The use of transfersomes dispersed in a carbopol-based gel has been observed to successfully enhance penetration through hypertrophic scar tissue to the dermal layer, even penetrating deeper skin layers without physical changes or allergic reaction [118]. Another report suggested that using Tween 80 as the EA in transfersome-loaded carbopol gel significantly improves skin deposition and penetration of 5-fluorouracil [119].

As a potent analgesic, ketorolac can be formulated for transdermal delivery, which has the advantage of gradual release, thus reducing the gastrointestinal side effects that often accompany it. To overcome the low permeability of ketorolac [120], Nava *et al.* [52] succeeded in formulating it into transfersomes consisting of Epikuron™ 200 and Tween 80 at a respective weight ratio of 86:14. The transfersome has a particle size of approximately 127.8 nm, with a low polydispersity index, a relatively neutral charge with a ζ-potential of -12 mV and high entrapment efficiency of 73.11%. Moreover, its release is delayed, causing it to remain in the skin for a long period, thus producing local therapeutic effects [52].

Transfersome vesicles possess the ability to modify the permeability of active ingredients due to encapsulation within the carrier which can change passive diffusion into active transport, allowing low permeable ketorolac-like active cosmetic ingredients, such as ascorbic acid [121], to permeate biological membranes. The use of biomimetic phospholipid as a component of transfersomes would enable vesicles to carry active ingredients via the paracellular or transcellular routes, among others, or through fusion with the cell membrane. This underpins the potential of transfersomes to deliver active ingredients promoting dermal repair and rejuvenation [122].

Active substances with low solubility & low permeability

In transdermal delivery, the active ingredients should be dissolved to maximally penetrate the skin. To overcome the problem of low solubility and low permeability of active ingredients, transfersomes are used as the carriers as they have been shown to successfully deliver active ingredients including curcumin, psoralen, cisplatin, paclitaxel and ketorolac to the deeper layers of the skin [36,38,44,52,123]. Numerous reports have demonstrated that curcumin can be a potential agent for reversing aging. Its high antioxidant capacity offers protection against the negative effects of free radicals, as well as anti-inflammatory effects which potentially stimulate the production of TGF-β and fibroblasts, while also inducing extracellular matrix production and angiogenesis, which both play a significant role in repairing skin and maintaining its health [124–127]. Curcumin has been seen to demonstrate low water solubility and poor permeability for oral and topical delivery [128]. The low bioavailability of curcumin can be increased by transfersomes prepared with purified phosphatidylcholine (Epikuron 200) as the phospholipid and sodium cholate as the surfactant, at a weight ratio of 85:15 using a thin-layer hydration method followed by extrusion. These nanovesicles' characteristics, including small and homogeneous particle size with high entrapment efficiency (up to 93.91%) and loading amount of 7.04% with improved skin permeability, proved useful in increasing antitumor activity [36].

Cisplatin is a platinum-based chemotherapeutic agent with extremely low skin penetration through the main route of skin appendages [129]. Moreover, it also demonstrates limited solubility in water and, consequently, often requires solubilizing agents as well as absorption enhancers to improve its effects [130]. Transfersomes composed of soya lecithin and sodium cholate at a weight ratio of 17:3 produced a gradual release of cisplatin, thereby reducing its side effects on healthy cells. Cisplatin, either alone or together with a stabilizer such as a combination of soya lecithin:Pluronic:sodium cholate at respective weight ratios of 17:1.5:1.5 or other antioxidants produced positive nanovesicle characteristics with small and homogenous particle size and high entrapment efficiency (up to 97.97%), thus increasing anticancer effectiveness in skin melanoma therapy [19,43,131]. The use of protransfersomes

and transfersomes also improved cisplatin levels in plasma during transdermal application, which proves these ultradeformable vesicles successfully enhance penetration of poorly soluble and poorly permeable active ingredients such as cisplatin [14].

The use of transfersomes for the transdermal delivery of methotrexate can increase the effect of drug deposition in the skin and can release the drug efficiently. Transfersomes prepared at a phosphatidylcholine:Tween 80 weight ratio of 7:3 were shown to be superior to conventional liposomes in delivering drugs into the deeper skin layers [132]. In combination with resveratrol, they can increase the anticancer activity of methotrexate against skin melanoma and some squamous cell carcinomas such as actinic keratosis, Bowen's disease and keratoacanthoma [45].

Methotrexate was formulated by an extrusion method using phosphatidylcholine and with two types of EAs (Tween 80 and sodium cholate) to compare its physicochemical characteristics and penetration abilities across skin [47]. From the study, it was clear that the resulting transfersome had a homogeneous and stable unilamellar structure and could increase the penetration of methotrexate into the skin layer by up to five-times. As the EA, Tween 80 was more effective at increasing vesicle deformability than sodium cholate [47].

According to these results, transfersomes and protransfersomes are able to improve the solubility and permeability of active cosmetic ingredients with low water solubility and poor permeability, such as kinetin [133,134] and superoxide dismutase, which also has a high molecular weight (30 kDa) [135]. Their ability to entrap hydrophobic molecules within the lipid domain of the bilayer membrane, as well as the amphiphilic properties of the phospholipids used in transfersomes, significantly improves the solubility and permeability of such compounds, rendering them useful in delivering active cosmetic ingredients.

In vitro evaluation of transfersomes & protransfersomes

Several nanocarrier lipids, both conventional and elastic liposomes, have different characteristics of vesicle shapes depending on their constituent components, namely surfactant for transfersomes and ethanol for ethosomes. From microscopic observation, it is clear that all of them are spherical vesicles, but have different vesicle sizes, as can be seen in transmission electron micrographs [61].

During hydration in the presence of water, the protransfersome gel with lamellar appearance transforms into transfersomes due to the hydrating fluid being absorbed by the gel system [136]. This hydrated gel forms spherical vesicular structures due to the different degrees of hydration between surfactants and phospholipids. Starting from the protransfersome with a limited amount of solvent, a mixture of lamellar liquid crystals is formed which resembles the interrelated palisade and vesiculated lamellae. The addition of excess water will cause swelling of the lipid bilayer due to the interaction of water with the surfactant hydrophilic groups above the solvent threshold concentration, with the result that the bilayer randomly forms a spherical structure which resembles a vesicle [22] and can be described as presented in Figure 2.

The increase in vesicle deformability is also evidenced by the increasing amount of active ingredients penetrating the skin, which is the important factor in efficient skin permeation. This deformability is highly influenced by the presence of an EA in the form of a single-chain surfactant with a high radius of curvature, which renders the vesicles unstable and enables the double layers of vesicles to change shape easily [137]. EAs reduce the energy required to deform the vesicles, with the result that transfersome vesicles can flex to pass through tiny pores in the skin or through intercellular gaps [26]. However, this deformability can be reduced when the amount of surfactant increases [73].

The lipid lamellae in the SC have a high proportion of negatively charged lipids [138]. Consequently, the ionically charged surfactant affects the penetration of the active substances. Vesicles with cationic surfactants can increase the penetration of active substances to a greater extent than anionic or non-ionic surfactants, as revealed by the considerable fluorescent intensity of labeling agents entrapped in transfersomes. This result is due to electrostatic attraction to the negative charge in the SC. This difference in charge can strengthen the interaction between cationic transfersomes and intracellular lipids [137].

Release studies of active substances from the carrier can be used to predict how the carrier can deliver active ingredients and produce therapeutic effects before being tested *in vivo*, which is an expensive process. In the *in vitro* release test using a Franz diffusion cell, the active substances' release from transfersomes is limited by two barriers, namely the phospholipid and the dialysis membrane. The concentration of EA has an effect on the release of active ingredients which is directly proportional. If the concentration is low, then the release of the active substances is similarly low. This is because the lipid membrane becomes regular and does not leak easily. Meanwhile, if the concentration of EA is excessive, the vesicles will be stiffer, with the result that they leak easily and are less sensitive

to osmotic gradients [27]. Pena-Rodríguez *et al.* [76] studied the penetration of retinyl palmitate by comparing transfersomes composed of phosphatidylcholine and Tween 80 with free active ingredients. They found that about 69% of conventional liposome-loaded retinyl palmitate could not penetrate the skin and that only 2% reached the epidermis to be retained in the SC. Lipid vesicles can act as a reservoir system for the continuous delivery of active cosmetic ingredients. However, the vesicles of the anionic surfactant deviate from the first-order kinetics of drug release following the diffusion flow of the skin [137].

El-Alim *et al.* [56] compared the release rate of diflunisal in solution with those of liposomes, ethosomes and transfersomes. The results showed that within 2 h the amount of diflunisal released from the solution was 84.52%, higher than that released from liposomes (68.10%) ethosomes (58.21%) or transfersomes (65.88%). The peak level of diflunisal release in solution was reached within 3 h, whereas diflunisal in vesicles continues for up to 5 h before reaching peak levels.

In vivo evaluation of transfersomes & protransfersomes

From several studies it is known that skin penetration by drugs can be via intercellular or transcellular routes. Transfersomes can pass through these routes due to their elastic properties and the water concentration gradient in the skin layer. The nature of this tendency to attract water triggers the vesicles' ability to penetrate the deeper layers of the skin because of their higher water content. After entering the dermis, the active substances will circulate through the blood vessels to the systemic blood circulation. Due to the higher drug penetration, effectiveness also increases.

The pharmacokinetic study in mice conducted by Jain *et al.* [22] indicated that levonorgestrel levels in blood plasma were very low for free active ingredient (0.015 ± 0.005 μg/ml), in contrast to the transfersome-loaded levonorgestrel, which reached levels of 0.139 ± 0.050 μg/ml after topical aplication. The level rose to approximately eight-times higher within 4 h and was maintained for up to 48 h. Therefore it can be proved that by using transfersomes, levonorgestrel can be gradually released over a protracted period.

A similar study was performed by Hussain *et al.* [72], who compared the plasma levels after oral administration of rifampicin and transdermal application of transfersome-loaded rifampicin. The comparative data for C_{max} and T_{max} indicated levels of 10.5 ± 1.4 μg/ml after 2.0 h and 6.9 ± 0.80 μg/ml after 10.6 h, respectively, for oral administration. Meanwhile, the AUC value of rifamipicin after 24 h for oral administration was 41.71 ± 5.2 μg/ml, while for transdermal application it was 56.23 ± 2.7 μg/ml. This suggests that the use of transfersomes for transdermal administration can increase the systemic availability of rifampicin by reducing the dose-related side effects and toxicity of the orally administered rifampicin.

An *in vivo* test using tape stripping was used by Fernández-García *et al.* [70] to compare amphotericin B levels in the SC and dermis after the application of amphotericin B transfersomes to undamaged skin and by microneedle. This study proved that amphotericin B transfersomes can penetrate to the deeper layers of the skin, while using a microneedle before the application of amphotericin B transfersomes resulted in increased penetration of the active ingredient during the first hour, especially in deeper skin areas. The use of microneedles produces temporary skin micropores that aid drug delivery throughout the skin. However, these micropores close within 2 h and scar tissue is formed which can reduce the surface area for the active ingredient [29]. In this study, there was no significant difference in the degree of skin penetration between transfersome-loaded amphotericin B and amphotericin B added to dimethyl sulfoxide as a skin penetration enhancer. This study proved that the transfersome is capable of acting as an enhancer in itself.

Transfersomes are largely evaluated *in vivo* through the use of both human and animal subjects. In human subjects, the transfersomes can be assessed for their transepidermal water loss value both before and after application. From the results of the tape strip, it is known that there is no significant difference in this value, therefore confirming that the transfersomes do not affect skin integrity [76]. Although transfersomes can act as a depot for epidermal absorption, the SC is desquamated, with the result that the active ingredient can be lost. In one study, by using transfersomes, about 63% of the retinyl palmitate successfully penetrated the epidermis [76]. Fluorescent photomicrographs showed that the transfersomes contained Nile red, indicating that transfersomes can deliver active ingredients penetrating the deeper layers of the skin [76]. Moreover, the fluorescence correlated with transfersomes was extensively observed in the space between the corneocytes in the epidermis [19].

Arora *et al.* [25] studied penetration of the antioxidant resveratrol by transfersome carriers composed of soya phospholipids and sodium cholate at a weight ratio of 85:15. At an appropriately high phospholipid content level, the lipophilic resveratrol can be trapped within the lamellar lipids of vesicles. The use of transfersomes successfully

increased the penetration of resveratrol, thus improving the *ex vivo* antioxidant activity as determined by the 2,2-diphenyl-1-picrylhydrazyl test. This improved effectiveness is due to an increased flux of active ingredients caused by disrupting the SC barrier through an amalgam effect of a combination of phospholipids and surfactants. In addition, the skin-penetrating amount of vesicle-entrapped active ingredients was increased due to the longer residence time in the skin.

In albino Wistar rat subjects, the application of timolol-loaded transfersomes composed of phosphatidylcholine:Span 80 and Tween 80 at a weight ratio of 3:1 to the shaved back skin was observed to reduce the occurrence of erythema and edema compared with conventional liposomes. Neither erythema nor edema occurred after this *in vivo* application [24].

Discussion

The formulation of ultradeformable vesicles (transfersomes and protransfersomes) can be seen to increase the effectiveness of active ingredients due to improvements in their physicochemical characteristics and skin penetration. With the combination of phospholipids that resemble skin membranes and the addition of surfactants as EAs, the formation of vesicles can reduce the particle size, enabling them to easily penetrate intercellular gaps and skin pores. The ability to deliver active ingredients with various characteristics of lipophilicity, solubility, permeability and high molecular weight – including proteins, RNA and hormones – also constitutes an advantage of this delivery system. Transfersomes can be applied in the cosmetics industry because the research conducted indicates that the use of a base preparation including gel and cream neither changes the skin penetration profile nor reduces the effectiveness of the active ingredient. Rather, it can increase the length of time the drug remains in the skin and product acceptability [8,94].

It is expected that transfersomes and protransfersomes can potentially be used in the cosmetic field with local biological effects, especially in anti-aging products. Skin aging is known to be caused by the presence of reactive oxygen species that induce oxidative stress in cells, reduce cell proliferation and disrupt the dermal extracellular matrix [139,140]. However, active cosmetic ingredients used in anti-aging therapy, such as CoQ10 and AMSC-MP, suffer from skin penetration-related drawbacks including low water solubility and high molecular weight. The use of transfersomes and protransfersomes may facilitate the penetration by active cosmetic ingredients of the deep skin layers, in particular the dermis, which is composed of almost 70% collagen [141]. With increased skin penetration, the effectiveness and stability of cosmetic products will be improved, providing potential use for beauty and health.

Conclusion & future perspective

Transfersomes and protransfersomes demonstrate encouraging potential for use in cosmetics, especially anti-aging products. The use of phospholipids and EAs in these carriers has benefits for producing nanovesicles with desirable characteristics supporting high skin penetration, thus increasing the effectiveness of active cosmetic ingredients.

Delivering cosmetic active ingredients to target sites, especially for agents affecting biological functions, can be ultimately supported by appropriate delivery carriers. This review represents the underlying researches in topical or transdermal delivery of active ingredients to the development of therapeutic products for esthetic medicines and cosmetics. A positive approach of the use of ultradeformable carriers (transfersomes) and their provesicular states (protransfersomes) has been largely explored to improve skin penetration by utilizing the natural characteristics of phospholipids and EAs to form intact flexible vesicles which pass through intercellular gaps. As delivery carriers, these deformable vesicles show great potential for transporting either hydrophobic or hydrophilic molecules with low or even high molecular weight (such as proteins) to penetrate into deeper skin tissues, which become the main target sites of most cosmetics, especially for anti-aging therapy. Further explorations and investigations are definitely required to comprehensively evaluate the potential use of ultradeformable vesicles in improving the efficacy of cosmeceuticals, which is currently still limited.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Transfersomes encapsulate various active ingredients

- Transfersomes are a vesicular drug carrier that consists of a bilayer membrane composed of phospholipids and biosurfactants at the appropriate ratio surrounding an inner aqueous phase.
- Active ingredients with hydrophilic properties will be encapsulated in the aqueous core, while lipophilic active ingredients can be trapped within the lipid membrane layer.
- Transfersomes also provide the possibility of encapsulating active ingredients with high molecular weight.

Ultradeformable liposomes as vesicular drug carriers for skin cosmetics

- Ultradeformable vesicles can change shape and pass through the pores intact by shrinking to five- to ten-times smaller than the original, due to the transepidermal osmotic gradient.
- Transfersomes can penetrate the skin layers by means of different routes: the intercellular pathway, transcellular route and appendageal route.

Ultradeformable liposomes improve skin delivery of active cosmetic ingredients

- The lipid vesicles of transfersomes can act as a reservoir system for the continuous delivery of active cosmetic ingredients.
- The transfersome is capable of acting as an enhancer in itself.
- The skin-penetrating amount of transfersome-entrapped active ingredients is increased due to the longer residence time in the skin.
- Neither erythema nor edema occurred after the *in vivo* application of transfersomes.

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Therapeutic Delivery

COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
United Kingdom Universities and research institutions in United Kingdom	Pharmacology, Toxicology and Pharmaceutics Pharmaceutical Science	Future Science	52

PUBLICATION TYPE	ISSN	COVERAGE	INFORMATION
Journals	20415990, 20416008	2010-2021	Homepage How to publish in this journal r.finnie@future-science.com

SCOPE

Delivering therapeutics in a way that is right for the patient - safe, painless, reliable, targeted, efficient and cost effective - is the fundamental aim of scientists working in this area. Correspondingly, this evolving field has already yielded a diversity of delivery methods, including injectors, controlled release formulations, drug eluting implants and transdermal patches. Rapid technological advances and the desire to improve the efficacy and safety profile of existing medications by specific targeting to the site of action, combined with the drive to improve patient compliance, continue to fuel rapid research progress. Furthermore, the emergence of cell-based therapeutics and biopharmaceuticals such as proteins, peptides and nucleotides presents scientists with new and exciting challenges for the application of therapeutic delivery science and technology. Successful delivery strategies increasingly rely upon collaboration across a diversity of fields, including biology, chemistry, pharmacology, nanotechnology, physiology, materials science and engineering. Therapeutic Delivery recognizes the importance of this diverse research platform and encourages the publication of articles that reflect the highly interdisciplinary nature of the field. In a highly competitive industry, Therapeutic Delivery provides the busy researcher with a forum for the rapid publication of original research and critical reviews of all the latest relevant and significant developments, and focuses on how the technological, pharmacological, clinical and physiological aspects come together to successfully deliver modern therapeutics to patients. The journal delivers this essential information in concise, at-a-glance article formats that are readily accessible to the full spectrum of therapeutic delivery researchers.

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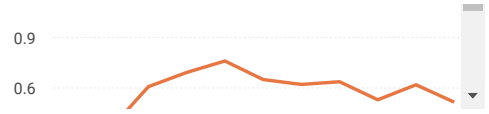

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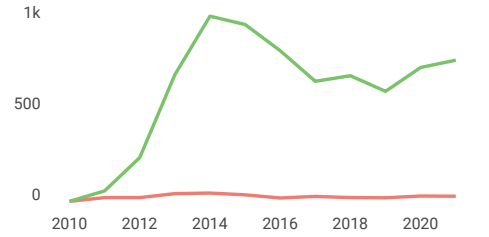

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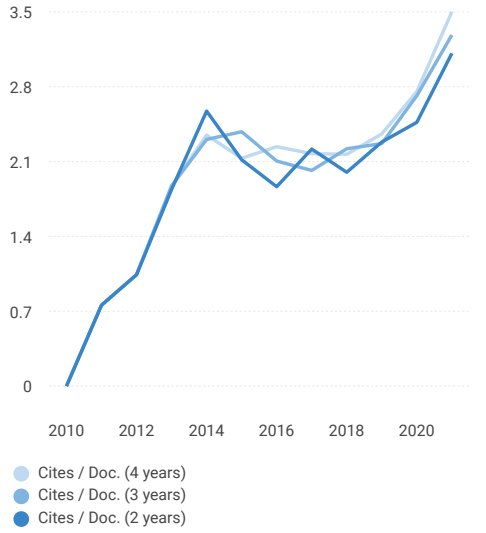

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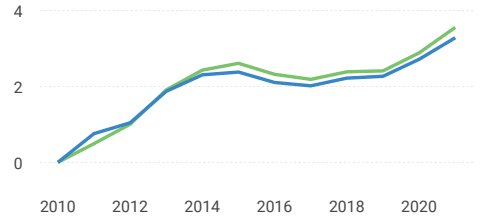

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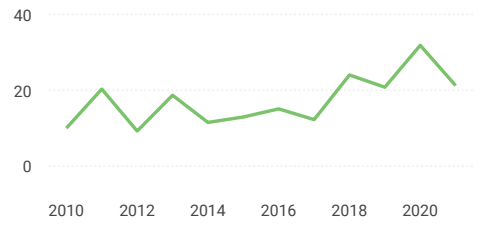

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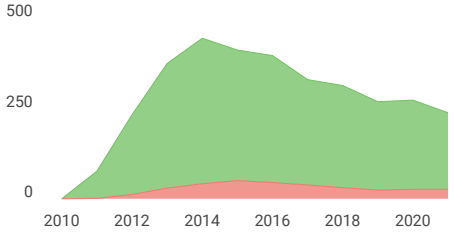

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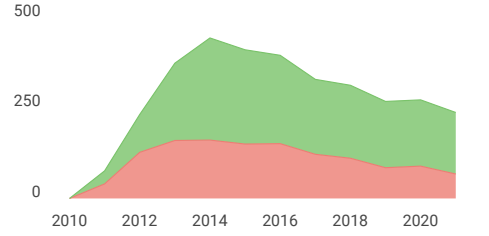

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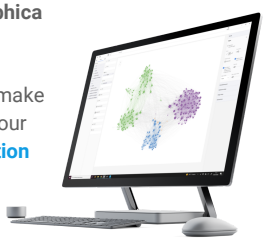

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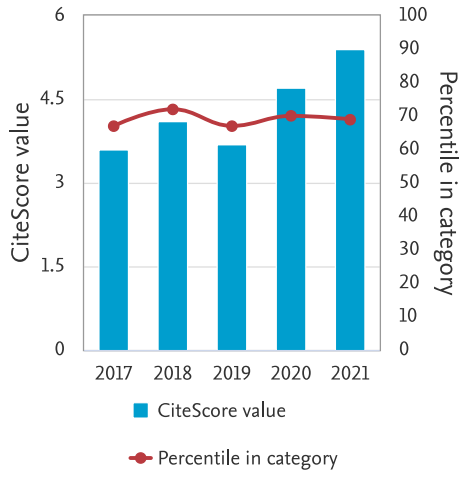

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☆	#76	Pharmaceutical patent analyst	3.7	55th percentile
☆	#77	Biological and Pharmaceutical Bulletin	3.7	55th percentile
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☆	#79	Journal of managed care & specialty pharmacy	3.6	54th percentile
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☆	#81	International Journal of Clinical Pharmacy	3.3	52nd percentile
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