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Nanocarriers: Architecture, Transport, and Topical Application of Drugs for Therapeutic Use

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Skin as the largest organ of the human body is taken in view by pharmacists for topical or transdermal drug delivery. The biological barrier of healthy skin, more specifically the stratum corneum layer (SC), limits the penetration of bioactive substances [1]. Various attempts have been performed to overcome this barrier including applications of ultrasound, electroporation, microneedles, magnetophoresis, or iontophoresis [2]. The successful treatment of inflammatory skin diseases requires an efficient transport of exact, clinically relevant dosage to the targeted site in a way that possible side effects of drugs can be avoided [3]. In this respect, nano-sized polymeric carrier systems for dermal drug delivery represent an elegant strategy to be explored in dermatology in order to increase the penetration depth of applied drugs into skin compared to conventional formulations. In fact, many morphological and physiochemical properties of nanocarriers, such as shape, charge, surface properties, size, and particle softness have an impact on their drug-loading efficiency, skin penetration depth, and interaction with various skin tissues [4]. These interrelated factors turn the task of finding the ideal nanocarrier system for topical treatment into a challenge, especially as the fundamental knowledge related to the interaction of different types of nanoparticles with different skin layers and subsequently to the drug release is still lacking. The development of nanocarriers for the delivery of bioactive molecules in a controlled way for specific treatment of inflammatory skin diseases requires a multidisciplinary approach [5]. The Collaborative Research Center (CRC) 1112 “Nanocarriers: Architecture, Transport, and Topical Application of Drugs for Therapeutic Use” has been established to address these challenges. This Special Issue of the *European Journal of Pharmaceutics and Biopharmaceutics*, was inspired by the International Conference on Dermal Drug Delivery by Nanocarriers, which was held on March 14-16, 2016 in Berlin Germany, bringing together an

international group of scientists from different disciplines, including chemists, biologists, physicists, pharmacists, pharmacologists, veterinarians, and dermatologists, as well as industry representatives. It is our pleasure to make some of the presented results accessible to the broader scientific community through this special issue, to support the progress in this challenging field.

Thermoresponsive nanogels (tNG) are promising candidates for drug delivery in dermatology as they are able to release the loaded cargo above a certain temperature, which could be the elevated temperature of inflamed skin. A comparison between penetration and release properties of tNG in presence or absence of a thermal stimulus upon topical application on intact or barrier-disrupted human skin *ex vivo* was carried out [6]. The studied nanocarriers revealed improved penetration and controlled release properties compared to conventional formulation with the ability to effectively reach dermal dendritic cells of barrier-disrupted skin. The follicular penetration and release properties of the model drug tetramethylrhodamine-labeled dextran (TRITC-dextran) loaded into fluorescein isothiocyanate(FITC)-labeled bovine serum albumin hydrogel nanocarriers (FITC-BSA) were followed using confocal laser scanning microscopy. The results showed that TRITC-dextran released from the FITC-labeled nanocarriers and penetrated in hair follicles significantly deeper than the FITC-BSA nano-hydrogel [7].

Micelles are widely used as nanocarriers for drug delivery applications as they have a small size which can be controlled by tailoring their chemical structure, and a long circulation time in blood. Micelles formed by mono methoxy poly (ethylene glycol)-*block*-poly (ε-caprolactone) (mPEG-PCL) diblock copolymers are able to encapsulate curcumin with a high drug loading capacity of 20 wt.% and with a remarkably enhanced drug half-life $t_{1/2}$ and low cytotoxicity compared to curcumin in solution [8]. Rhamnolipids have been explored as nanocarriers for dermal treatment mimicking bacterial bio-surfactants [9]. Eight different structurally defined rhamnolipids formed micelles with spherical structure and well-defined sizes in the range of 10-100 nm. They were able to incorporate hydrophobic drugs with drug loading efficiency up to 30 wt.%. Nanoemulsions are widely used as nanocarriers system for psoralens, i.e. a natural product used for the treatment of psoriasis and vitiligo, as they can increase skin penetration, controlled release, and reduce the dosage of psoralens which thereby reduces their adverse effects. The low viscosity of nanoemulsions, however, limits their application in topical administration. To

overcome this challenge, chitosan was added as hydrogel-thickener to oil-based nanoemulsions, which improved the transdermal delivery of psoralens [10].

Despite many advantages of using micelles as nanocarriers, their stability during topical treatment remains a challenge. Polymeric nanoparticles represent an alternative to prepare nanocarriers with enhanced stability. Five semi-solid formulations containing fluorescent poly(lactic acid) (PLA) nanoparticles were prepared using five different polymeric excipients [11]. These formulations were compared with regard to their physico-chemical properties, toxicity, and delivery efficacy. Utilization of Avicel or Viscarin as polymeric excipients for the formulation with PLA nanoparticles showed satisfying results in terms of physico-chemical properties and safety profile. Oligodepsipeptide-based submicron particles were prepared by a single oil-in-water emulsion process followed by solvent evaporation [12]. A four-armed star-shaped oligo(ethylene glycol) functionalized with tyrosine-derived aromatic moieties (sOEG-DAT) was used as a surfactant during the preparation and enabled tailoring of particle size in the range of 300-900 nm with narrow polydispersity, surpassing common surfactants, such as poly(vinyl alcohol) (PVA) or Tween 20. A series of polymeric rigid model nanoparticles with various sizes and matrix compositions was prepared from poly[acrylonitrile-co-(N-vinyl pyrrolidone)] and loaded with Nile Red or Rhodamin B, in order to investigate their penetration in human skin [13]. The results revealed that the hydrophilicity of these nanocarriers can influence their cellular uptake while penetration in skin can be enhanced by utilization of small-sized nanocarriers ($\leq$ 50 nm) with increased hydrophilicity.

Non-destructive analytical techniques enable tracking the penetration of nanocarriers and exploring their interactions with skin tissues. Advanced Raman techniques have gained increasing attention as label-free spectromicroscopy to study the distribution of substances in biological samples. However, the cross-sensitivities caused by blended Raman bands are considered as a major hurdle in advancing the use of these techniques. By combining stimulated and spontaneous Raman spectromicroscopy the cross-sensitivity caused by the bands of lipids and proteins can be reduced by a factor of eight in human skin samples, which could finally improve the understanding of the lipid distribution in human skin [14]. Vibrational spectroscopies are efficient techniques to study the interaction of skin with plasmonic nanoparticles [15]. Electron paramagnetic resonance (EPR) allows studying the localization of a

drug within a carrier and following its penetration in different skin layers. Dexamethasone (Dx)-labeled with 3-carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxy (PCA), (DxPCA), was incorporated in core-multishell nanocarriers and its penetration and release in porcine ear skin was explored [16]. By combination of EPR, confocal Raman, and laser scanning microscopy the penetration in porcine ear skin of DxPCA loaded into nano-sized lipid particles (NLP) was compared with DxPCA dissolved in a base cream. This resulted in the finding that NLP increased the penetration of Dx by a factor of two and were able to form a reservoir within SC and hair follicles [17]. Fluorescence lifetime microscopy (FLIM) has emerged in the recent years as an important non-invasive imaging technique to study the interaction and penetration in skin layers due to its ability to distinguish fluorescently tagged nanocarriers from the tissue autofluorescence background. It provides valuable information on the local environment of nanocarriers and their interaction with other biomolecules [18].

Follicular transport has been found to be a significant pathway for drug penetration. By using a two-dimensional stochastic model, the movement of single nanoparticles inside a hair follicle was studied in order to mimic the effect of massaging or other external forces acting on the hair [19]. Radial movement of the hair resulted in a direct transport of nanoparticles into the hair follicles, while the axial motion parallel to the hair axes caused a reversal of transport direction, i.e. out of the hair follicles. Dialysis is a common route to study the kinetic of drug release from nanocarriers. The time required for drug molecules to pass through the dialysis membrane is usually ignored and thus the results need to be considered in the view of this. A two-step approach was developed in order to study the drug release of dexamethasone capsulated in core-multishell nanocarriers using a dialysis membrane where the effect of dialysis membrane on the release kinetic was taken into account, which resulted in an improved understanding for the process [20]. An interesting and reproducible pre-clinical model was developed by combination of short-term cultured human skin with tape-stripping and 4 h sodium lauryl sulfate pre-treatment. The suggested model mimics the skin barrier during inflammatory processes in order to evaluate the efficacy and penetration of any anti-inflammatory drug in dermatology [21].

Direct effects of senescent keratinocytes on the skin barrier were studied on a reconstructed human epidermis from UVB-irradiated keratinocytes (UVB-RHE) [22]. The permeation of testosterone, caffeine, and dendritic core-multishell nanocarriers into UVB-RHE was increased

compared to non-irradiated keratinocytes. tNGs exist usually in hydrophilic state below their cloud point temperature (T_{cp}). Therefore, caveolae-mediated endocytosis and micropinocytosis were observed as cellular uptake mechanisms for tNGs below T_{cp} [23]. Above T_{cp}, tNGs show usually a hydrophobic nature and thus only a caveolae-mediated endocytosis mechanism was observed.

Despite recent achievements in the field of nanocarriers for topical treatments, it still requires much effort in order to design and produce an ideal nanocarrier, which will be able to carry a sufficient amount of drug, transport it efficiently to the targeted tissue, and release it on demand, while avoiding any adverse effects of this treatment.

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References

[1] A. Alexander, S. Dwivedi, Ajazuddin, T.K. Giri, S. Saraf, S. Saraf, D.K. Tripathi, Approaches for breaking the barriers of drug permeation through transdermal drug delivery, J. Control. Release, 164 (2012) 26-40.

[2] W.W. Ting, C.D. Vest, R.D. Sontheimer, Review of traditional and novel modalities that enhance the permeability of local therapeutics across the stratum corneum, Int. J. Dermatol., 43 (2004) 538-547.

[3] L. Brannon-Peppas, J.O. Blanchette, Nanoparticle and targeted systems for cancer therapy, Adv. Drug Delivery Rev., 56 (2004) 1649 -1659.

[4] T.W. Prow, J.E. Grice, L.L. Lin, R. Faye, M. Butler, W. Becker, E.M. Wurm, C. Yoong, T.A. Robertson, H.P. Soyer, M.S. Roberts, Nanoparticles and microparticles for skin drug delivery, Adv. Drug Delivery Rev., 63 (2011) 470-491.

[5] A. Vogt, C. Wischke, A.T. Neffe, N. Ma, U. Alexiev, A. Lendlein, Nanocarriers for drug delivery into and through the skin—Do existing technologies match clinical challenges?, J. Control. Release, 242 (2016) 3-15.

[6] F. Rancan, M. Giulbudagian, J. Jurisch, U. Blume-Peytavi, M. Calderón, A. Vogt, Drug delivery across intact and disrupted skin barrier: Identification of cell populations interacting with penetrated thermoresponsive nanogels, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.11.017.

[7] N.B.N.N. Tran, F. Knorr, W.C. Mak, K.Y. Cheung, H. Richter, M. Meinke, J. Lademann, A. Patzelt, Gradient-dependent release of the model drug TRITC-dextran from FITC-labeled BSA hydrogel nanocarriers in the hair follicles of porcine ear skin, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.09.016.

[8] H. Kheiri Manjili, P. Ghasemi, H. Malvandi, M.S. Mousavi, E. Attari, H. Danafar, Pharmacokinetics and in vivo delivery of curcumin by copolymeric mPEG-PCL micelles, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.10.003.

[9] F. Müller, S. Hönzke, W.-O. Luthardt, E.L. Wong, M. Unbehauen, J. Bauer, R. Haag, S. Hedtrich, E. Rühl, J. Rademann, Rhamnolipids form drug-loaded nanoparticles for dermal drug delivery, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.12.013.

[10] T.N. Barradas, J.P. Senna, S.A. Cardoso, S. Nicoli, C. Padula, P. Santi, F. Rossi, K.G. de Holanda e Silva, C.R.E. Mansur, Hydrogel-thickened nanoemulsions based on essential oils for

topical delivery of psoralen: Permeation and stability studies, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.11.018.

[11] A.S. Boisgard, M. Lamrayah, M. Dzikowski, D. Salmon, P. Kirilov, C. Primard, F. Pirot, B. Fromy, B. Verrier, Innovative drug vehicle for local treatment of inflammatory skin diseases: Ex vivo and in vivo screening of five topical formulations containing poly(lactic acid) (PLA) nanoparticles, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.09.021.

[12] N. Brunacci, C. Wischke, T. Naolou, A.T. Neffe, A. Lendlein, Influence of surfactants on depsipeptide submicron particle formation, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.11.011.

[13] N. Zhang, A. Said, C. Wischke, V. Kral, R. Brodwolf, P. Volz, A. Boreham, C. Gerecke, W. Li, A.T. Neffe, B. Kleuser, U. Alexiev, A. Lendlein, M. Schäfer-Korting, Poly[acrylonitrile-co-(N-vinyl pyrrolidone)] nanoparticles – Composition-dependent skin penetration enhancement of a dye probe and biocompatibility, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.10.019.

[14] A. Klossek, S. Thierbach, F. Rancan, A. Vogt, U. Blume-Peytavi, E. Rühl, Studies for improved understanding of lipid distributions in human skin by combining stimulated and spontaneous Raman microscopy, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.11.001.

[15] A. Jeništová, M. Dendisová, P. Matějka, Study of plasmonic nanoparticles interactions with skin layers by vibrational spectroscopy, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.12.011.

[16] S. Saeidpour, S.B. Lohan, M. Anske, M. Unbehauen, E. Fleige, R. Haag, M.C. Meinke, R. Bittl, C. Teutloff, Localization of dexamethasone within dendritic core-multishell (CMS) nanoparticles and skin penetration properties studied by multi-frequency electron paramagnetic resonance (EPR) spectroscopy, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.10.001.

[17] S.B. Lohan, S. Saeidpour, A. Solik, S. Schanzer, H. Richter, P. Dong, M.E. Darvin, R. Bodmeier, A. Patzelt, G. Zoubari, M. Unbehauen, R. Haag, J. Lademann, C. Teutloff, R. Bittl, M.C. Meinke, Investigation of the cutaneous penetration behavior of dexamethasone loaded to nano-sized lipid particles by EPR spectroscopy, and confocal Raman and laser scanning microscopy, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.12.018.

[18] U. Alexiev, P. Volz, A. Boreham, R. Brodwolf, Time-resolved fluorescence microscopy (FLIM) as an analytical tool in skin nanomedicine, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2017.01.005.

[19] M. Radtke, A. Patzelt, F. Knorr, J. Lademann, R.R. Netz, Ratchet effect for nanoparticle transport in hair follicles, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.10.005.
[20] R. Schwarzl, F. Du, R. Haag, R.R. Netz, General method for the quantification of drug loading and release kinetics of nanocarriers, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.12.015.
[21] N. Döge, A. Avetisyan, S. Hadam, E.K.B. Pfannes, F. Rancan, U. Blume-Peytavi, A. Vogt, Assessment of skin barrier function and biochemical changes of ex vivo human skin in response to physical and chemical barrier disruption, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.12.012.
[22] L.J. Löwenau, C. Zoschke, R. Brodwolf, P. Volz, C. Hausmann, S. Wattanapitayakul, A. Boreham, U. Alexiev, M. Schäfer-Korting, Increased permeability of reconstructed human epidermis from UVB-irradiated keratinocytes, Eur. J. Pharm. Biopharm. DOI: 10.1016/j.ejpb.2016.12.017.
[23] A. Edlich, C. Gerecke, M. Giulbudagian, F. Neumann, S. Hedtrich, M. Schäfer-Korting, N. Ma, M. Calderon, B. Kleuser, Specific uptake mechanisms of well-tolerated thermoresponsive polyglycerol-based nanogels in antigen-presenting cells of the skin, Eur. J. Pharm. Biopharm. 10.1016/j.ejpb.2016.12.016.