European Journal of Pharmaceutics and Biopharmaceutics 77 (2011) 1–2

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Short review (expert opinion)

Potentials of new nanocarriers for dermal and transdermal drug delivery

Reinhard H.H. Neubert *

Institute of Pharmacy, Martin Luther University Halle-Wittenberg, Halle, Germany

ARTICLE INFO

Article history:
Received 11 August 2010
Accepted in revised form 5 November 2010
Available online 24 November 2010

Keywords:
Nanocarriers
Microemulsions
Liposomes
Vesicles
Nanoparticles
Dermal and transdermal drug delivery

ABSTRACT

Nanocarriers (NCs) are colloidal systems having structures below a particle or droplet size of 500 nm. In the previous years, the focus for the application of NCs was primarily placed on the parenteral and oral application. However, NCs applied to the skin are in the center of attention and are expected to be increasingly applied as the skin offers a lot of advantages for the administration of such systems. For the use of NCs to the skin, one has to differentiate between the desired effects: the local effect within the skin (dermal drug delivery) or a systemic effect accompanied by the permeation through the skin (transdermal drug delivery).

Both for dermal and transdermal drug delivery, the stratum corneum (SC), the main barrier of the skin, has to be overcome.

SC is one of the tightest barriers of the human body. Therefore, it is the primary goal of new NC to overcome this protective and effective barrier. For that purpose, new NCs such as microemulsions, vesicular (liposomes) and nanoparticular NCs are developed and investigated. This article evaluates the potentials of these NCs for dermal and transdermal drug delivery.

1. Microemulsions (MEs)

MEs are defined as colloidal, optically isotropic, transparent or slightly opalescent formulations of low viscosity consisting of surfactant, co-surfactant, oil and water. They are thermodynamically stable colloidal dispersions and they are formed without any energy input. The formation process requires a highly fluid interfacial film and the creation of low interfacial tension between the colloidal and the external phase.

MEs have different microstructures depending on the surfactant system used. The MEs are categorized as water-in-oil (w/o) or oil-in-water (o/w) MEs with droplet-like colloidal structure (with diameters in the range of 20–100 nm) embedded in a mono-continuous external phase and both are separated by surfactant-rich interfacial layers. MEs have some substantial advantages for pharmaceutical use: ease of preparation, long-term stability, high solubilization capacity for hydrophilic and lipophilic drugs, and in consequence, improved drug delivery. MEs are already used in oral drug delivery.

The administration of MEs offers a lot of advantages in dermal and transdermal drug delivery. They present a high solubilization capacity even for poorly soluble drugs. MEs have substantial penetration enhancing effects for extremely lipophilic drugs when using a lipophilic colloidal phase. Up to date, however, main point of criticism is the necessity of large amounts of surfactants to form MEs. Therefore, a successful extended use of these colloidal carrier systems in the future depends on the choice of well-tolerated surfactants and the restriction of their amounts [1–6].

The challenge for the future is the use of MEs for hydrophilic biopharmaceuticals such as peptides, proteins and RNA and DNA derivatives in dermal and transdermal drug delivery. For that purpose, MEs have to be developed with an aqueous colloidal phase [7].

2. Vesicular transport systems

In the past two decades, colloidal lipid aggregates called liposomes (LIPs) are developed as vesicular drug carrier systems.

LIPs consist of lipids, typically cholesterol and phospholipids, but also other amphiphilic components are possible [8]. Depending on the preparation method used, different LIPs result. Multivesicular vesicles (MVV) contain several vesicles embedded in one surrounding spherical lipid bilayer; multilamellar vesicles (MLV) comprise several concentric bilayers; and large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV) are made up of only one lipid bilayer. The objective of the administration of LIPs is an optimal localized effect with minimized systemic absorption or transdermal drug delivery with the goal of a pronounced systemic effect. It is possible to influence the physicochemical properties of the LIPs to receive a specialized system in terms of drug transport and protection of the active agent.

Classical LIPs (MLV) are already used for the dermal delivery of heparin, diclofenac Na and iodide.

* Tel.: +49 345 5525000; fax: +49 345 5527292.
E-mail address: reinhard.neubert@pharmazie.uni-halle.de

0939-6411/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2010.11.003

However, there are several new vesicle types, depending on the additives used for the vesicle preparation: *transfersomes, flexosomes, ethosomes, niosomes, vesosomes, invasomes and polymerosomes*.

There are several remarkable results regarding the potential of liposomal carrier systems for targeted skin delivery as well as for transdermal drug delivery. Especially, elastic ultra-deformable vesicles (transfersomes) and ethosomes led to promising results [9–13]. In principle, there are two ways for influencing drug penetration across the SC by LIPs and transfersomes. Discussions are still running whether the LIPs or the transfersomes are penetrating across the SC as intact aggregates or is there an incorporation of the liposomal lipids into the SC lipids [14–16]. Therefore, further elucidation of concrete mechanisms of the penetration of LIPs as well as transfersomes into and through the SC is needed until new products for dermal and transdermal delivery can be developed, and the potentials of these systems have to be validated.

3. Nanoparticles for dermal delivery of drugs and active compounds

The use of micro-(MPs) and nanoparticles (NPs) in dermatopharmaceutics as well as in cosmetics appears to be an interesting alternative to the application of other colloidal systems.

In principle, two directions were identified in the use of MPs and NPs for dermal drug delivery:

1. Dermal application of MPs and NPs and
2. Follicular application of NPs.

The advantages of the application of MPs and NPs are still a matter of debate. Particularly, the size of the MPs appears to be important for the penetration depth; therefore, the dermal application of NPs seems to be preferable compared to MPs. The development of solid lipid NPs and nano-structured lipid carriers for the dermal application in combination with occlusion is an interesting research topic [17–19]. However, it is necessary to validate the results concerning drug penetration from these systems in comparison with standard and other colloidal systems such as ME and LIPs.

New and promising results were obtained by studying the penetration of NP into the hair follicles, where a high increase in penetration depth was observed. Within the hair follicles, the NPs can also be used as depot for the active agents. However, massage after application of the NPs is necessary. Based on the surface structure of the SC of human hair follicles, it was assumed that the movement of the hairs caused by massage pumps the NPs deeper into the hair follicles [20–23].

4. Summary and conclusion

During the last years, many new insights into the structural properties of the SC, in particular its lipid matrix, prompted the development of new dermal and transdermal drug delivery systems such as NCs. The ultimate aim is to understand the interactions between the SC lipid membranes and the different dermal and transdermal NCs, thereby creating the most efficient drug NCs and causing the least damage in respect of the SC barrier.

Taken together, the presented NCs have different potentials concerning dermal and transdermal drug delivery. Up to date, MEs appear to be most promising concerning dermal drug delivery. Most challenging is the use of NPs concerning follicular drug administration as well as concerning deposition of these systems in the hair follicles.

Nevertheless, it is necessary to fully understand the transport mechanism of each NC category.

References

[1] S. Heuschkel, A. Goebel, R.H.H. Neubert, Microemulsions – modern colloidal carrier for dermal and transdermal drug delivery, J. Pharm. Sci. 97 (2008) 603–631.
[2] M. Kreilgaard, E.J. Pedersen, J.W. Jaroszewski, NMR characterisation and transdermal drug delivery potential of microemulsion systems, J. Controlled Release 69 (2000) 421–433.
[3] M. Kreilgaard, Influence of microemulsions on cutaneous drug delivery, Adv. Drug Deliv. Rev. 54 (2002) S77–S98.
[4] M. Kahlweit, G. Busse, B. Faulhaber, Preparing nontoxic microemulsions with alkyl monoglucosides and the role of alkanediols as cosolvents, Langmuir 12 (1996) 861–862.
[5] S. Heuschkel, J. Wohlrab, R.H.H. Neubert, Dermal and transdermal targeting of dihydroavenanthramide D using enhancer molecules and novel microemulsions, Eur. J. Pharm. Biopharm. 72 (2009) 552–560.
[6] B. Biruss, C. Valenta, The advantage of polymer addition to a non-ionic oil in water microemulsion for the dermal delivery of progesterone, Int. J. Pharm. 349 (2008) 269–273.
[7] M.B. Delgado-Charro, G. Iglesias-Vilas, J. Blanco-Mendez, M. Arturo Lopez-Quintela, J.P. Marty, R.H. Guy, Delivery of a hydrophilic solute through the skin from novel microemulsion systems, Eur. J. Pharm. Biopharm. 43 (1997) 37–42.
[8] B.W. Barry, Novel mechanisms and devices to enable successful transdermal drug delivery, Eur. J. Pharm. Sci. 14 (2001) 101–114.
[9] G. Cevc, D. Gebauer, Hydration driven transport of deformable lipid vesicles through fine pores and the skin barrier, Biophys. J. 84 (2003) 1010–1024.
[10] G. Cevc, Lipid vesicles and other colloids as drug carriers on the skin, Adv. Drug Deliv. Rev. 56 (2004) 675–711.
[11] G. Cevc, D. Gebauer, J. Stieber, A. Schaetzlein, G. Blume, Ultraflexible vesicles, Transfersomes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin, Biochim. Biophys. Acta 1368 (1998) 201–215.
[12] B. Godin, E. Touitou, Mechanism of bacitracin permeation enhancement through the skin and cellular membranes from an ethosomal carrier, J. Controlled Release 94 (2004) 365–379.
[13] G.M.M. El Maghraby, A.C. Williams, B.W. Barry, Skin delivery of oestradiol from lipid vesicles: importance of liposome structure, Int. J. Pharm. 204 (2000) 159–169.
[14] G.M.M. El Maghraby, A.C. Williams, B.W. Barry, Interactions of surfactants (edge activators) and skin penetration enhancers with liposomes, Int. J. Pharm. 276 (2004) 143–161.
[15] G.M.M. El Maghraby, A.C. Williams, B.W. Barry, Can drug bearing liposomes penetrate intact skin?, J Pharm. Pharmacol. 58 (2006) 415–429.
[16] G.M.M. El Maghraby, B.W. Barry, A.C. Williams, Liposomes and skin: from drug delivery to model membranes, Eur. J. Pharm. Sci. 34 (2008) 203–222.
[17] R.H. Muller, M. Radtke, S.A. Wissing, Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations, Adv. Drug Deliv. Rev. 54 (Suppl. 1) (2002) S131–55.
[18] C.S. Maia, W. Mehnert, M. Schaller, H.C. Korting, A. Gysler, A. Haberland, M. Schafer-Korting, Drug targeting by solid lipid nanoparticles for dermal use, J. Drug Target. 10 (2002) 489–495.
[19] S. Lombardi Borgia, M. Regehly, R. Sivaramakrishnan, W. Mehnert, H.C. Korting, K. Danker, B. Roder, K.D. Kramer, M. Schafer-Korting, Lipid nanoparticles for skin penetration enhancement-correlation to drug localization within the particle matrix as determined by fluorescence and parelectric spectroscopy, J. Controlled Release 110 (2005) 151–163.
[20] J. Lademann, H. Richter, A. Teichmann, N. Otberg, U. Blume-Peytavi, J. Luengo, B. Weiss, U.F. Schaefer, C.M. Lehr, R. Wepf, W. Sterry, Nanoparticles – an efficient carrier for drug delivery into the hair follicles, Eur. J. Pharm. Biopharm. 66 (2007) 159–164.
[21] F. Knorr, J. Lademann, A. Patzelt, W. Sterry, U. Blume-Peytavi, A. Vogt, Follicular transport route – research progress and future perspectives, Eur. J. Pharm. Biopharm. 71 (2009) 173–180.
[22] J. Lademann, F. Knorr, H. Richter, U. Blume-Peytavi, A. Vogt, C. Antoniou, W. Sterry, A. Patzelt, Hair follicles – an efficient storage and penetration pathway for topically applied substances, Skin Pharmacol. Physiol. 21 (2008) 150–155.
[23] J. Lademann, H. Richter, U.F. Schaefer, U. Blume-Peytavi, A. Teichmann, N. Otberg, W. Sterry, S Hair follicles – a long-term reservoir for drug delivery, Skin Pharmacol. Physiol. 19 (2006) 232–236.