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Solid lipid nanoparticles as drug carriers for topical glucocorticoids

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Abstract

Recent investigations both in vitro and in human subjects proved the benefit/risk ratio of prednicarbate (PC) to exceed those of halogenated topical glucocorticoids about 2-fold. To obtain a further highly desired increase by drug targeting to viable epidermis, PC was incorporated into solid lipid nanoparticles (SLN). Keratinocyte and fibroblast monolayer cultures, reconstructed epidermis and excised human skin served to evaluate SLN toxicity and PC absorption. Well-tolerated preparations (e.g. cellular viability 94.5% following 18 h incubation of reconstructed epidermis) were obtained. PC penetration into human skin increased by 30% as compared to PC cream, permeation of reconstructed epidermis increased even 3-fold. The present study shows the great potential of SLN to improve drug absorption by the skin.

Keywords: Prednicarbate; Benefit-risk ratio; Solid lipid nanoparticles; Dermal absorption; Drug targeting

Topical corticosteroids are first-line drugs in the therapy of acute exacerbations of atopic dermatitis and contact dermatitis. Prednicarbate (prednisolone 17-ethylcarbonate, 21-propionate, PC) is superior to the halogenated glucocorticoids because of an improved benefit/risk ratio (Schäfer-Korting et al., 1993; Lange et al., 1997). The present separation of the antiinflammatory effect on the epidermis and the unwanted antiproliferative action mainly in the dermis, however, does not satisfy completely. For a further improvement due to a selective PC targeting to eczematous viable epidermis the drug was incorporated into SLN to study the potential of this carrier system in topical glucocorticoid therapy. Drug targeting to the skin by special drug delivery systems has been suggested already with liposomes (Mezei et al., 1994) and SLN (Zur Mühlen and Mehnert, 1998). The latter combine several advantageous characteristics for drug delivery: good local tolerability (GRAS status for many components), a high inclusion rate for lipophilic substances (Müller et al., 1995) and small particle size providing close contact to the stratum corneum. Moreover, their ability to form a film on the skin surface appears desirable in chronic atopic eczema.

Prednicarbate (PC) and its metabolites prednisolone 17-ethylcarbonate (P17EC), prednisolone 21-ethylcarbonate (P21EC), prednisolone (PD), as

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Table 1
Prednicarbate (PC)-solid lipid nanoparticles (SLN): technological characteristics and toxicity data (MTT test keratinocyte monolayer cultures; mean value ± S.D. ($n = 9$).

Formulation			Size (nm)	Polydispersity index (PI)	Viability (%) 6 and 24 h
A	Compritol ATO 888	5.0%	144	0.339	87.5 ± 4.7
	Poloxamer F68	2.5%			79.4 ± 9.3
	Water	ad 100.0%			
B	Precirol	2.5%	145	0.537	87.3 ± 7.0
	Poloxamer F68	5.0%			80.1 ± 7.0
	Water	ad 100.0%			
C	Dynasan 114	10.0%	206	0.166	35.6 ± 1.7
	Lipoid S75	1.0%			27.0 ± 3.3
	Poloxamer F68	0.5%			
	Water	ad 100.0%			

well as Dermatop® cream and the respective glucocorticoid-free cream were a gift from Hoechst Marion Roussel. PC-SLN 0.25 and 0.125% were produced as described in Table 1 (Zur Mühlen and Mehnert, 1998). Entrapment efficiency was determined by HPLC analysis (Gysler et al., 1997) of PC concentrations in the dispersion medium. Particle size and polydispersity index (PI) were determined by photon correlation spectroscopy (PCS). The cytotoxicity of PC solution (2.5 μM), of the SLN formulations (with/without PC 0.25%, dilution 1:2000) and of other ingredients was determined in keratinocyte and fibroblast monolayer cultures with MTT test (Lange et al., 1997). The formulation A was also tested for cytotoxicity with MTT test in reconstructed epidermis (Doucet et al., 1996). PC penetration and metabolism was studied in freshly excised human skin obtained as the waste from cosmetic surgery and reconstructed epidermis (Skinethic™ Laboratory, Nice, France) by means of Franz flow-through diffusion cells (Gysler et al., 1999). 50 mg of PC cream (0.25%) or 100 μl of PC-SLN (0.125%) were applied on the skin. After 24 h the skin samples were sliced (100 μm) horizontally and homogenized. PC and metabolites were extracted with ethyl acetate and subjected to HPLC analysis (Gysler et al., 1997).

PC is a highly lipophilic diester of PD, allowing a high SLN inclusion exceeding 90.0% for all test preparations. The good thermostability of PC during the production process (80°C) is demonstrated by the absence of degradation products. Keratinocyte and fibroblast viability was only slightly reduced by formulations A and B, while formulation C turned out less favourable. Lipoid S75 and Poloxamer F68 were well tolerated, too (viability > 90.0% at 24 h). PC incorporation did not increase SLN toxicity. Formulation A was also tested for cytotoxicity in reconstructed epidermis. After 18 h incubation cell viability was 94.5%. Therefore a protective effect is induced by the horny layer (skin model) which is lacking in monolayer cultures.

PC penetration into human skin increased by 30.0% as compared to PC cream (Fig. 1) possibly due to the small particle size and close interaction of SLN with the stratum corneum. The amount of

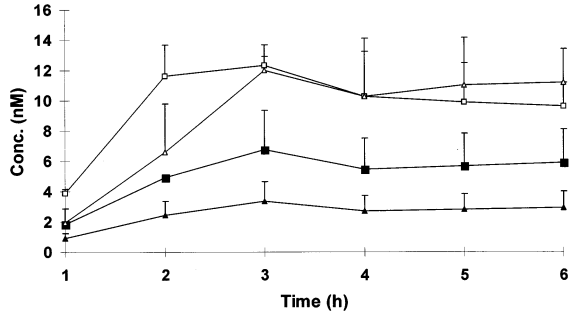

Fig. 1. Permeation of reconstructed epidermis following solid lipid nanoparticles (SLN) (open symbols) and prednicarbate (PC) cream (closed symbols) by PC metabolites (□, P17EC; P21EC). Native PC and metabolite prednisolone (PD) were just detectable. Mean values ± S.D. ($n = 3$).

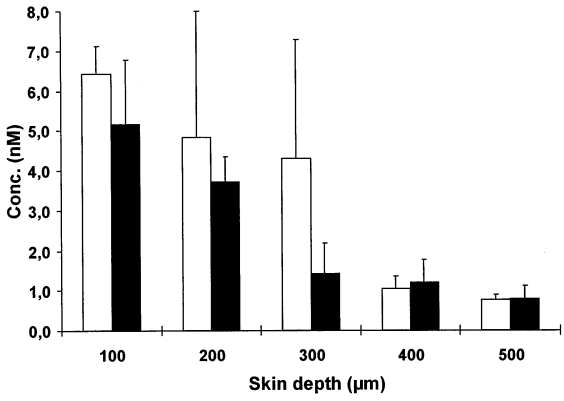

Fig. 2. Distribution of prednicarbate (PC) and its metabolites in human skin after 24 h with PC-solid lipid nanoparticles (SLN) (open columns)and PC cream (closed columns). Mean values ± S.D. ($n = 3$).

PC reaching the dermis (slices 2–5), however, even more (6.1 vs. 3.4 nM). The spectrum of PC and its metabolites, however, remained unchanged. With reconstructed epidermis 8.0% of the applied drug (and metabolites) was recovered from the acceptor medium but only 2.8% with PC cream (Fig. 2) which means even an about 3-fold increase. PC penetration of excised skin following SLN and cream was clearly less than the penetration of reconstructed epidermis. The penetration study of PC-SLN showed that the biotransformation of PC did not change by SLN-incorporation.

The present study clearly shows the potential of SLN as drug carriers for topical glucocorticoids. As many of these drugs are steroid diesters they should be efficiently entrapped into these particles which are well-tolerated by human skin. In contrast to the authors' expectations, however, PC concentration in the dermis increased considerably. Until now we only tested SLN dispersions, yet incorporating PC-SLN into a cream or gel may improve targeting to the viable epidermis. If this will be obtained SLN offer the chance to improve the benefit/risk ratio also of betamethasone dipropionate which does not only belong to the most potent (and therefore needed for severe dermatitis) but also to the most atrophogenic topical glucocorticoids currently under use. Moreover, due to the 3-fold increase in PC permeation observed, SLN also may be a suitable device for a transdermal drug application.

References

Doucet, O., Robert, C., Zastrow, L., 1996. Use of a serum-free reconstituted epidermis as a skin pharmacological model. Toxicol. In Vitro 10, 305–313.

Gysler, A., Kleuser, B., Sipp, W., Korting, H.C., Höltic, D., Schäfer-Korting, M., 1999. Skin penetration and metabolism of topical glucocoticoids in reconstructed epidermis and in excised human skin. Pharm. Res. 16, 1386–1391.

Gysler, A., Lange, K., Korting, H.C., Schäfer-Korting, M., 1997. Prednicarbate biotransformation in human foreskin keratinocytes and fibroblasts. Pharm. Res. 14, 797–801.

Lange, K., Gysler, A., Bader, M., Kleuser, B., Korting, H.C., Schäfer-Korting, M., 1997. Prednicarbate versus conventional topical glucocorticoids: pharmacodynamic characterization in vitro. Pharm. Res. 14, 1744–1749.

Mezei, M., Touitou, E., Junginger, H.E., Weiner, N.D., Tagai, T., 1994. Liposomes as carriers for topical and transdermal delivery. J. Pharm. Sci. 9, 1189–1203.

Müller, R.H., Mehnert, W., Lucks, J.-S., Schwarz, C., zur Mühlen, A., Weyhers, H., Freitas, C., Rühl, D., 1995. Solid lipid nanoparticles (SLN) — an alternative colloidal carrier system for controlled drug delivery. Eur. J. Pharm. Biopharm. 41, 62–69.

Schäfer-Korting, M., Korting, H.C., Kerscher, M.J., Lenhard, S., 1993. Prednicarbate activity and benefit/risk ratio in relation to other topical glucocorticoids. Clin. Pharmacol. Ther. 54, 448–456.

Zur Mühlen, A., Mehnert, W., 1998. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. Pharmazie 53, 2–55.