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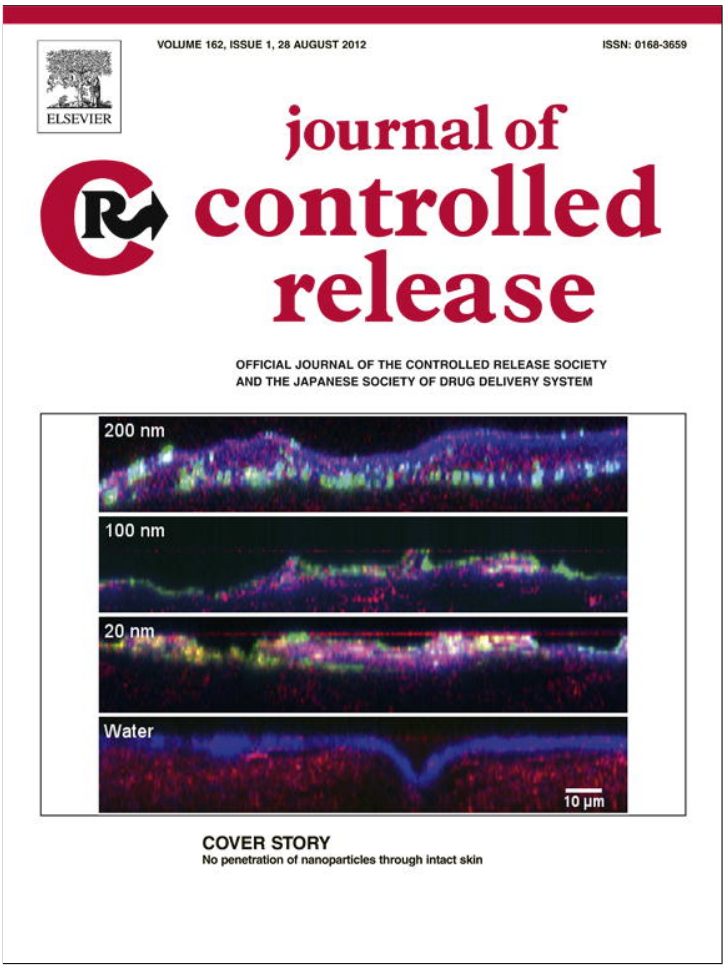

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Cover story

No penetration of nanoparticles through intact skin

The use of nanoparticles as drug delivery vectors is presently undergoing intense scrutiny. The topical–transdermal route of drug administration has not escaped the attention of the nanoparticle community, initially because of potential toxicity concerns resulting from exposure to such structures in sunscreens, for example. Subsequently, the drug delivery community recognized a more positive opportunity and several studies have appeared in which improved skin penetration/permeation of active substances associated with nanoparticle-containing formulations have been reported. These results have led to claims that nano-sized objects are, somehow, able to make their way across this most resilient of membranes. These claims were made despite the acknowledged, superlative nature of the skin's barrier function to the ingress of just about any small drug, let alone even the tiniest of particles.

In this issue, Professor Richard Guy and his colleagues [1] objectively assess the disposition of nanoparticles on mammalian skin after prolonged topical application. The paper focuses particular attention on the interface between the applied nanoparticle formulations and the outermost layer of the skin, the stratum corneum. The over-riding function of the thin layer (on average only 10–20 μm) of stratum corneum is to constrain the outward transport of water from inside the body. To address the conflicting points of view in the literature about nanoparticle transport across skin, Professor Guy and his team have used laser scanning confocal microscopy to track the fate of fluorescently-labeled polystyrene beads ranging in diameter from 20 to 200 nm. Aqueous suspensions of these particles have been applied to mammalian skin for periods of up to 16 h before microscopic examination. Experiments have been performed both on normal, intact skin and on skin from which several layers of the stratum corneum were first removed by the repeated application of adhesive tape. The latter approach is recognized to remove both the stratum disjunctum (the most exterior layer of the stratum corneum that is in the final process of desquamation) as well as, progressively, the functional component of the barrier itself.

Importantly, the analysis of the confocal images obtained has been undertaken in an objective and statistical manner so as to minimize or indeed eliminate investigator bias. Specifically, regions of interest were selected as coordinates from fields of view using true random numbers generated from atmospheric noise. At least three random regions of interest were recorded for each skin sample, thereby preventing selection bias towards those offering the most attractive images. The entire acquired image was analyzed and a profile of the fluorescence distribution emanating from the nanoparticles (which, individually, were too small to resolve optically) was generated. This process required essentially no human decisions, and thus, the subjectivity inherent in image interpretation was considerably decreased. Consequently, the profiles from independent skin samples could be compared to assess whether the nanoparticles could actually penetrate beyond the skin surface or not.

Confocal imaging permits the effect of an uneven skin surface to be visualized unambiguously, and the apparent "deep" penetration of particles that have, in fact, been deposited into an invagination of the sample to be interpreted correctly. The results show clearly that polymeric nanoparticles (of diameters from 20 to 200 nm) only penetrated into the surface layers (to a depth of ~2–3 μm) of the stratum corneum, suggesting simple infiltration along fissures in the stratum disjunctum. The quantitative assessment of bulk particle location demonstrated no time-dependent penetration of any nanoparticle, even when the stratum corneum was partially compromised by adhesive tape-stripping. As one might have intuitively predicted, therefore, mammalian skin is as good a barrier to the ingress of nano-sized objects from the external environment as it is to the "escape" of endogenous nanoparticles (e.g., proteins) from the body! However, as intimated by Professor Guy and his group, it is interesting to speculate whether appropriate formulations of carefully designed nanoparticles may offer potential reservoirs on or near to the skin surface that may sustain controlled drug release over long periods of time. The research from Professor Guy's laboratory in this issue is perhaps the first investigation which has determined the value of using nanoparticles in drug delivery with an open minded and unbiased approach. Obviously, such objective criteria should be applied to the analysis of all nanoparticle formulations under development. It is time for researchers in this field to examine the potential and limitations of nanoparticle formulations with a more critical eye.

Reference

[1] C. Campbell, L.R. Contreras-Rojas, M.B. Delgado-Charro, R.H. Guy, Objective assessment of nanoparticle disposition in mammalian skin after topical exposure, J. Control. Release 162 (2012) 201–207.

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