Editorial

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Is the New Class of Cosmeceuticals–Percutaneously Delivered Dermal Fillers-Scientifically Feasible?

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Editorial

At times when countless claims of "successful" wrinkles reduction for filling, skin plumping, and smoothening can be found in marketing materials, digital media sources, even in peer review articles, the question arises whether true percutaneous, without injection, dermal filler delivery is possible? To answer this question deliberation on the newest scientific developments on this hot topic seem warranted and inspires this editorial.

To discuss the feasibility of such a prospect, differences between volumizing and filling have to be delineated. Skin wrinkles and crevices reducing filling injectables expand deeper layers of the skin (dermis) by their administration. Volumizing products work at the epidermal layers of the skin for a plumping appearance (mostly by hydration) with different, depending on the product, timelines to produce the desired effect. From the consumer standpoint, both filling and volumization initial effects can be, to a degree, similar. The volumization effect is typically shorter (e.g. hours to days) and requires maintenance by repeated applications (in order to last). Dermal fillers are currently administered by injections (traditional injection, or recently by means of microneedling) and effects are immediate, proportional to volume administered, and normally relatively long lasting (months). The most common ingredient of injectables is larger molecules of collagen (and its modifications) or larger molecules of hyaluronic acid, although other substances (such as synthetic calcium hydroxyapatite, poly L-lactic acid and polymethylmethacrylate) are also used as fillers.

Regarding tissue contouring methods, it is worthy to mention that certain bioactive, with relatively low molecular weight peptides, are known to penetrate the epidermal barrier and stimulate production of the extracellular matrix and specifically collagen by dermal fibroblasts, thus indirectly increasing the thickness of the skin, creating a "filling" effect and reducing signs of aging. Stem cell and other regenerative cellular elements are also a separate promising class of rejuvenating agents but not true fillers [1,2].

The question arises whether it is possible to deliver percutaneously injectable grade, high molecular weight, and dermal fillers? Ideally such agents would not only fill but also volumize subepidermal skin layers by water retention. For example, high molecular weight hyaluronic acid particles or cross-linked collagen could play aforementioned, dual roles. Such a concept poses scientific and technological challenges. The *stratum corneum* is normally an effective barrier on one hand to trans-epidermal water loss, and on the other hand prevents penetration of exogenous substances such as cosmeceuticals from outside. Water soluble ingredients with molecular weight in excess of 1,000 Daltons have difficulty penetrating the epidermis [3].

The difficult task of high molecular weight cosmeceutical delivery to the dermal layer can be eased by simple physical modalities such as heat (sauna, heat patches) or even scrubbing, all increasing size of skin pores, freeing spaces in hair follicles and sweat glands, and also by reducing tightness of cellular layers thus increasing epidermal cosmeceuticals penetrability through skin appendages or intercellular route. Skin preparation by reduction of the *stratum corneum* thickness by chemical peels or laser assisted skin resurfacing would obviously ease the epidermal repellence and somewhat increase the effectiveness of such compound cosmeceuticals. However regardless, the epidermal capability to repel water-soluble agents is enormous!

Considering that the epidermis allows the penetration of lipids or lipid soluble more readily than water-soluble compounds, lipid coating of water-soluble agents becomes a critical component of technologies allowing transepidermal delivery of agents which would normally not penetrate *stratum corneum*. Acting in concert with agents temporarily reducing the barrier resistance of *stratum corneum*, a lipophilic coating surrounding water-soluble molecules allows not only penetration of normally repelled agents but also transepidermal delivery of large, even injectable grade, molecules [3,4]. Therefore, these promising technologies designed to overcome the 500 Dalton rule are the focus of cosmetology research.

However, the successful "entrapment" of water soluble cosmeceutical into lamellar lipid vesicle and its transepidermal transport is only part of the process. In order to release the agent "smuggled" into the dermis, these lipid films must be erodible or degradable when they reach the target skin layer. The challenge is to assemble a functional system capable of controlled encapsulation, transepidermal delivery, and then release of the intact cosmeceutical molecule. The multilamellar processing has recently been optimized allowing creation of robust lipid nanocapsules with the aim of increasing their water-soluble agent–e.g. to enable high molecular collagen or injectable grade hyaluronic acid-loading capacity. These films allow for biological cargos to be entrapped in native aqueous conditions, and provide triggered release of materials through programmed vesicle disruption. A key issue for incorporation of liposomal carriers in multilayer films is the need for stabilization of vesicles against rupture during the assembly process and during the transepidermal passage and then controlled disintegration and agent release [4,5].

The aforementioned thoughts and references from different lines of research allow us to conclude that percutaneous delivery of fillers and dermis rejuvenating agents- in general- is an imminent reality and worthy of further investigation. The future will show if in addition to such natural ingredients as high molecular weight collagen and hyaluronic acid, other compounds may join the class of percutaneously delivered dermal fillers.

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