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Safety of Microneedles for Transdermal Drug Delivery

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Transdermal delivery is an attractive route of administration, allowing the therapeutic agents to bypass first pass-hepatic metabolism to minimize the drug toxicity and enhance the treatment efficacy, especially for drugs that are unstable in the acidic environment in the stomach or those cause irritation in the gastrointestinal tract [1-3]. Despite these advantages, a drawback is observed in skin delivery: numerous drugs have extremely low skin permeability due to the outermost lipophilic stratum corneum layer of skin. Passive diffusion is generally limited to small molecules (molecular weight less than 500 Da) with a low dose (highly potent), and moderate lipophilicity (log P 1-3) [2-5]. The drug delivery can be enhanced by optimizing the drug formulations or disrupting the skin barrier function using either chemical penetration enhancers or physical enhancement technologies including microneedles, laser, sonophoresis, iontophoresis, and thermal energy [6,7]. Microneedles application is a minimally invasive, cost-effective, and patient-compliant technique to significantly enhance the drug delivery into and across skin [8-10]. Upon being inserted into the skin, microneedles disrupt the stratum corneum and penetrate the epidermis layer to create interstitial fluid-filled and micron-sized channels in skin. These microchannels allow the penetration of therapeutic agents of any size (monoclonal antibody, vaccines, proteins and peptides, microparticles, and cosmeceuticals) [8,11-13] without causing irreversible damage to skin, irritation, or infection [14-16]. The safety of microneedles could be evaluated on various factors including pore closure, potential infection, risk of bleeding, local reactions, needle breakage, biocompatibility of needle materials, concerns related to microneedles reuse, and safe disposal.

Several researchers have compared and calculated the ratio of fracture force and insertion force of microneedles-margin of safety [17]. Microneedles arrays should possess a fracture force greater than the insertion force, required for a successful microporation. These forces could be recorded using a force-displacement measurement [18,19], electrodes-integrated microneedles [20], or electrical impedance measurements on human skin of volunteer subjects [18] or animal skin models *in vitro* [20]. The forces were found to be dependent on the sharpness of the tips and microneedles length. The higher the fracture force, the safer the microneedle insertion since microneedle arrays are designed for manual application by patients using a wide range of pressure. Multiple studies have demonstrated that minimally invasive microporation led to reduced pain and less tissue trauma in human subjects with a very low average pain score on a 0-100-mm visual analog pain scale as compared to hypodermic needle. Pain sensation varied based on drug candidate, formulation components, occlusion, microneedle geometry (length and density), and applied pressure. The sensory perception of microneedle insertion was 'pressing' and 'heavy' while the pain caused by hypodermic needles was described as 'sharp' and 'pricking' sensation. The observation of microneedle-induced bleeding was absent or rare in human studies with a significantly lower probability as compared to hypodermic needles. This helps to facilitate the regulatory approval and patient's acceptability. Technically, the risk of bleeding depends on the microneedle length and the penetration depth.

The acceptability of microneedles has been assessed based on the degree of adverse effects such as erythema, burning, edema, itching, stinging, scaling, tightness, and prickling sensation. Kim et al revealed that the use of retinyl retinoate- and ascorbic acid-loaded hyaluronic acid microneedles led to no allergic or irritant contact dermatitis, thus, be regarded as safe products for human use. Skin irritation is primarily determined by the microneedle materials or residual solvents in the needles. Various biophysical characterization methods could be employed to evaluate potential skin irritation such as transepidermal water loss, laser Doppler flowmetry, high-frequency ultrasound, chromametry, capacitance reflectance spectroscopy, and Draize dermal scoring. Several studies have been performed to suggest the absence or unsubstantial occurrence of redness (erythema), swelling, visible sign of inflammation, or local skin reactions, following microneedle insertion. This observation was validated with various microneedle designs (dimensions, sharpness, and configuration), type of microneedle array (hollow, coated, silicon, or drug-loaded microneedles), and different skin models (Human or animal skin).

The skin acts as the primary barrier against environmental organisms, thus, any breach in the skin poses a risk of infection. Being minimally invasive, microneedles cause an insignificant damage to skin barrier and lower microbial penetration. None of the animal and human studies revealed microneedle-related local infection. Modepalli et al evaluated the safety and toxicity of ferric pyrophosphate-incorporated hydrogel-forming microneedles on human skin fibroblast cell lines and reported no toxicity in the cell lines caused by the microneedles. Cytotoxicity of polymers (Sodium hyaluronate and polyvinyl pyrrolidone) used to make dissolving microneedles was examined by MTT assay using HaCaT and HEK293 cell lines to report the cell viability of more than 87% after 72 hours. McCrudden et al conducted a biological safety of hydrogel-forming ibuprofen sodium-loaded microneedles and concluded that no bioburden was detectable and the endotoxin concentrations were significantly lower than the accepted FDA limits for medical devices. Extensive research has validated the safety and efficiency of microneedles, thus indicated the patient's acceptance and product popularity.

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