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Dissolving polyvinylpyrrolidone-based microneedle systems for *in-vitro* delivery of sumatriptan succinate

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ABSTRACT

In-vitro permeation studies were conducted to assess the feasibility of fabricating dissolving-microneedle-array systems to release sumatriptan succinate. The formulations consisted mainly of the encapsulated active ingredient and a water-soluble biologically compatible polymer, polyvinylpyrrolidone (PVP), approved by the U.S. Food and Drug Administration (FDA). Tests with Franz-type diffusion cells and Göttingen minipig skins showed an increase of the transdermal flux compared to passive diffusion. A preparation, containing 30% by mass of PVP and 8.7 mg sumatriptan, produced a delivery rate of 395 ± 31 μg/cm^2 h over a 7-hour period after a negligible lag time of approximately 39 min. Theoretically, a 10.7 cm^2 microneedle-array patch loaded with 118.8 mg of the drug would provide the required plasma concentration, 72 ng/mL, for nearly 7 h.

1. Introduction

It was recently determined that 11.6% of the world's population (1 in 10 people) are affected by migraines. The average age, of those afflicted, is 35 years with females (13.8%) twice as likely as males (6.9%) to suffer this malady (Woldeamanuel and Cowan, 2017; Hawkins et al., 2007). Symptoms include throbbing headaches, nausea, vomiting and abnormal sensitivity to light, noise and smell (Burstein et al., 2015). A separate study found that 31.8% of all patients experience three or more migraines per month. More than half (53.7%) of the migraines were considered severe and required bed rest (Lipton et al., 2007).

In the US, the high prevalence of the disease is a major contributor to the rise in healthcare costs. From 2004 to 2013, the average annual adjusted healthcare expenditure for patients with migraines was $9.2 billion more than patients without this ailment (Raval and Shah, 2017). Most individuals, affected by this debilitating illness, are in their productive working years which imposes high costs on employers. In 2003, the indirect costs to US companies amounted to $12 billion due largely to absenteeism (Hawkins et al., 2007). These central factors are now motivating research and innovation in the migraine drug market, which is projected to increase from roughly $3 billion in 2015 to over $10 billion in 2025 (Grover, 2016).

Sumatriptan succinate, or sumatriptan (the active pharmaceutical ingredient, API), developed in 1991, is still considered the gold standard in prescription anti-migraine therapy. It was the first of several triptan compounds discovered to bind to serotonin (5-hydroxytriptamine) receptors and induce vasoconstriction of arteries in the brain to reduce neurogenic inflammation and relieve migraine headaches (Jhee et al., 2001; Moskowitz and Cutrer, 1993). Sumatriptan is delivered in several dosage forms (intranasal, oral, subcutaneous, and iontophoresis). However, each method has its own limitation that reduce patient willingness to comply with the treatment. The subcutaneous injection is difficult to administer when an individual is incapacitated by a migraine headache. The oral tablet and nasal spray have low bioavailability of 15% and 14%, respectively, and are likely accompanied by side effects of nausea and vomiting (Jhee et al., 2001). The iontophoretic device, Zecuity® (formerly NP1010, Zelrix™), has C_{max} values that are between those reported for nasal and oral administrations (bioavailability not reported) and decreases side effects (Pierce, 2010; Vikelis et al., 2012; Siegel et al., 2007). However, it was voluntarily removed from the market because of an FDA safety communication related to patient complaints of burns and scarring (US Food and Drug Administration, 2016).

A microneedle-array-dosage form is proposed as a suitable option for the delivery of the API. This alternative method would be cost effective and produces negligible side effects. Microneedles have been developed as minimally invasive transdermal systems capable of delivering macromolecules through the skin. The microneedles successfully bypass the skin's primary barrier (*i.e.*, stratum corneum) to achieve systemic uptake of the medication in the dermis. An array of micron-sized needles is designed to puncture the epidermis with micron-sized 'holes'. Channels are therefore created for the drug molecules to flow

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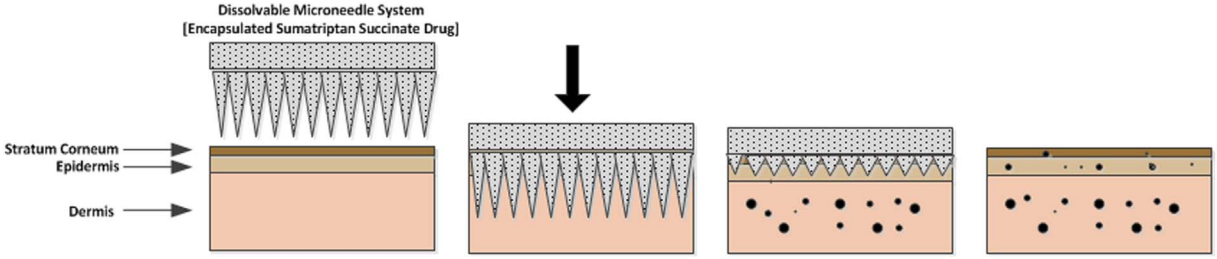

Fig. 1. Dissolvable microneedle schematic representation for rapid or controlled release of the drug encapsulated within the microneedles.

into the capillary-rich dermis and reach the systemic circulation. Individual microneedles are fabricated with a height ranging from 50 to 900 μm and a surface density < 2000 needles/cm^2. These dimensions allow the needles to penetrate the dermis but not to extend to nerves and blood vessels (Larraneta et al., 2016; Prausnitz and Langer, 2008; Prausnitz, 2004).

Dissolving microneedles (DMNs) are made of water-soluble biologically compatible polymers that incorporate the API within the microneedle array. The needles are inserted into the epidermis where they dissolve in minutes, releasing the API into the skin and dermis layers for rapid distribution into the body fluid (Fig. 1). No sharp medical waste is left for disposal after use. It has been shown that the skin punctures, created in the process, are painless and heal within 3 days (Larraneta et al., 2016; Lee et al., 2008; Sullivan et al., 2010; Haq et al., 2009).

Nalluri et al. observed that, before beginning transdermal *in-vitro* studies, skin treatment with AdminPatch® microneedle arrays or Dermaroller® microneedle rollers, significantly increased the cumulative amount of sumatriptan released, the steady-state flux, the permeability and diffusion coefficient. The *in-vitro* flux values suggest that, after treatment with AdminPatch® microneedle array containing 1.5 mm needles, a 2.5 cm^2 transdermal patch is sufficient for effective therapy (Nalluri et al., 2015). More recently, a few research groups have developed sumatriptan containing DMN formulations based on the polysaccharide sodium hyaluronate or dextran polymers. *In-vivo* studies with DMNs from both polysaccharides microneedles demonstrated > 90% bioavailability as compared to subcutaneous injections (Wu et al., 2015; Ito et al., 2011). Finally, Kellerman et al. have designed a polyvinylpyrrolidone based microneedle system, ZP-Zolmitriptan, for the delivery of zolmitriptan, a triptan compound. Phase I clinical trials demonstrated an equivalent or greater Cmax following the microneedle application of various dosages (0.96 mg, 1.9 mg, and 3.8 mg) compared to 2.5 mg of oral zolmitriptan (Kellerman et al., 2016).

This contribution focuses on evaluating dissolving polyvinyl pyrrolidine (PVP)-based microneedles formulated to release sumatriptan. The polymer is water soluble, biologically compatible, FDA-approved and is often used in pharmaceutical applications. Franz cell diffusive studies were performed using a Göttingen minipig skin, which is considered a good model for *in-vitro* permeation through human skin (Barbero and Frasch, 2009; Qvist et al., 2000).

2. Materials and methods

2.1. Chemicals and reagents

The sumatriptan succinate [3-[2-(dimethylamino) ethyl]-*N*-methylindole-5-methane-sulfonamide succinate (1:1)] (MW = 413.5) was purchased from Meohs Fine Chemicals (Iberica SL). Polyvinyl pyrrolidone (Kollidon K30, MW = 51,000) was bought from BASF (Ludwigshafen, Germany). Glycerine was acquired from P&G Chemicals (Cincinnati, OH). Polysorbate 80 and Nitrazine yellow were bought from Croda (New Castle, DE) and Alfa Aesar (Ward Hill, MA), respectively. All other chemicals and reagents were of analytical grade.

2.2. Preparation of sumatriptan microneedle arrays

To prepare the soluble microneedle formulations with encapsulated sumatriptan succinate; PVP, glycerine, polysorbate 80, and sumatriptan succinate were dissolved in water to form 2.0 mL solution.

Negative molds of a platinum-cured silicon microneedle array were acquired from LTS Lohmann Therapie-Systeme AG (Andernach, Germany). The silicone molds were filled with PVP-sumatriptan solution using method described by Ripolin et al. (2017). Next, the molds were dried overnight on benches under ambient conditions and room temperature. The dried microneedle arrays were carefully peeled from the PDMS molds and stored in sealed moisture resistant containers. This procedure was adopted to prepare four PVP-sumatriptan (PVP-S) microneedle formulations (Table 1).

2.3. Microscope characterization of microneedle arrays

A visual characterization of the microneedle arrays was performed using light microscopes (Nikon Optiphot-2, Nikon, Japan), digital sight (Nikon D5-Fi1, Nikon Corp, Japan) and imaging software (NIS-Elements, Nikon, Japan). Fig. 2 was produced with a light microscope (Swift-Duo. Vision Engineering, Woking, UK) and imaging software (M3 Metrology, Vision Engineering, Woking, UK).

2.4. Mechanical testing of microneedle arrays

A tensile test machine (TA.XTPlus, Stable Microsystems Ltd., Godalming, UK) was required to assess whether DMNs are able to penetrate the skin. The mechanical failure force of microneedle arrays was measured using the instrument in compression mode fitted with a 3-point bend apparatus (HPD/3 PB, Stable Microsystems Ltd., Godalming, UK). The microneedles were stored for > 24 h at 25 °C and 45% relative humidity before conducting the tests. Once a single microneedle array was loaded onto the stationary mount, a sensor probe applied an axial force to the DMNs at a speed of 0.1 mm/s. The test was aborted when a maximum displacement (5 mm) was attained or force decreased below the threshold (< 0.1 N).

2.5. Skin preparation

Whole female Göttingen minipig skin tissue samples were acquired from Ellegaard Göttingen Minipigs Agricultural Service (Dalmose, Denmark). Tissues were thawed at room temperature and rinsed with

Table 1
Microneedle array wet composition (%, w/w).

Formulation	Water	SS	PVP	Glycerin	PS 80
F1	58	10	30	1	1
F2	64	5	30	1	1
F3	74	5	20	1	1
F4	54	15	30	1	1

SS, sumatritpan succinate; PVP, polyvinyl pyrrolidone, PS, polysorbate.