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# Non-Ablative Fractional Laser to Facilitate Transdermal Delivery

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ABSTRACT

The advances in laser technology have led to its rapidly expanding applications in dermatology. This study aims at the novel use of a non-ablative fractional laser to enhance transdermal permeation of diclofenac sodium and sumatriptan succinate. The effects of the laser on skin were characterized visually with dye binding, scanning electron microscopy, pore permeability index, and histology. *In vitro* transdermal permeation of drugs through laser treated and untreated human dermatomed skin was analyzed over 24 h and quantified by HPLC. Drug transport through untreated skin resulted in transdermal delivery of 72.61 μg/cm$^2$ ± 50.35 and 22.80 ± 0.64 μg/cm$^2$ of diclofenac sodium and sumatriptan succinate, respectively. Laser treatment of skin significantly increased ($p < 0.005$) delivery of diclofenac sodium to 575.66 ± 207.18 μg/cm$^2$ and sumatriptan succinate to 498.32 ± 97.54 μg/cm$^2$. This is a first of its kind study that demonstrates the use of 1410 nm non-ablative fractional laser to enhance transdermal permeation of 2 small molecular weight drugs.



## Introduction

The diversity of laser technologies and the versatility of treatments available have resulted in their rapidly expanding spectrum of applications. Lasers emit narrow, high-intensity monochromatic light of discrete wavelength that interacts with specific chromophores such as melanin, water, hemoglobin, or tattoo ink in the skin to produce precise tissue destruction of a few micrometers in depth, resulting in clinical benefits with reduced adverse effects. When a chromophore in the skin absorbs the corresponding wavelength of energy, the energy is converted into heat causing thermal destruction of the target site known as photothermal effect. The depth of laser penetration into the skin depends upon absorption and scattering of the wavelength used. Certain wavelengths target tissue water resulting in selective vaporization of water containing tissues; this principle is the basis of ablative laser technology.[1]

Ablative laser technology shows good clinical results by generating thermal injury that essentially vaporizes the water in skin to create microscopic vertical channels in the epidermis that serve as open channels into which topically applied drugs can migrate down to the dermis and then into the systemic circulation. The technique comes with undesired residual thermal effects such as prolonged oozing, pain, swelling, persistent skin redness, and longer recovery times in comparison to the non-ablative fractional laser (NBFXL) technology.[2,3]

Fractional ablative lasers were introduced as an alternative to full ablative lasers to reduce the thermal side effects of full ablative lasers. Fractional ablative lasers use fractional photothermolysis to create what was first described as “microscopic thermal wounds”, or now known as microscopic treatment zones (MTZs).[4] These MTZs are zones of ablation that penetrate the stratum corneum and extend into the epidermis and dermis. A zone of coagulation is a group of necrosed thermally damaged cells around the microchannels and surrounded by normal skin that has not been affected by the laser beam.[4] Fractional ablative lasers can achieve similar skin resurfacing effects as full ablative lasers but with shorter recovery times. The major difference between full ablative and fractional ablation being the presence of unaffected skin around the ablated parts, which help, promote faster healing.[3] Previous literature has explored the use of ablative lasers and fractional ablative lasers to enhance drug delivery but clinical use of these lasers for drug delivery is limited.[5-9]

NBFXLs were introduced to further reduce thermal side effects and downtime by using controlled dermal heating without significant structural damage of the superficial layers. In this technique, heat is generated within the dermal connective tissue without necessarily removing the overlying skin surface in contrast to ablative techniques. Superficial damage is prevented by delivering the appropriate wavelength of light capable of penetrating deep

*Abbreviations used:* H&E, hematoxylin and eosin; MTZ, microscopic treatment zones; NBFXL, non-ablative fractional laser; PPI, pore permeability index; SEM, scanning electron microscopy.

*Conflicts of interest:* The authors declare no conflict of interest.

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enough through the surface while cooling the epidermis during the light-tissue interaction.[1,10] The advantages of non-ablative techniques are the preservation of stratum corneum and retaining a confined epidermal and dermal coagulation.[10] Non-ablative lasers emit light within the infrared range (1000-1500 nm) of the electromagnetic spectrum. These wavelengths are weakly absorbed by the superficial layers of skin, thereby penetrating the deeper tissues creating a dermal wound without disruption of the epidermis.[1] In comparison to ablative lasers, NBFXL technology is less expensive, less labor-intensive, safer with minimum side effects, and results in reduced healing time.

The use of 2 home use NBFXL devices has been reported, namely PaloVia (Palomar Medical Technologies, Inc., Burlington, MA) and ReAura (Solta Medical, Inc., Hayward, CA). The thermal damage produced by the former is characterized and used in this study for enhancing transdermal permeation of 2 model small molecular drugs. The PaloVia device used in our research has demonstrated usability and well-established safety during clinical trials. Clinical testing exhibited high subject compliance, well-tolerated self-application treatments with minimal and transient side effects. In addition to safety testing, the device has inbuilt safety design elements that prevent the device from misfiring or overheating. The contact sensor array ensures that full contact around the optical window must be met and maintained for emission of laser energy. The selected wavelength and beam divergence eliminates potential damage to the eye retina and can only be activated a maximum of 25 times per day.[11]

Current use of lasers includes treatment for cutaneous disorders of blood vessels, pigmentation, hair growth, photo-ageing, scarring, and skin rejuvenation.[1] Previous literature has confirmed the therapeutic efficacy of NBFXL in acne scars, burn scars, and skin rejuvenation but only one previous study has demonstrated its use to enhance drug penetration.[3,11-17] Our study is the first of its kind that employs a 1410 nm NBFXL technique to enhance drug delivery of 2 model drugs, namely diclofenac sodium and sumatriptan succinate.

Sumatriptan succinate is the most commonly prescribed selective serotonin receptor agonist to alleviate symptoms of migraine headaches. Diclofenac sodium is an over-the-counter non-steroidal anti-inflammatory agent commonly used to allay mild to moderate pain including pain associated with migraine headaches.[18] Migraine is a common debilitating disorder that affects more than 28 million people in the United States alone.[19] It is ranked among the 20 most disabling diseases in the world affecting 1 in every 7 adults, and interferes with the sufferer's ability to function in everyday life resulting in loss of work or school days.[20,21] Every 10 s, someone in the United States goes to the emergency room with a headache or migraine, resulting in a cost of an estimated $50 billion each year on medical services rendered.[21] The 2 drugs have a variety of formulations ranging from gels, ointments, tablets, capsules, patches, suppositories, injections, and nasal sprays. However, each formulation is not without limitations. Oral forms have poor patient compliance and low efficiency when migraine is accompanied by nausea. It is estimated that in half of migraine attacks, 49.5% of these patients experience concomitant nausea.[19] Oral administration of diclofenac sodium causes gastric irritation and undergoes substantial hepatic first-pass metabolism resulting in low bioavailability ($F = 0.50$).[19,22] Intravenous route is the best route to achieve quick and immediate relief but is accompanied by pain at injection site, paresthesias, and requires medical supervision. Sumatriptan nasal spray is known to alleviate pain within 15 min of administration but leaves an unpleasant aftertaste, has low bioavailability, and is less effective when patient has nasal congestion or nausea.[19] Transdermal route of drug delivery is a good alternative to overcome the limitations of conventional routes; however, it is limited by low skin permeability of the stratum corneum. Stratum corneum is the protective outermost layer of skin.[23-25] In this study; we use an NBFXL technique in an effort to enhance existing topical and transdermal drug delivery where skin permeability is a barrier. In addition, the study may open avenues to new therapeutic applications by adding a safe and effective technique to the existing enhancement techniques such as chemical enhancers, iontophoresis, microporation with microneedles, and ablative laser techniques.[5,26-28]

Despite the overwhelming research on sumatriptan succinate and diclofenac sodium and the numerous formulations available, there is a need for an easy to use, minimally invasive, low risk, and effective formulation to alleviate pain associated with migraine headaches. The goal of this study was to investigate an alternative use of NBFXL to enhance transdermal drug delivery of sumatriptan succinate and diclofenac sodium, thereby addressing the limitations of existing conventional formulations. The objective of the study was further extended to visually confirm and characterize the effects of NBFXL on skin with dye binding studies, scanning electron microscopy (SEM), pore permeability index (PPI), and histology.

## Materials and Methods

### *Materials*

Diclofenac sodium and sumatriptan succinate were obtained from Sigma Aldrich (St. Louis, MO). Potassium dihydrogen phosphate, sodium hydroxide, phosphate buffered saline, orthophosphoric acid, and sodium phosphate monobasic monohydrate were purchased from Fisher Scientific (Waltham, MA). HPLC grade methanol and acetonitrile were obtained from Medsupply Partners (Atlanta, GA). Dermatomed human skin was obtained from New York firefighters skin bank (New York, NY). PaloVia skin renewing laser (Palomar Medical Technologies, Inc.) was purchased from Amazon.com, Inc. (Seattle, WA).

### *Exposure to Non-Ablative Fractional Laser*

Dermatomed human skin with a skin thickness of approximately 0.4 ± 0.1 cm was used for all the interventions. The skin samples were pre-treated with laser micropulses using an NBFXL. The laser device applied a stamping or scanning mode of treatment on a predetermined area of the skin. Each scan consisted of a series of laser micropulses with energy ranging between 8 and 15 mJ/μb (low to high) delivered on a rectangular grid with a pitch between 0.9 and 2.0 mm and an output window of 9 × 13 mm dimensions.[11] Skin samples were placed on aluminum foil and exposed to NBFXL by placing the scanning window over the surface of skin with minimum pressure until a blue light was visible. Once the blue light was visualized, the irradiation was activated resulting in the exposure of skin to a 1410 nm (±5 nm) wavelength beam for 10 ms with a maximum energy of 15 mJ/μb. This procedure was repeated 5 times on each skin sample, each with exposure at different locations but within the predetermined array.

### *Skin Barrier Impedance Measurement*

Skin integrity for all skin samples used in this study were assessed prior to the addition of drug for *in vitro* permeation study. Human dermatomed skin was clamped between the donor and receiver compartments followed by the addition of 1× phosphate buffered saline to the donor and receptor compartment of the vertical Franz diffusion cell setup and allowed a 15-min equilibration time. Equilibration was followed by measurement of skin