



## A Comprehensive Review on Laser-Assisted Drug Delivery

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### ABSTRACT

The barrier function of the skin restricts the amount of topical applications that can be absorbed through the epidermis. To improve penetration, a variety of methods and materials, including radiofrequency, lasers, dermabrasion, and microneedling, have been employed as part of a strategy called transdermal drug delivery system. Laser-assisted drug delivery (LADD) is one of these methods. Because ablative fractional lasers, such as CO<sub>2</sub> or erbium:YAG lasers, can create minuscule ablated channels, LADD frequently uses these lasers. The patient, the medicine, and the location and state of the skin all require adjustments to the LADD parameters. LADD has been utilized in conjunction with a range of topical medications, including corticosteroids, photosensitizers, and immunotherapy drugs (imiquimod or 5-fluorouracil) to treat a variety of ailments, including photodamage, scarring, and nonmelanoma skin cancer.

**Keywords:** Laser-assisted drug delivery, Ablative fractional laser, CO<sub>2</sub> laser, Microneedling; Micro ablation zones.

### INTRODUCTION

Laser-assisted transdermal drug delivery (LADD) system is a cutting-edge technology that offers a non-invasive method for delivering drugs through the skin. By utilizing laser energy to create microscopic channels in the skin, this system enhances the permeation of drugs, allowing for efficient and targeted delivery. This approach has the potential to revolutionize drug delivery by improving the absorption and bioavailability of medications, leading to enhanced therapeutic outcomes for patients.<sup>[1]</sup> The use of laser technology in transdermal drug delivery has garnered significant attention due to its ability to overcome the limitations of traditional delivery methods. By precisely controlling the depth and density of the channels created in the skin, this system enables the delivery of a wide range of drug molecules, including large and hydrophilic compounds that may otherwise have difficulty permeating the skin barrier.<sup>[2]</sup> Moreover, the non-invasive nature of this approach minimizes patient discomfort and reduces the risk of infection, offering a promising alternative to conventional drug administration routes.<sup>[1,3]</sup> In this article, we will delve into the underlying principles of laser-assisted transdermal drug delivery, explore its potential applications across various medical fields, and examine the current challenges and future prospects of this innovative technology.

### Transdermal Drug Delivery System

TDSS is a painless technique to apply a drug formulation to healthy and intact skin in order to deliver medications systemically. Without accumulating in the dermal layer, the medication first enters the stratum corneum before moving on to the deeper layers of the

epidermis and dermis. A medication can be absorbed systemically by the dermal microcirculation once it has reached the dermal layer.<sup>[2]</sup> TDD provides a range of benefits over other traditional medication delivery techniques. It can avoid difficulties like needle phobia by offering a non-invasive substitute for parenteral administration. Many placement possibilities for transdermal absorption on the skin are made possible by the skin's large surface area and ease of access. Furthermore, oral administration frequently results in issues with true bioavailability because of the first-pass metabolism and may be constrained by a higher risk of side effects. Research on pressure waves, vacuum effects, microneedling, dermabrasion, scraping, and lasers have all been studied in relation to transdermal drug administration. Drugs and chemicals, including triamcinolone, methyl aminolevulinic acid (MAL), 5-fluorouracil, and methotrexate, have all been delivered using these modalities.<sup>[4,5]</sup>

### Laser-Assisted Drug Delivery

Laser is a device that stimulates the emission of photons from excited atoms or molecules, producing a strong beam of coherent monochromatic light (or other electromagnetic radiation). Various kinds of lasers have been employed in LADD. While it's crucial to understand each type's specific safety profile, each type is generally effective. The four groups of lasers utilized in LADD can be categorized practically as follows:<sup>[2,6]</sup>

- **Fully ablative lasers:** These heat and completely evaporate skin like the carbon dioxide (CO<sub>2</sub>) laser (10 600 nm) or the Er:YAG laser (2940 nm).
- **Ablative Fractional Lasers:** These are similar to the previous type but produce microscopic treatment zones (MTZs) called

columns of thermal injury when used fractionally.

- **Non-Ablative Fractional Lasers:** These are the same as the AFLs and include lasers like the erbium fiber laser (1550 nm). The primary chromophore of both lasers is water. These likewise result in MTZs, but the dermal-epidermal interface is not ablation-only. Skin heating is seen in the columns (Table 1).
- **The non-Ablative dermal remodeling:** This category comprises all lasers that have been used to increase medication absorption but have chromophores other than water. They also include lasers for treating vascular abnormalities, including the neodymium-doped YAG laser (1064 nm) and the pulsed dye laser (585/595 nm). Due to its unique qualities, AFL has been examined more than any other LADD topic, with NAFL coming in second (Table 2).

The adverse effects like erythema, scarring, vesiculation and, crusting etc. associated with fractional lasers are less compared to conventional ablative lasers. The amount of tissue that the MTZs cover is referred to as the fractional laser density. Both the number of channels and the laser beam's size influence the total density. The depth of the channel itself is another important factor that is directly influenced by laser fluence. In general, if we want to treat diseases like alopecia or scarring, we should use greater fluences to go to the deeper layers of the dermis. Treatment of photodamage, melasma, or superficial scarring would be appropriate for the outermost layers of the dermis. When treating patients with vitiligo, superficial nonmelanoma skin cancer, or melasma, ablation limited to the epidermis may be adequate.<sup>[7,8]</sup>

## Background Information

R. R. Anderson *et al.* initially presented the concept of ablative fractional laser treatment (AFXL) in 2004.<sup>[6,9]</sup> Ablative laser pulses are divided into several micro pulses that are grouped in a regular grid pattern using microlens prisms or scanners. The micro ablation zones (MAZ) are vertical, cone-shaped channels formed by the impact of these micro pulses on the skin. The ablation width (AW), ablation depth (AD), and surrounding coagulation zone of MAZs, which are more prominent when using CO<sub>2</sub> lasers, are all characteristics of thermal laser effects. By modifying the numerous treatment parameters, such as stacks (number of delivered pulses) and fluence (energy density), the desired AW and AT of the MAZ can be specified. Healthy skin bridges (often greater than 50%) remain to exist between individual MAZ, ensuring fast and scar-free wound healing. In contrast with conventional laser resurfacing, patients experience significantly less downtime.<sup>[10]</sup> When topical treatments are applied immediately following AFXL treatment, the active components have a greater probability of penetrating through the MAZ and accumulating in the skin, increasing their bioavailability under the stratum corneum.<sup>[11]</sup> According to recent research, LADD may also be treated with non-ablative fractional laser systems (NAFXL). NAFXL is frequently used in therapeutic practice to treat scars and rejuvenate skin. NAFXL, like the fractional 1,550 nm erbium-glass laser, may cause thermal injury to the skin's deeper layers without significantly damaging the stratum corneum, according to certain theories. However, it is possible that intracellular gaps increase as a result of generating a photomechanical wave, momentarily affecting the integrity of the stratum corneum.<sup>[12]</sup>

## Mechanism of LADD

Traditionally, laser devices have been employed in continuous mode, which ablates the entire water-containing epidermis under treatment. Ablative fractional laser technologies have emerged more recently.<sup>[13,14]</sup> (AFXL) is now in development. AFXL uses fractional photothermolysis, a process that produces unhindered channels of communication with the stratum corneum's outermost layer by thermally destroying several vertical columns of tissue. A cuff of dense, thermally-coagulated tissue, known as microscopic treatment zones (MTZs), envelops each channel.<sup>[6]</sup>

MTZs help topical compounds penetrate from the skin's surface to the layer of interest, but they leave the majority of the skin's surface area untreated and unaltered. This means that only a small portion of the skin's surface is treated.<sup>[6]</sup> The skin that has not been treated works as a reservoir for stem cells, growth factors, and inflammatory cells that can quickly migrate to injured skin to promote quicker healing with less scarring. The fluence that is applied can be utilized to determine the depth of these ablated channels.<sup>[15]</sup>

The rationale behind the increased penetration of drugs or molecules via MTZs can be explained by applying Fick's first law of physics, which states, in its simplest form, that the concentration difference of that molecule on either side of that barrier ( $\Delta C$ ), divided by the path length ( $L$ ), is the product of the partition coefficient ( $K_m$ ), which reflects the number of molecules available for diffusion across a membrane, the diffusion constant ( $D_m$ ), and the degree of flux of a molecule ( $J$ ) across a barrier.

$$J = \frac{K_m \times D_m \times \Delta C}{L}$$

The total flux of the molecule increases when the stratum corneum's permeability is increased through MTZs, which also raises  $K_m$ . The drug's total flow decreases as its molecular size grows because there is more frictional resistance to molecule movement and  $D_m$  lowers.<sup>[16]</sup>

## Vitiligo

The auto-immune disease vitiligo causes skin areas to become depigmented. In a half-body comparative analysis, patches of vitiligo on one side of the body (control) received CO<sub>2</sub>-AFXL and NB-UVB alone; patches on the other side (study) received topical application of betamethasone (corticosteroids) solution under occlusion and a course of NB-UVB phototherapy (treatment).<sup>[17]</sup> The study involved 25 patients with stable, symmetrical vitiligo who were resistant to other therapies. Half-monthly CO<sub>2</sub>-AFXL treatments were administered, whereas NB-UVB treatments were administered two to three times per week for a period of six months. Due to increased topical corticosteroid penetration, 44% of patients on the treatment arm experienced more than 50% re-pigmentation, which was considerably better than the control arm. Although the results are fascinating, the lengthy course of treatment and related costs might prohibit this treatment in other healthcare systems; however, the study adds more evidence in favor of using this idea.<sup>[13,17]</sup>

## Hypertrophic and Keloid Scars

After AFXL treatment, scar appearance is frequently improved. This is probably because part of the fibrotic scar is removed and the

structure and composition of collagen are somewhat restored.<sup>[18]</sup> Waibel examined fifteen patients who had burns, injuries, or trauma that left them with hypertrophic scars. Using the UltraPulseLumenis machine, each patient underwent up to five treatments of CO2-AFXL (10–15% density), which were followed by topical triamcinolone application (10 or 20 mg/mL).<sup>[19]</sup> Six months after the last treatment session, 23 blinded observers observed improvements in texture, degree of hypertrophy, and dyschromia.<sup>[20]</sup>

### Atrophic Scars

In order to restore facial volume, poly-L-lactic acid (PLLA; Sculptra) is frequently used as a subcutaneous filler. It is believed to promote the proliferation of fibroblasts and the synthesis of collagen. CO2-AFXL was used to treat 19 patients who had atrophic scars from a variety of conditions, such as acne, trauma, and surgery. PLLA was then applied topically to the patients.<sup>[21]</sup> The most often mentioned concerns were erythema and edema, although the treatments seemed to be well-tolerated with relatively slight post-procedural pain. On average, each patient only needed one therapy. Three months following treatment, four observers who were blinded to the results noted improvements in scar color, atrophy, and color.<sup>[22]</sup>

### Applications of Laser-Assisted Drug Delivery in Fields Other than Dermatology

In addition to its uses in dermatology, LADD has been employed to deliver medications and chemicals into the body for a wide range of purposes. Research on both humans and animals has demonstrated the effectiveness of completely ablative and fractional lasers in introducing

antibodies and small interfering RNA molecules (siRNA). siRNA has shown promise in treating a wide range of disorders by blocking the translation of different genes. Even though mice have been the subject of the sole studies on LADD with siRNA yet, this route may one day be investigated in dermatological illnesses utilizing siRNA, as has been the case with microRNA 21 in psoriasis, for instance.<sup>[2,23]</sup> Pilot investigations using hematopoietic stem cells topically combined with an ablative laser in mice are much more sophisticated, opening the way for the potential use of LADD as a substitute in hematopoietic progenitor transplants.<sup>[24]</sup>

### Potential Risks and Limitations

The incidence of AFXL side effects and problems is minimal when used as directed.<sup>[25]</sup> But it's important to remember that when AFXL is used with topically applied medicines, the cutaneous bioavailability of these medications increases, which could potentially raise the risk of problems. This is especially true in situations when the medications being administered like ALA, MAL, 5-FU, or IM—have the potential to cause cutaneous inflammatory reactions. For example, following AFXL-PDT, one of the patients experienced a widespread chronic erosion on the scalp that later progressed into a superinfection with *Staphylococcus aureus*. After several weeks of topical treatment with a mixture of betamethasone and fusidic acid, the wound finally healed.<sup>[9]</sup> Adverse effects can also result from active chemicals penetrating too deeply. Drugs given topically may, therefore enter the capillary circulatory system through the MAZ directly. Medications whose safety profile is often limited to topical application may potentially have systemic effects.<sup>[26]</sup>

**Table 1:** Evidence for ablative fractional laser-assisted drug delivery<sup>[27]</sup>

| S. No. | Drug delivery assisted by ablative fractional laser            | Year of study | Study given by    | Laser used   | Study conducted  | Study outcomes  |
|--------|--|---------------|-------------------|--|--|---|
| 1      | Aminolevulinic Acid (ALA) and Methyl-aminolevulinic Acid (MAL) | 2010          | Haederstal et al. | CO <sub>2</sub> laser                                | Pig skin   | The results showed deep and uniform drug distribution after pretreatment with lasers due to radial diffusion of the product which was deposited on the MTZs.  |
|        |  | 2015          | Choi SH et al.    | 2,940 nm Er:YAG Laser followed by application of MAL | 33 patients diagnosed with actinic cheilitis were randomized to receive either 1 session of pretreatment with laser immediately followed by PDT or two sessions of traditional PDT with an interval of 7 days  | In both the first 3 months of follow-up (92 vs 59% of full cure) and the 12-month follow-up (85 vs 29%), the group that received laser pretreatment showed a more successful response. In the year following the procedure, there was a decreased recurrence rate due to the pretreatment method. |
| 2      | Diclofenac   | 2011          | Bachhav et al.    | 2,940 nm Er:YAG Laser                                | Use of 2,940nm Er:YAG laser followed by the application of diclofenac in Gel and Aqueous form on pig skin.   | The application of a laser increased the distribution of diclofenac in both its aqueous and gel forms by a factor of 13. Moreover, the fluence of the laser affected penetration but not the skin's deposition of diclofenac.   |
| 3      | Betamethasone  | 2015          | Li et al.         | CO <sub>2</sub> Laser                                | 25 patients underwent a split-body treatment. The lesions on one side of the body were treated with a laser, betamethasone solution, and narrowband UVB phototherapy. On the other side, phototherapy was carried out after laser treatment (control). | In comparison to the control side, the side treated with betamethasone solution right after the laser surgery showed higher rates of re-pigmentation, with proportions of 40% (against 8%) for patients with re-pigmentation >50%.  |

|    |  |      |                |   |  |   |
|----|--|------|----------------|---|--|---|
| 4  | Triamcinolone acetonide                                | 2013 | Waibel et al.  | CO2 Laser   | 15 patients with hypertrophic scars underwent this study. 3–5 sessions of fractional CO <sub>2</sub> laser were performed. The time interval between the procedures was 2–3 months. Right after the laser treatment, 10–20 mg/mL of Triamcinolone Acetonide was applied. | According to the Manchester modified scoring method, which has a maximum score of 3, the improvement in the parameters of scars, atrophy, dyschromia, and contour six months after assessment was 2.73. The dyschromia parameter received the lowest improvement scores, whereas the parameter texture demonstrated the best results. |
| 5  | Methotrexate   | 2008 | Lee et al.     | Either 2,940nm Er:YAG Laser or electroporation.                               | In-vitro evaluation in rodent's healthy skin (nude mouse)  | The results showed an increase in absorption of the drug by 3 to 80 times after the use of the laser.   |
| 6  | Vitamin C  | 2016 | Waibel et al.  | CO <sub>2</sub> Laser   | A split-face study was conducted to evaluate the use of CO <sub>2</sub> laser in a non-sterile formulation that contained vitamin C (15%), vitamin E (1%) and ferulic acid (0.5%) in serum vehicle.  | The biopsy specimens, which were harvested after five days of the treatment, on molecular analysis, showed an increase in fibroblast growth factor responsible for stimulating tissue repair.   |
| 7  | 5- Flourouracil (5-FU)                                 | 2015 | Nguyen et al.  | Ablative fractional CO <sub>2</sub> Laser with drug delivery under occlusion. | <i>In-situ</i> evaluation in 30 lesions of superficial basal and squamous cell carcinoma present in the trunk and extremities. After the treatment, the drug was administered daily for the first 7 days under occlusion.  | The biopsies of the treated areas, which were harvested after 4-8 weeks of treatment, showed histologic healing in 87% of the lesions that were treated.  |
| 8  | Topical Antifungals (Terbinafine and Amorolfine cream) | 2014 | Yang et al.    | Ablative fractional laser   | Evaluation of laser on drug administration on the nail plate that used optical coherence tomography in an effort to determine the ideal parameters to prevent harm to the tissues beneath the nail plate.  | The use of tomography was proved effective in performing the analysis. It ensures the safety of the procedure as well.  |
| 9  | Poly lactic acid                                       | 2014 | Rkein et al.   | Ablative fractional CO2 Laser   | Ten patients with atrophic scars.  | On a scale ranging from 0 to 3, 95% of the scars secured an improvement score of 2.18 after three months.   |
| 10 | Botulinum toxin  | 2015 | Mahmoud et al. | Ablative fractional CO <sub>2</sub> Laser                                     | Ten patients underwent a split-face study in the periorbital area.   | A significant improvement was seen on the side associated with botulinum toxin after 30 days of follow-up.  |

**Table 2:** Evidence for non-ablative fractional laser-assisted drug delivery<sup>[27]</sup>

| S.No | Drug delivery assisted by non-ablative fractional laser       | Year of Study | Study given by | Laser used                                      | Study conducted  | Study outcomes  |
|------|---|---------------|----------------|---|--|---|
| 1    | Aminolevulinic Acid (ALA) and Methylaminolevulinic Acid (MAL) | 2016          | Lee et al.     | Non-ablative fractional 1,550 nm Er:glass laser | Comparison study of skin pretreated with laser to the untouched skin.  | An increase of up to 1200 times in the skin's permeability to ALA was reported as compared to the untouched skin.   |
| 2    | Topical Antifungal  | 2016          | Kim et al.     | 1,064 nm Nd:YAG Laser                           | Three groups of patients were created: Group 1 (which only received laser treatment); Group 2 (which also received topical antifungal medicine in addition to laser treatment); and Group 3 (which had only received antifungal treatment). Each month, 3-4 laser sessions were carried out. | Clinical and mycological studies showed that the laser treatment, either alone or combined with topical medication, produced better outcomes than topical antifungal treatment. Moreover, individuals who received the combined treatment seemed to be able to avoid reinfection with the addition of topical antifungal. |
| 3    | Tretinoin   | 2016          | Lee et al.     | Non-ablative fractional 1,550 nm Er:glass laser | Tretinoin penetration into skin treated with a non-ablative fractional 1,550 nm Er: glass laser <i>in-vitro</i> evaluated  | When compared to the skin that was left untreated, they observed a two-fold increase in the active principle's permeation.  |

|   |                        |      |              |  |  |  |
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| 4 | 5- Fluorouracil (5-FU) | 2008 | Gomez et al. | 1,064 nm Q-switched Nd:YAG laser               | <i>In-vitro</i> Study  | In investigation on animal skin, the application of this laser proved to be beneficial for promoting the active principle's permeation.  |
| 5 | Vitamin C              | 2013 | Lee et al.   | Q- switched laser associated with sonophoresis | Patients with melasma underwent this study.  | As per the visual analog scale for treating melasma, the results showed a significant improvement in the hemiface where the drug delivery was performed.   |
| 6 | Cosmeceuticals         | 2015 | Kalil et al. | Q- switched laser                              | Four sessions of laser with an application of a formula of the drug were carried on four patients fortnightly. | In comparison to a placebo group, the results showed improvement in acne, spots, pores, texture, and UV index using a formula including Hyaxel®, Hidroxiprolisilane®, DMAE Pidolato®, Nano Vit C®, and Matrixyl 3000®. |

## Future Prospectives

For all of the suggested therapies to confirm their efficacies and side effects, larger trials with more participants in both the treatment and control arms are needed. Various body sites and treatment efficacy among age groups, genders, and ethnicities will need to be taken into consideration in future cohorts. To achieve maximum medication penetration and rapid skin recovery, optimal laser parameters such as fluence, density, and treatment schedule must be established. Improved therapeutic results are the ultimate goal of using fractional LADD to increase topical medication cutaneous absorption, which has demonstrated considerable promise thus far. Significantly shorter treatment durations and incubation periods are other benefits of AFXL-assisted medication delivery. Apart from the advantages of using current regimens, systemic medications that were not previously able to be delivered through the skin, such as methotrexate and cisplatin, can now be applied topically.<sup>[13]</sup> Convenient in-office treatments can take the place of difficult, patient-dependent therapy plans. Although in its early stages of development, AFXL-assisted medication administration is a potentially helpful, broadly applicable, and minimally invasive delivery method that has applications not just in dermatology but also in other fields.<sup>[28]</sup>

## CONCLUSION

In conclusion, the combination of LADD with topical treatments shows immense promise in enhancing treatment outcomes by promoting absorption and synergistic effects. Laser-assisted drug delivery has shown mostly local reactions consistent with laser therapy, underscoring its general tolerability. However, severe systemic effects like depigmentation and scarring, albeit rare, warrant careful consideration. While safety and technique remain contentious, ongoing research and advancements in technology are expected to address these concerns in the near future. The potential of this approach in improving patient care and treatment efficacy is undeniable, signaling a hopeful future for medical and physical treatment integration.

## CONFLICT OF INTEREST

None.

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