Development of Bio-ballistic Device for Laser Ablation-induced Drug Delivery

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Transdermal and topical drug delivery with minimal tissue damage has been an area of vigorous research for a number of years. Our research team has initiated the development of an effective method for delivering drug particles across the skin (transdermal) for systemic circulation, and to localized (topical) areas. The device consists of a microparticle acceleration system based on laser ablation that can be integrated with endoscopic surgical techniques. A layer of microparticles is deposited on the surface of a thin metal foil. The rear side of the foil is irradiated with a laser beam, which generates a shockwave that travels through the foil. When the shockwave reaches the end of the foil, it is reflected as an expansion wave and causes instantaneous deformation of the foil in the opposite direction. Due to this sudden deformation, the microparticles are ejected from the foil at very high speeds, and therefore have sufficient momentum to penetrate soft body tissues. We have demonstrated this by successfully delivering cobalt particles 3 μm in diameter into gelatin models that represent soft tissue with remarkable penetration depth.

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1. Introduction

Recently, the biolistic (bio-ballistic) process has emerged as an effective technique to transfer adequate concentrations of pharmacological agents directly into delicate and unapproachable sites within the body with minimal side effects. Moreover, the direct use of drugs in powder form can be useful in the treatment of certain types of cancer, thromboses, and in gene therapy. Therefore, several devices have been designed and tested for delivering microparticles at controlled velocities into soft targets; examples of such devices include a detonation-driven particle gun,[1] and a needle-free vaccine delivery system, which uses pressurized helium gas in conjunction with a miniature nozzle.[2-4] The emergence of these localized drug delivery techniques has opened up new avenues in gene therapy and pharmacological treatments. However, these drug delivery methods have various shortcomings. The detonation-driven particle gun may not be suitable for clinical/surgical procedures as an explosive charge is used for detonation. In addition, the miniaturization of such a device may not be possible. The needle-free vaccine delivery system may not be useful in delivering vaccines to internal treatment sites in the body because the device causes a substantial amount of helium gas to flow along with the particles.

Despite the significant advances described above, these devices cannot be easily integrated with medical or surgical procedures for either topical (*i.e.*, localized internal and external areas on the skin) or transdermal (*i.e.*, across the skin) delivery of drug particles.

Therefore, we have initiated the development of a biolistic device that makes use of a shockwave generated by laser ablation[5]. This device has a number of distinct advantages over existing drug delivery systems. The laser system is relatively safe for use in medical procedures as the laser can be precisely controlled. In addition, it is minimally invasive and can be miniaturized by integration with other devices, such as the endoscope. Thus, the device can be used for endoscopic surgical procedures when treatment sites cannot be approached easily.

Here, we present the results of experiments using laser ablation-induced microparticle acceleration as an innovative drug delivery system.

2. Laser Ablation

The term "laser ablation" is generically used to describe the laser–material interaction, which involves coupling of optical energy into a solid. This results in several processes, such as vaporization, the ejection of atoms, ions, molecular species, and fragments, shockwaves, plasma initiation, and expansion, and a combination of these and other processes. The laser irradiance and the thermooptical properties of the material are critical parameters that influence these processes.[6]

To choose the most efficient conditions for particle acceleration, we first performed direct laser ablation experiments to generate shockwaves and to measure their velocities under different conditions. Subsequently, particle acceleration experiments were performed with both direct and confined ablation, and the results were used to make qualitative penetration depth comparisons.

2.1 Direct laser ablation

In direct laser ablation, the target material is directly irradiated with a laser beam, which causes evaporation of part of the material and generates a plasma. This plasma expands supersonically with the generation of a shockwave.

An Nd:YAG laser with a wavelength of 532 nm and pulse duration of 10 ns was used for the experiment. The energy was set to 200 mJ/pulse and the target materials were foils of copper, aluminum, and brass 1 mm thick. The velocities of the shockwaves were determined from the shadowgraph images and were compared with Sedov's blast wave theory.[7,8] As shown in Figure 1, the experimental and theoretical values were in good agreement, and thus the theory was used to analyze the amount of energy transmitted from the laser beam to the shockwave.[9]

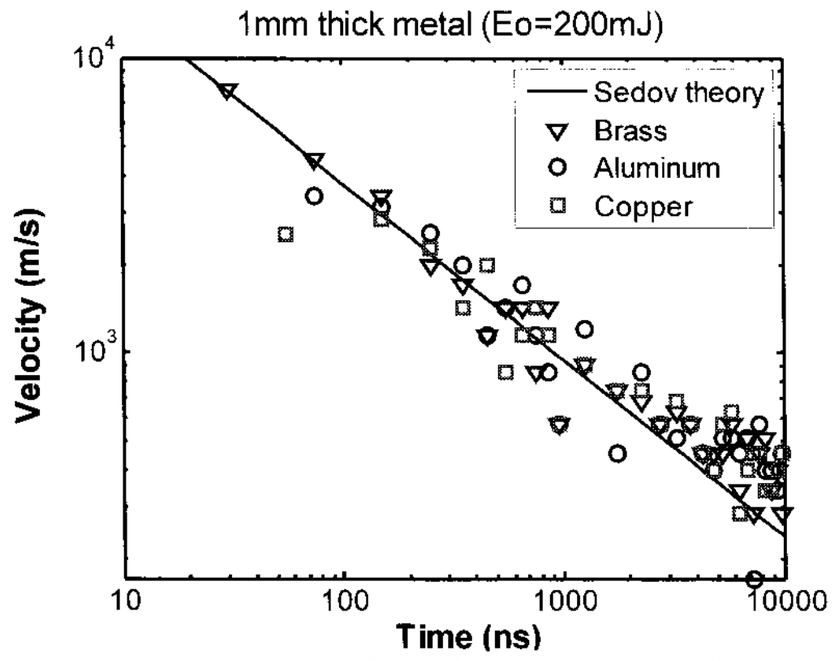


Fig. 1 Propagation velocities of the shockwaves at different times[9]

As Sedov's theory describes the propagation of a shockwave from the explosion of a point source, the atmospheric pressure p_1 can be neglected as it is much less than the shockwave pressure p_2. Therefore, the shockwave problem can be expressed in terms of air density ρ_1, shockwave energy E_0, specific heat ratio γ, and time t. Defining r_2 as the shockwave radius, we obtain the following equation:

$$r_2 = \left(\frac{E_0}{\rho_1}\right)^{1/(2+\nu)} t^{2/(2+\nu)} \lambda_0 \tag{1}$$

where ν represents the dimensionality of the propagation ($\nu = 1$ for planar, $\nu = 2$ for cylindrical, and $\nu = 3$ for spherical propagation), and λ_0 is a non-dimensional coefficient. In the above equation, $E_0 = \alpha E$, where E is the laser energy. Rearranging Eq. (1) to obtain the value of E_0 we obtain:

$$E_0 = \frac{r_2^{(2+\nu)} \rho_1}{t^2} \tag{2}$$

Hence, using Eq. (2), the energy transferred to the shockwave can be estimated by substituting the measured propagation distance r_2.

Table 1 shows the calculated values of absorptivity α of each metal, and their melting and boiling temperatures, T_m and T_b, respectively.

Table 1 Absorptivity and temperatures of the metals tested in this study

	Aluminum	Brass	Copper
α	0.5534	0.4877	0.4655
T_m	~ 650°C	~ 915°C	~ 1083°C
T_b	~ 2200°C	~ 2300°C	~ 2310°C

Among the three metals tested, aluminum showed the largest energy transfer to the shockwave. This was because of its low melting/boiling point. Assuming that the metals are irradiated with the same energy, when the melting/boiling point is low, the amount of metal vapor produced will increase. This causes the ambient air to be pushed more strongly. Thus, aluminum is considered the most efficient metal for accelerating particles.

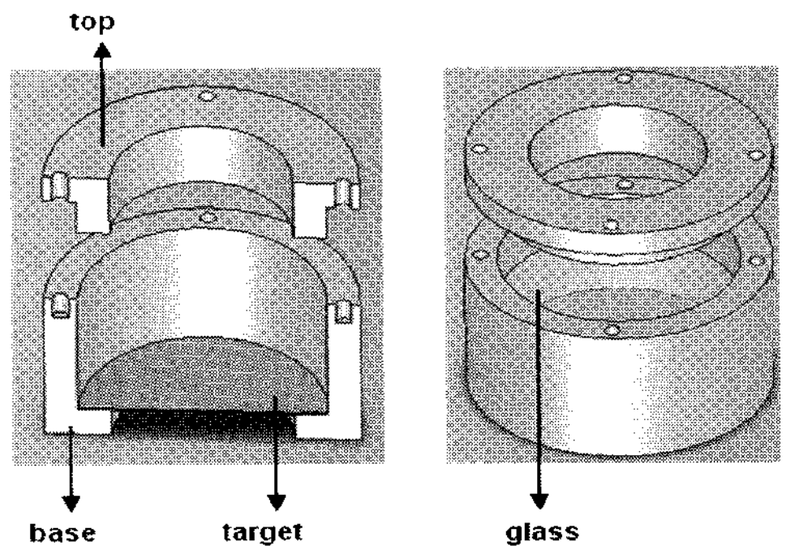


Fig. 2 Design of the holder for confined ablation

2.2 Confined laser ablation

In comparison to direct ablation, confined ablation is a more effective method of enhancing momentum transfer to the metal target. When the target is irradiated, it absorbs energy and generates plasma that expands supersonically. If the target is covered with a transparent material, the plasma generated will be confined. This greatly enhances the momentum transfer and coupling coefficient. Some of the factors that contribute to this enhancement are as follows: 1) the interaction takes place in a very small area, thus enhancing the plasma density and temperature; 2) the plasma is confined in one direction instead of two opposite directions, thus doubling the coupling coefficient; 3) the expansion of the heated air on the interface also adds more momentum to the target. These factors result in a high coupling coefficient.

It was reported previously that the momentum transfer in confined ablation could be as much as ten times the amount from direct ablation.[10] Based on this evidence, we designed the holder shown in Figure 2 to accelerate particles using the confined ablation technique.

3. Microparticle Acceleration

Figure 3 shows a schematic diagram of the particle acceleration process using confined ablation. A thin layer of microparticles is deposited on one surface of the metal foil, and the other surface is irradiated with the laser beam. The laser beam passes through a transparent material, which is BK7 glass in this case. The deposited laser energy causes a small portion of the foil to vaporize. This ionized vapor expands and generates a shockwave that travels through the metal target. When the shockwave reaches the end of the foil surface, it is reflected as an expansion wave due to the acoustic impedance mismatch between the air and the metal foil. The backward propagation of the expansion wave causes the metal foil to deform suddenly, and this instantaneous deformation ejects the particles from the deposited layer at very high speeds. The BK7 glass overlay helps to confine the laser ablation, making the shockwave stronger.[11]

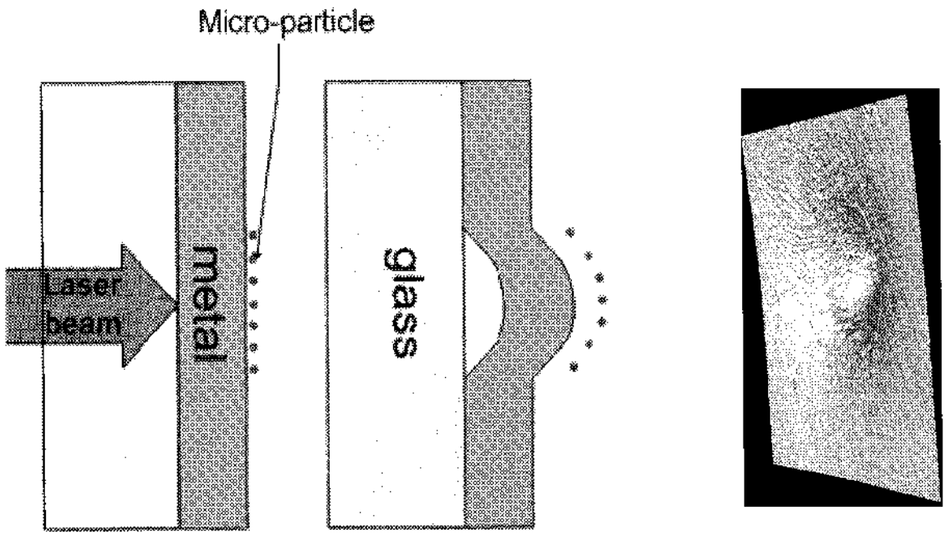
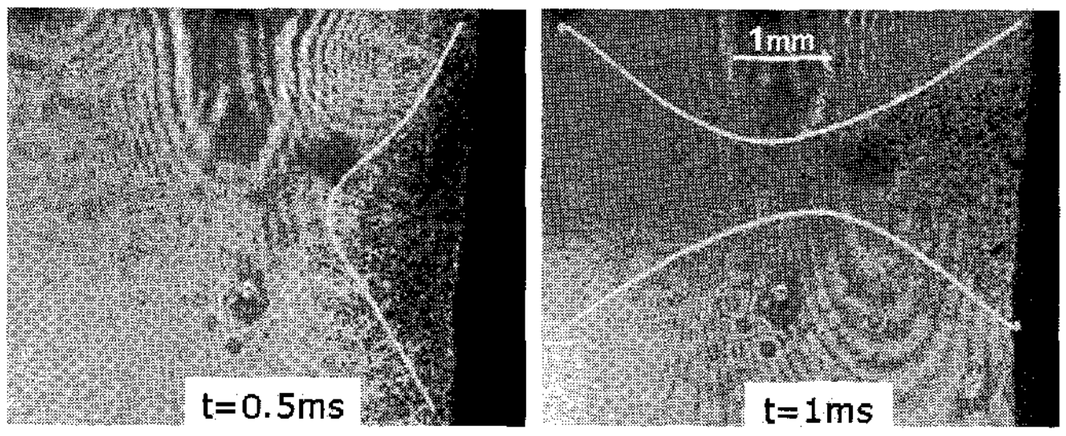


Fig. 3 Schematic diagram of the particle acceleration process through confined ablation (left) and an image of metal foil deformation using a 3D surface profiler (right)



(a) (b)

Fig. 4 Accelerated particles from particle-coated metal foil (right) to air (left) through "confined" ablation at (a) t=0.5 ms and (b) t=1 ms

We performed experiments using copper foil 0.05 mm thick as the target material, BK7 glass 3 mm thick as the confinement layer, and a laser energy of about 11 mJ/pulse. We used fluorescent polymer microspheres with a density of 1.05 g/cm³ as the particles to be ejected. Figure 4 shows sequential images of the particle acceleration process. These images show that the particles were ejected from the foil at very high velocity with a millisecond timeframe. In addition, they rapidly decelerated after ejection. As an ICCD camera was used, each frame represents an individual experiment. In addition, because the particles were not equally distributed over the surface, precise quantification could not be done based on these images.

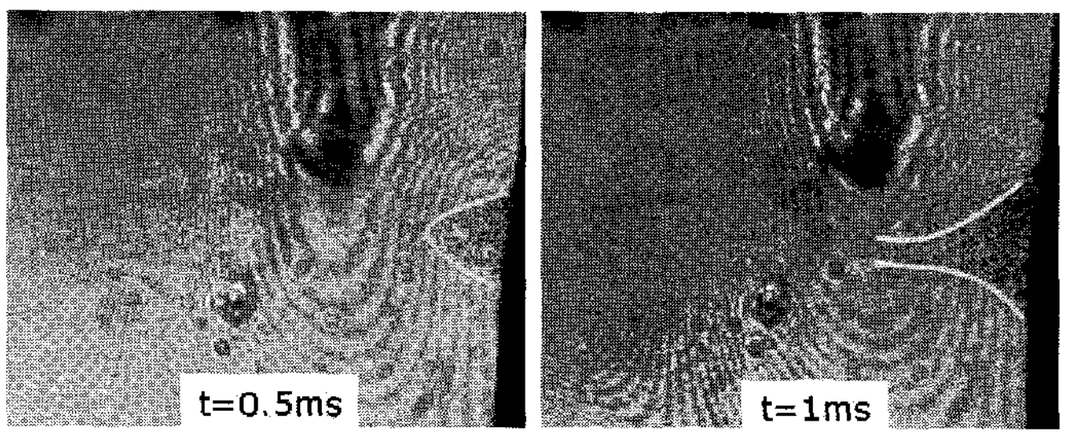
Instead, we estimated the surface velocity of the foil from first principles using continuum mechanics based on plastic deformation in the foil due to shockwave loading. As the shockwave propagation through the metal foil is a longitudinal compressive wave, its velocity inside a thin metal foil, C_l is given by:

$$C_l = \sqrt{\frac{E_m(1-\nu_m)}{\rho_m(1+\nu_m)(1-2\nu_m)}} \tag{3}$$

where E_m is the Young's modulus, ρ_m is the density, and ν_m is the Poisson's ratio of the metal. Assuming that the shockwave increases the metal foil's pressure P, the displacement S is expressed as:

$$S = \frac{2PC_l\tau}{E_m} \tag{4}$$

where τ is the time needed for the wave to travel once through the foil. As the displacement of the foil is a plastic event that can be physically measured, the pressure induced can be estimated. As the values of P and C_l are known, the velocity of the foil can be determined by differentiating Eq. (4); it was found to be 4973 m/s. As the foil is very thin, the surface of the metal target on which the particles were deposited was expected to accelerate to this velocity, and the particles deposited on it would also have the same velocity. Hence, we estimated the initial velocity of the particles to be about 4900 m/s.



(a) (b)

Fig. 5 Accelerated particles from particle-coated metal foil (right) to air (left) through "direct" ablation at (a) t=0.5 ms and (b) t=1 ms

To qualitatively verify that the confined ablation was an enhanced way of accelerating particles, we also performed direct ablation experiments. As shown in Figure 5, the particles were ejected at a much slower speed as compared to Figure 4. The foil also showed reduced deformation.

After we verified that confined ablation enhanced the acceleration of the particles, we performed dry particle injection into gelatin. Gelatin was used as a model of soft tissue as it is derived from collagen, a natural protein present in the tendons, ligaments, and tissues of animals, in which its strength and viscosity can be varied. The laser energy was 710 mJ/pulse with a spot diameter of 1.4 cm. The metal target used was aluminum with a thickness of 0.05 mm and the confining BK7 glass was 3 mm thick. The particles to be accelerated were made of cobalt and had a particle size of 3 μm.

As shown in Figure 6, the particles were successfully accelerated into gelatin, and the penetration depth was estimated to be 6 mm. As the acceleration of the particles is controlled by the laser energy, this means that the penetration can be controlled by adjusting the irradiated laser energy. However, the main difficulty in controlling both the penetration depth and the amount of particles delivered is due to the lack of a uniform distribution of the particles on the foil. Hence, further studies and experiments on the effects of the distribution of particles and the effects of penetration depth on the characteristics of the targets and the particles are required.

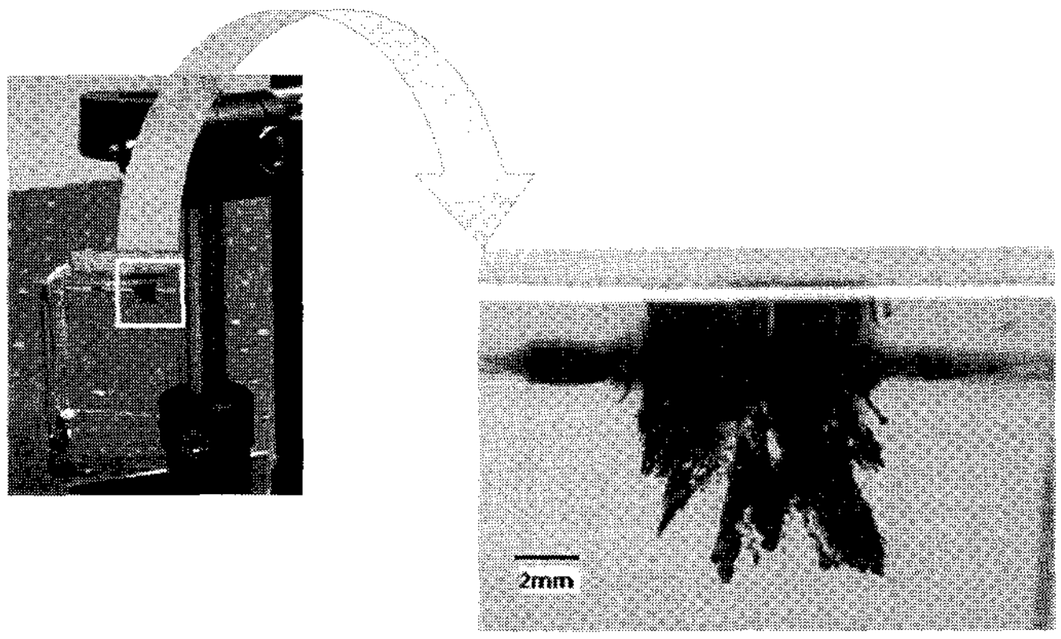


Fig. 6 The penetration of particles into gelatin as a model of human tissue

4. Conclusions

We have developed a needle-free, painless biolistic device based on laser ablation of particle-coated metal foil. Integrating such a device with endoscopes or optical fibers may enable it to be miniaturized and allow localized *in vivo* drug therapy to be performed. The most immediate potential applications of this device are in the topical delivery of lidocaine for local anesthesia and the transdermal injection of insulin for treating diabetes mellitus.

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