Localized, needle-free drug delivery is emerging as an effective technique to transfer adequate concentrations of pharmacologic agents directly to delicate and nonapproachable treatment sites in the body with minimum side effects. Moreover, the direct use of drugs in powder form can be very useful in the treatment of certain cancer cells, thrombosis, and in gene therapy. In recent years, several devices have been configured and tested for delivering microparticles at controlled velocities into soft targets. Klein et al.1 have developed and tested, in a detonation driven particle gun to deliver drug adsorbed microwolfram particles into gelatin models. A thin metal foil, with a deposition of a layer of microparticles is subjected to laser ablation on its back face such that a shock wave propagates through the foil. Due to shock wave loading, the surface of the foil containing microparticles is accelerated to very high speeds, ejecting the deposited particles at hypersonic speeds. The ejected particles have sufficient momentum to penetrate soft body tissues, and the penetration depth observed is sufficient for most of the pharmacological treatments. We have tried delivering 1 μm tungsten particles into gelatin models that represent soft tissues, and liver tissues of an experimental rat. Sufficient penetration depths have been observed in these experiments with minimum target damage. © 2005 American Institute of Physics. [DOI: 10.1063/1.2093930]
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The velocity of the compressive wave in aluminum foil works

based on the plastic deformation in the foil due to shock wave loading, the surface velocity of the foil can be estimated from the first principles using basic continuum mechanics. The shock wave propagating through the foil is a longitudinal compressive wave, and its velocity \( C_l \) in a thin metal foil can be given by

\[
C_l = \sqrt{\frac{E(1-\nu)}{\rho(1+\nu)(1-2\nu)}},
\]

where \( E \) is the Young’s modulus, \( \rho \) is the density, and \( \nu \) is the Poisson’s ratio of the material in which the compressive wave is propagating. For an aluminum foil, these values are \( E \sim 70 \text{ GPa}, \) \( \rho \sim 2700 \text{ kg/m}^3, \) and \( \nu \sim 0.33, \) respectively. So the velocity of the compressive wave in aluminum foil works out to be \( (C_l) \sim 6198 \text{ m/s}. \)

If the compressive/shock wave causes a step increase in pressure \( (P) \) in the foil, then the displacement \( (S) \) of the foil due to shock wave loading can be given by

\[
S = \frac{2PC_l\tau}{E},
\]

where \( \tau \) is the time needed for the wave to travel once through the thin foil. The displacement \( (S) \) of the foil is the plastic deformation in the foil due to shock wave loading, and can physically be measured. Knowing the value of \( C_l, \) the value of \( \tau \) can be calculated for a 100-\( \mu \text{m} \)-thick aluminum foil. The measured plastic deformation in the foil for a confined laser ablation with an energy deposition of 0.25 GW is about 185 \( \mu \text{m}, \) and with this, the pressure \( (P) \) induced in the foil is estimated to be about 65.3 GPa from

\[
V = \frac{PC_l}{E},
\]

where the value of \( V \) works out to be 5782 m/s. Since the foil thickness is very small, the surface of the foil on which the particles are deposited is expected to accelerate to this velocity and so are the particles. Hence, the deposited particles will initially accelerate to about 5782 m/s with a confined energy deposition of 0.25 GW. The deformed 100-\( \mu \text{m} \)-thick aluminum foil after shock wave loading is shown in Fig. 2.

The particles to be deposited are suspended in a solvent (\( \text{C}_2\text{H}_5\text{OH} \) or 2-propanol) and a small volume (typically 2.5–5 \( \mu \text{L} \)) of this suspension is deposited on the thin foil. The solvent evaporates leaving behind a thin trace of suspended particles. Depending upon the desired distribution and number of particles, the concentration (ppm level) of the particles and the volume to be deposited are varied. A thin layer of 1 \( \mu \text{m} \) tungsten particles deposited on a 100-\( \mu \text{m} \)-thick aluminum foil is shown in Fig. 3.

1 \( \mu \text{m} \) tungsten particles are delivered into soft targets such as 3% gelatin and liver tissue of an experimental rat (Sprague Dawley male). The 3% gelatin (20–25 bloom, cooled at 10 °C for 1 h) represents a human thrombus model and a penetration of about 1 mm has been observed in this case. The percentage of gelatin is determined by weight ratio of gelatin to water. A gelatin model with the penetrated tungsten particles is shown in Fig. 4. Figure 5 shows 1 \( \mu \text{m} \) tungsten particles delivered into liver tissues of Sprague Dawley male rat. The sections shown are hematoxylin-eosin stained and are 30–50 \( \mu \text{m} \) thick. Most of the penetration is observed along the focal point of the laser beam. Four experimental animals (rats) have been used for this study so far, and a good repeatability has been observed in the results.

Knowing the initial velocity of the particles from Eq. (3), the velocity of the particles at or near the surface of the target can be deduced from the equations of motion, assuming an appropriate size for the particles. If we assume a particle sphere of about 3 \( \mu \text{m} \) diameter (in the case of cluster-
ing), flying at 5700 m/s ($V_0$) in atmospheric air (density, $\rho_a = 1.18$ kg/m$^3$), its coefficient of drag ($C_d$) can be given by the following equation:

$$C_d = \frac{D}{0.5 \rho_a V_0^2 A},$$  

(4)

where $D$ is the drag force and $A$ is the frontal surface area of the sphere. At hypersonic speeds, the $C_d$ for a sphere can be assumed to be unity. With this, from Eq. (4), the drag force on the particle can be calculated. The equation of motion for such a particle can be given as later

$$-D + w = m \frac{dV}{dt},$$  

(5)

where $w$ is the weight, $m$ is the mass and $dV/dt$ is the deceleration of the particle. Weight of the particle in this case is negligible and, hence, knowing the density of the particle, the deceleration of the particle can be found out. The final velocity of the particle ($V_p$) can be computed using the following expression:

$$V_p = \left[ V_0^2 - \left( 2 \times \frac{dV}{dt} \times Sd \right) \right]^{1/2},$$  

(6)

where $Sd$ (stand-off distance) is the distance of the target from the thin metal foil. In this case, for a particle size of 3 $\mu$m diameter and target stand-off distance of 10 mm, $V_p$ works out to be about 4700 m/s.

A theoretical penetration model proposed by Dehn$^6$ has been used to determine the penetration depth of microparticles in rat liver. The force of deceleration acting on each particle is split into an inertial force, required to accelerate the target material up to the speed of the particle, and a static force required to yield the target material

$$F = \frac{1}{2} \rho A V^2 + 3 \rho_1 \sigma_1,$$  

(7)

where $F$ is the force acting on the particle, $V$ is the instantaneous particle velocity, $A$ is the projected area of the projectile, $\sigma_1$ is the yield strength, $\rho$ is the density, and subscripts $p$ and $t$ apply to the particle and target, respectively. Integration of Eq. (7) yields a theoretical penetration depth relation as later

$$d = \frac{4 \rho_r \rho_p}{3 \rho_t \left[ \ln \left( \frac{1}{2} \rho_t V_t^2 + 3 \sigma_1 \right) - \ln(3 \sigma_1) \right]},$$  

(8)

In expression (8), $d$ is the penetration depth, $\rho$ is the density, $r$ is the radius of the particle, $V_t$ is the particle impact velocity, and $\sigma$ is the yield strength. Subscripts $p$ and $t$ apply to the particle and target, respectively. Assuming that the target is humid (with a lot of water/liquid content), and the liver tissue fails along its cell boundaries considering the particle size (clusters), an yield strength of 1 MPa is assumed for the rat liver. This is a typical value for the yield strength of a humid soft body tissue.$^7$ Density for the rat liver is measured to be 1120 kg/m$^3$. For the tungsten particles used, the density is 19 250 kg/m$^3$ and the particle diameter is assumed to be 3 $\mu$m (assuming clusters). The impact velocity at the target surface is taken as 4.7 km/s as obtained from expression (6). With these values, the theoretical penetration depth of tungsten particles in rat liver tissue works out to be about 287 $\mu$m, which is close to the one shown in Fig. 5 as far as the order of magnitude of the penetration depth is concerned.

Delivery of the microparticles into the rat liver substantiates the usability of the device on internal body organs. The proposed device can also be used to deliver vaccines into human skin. For a successful delivery of vaccines into skin, the drug-coated particles should penetrate the stratum corneum of the skin and reach the viable epidermis. Considering an yield strength and a density of 3.2 MPa (under humid conditions) and 1500 kg/m$^3$, respectively, for the stratum corneum,$^8$ expression (8) gives a penetration depth of about 191 $\mu$m for the earlier particle size and impact velocity. The estimated penetration depth in skin is 33% lower when compared to the liver. Based on the experimentally observed penetration depth in liver (Fig. 5), a 33% lower penetration depth would amount to about 50 $\mu$m, which is sufficient to reach the viable epidermis of the skin, considering a maximum thickness of 16 $\mu$m for the stratum corneum.$^9$

In conclusion, we have demonstrated a laser ablation based particle delivery device to deliver drug coated dry microparticles into soft body targets. Particle penetration depth in the target observed in the preliminary experiments is believed to be sufficient for most of the pharmacological treatments. The device being proposed is supposed to be totally noninvasive and is likely to have potential applications in medical surgical procedures. Further, it is intended to have a very uniform and controlled distribution of the particles on the foil, such that the particles enter the target as individual drug coated spheres so that a good distribution of drug can be had in the target tissue. It would be very effective if an individual drug coated particle enters a cell in the tissue by rupturing cell membrane, without collapsing the cell boundaries. Also, to apply this device to clinical procedures, it has to be handy and, hence, has to be miniaturized and also has to be integrated with devices like endoscopes. Laser focusing/irradiation in such a case can conveniently be done by drawing an optical fiber from the laser. And if the lenses are miniaturized, then they can easily be integrated with an endoscope, and the device can suitably be used for even endoscopic surgical procedures, when the treatment sites are nonapproachable. These further thoughts would be implemented in the next phase of research.


$^5$L. Brekhovskikh and V. Goncharov, Mechanics of Continua and Wave Dynamics (Springer, Tokyo, 1982).

