

Novel applications of micro-shock waves in biological sciences

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Abstract

Spherical micro-shock waves of a few mm radii can be generated both in ambient air and in water by expending a small amount of energy (~1 J). Various techniques such as focusing of laser beam, energy deposition using electrical discharge in water, micro-explosion of silver azide pellets and simultaneous actuation of piezo-ceramic/electrical crystal array can be used for creating micro-shock waves of requisite intensity. The nonlinear instantaneous pressure spike (1 MPa – 100 MPa) generated by the micro-shock waves can be used in applications such as particle delivery systems for gene therapy, food preservation, wood preservation and conditioning, and also in cancer treatment. The visualization studies of micro-shock waves generated using laser beam focusing in ambient air, various types of micro-shock wave generators, the status of current research on various applications along with some experimental results on micro-shock wave-assisted particle delivery systems are discussed in this paper.

Keywords : Micro-shock waves, laser beam focusing, micro-explosion, lithotripsy, food preservation, wood preservation, gene therapy, drug delivery and cancer treatment.

1. Introduction

Shock waves are commonly associated with supersonic flight. However, in recent times, utilizing the nearly instantaneous changes in fluid velocity and pressure produced by these waves, many innovative techniques have been developed or are being developed for medical and biological applications. It is possible to generate spherical shock waves with typical radius of a few mm, both in ambient air as well as in water expending energy of the order of a few joules. For example, in the laboratory, spherical shock waves can be generated by focusing an Nd:Glass laser beam in ambient air and the energy expended in this process is typically ~ 1.38 J, which is equivalent to 0.3 mg of conventional TNT explosive. Considering the small amount of energy spent in generating such shock waves they deserve to be referred to as micro-shock waves [1]. However, these waves travelling at supersonic velocity exhibit highly nonlinear pressure profile with ultra short rise times (~ a few μ s) and are completely different from conventional acoustic waves wherein the pressure profiles are more linear with slower rise time (~ tens of ms).

Shock wave-assisted lithotripsy, probably one of the most useful and proven treatments for kidney stones [2], [3] and gall bladder diseases, is now widely used by doctors in many countries. Shock waves for lithotripsy are usually of microsecond duration with peak pressures ranging from about 35 to 120 MPa in a single pressure pulse. The other applications include treatment of pancreatic and salivary stones, and also in orthopaedics [4]. While substantial progress has been made in the research related to medical applications of shock waves [5] no work has been reported

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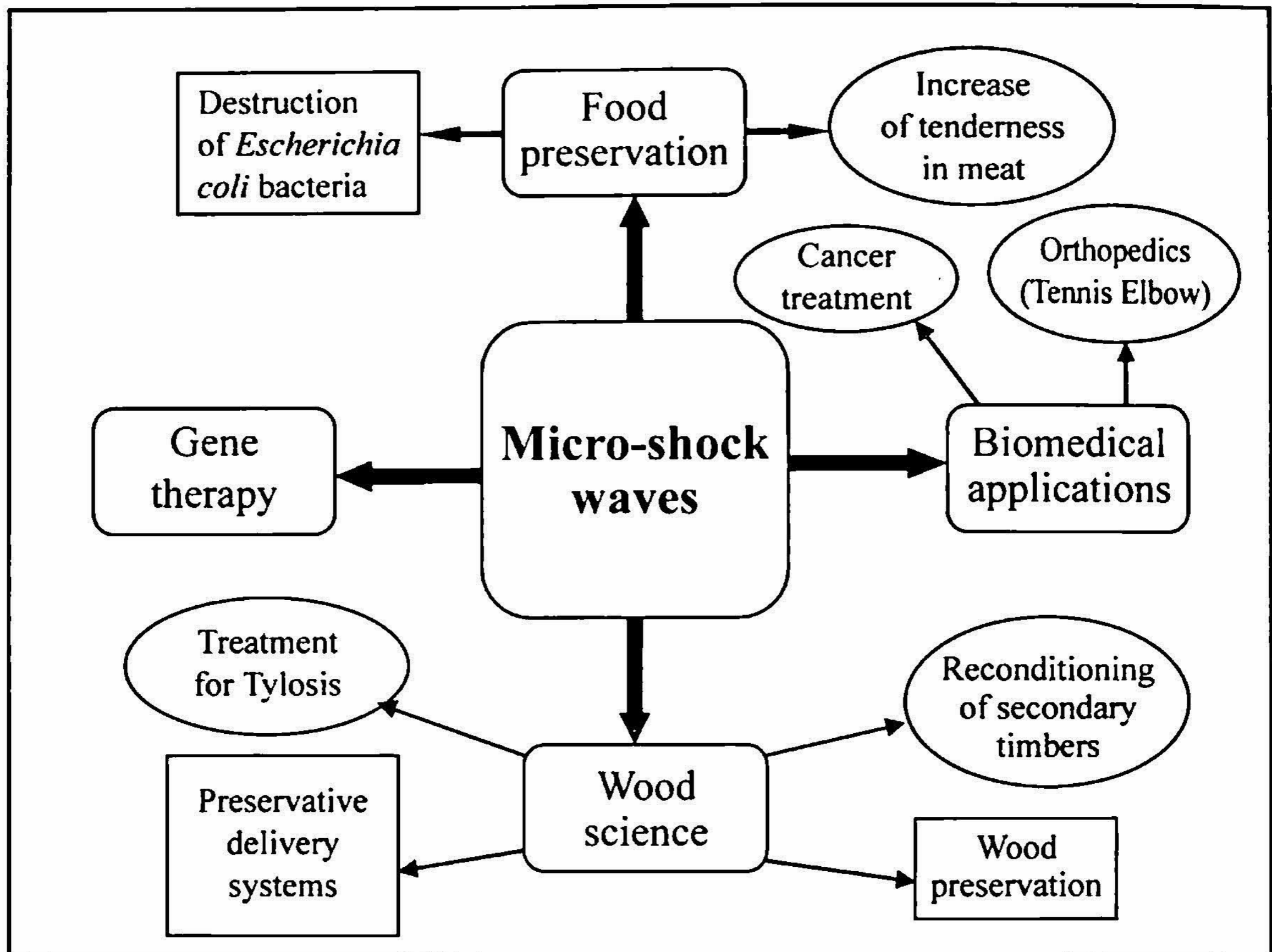


Fig. 1. Schematic representation of possible applications of micro-shock waves in medical and biological sciences.

to the best of our knowledge on micro-shock wave-based applications in agriculture and biological sciences. The nonlinear instantaneous pressure spike produced for very short time can be used for a variety of applications in biological and medical sciences. Figure 1 schematically represents a number of possible applications of shock waves currently being explored at the Department of Aerospace Engineering at IISc, Bangalore. The gambit of applications that have been developed or are being explored include micro-particle delivery system for gene therapy and drug delivery, destruction of *E. coli* bacteria for food preservation, meat preservation and conditioning, shock-wave assisted water-soluble preservative delivery systems, treating vessel blockage (Tylosis) problems in timber for better wood preservation, and shock wave-assisted induction of dry preservatives for protecting agricultural products like pulses from pests. In most of these applications, shock waves are generated in a controlled manner using different types of shock wave generators and diaphragmless shock tubes. The peak pressure of the shock wave ranges from a few MPa to ~ 100 MPa and the typical pulse width can be anywhere from a few μs to $\sim 50 \mu\text{s}$. Whenever the required peak pressure is more than a couple of MPa, the generated spherical or planar shock waves are focused using either parabolic or ellipsoidal reflectors. Different techniques such as pulsed laser beam focusing, explosion of micro-explosives like silver azide or lead azide under water, simultaneous actuation of piezo-electric crystal array and electric discharge in water are used to generate micro-shock waves. In the following sections, different types of micro-shock wave generators are explained first followed by a brief discussion of some

of the recent results from the shock wave-assisted micro-particle delivery experiments carried out at the Shock Wave Research Center, Sendai, Japan.

2. Generation of micro-shock waves

In this section, we present a brief description of four important techniques commonly used for generating micro-shock waves. In addition, the spherical micro-shock waves generated by pulsed-laser focusing and underwater micro-explosions visualized using double-exposure holographic interferometry are explained.

2.1. Pulsed laser beam focusing

Micro-shock waves can be generated in ambient air by focusing the energy from a pulsed laser beam into small area ($\sim 300 \mu\text{m}^2$). Once the deposited energy of the focused laser beam exceeds the threshold value for optical breakdown, ambient air breaks down with subsequent formation of laser plasma. The energy deposition immediately creates a primary spherical micro-shock wave travelling outwards from the focal point. Since the energy in the laser pulse is finite, the primary micro-shock wave velocity decays with elapse of time eventually turning into a Mach wave.

An Nd:YAG laser beam focusing is a very useful and reliable technique for generating micro-shock waves in ambient air with high degree of repeatability. In the present experiments, an Nd:YAG laser beam with 1.38 J pulse and 18 ns pulse duration is focused on a very tiny spot of about $300 \mu\text{m}$ in diameter to generate micro-shock waves. The optical arrangement used for the generation of the micro-shock wave and double-exposure holographic interferometry for visualizing them has been explained by Jiang *et al.* [6]. The Nd:glass laser system with a beam diameter of 12 mm is expanded to 25 mm using a combination of concave and convex lenses. The expanded beam is then focused on to a spot using an achromatic lens of 70 mm focal length. A double-pulse holographic laser (Apollo Laser, Model 22HD) with a pulse width of 25 ns and 2 J of energy per pulse with 694.3 nm wavelength is used for quantitative flow visualization in the experiments. The visualized interferograms with a standoff distance of 4 mm (between a flat surface and the laser focal point) at different times are shown in Fig. 2. Only regular reflection of the shock wave is observed in the initial stages of interaction. However, Mach reflection is observed at $\sim 20 \mu\text{s}$ from where a very clearly defined triple point and Mach stem are observed. The Mach stem grows with time and later the micro-shock wave transforms itself into Mach wave. The $r-t$ diagram of the micro-shockwave propagation in air is shown in Fig. 3. The radius (r) of the primary spherical micro-shock wave is plotted along the Y-axis and the corresponding time (t) on the X-axis. It has been observed that the radius of the shock wave generated scales as a function of time. This method of generation of micro-shock waves is very useful and is highly repeatable since the energy deposited is virtually constant and depends on the quality of laser. Although both energy density and temperature are very high in the vicinity of laser focal point, this method is very useful in applications where the energy dissipated by the shock formation can be converted into useful work.

2.2. Micro-explosives for underwater shock wave generation

The use of micro-explosives for underwater shock wave generation is probably one of the most

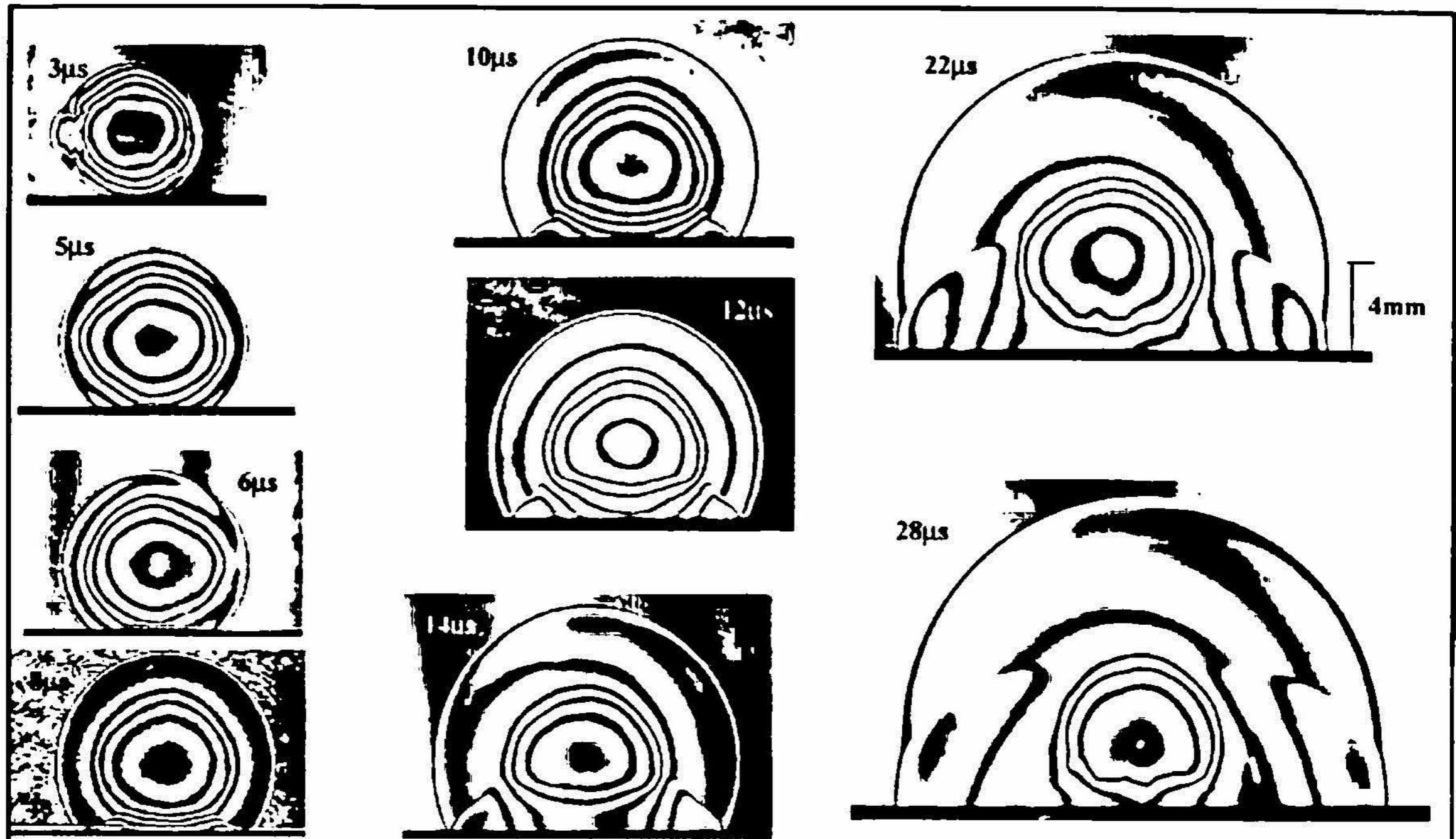


Fig. 2. Evolution of spherical micro-shock waves generated using pulsed laser beam focusing in ambient air, visualized using double exposure holographic interferometry.

popular methods in practice for a long time [7]. Figure 4 shows the typical underwater spherical shock wave generated using a 4 mg lead azide pellet, which was detonated instantaneously by irradiation of a Q-switched ruby laser. The interferogram shown in Fig. 4 was recorded $34 \mu\text{s}$ after detonation. In this case, the first exposure was recorded before the actual event, while the second synchronized with detonation. The dark spot seen at the center of the photograph is the lead azide pellet which occupies $\sim 1 \text{ mm}^3$ volume. The micro-explosive is coated with acetone-acetocellulose solution for waterproofing and is fixed to a very thin cotton thread with adhesive. Careful fixing of the lead azide pellets, the weight of the explosive, the shape and orientation of pellet during energy deposition are some of the important aspects which dictate consistent and successful generation of the shock wave. In lithotripsy applications, usually the micro-explosives are placed near one of the focal points of an ellipsoidal reflector and pressure spike produced at the other focal point of the ellipsoid is used to treat kidney stones. Silver azide pellets can also be used in place of lead azide. Instead of micro-explosives, a holmium:YAG laser beam (typical energy of 300 mJ and 16 ns pulse duration) can be focused at the end of an optical fibre in water to produce the shock waves. In this case, the instantaneous deposition of energy locally creates a vapour bubble, which in turn bursts creating the shock wave. This propagates faster in water compared to air.

2.3. Electro-hydraulic underwater shock-wave generator

The electro-hydraulic shock-wave generator [8] used in shock-wave-assisted food preservation is shown schematically in Fig. 5. An electric discharge is created between a pair of electrodes placed inside water and the instantaneous energy deposited by the electric discharge locally vaporizes the water, which, in turn, creates a vapour bubble. This bubble grows with time before

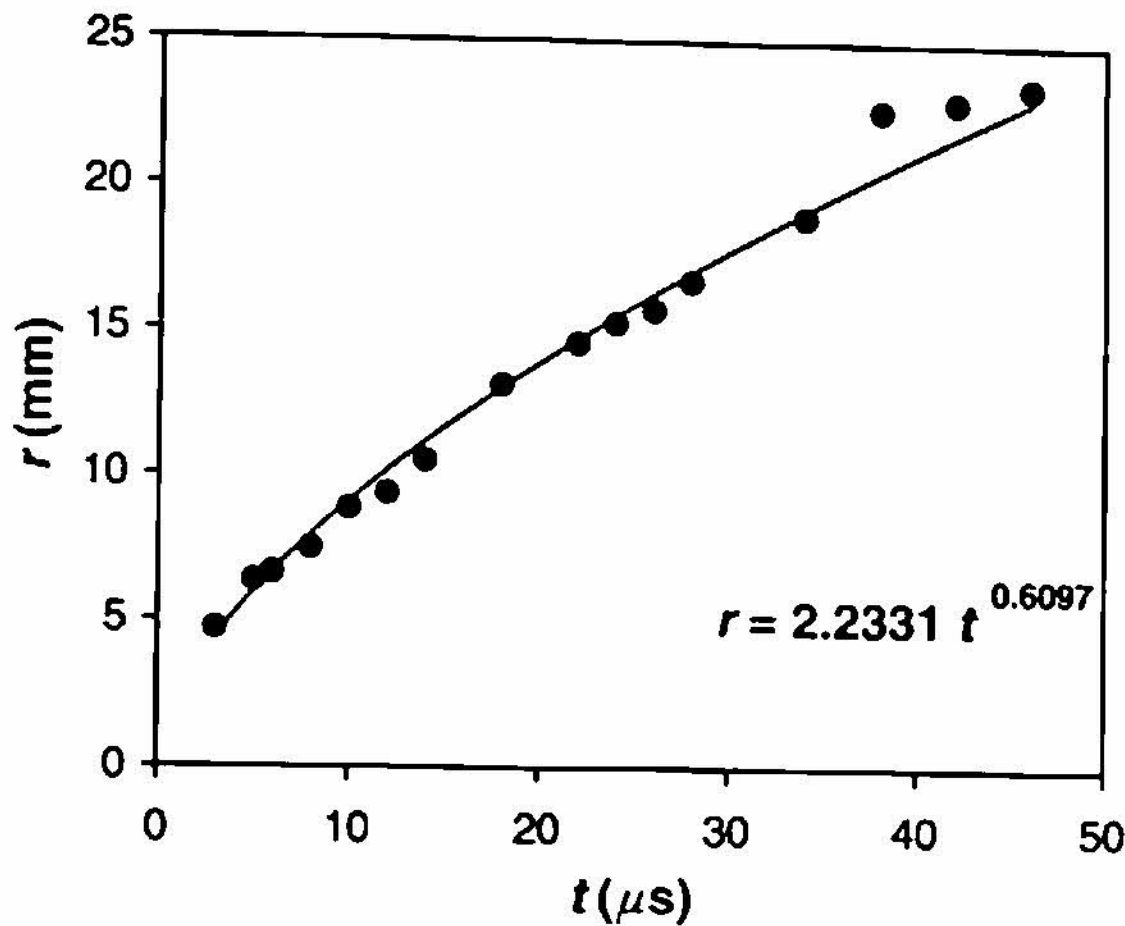


Fig. 3. The $r-t$ diagram for the spherical micro-shock waves generated by focusing an Nd:glass laser beam in ambient air.



Fig. 4. Typical underwater micro-shock wave generated by lead azide explosion visualized using double-exposure holographic interferometry.

rupturing resulting in the creation of shock wave. Parabolic or ellipsoidal reflectors are used to focus the shock wave either along a line or at a point where peak pressures of ~ 40 MPa can be generated with a pulse width of $\sim 5 \mu s$. Typical values of capacitance and voltage used in this electric discharge circuitry are ~ 80 nF and 20 kV, respectively. The spark gap is set at 1 mm and truncated cones are used as electrodes.

2.4. Piezo-ceramic shock-wave generator

Another type of shock-wave generator which employs an array of piezo-ceramic crystal array [9] is shown in Fig. 6. Here, individual piezo-ceramic crystals are placed in a parabolic reflector and are simultaneously subjected to high voltage. The compressive wave fronts produced by the vibration of individual piezo crystals coalesce to form the shock wave along the focal axis of the

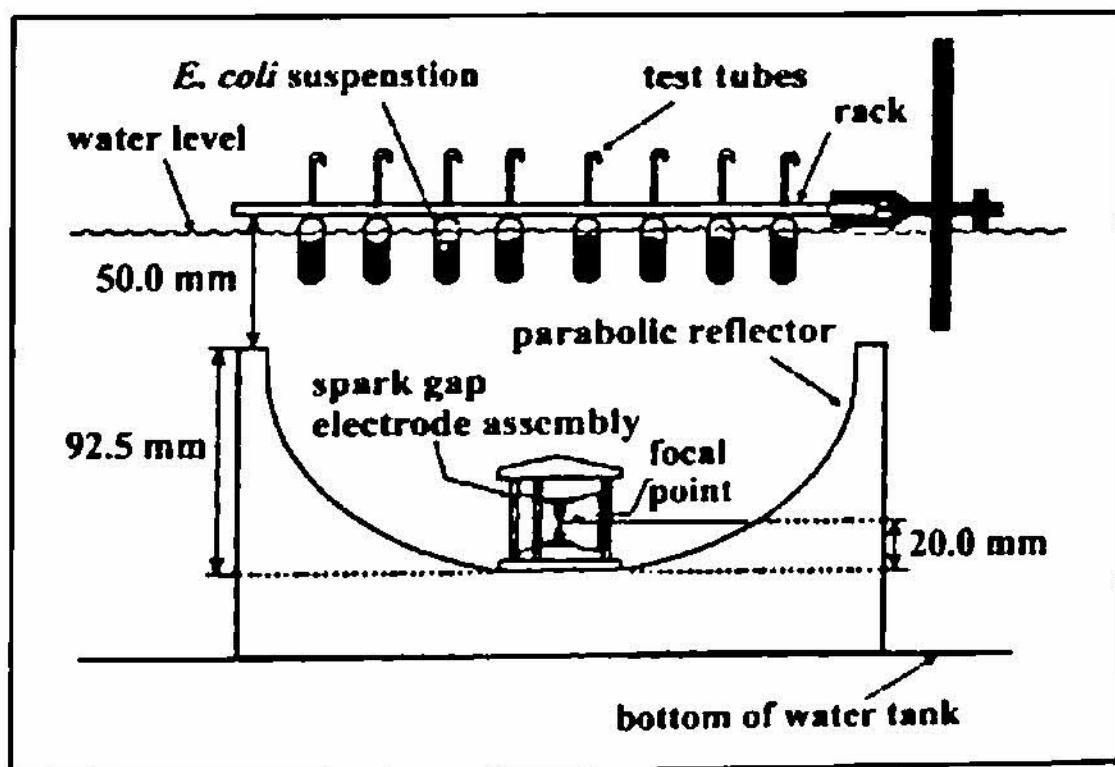


Fig. 5. The electro-hydraulic shock wave generator used for shock wave-assisted food preservation experiments [8].

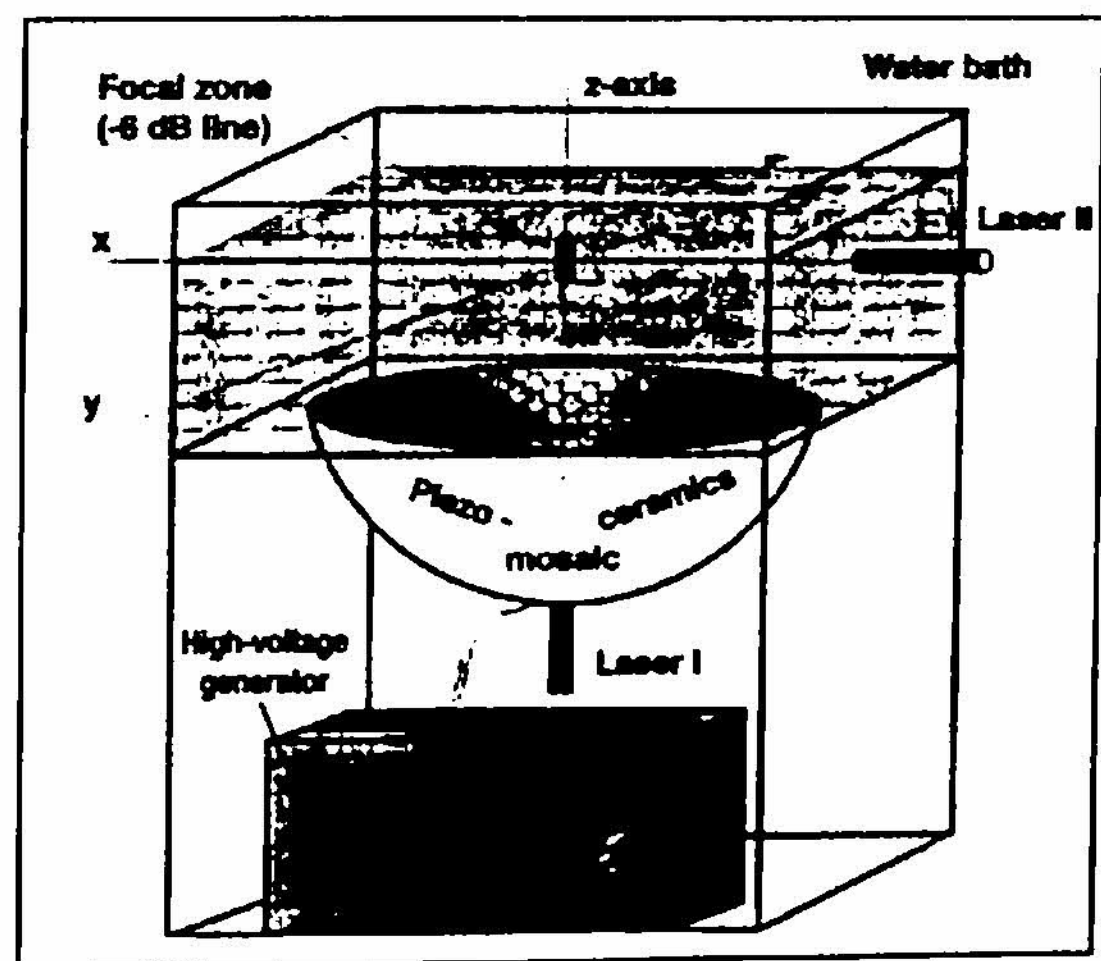


Fig. 6. Schematic representation of a piezo-ceramic crystal array-based micro-shock wave generator [9].

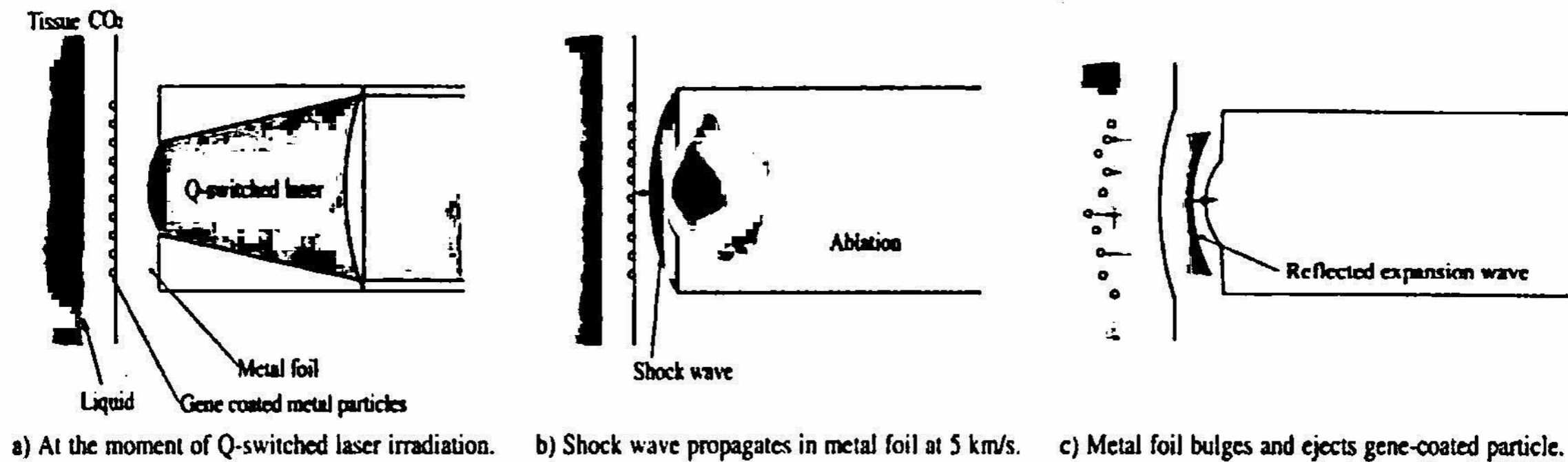


Fig. 7. Schematic representation of various processes taking place in the shock wave-assisted micro-particle delivery system.

reflector. However, this arrangement is not suitable for generating very high instantaneous pressure pulses. But the advantage of this method is that there is no need for additional focusing element and is widely used in lithotripsy. An improved variation of this type is a self-focusing electromagnetic underwater shock-wave generator developed by Mortimer and Skews [10]. This is also very useful for shock-wave generation in liquids of different viscosities. The main advantage of this generator is that there is no need for focusing elements like lens or concentrators for enhancement of overpressure.

Precise calculation of the energy conversion efficiencies in different types of shock-wave generators is rather difficult because of the numerous complex physical processes influencing the creation of shock waves. However, it is between 15% and ~ 20% in the case of explosives and about 25% in the case of laser focusing. In the case of electro-hydraulic and piezo-ceramic-type shock-wave generators the energy conversion efficiency ranges from 10% to 25%.

3. Shock wave-assisted micro-particle delivery system for gene therapy and drug delivery applications

A new laser ablation-assisted micro-particle delivery system has been developed [11] for subcutaneous drug delivery and gene therapy applications. An Nd:YAG laser pulse is focused in ambient air for generating the micro-shock wave. Gold/tungsten particles (~1 μm diameter) deposited on the back face of a metal foil (~ 0.1 mm thick) are ejected at hypersonic velocities when the front face of the foil is subjected to shock wave loading. The physical processes that occur during the shock wave loading are schematically shown in Fig. 7 and the optical arrangement is represented in Fig. 8. The measured average velocity of the ejected gold particles during shock wave loading is around ~2000 m/s. Micro-shock waves under ambient conditions are produced by focusing a Q-switched Nd:YAG laser pulse (~ 1.65 J/pulse; ~ 6.4 ns pulse duration) on a metal foil. A ~ 5 mm thick BK7 glass overlay is also used over the metal foil to enhance the peak pressure during shock wave loading. The introduction of the transparent overlay essentially creates situations similar to confined ablation. The effectiveness of the particle delivery system is investigated using agarose gel targets. The depth of penetration of gold particles measured in the agarose gel at a standoff distance of 6 mm is shown in Fig. 9. Successful particle delivery is also achieved in the skin and liver tissue of a mouse. Figures 10a and b show the successful delivery of micro-particles into skin and liver of mice. The maximum penetration depth measured in

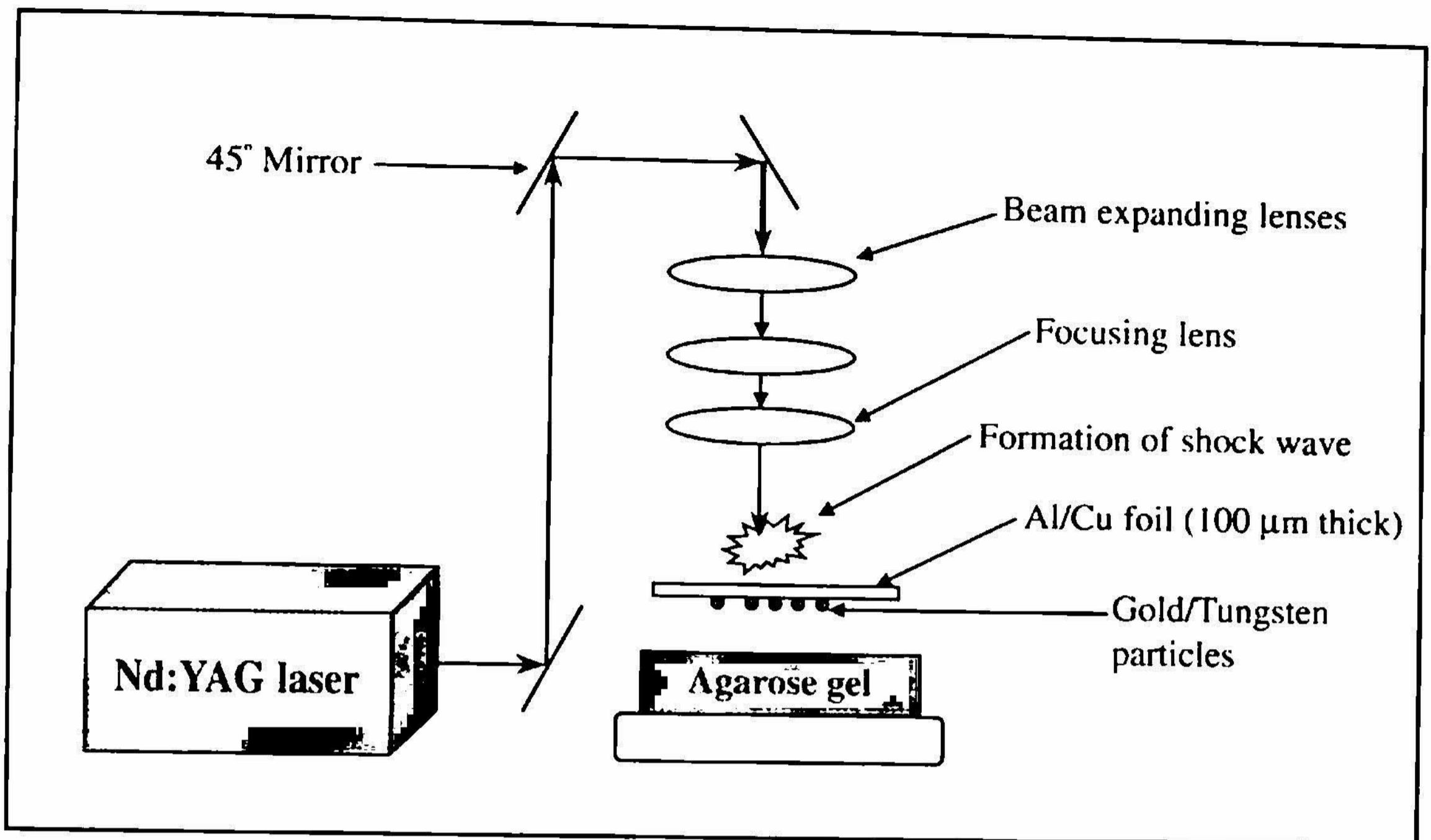


Fig. 8. Depth of penetration of gold micro-particles in agarose gel targets at 6 mm standoff distance.

mouse skin is ~ 0.75 mm, while it is ~ 1.25 mm in the liver. Further experiments are underway to demonstrate the use of the present technique for gene therapy in endoscope-assisted neurosurgery.

4. Micro-shock waves in agriculture

In food industry, heat treatment is usually used to inactivate pathogenic microorganisms, but it may affect the nutritional characteristics of food and hence there has been considerable interest in nonthermal processes. *Escherichia coli* in suspension is exposed to repeated application of micro-shock waves. Test tubes filled with the bacterial suspension are placed along the focal axis of the parabolic reflector. Recent results [8] indicate an exponential decrease in the *E. coli* population with increase in the number of shock exposures. Efforts are also underway at SWRC, Japan, to look at conditioning of beef strip loins to increase the storage lifetime and also to maintain acceptable tenderness.

Experiments are currently underway to explore the possibility of micro-shock wave-assisted clearing of vessel blockages in timber to ensure the infiltration of water-soluble preservatives which will enhance the life of wood. This type of blockage of vessels and conducts in timber is called Tylosis. In addition, shock wave-assisted preservative delivery systems are under development at the Department of Aerospace Engineering, IISc, for improved infiltration of preservatives into woods like catamarans which are used in the fabrication of fisherman boats. Shock wave-assisted induction of dry preservatives to protect agricultural products like pulses from pests is also being explored. A diaphragmless shock tube with parabolic end wall shock-wave-focusing unit and an electro-hydraulic underwater shock-wave generator are used for these experiments.

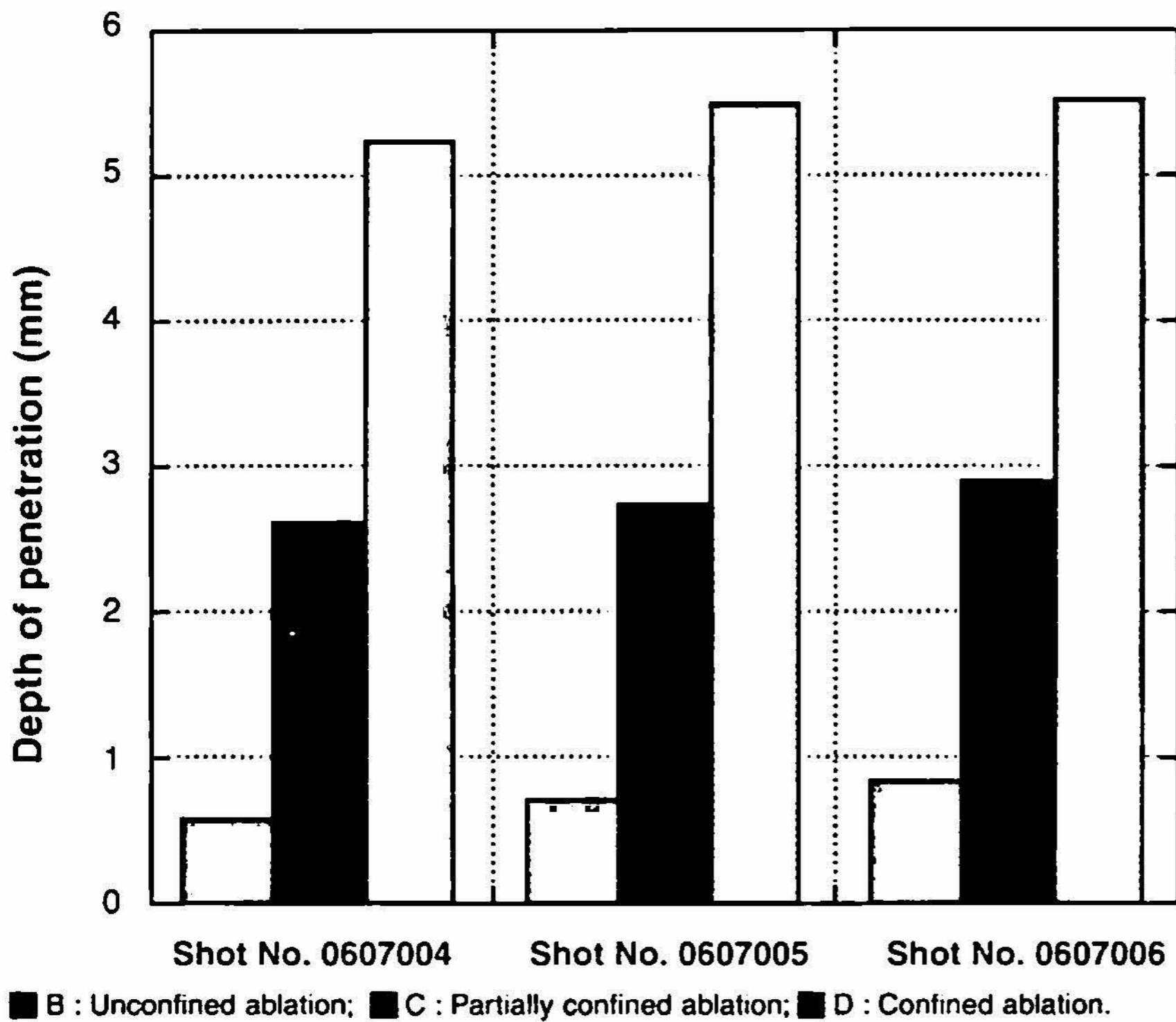


Fig. 9. Optical arrangement used in the micro-particle delivery system for generating shock waves.

5. Conclusions

Spherical micro-shock waves with requisite pressure intensity can be generated both in ambient air and in water using different techniques like pulsed laser beam focusing, electric discharge, simultaneous perturbation of piezo-crystal array and also diaphragmless shock tubes. A new micro-particle delivery system has been developed using laser-driven shock waves for gene therapy applications. Gold and tungsten micro-particles are propelled to penetrate both the skin and the liver of mice using micro-shock waves. Penetration depth of ~ 0.75 mm in skin and ~ 1.25 mm in the liver tissue of mice has been measured in the experiments at a standoff distance of 6 mm. Further experiments are underway to demonstrate the use of the present technique for gene therapy in endoscope-assisted neurosurgery. Wood and food preservation, cancer and bone



Fig. 10a. Micro-particle delivery into the skin of mice.

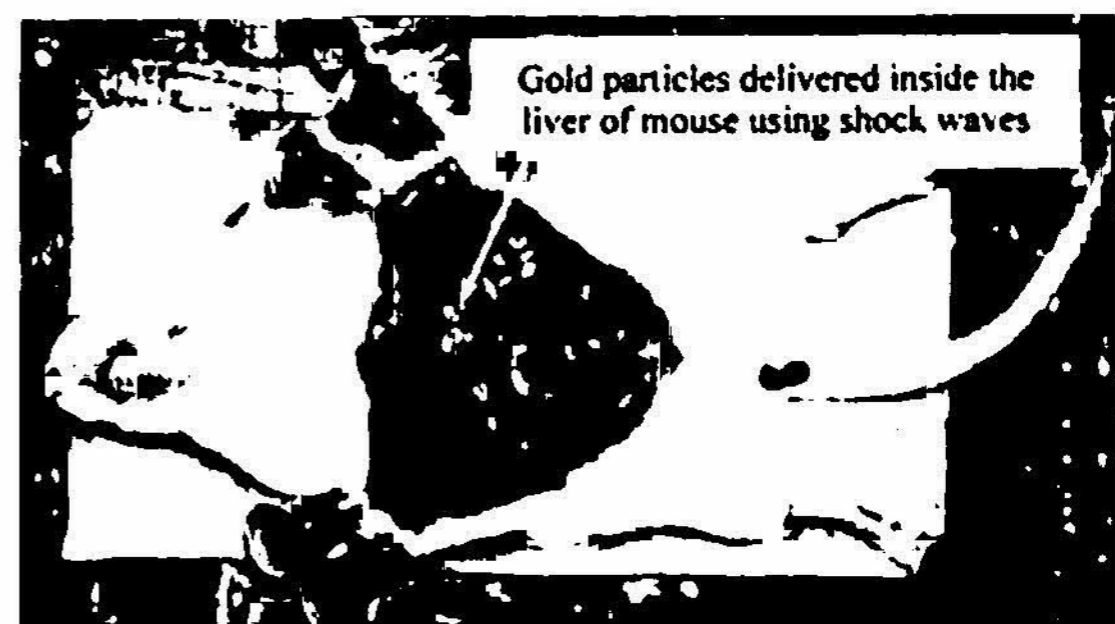


Fig. 10b. Gold particles delivered to the liver of mice.

fracture treatment are some of the other exciting applications of micro-shock waves currently being pursued at the Department of Aerospace Engineering, Indian Institute of Science.

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