INTRODUCTION

Nanometre-sized gold (Au) structures find widespread use for application in optics in the visible range thanks to their remarkable ability to enhance local electromagnetic fields through plasmon resonance effects (Fazio, Trusso, & Ponterio, 2013; Indrasekara et al., 2013; Tian et al., 2015). Conventional fabrication of gold colloids is often accomplished by multistep chemical synthesis that results in rather long production times (hours to days) and requires multiple purification steps. Although 5–100 nm NPs are produced by a fairly direct chemical reduction method, their surface is likely to be covered by reaction by-products such as anions and reducing agents that can affect the subsequent stabilization and functionalization steps (Zeng et al., 2011).

By photo-assisted synthesis methods, a comparatively fast production of metal NPs is possible. The methods can be split into photophysical and photochemical. In photochemical methods (Sakamoto, Fujistuka, & Majiam, 2009), light, usually in the UV region, induces photoreduction of a metal salt. Gold and silver NPs are generated by photoreduction of AuCl$_4^-$ and AgClO$_4$ respectively (Hada, Yonezawa, Yoshida, & Kurakake, 1976; Kurihara, Kizling, Stenius, & Fendler, 1983). For both metals, NPs are generated in a medium containing chemical residues of the reduction reaction.

Photophysical methods are based on the vaporization of a solid target by high-energy laser pulses. The process is performed in an ambient fluid, either gas or liquid, whose role is to confine the vaporized species and to induce their aggregation in clusters and NPs.
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The method has the advantage to produce NPs free from any chemical precursor. When the process is performed in an ambient gas at high pressure (Fazio, Neri, Ossi, Santo, & Trusso, 2009), NPs possibly coalesced are grown as arrays onto appropriate rigid flat supports; when liquids are used as the confining medium, a colloidal solution is obtained. The conceptually simple pulsed laser ablation in liquid (PLAL) technique, using nano/picosecond laser pulses, allows to produce surfactant-free NPs in a single step within a time scale of a few minutes (Acacia et al., 2010; Mafuné, Kohno, Takeda, & Kondow, 2000). The laser pulse deposits a large energy density at a focused spot on the target surface leading to ablation from the target of matter that immediately converts to a plasma that consists of both ablated species and a small amount of water molecules. Such a plasma plume expands through the liquid that spatially confines it. The high temperatures (of the order of thousands of Kelvin) and pressures (in the range of GPa) attained inside the plume during the regime of collisional expansion allow for NP formation. The low production yield of NPs, the purity and redispersibility from agglomerates is present limitations of PLAL (Barcikowski, Hahn, Kabashin, & Chichkov, 2007). Over the last decade, major efforts were directed to produce stable solutions of small NPs with narrow size distributions and controlled surface chemistry for biomedical applications (Dreaden, Alkilany, Huang, Murphy, & El-Sayed, 2012). Pulsed laser ablation in liquid appears among the most flexible and promising methods of NP synthesis because of the independent control of relevant process parameters such as irradiation time, energy density, laser wavelength, and because the ultra-high deposited energy density permits to ablate almost all kinds of materials. For ns-PLAL, we analysed the irradiation geometry, finding optimal focusing conditions to maximize the ablation rate (Fazio & Neri, 2013). For noble metals and ceramics, more recent systematic investigations compared the morphology, size, size distribution, production yield, absorption spectra of NPs produced by ns-, ps- and fs-PLAL at different laser wavelengths (Hamad, Li, & Liu, 2015). Compared to ns lasers, high repetition rate ps lasers are advantageous whenever the total thermal load produced by laser irradiation can be redistributed over a larger area (Östendorf, Kamlage, Klug, Korte, & Chichkov, 2005). When laser ablation is carried out in a polar liquid (typically, water), surface-charged NPs are produced. These are solvated by a shell of dipolar molecules (e.g., water) and do not agglomerate because of the Coulomb repulsion generated by their surface charge (Fazio et al., 2016).

The SPR depends on the structural and morphological properties of the noble metal NPs, thus it is necessary to determine the appropriate ablation parameters to obtain NPs with tailored size distributions and concentration (Fazio et al., 2009; Ossi & Bailini, 2008). In this work, moving from our previous results (Fazio & Neri, 2013), we report on the use of ns (λ = 532 nm; τ = 5 ns) and ps (λ = 532 nm; τ = 6 ps) PLAL at optimized fluence and irradiation times to synthesize Au NPs in water. By ns- and ps-PLAL, we obtained stable and pure NPs in colloidal state, with variable size and optical properties. After ultrasonically spraying a fraction of such Au colloids on inert glass or (100) Si supports, we obtained Au NP arrays with specific surface nanostructure. Such films were tested as SERS substrates against the antiepileptic drug perampanel which is the active pharmaceutical ingredient (API) of Fycompa® (Patsalos, 2015). Fycompa is indicated for the adjunctive treatment both of partial-onset seizures with or without secondarily generalized seizures and of primary generalized tonic-clonic seizures in adult and young patients from 12 years of age. The European Commission authorized Fycompa commercialization throughout EU Countries on 2 July 2015. Perampanel, being the progenitor of a new class of antiepileptic drugs, offers to epileptologists new therapeutic opportunities in the treatment of farmaco-resistant epilepsy (Krauss et al., 2013). As an example, 90 adult patients are presently treated with Fycompa at I.R.C.C.S. Fondazione Istituto Neurologico “C. Besta,” Milano, Italy (data provided by UO Neurofisiopatologia, I.R.C.C.S. Fondazione Istituto Neurologico “C. Besta,” Milano, Italy). Perampanel is a first-in-class selective, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons (Rogawski, 2011). Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over-excitation (Rogawski & Hanada, 2013). Activation of AMPA receptors by glutamate is thought to be responsible for most fast-excitatory synaptic transmission in the brain (Patsalos, 2015). In vivo, perampanel significantly prolongs seizure latency in an AMPA-induced seizure model. Presently, the detailed mechanism by which perampanel exerts its antiepileptic effects in humans is still to be fully elucidated (Patsalos, 2015).

2 | METHODS

Au colloids were prepared by pulsed laser ablation using 532 nm radiation provided by the second harmonic of a Nd:YAG source with a repetition rate of 10 Hz and pulse width of 5 ns as well as by an ultra-fast Nd:YVO₄ source with repetition rate of 10² kHz and pulse duration of 6 ps. The pulsed, high-power laser beam impacts onto a rod-shaped Au target (99.99% purity) immersed in demineralized water (see Figure 1). The optimized ablation times ensuring high NP productivity were 20 min (ns-PLAL) and 5 min (ps-PLAL); for both conditions, the laser fluence was F = 1.5 J/cm² (Fazio & Neri, 2013).

The Au content in colloids was determined by graphite furnace atomic absorption spectroscopy (GF-AAS) using a Varian 220/Zeeman atomic absorption spectrometer, equipped with a single-element hollow cathode lamp and a Varian PSD autosampler. The quantification of Au was carried out using the external standard method. The analytical method was validated according to the ICH guidelines (ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: Text and Methodology Q2(R1), 2005). The linearity was >0.999, the precision (expressed as relative standard deviation) 0.560, and the detection limit 8.0 ng/ml. The reported data are the average out of three determinations.

We recorded UV–Vis spectra of the colloids using quartz cells and a Perkin Elmer Lambda 750 UV-Vis spectrometer working in
the 300–900 nm range. Colloids were deposited on a nickel grid to carry out scanning transmission electron microscopy (STEM) using a Merlin model ZEISS-Gemini 2 instrument operating at primary voltage of 30 kV at the working distance of 4 mm.

FT-Raman measurements were carried out with a Nicolet NXR9650 instrument equipped with a solid-state Nd-YVO₄ laser providing the excitation wavelength of 1064 nm with the laser power at the sample of about 5 mW. The beam was focused by an Olympus BX41 microscope in a spot of about 1 μm diameter. For SERS measurements, the core of a 6 mg Fycompa tablet was ground to obtain about 5 mg of API (perampanel) mixed together with slightly less than 200 mg of excipients (predominant excipient, lactose monohydrate (http://www.ema.europa.eu/docs/it_IT/document_library/EPAR_Product_Information/human/002434/WC500130815.pdf); see Figure 6 for details on the other excipients). The obtained powder was cast in 10 ml of methanol, to which 0.2 ml of HCl 37% was added to foster protonation of perampanel and help solubilizing it. The insoluble solid deposit was removed from the suspension by centrifugation. Based on the adopted solvent volumes, and supposing that the whole 5 mg of perampanel was dissolved, we estimate a (maximum) final 1.4 × 10⁻³ M concentration of perampanel in methanol. The Au SERS sensor supported on Si (see spraying procedure) was fully dip into a few ml of the 1.4 × 10⁻³ M perampanel solution for 1 minute. Then, the sensor was extracted from the solution and let dry in ambient air for 10 minutes before carrying out micro-Raman measurements.

X-ray diffraction (XRD) was performed by a Bruker instrument using Cu Kα radiation (0.15406 nm). We obtained Au NPs with narrow size distribution using both ns and ps laser pulses. The latter allow for a higher NP productivity, as indicated by the SPR profile (Figure 2e, red line) which is more intense and slightly narrower than that collected from NPs produced by ns pulses.

Compared with ns-NPs, a narrowing of the SPR peak for the ps-NPs as well as an increase in the background is observed, while the SPR position is practically unaffected (Figure 2e). The narrowing depends on the presence of small, isolated NPs, while the background increase is due to a larger NP yield. Both features agree with STEM images (Figure 2a,b) and the size histograms in Figure 2c,d (see Table 1 for details on the fitting procedure of the size distribution).

We remark that we kept fixed the laser fluence and wavelength so that we could better compare NP sizes and production yields between ns and ps synthesis conditions with respect to previous studies (Hamad et al., 2015), assuming that NP size is mostly affected by the laser wavelength, whereas production yield is mostly affected by the laser fluence (Hamad et al., 2015).

Our results can be interpreted by considering that laser ablation in a stationary liquid involves the simultaneous production of NPs by ablation of the target material and the fragmentation/assembling of dispersed NPs by continuous irradiation of the already synthesized particles. In this respect, pulse duration is a relevant parameter for NP generation (Schwenke, Wagener, Nolte, & Barcikowski, 2011). By changing the pulse duration from ns to ps, the relevance of melting and thermal evaporation among ablation mechanisms significantly decreases. The shorter the pulse duration, the more efficient the ablation process that involves a nearly instantaneous evaporation with a minimized heat affected zone (Kelly & Miotello, 1996; Momma et al., 1996), thus resulting in a shorter time to produce the colloids. Furthermore, primary plasma shielding that is detrimental to ablation efficiency is much reduced with ps laser pulses, as compared to ns pulses (Pathak & Povitisky, 2008).

X-ray diffraction data in Figure 3 show that the NPs prepared by ps-PLAL are crystalline, as confirmed by the (111), (200), (220) and (311) Bragg reflections of fcc Au (see card JCPDS 04-0784). (111) texture is present. The XRD features are broader than those in Au nanocrystals (Sneha, Sathishkumar, Kim, & Yun, 2010). Most likely, this is due to a combination of the small size of such particles (see Figure 2d) with the associated residual stresses.

3.2 | Time evolution of colloids

Dynamic light scattering (DLS) allows to estimate the changes in size and size distribution of the particles. DLS data systematically correlate with the changes in the SPR lineshapes observed by UV-Vis spectroscopy. Au colloids produced by both ns- and ps-PLAL were stored for 3 months at atmospheric conditions; thereafter,
their optical properties were tested by UV–Vis spectroscopy and DLS, and compared to those of freshly prepared colloids. We show in Figure 4 the optical characterization of colloids prepared by ns-PLAL; the results for colloids produced by ps-PLAL are very similar, and are not discussed. After 3 months of storage in dark, at ordinary laboratory conditions, we observed no colour change of the colloids and no evidence of colloid instability. The intensity decrease with time of the SPR (Figure 4a) indicates gravity-induced sedimentation. Accordingly, changes in DLS (Figure 4b) occur at high delay times that correspond to larger NPs that are more sensitive to gravity. The estimated average size of NPs deduced from DLS reduces from 85 nm (fresh NPs) to about 45 nm (NPs stored for 3 months). Particle
sedimentation induces a decrease in the optical density of the colloid and a corresponding change in its refractive index. The evident discrepancy between NP size estimated by DLS and STEM data is due to detection limits of DLS in the presence of poly-disperse colloids. Sample polydispersity can affect DLS data because the fraction of non-precipitated large NPs can shield the smaller ones, thus altering the true NP size population (Tomaszewska et al., 2013). Notice that the particle size determined by STEM after three months does not change with respect to the fresh colloids (compare inset of Figure 4b with Figure 2a).

### 3.3 | SERS substrates made of colloids obtained from ps-PLAL

A fraction of the Au colloids produced by ps-PLAL was ultrasonically sprayed on glass or on (100) Si supports to obtain thin films suitable for SERS measurements. Before performing the SERS tests, we characterized with UV-Vis spectroscopy the films supported on glass, and we examined by SEM the morphologies of the films supported on Si (Figure 5). Comparing the upper absorbance spectrum in Figure 2e (colloids prepared by ps-PLAL) with the homologous spectrum in the inset of Figure 5, we see that the SPR red shifted from 517 nm (Figure 2e) to 522 nm (Figure 5). The FWHM changed from 47 nm (Figure 2e) to 79 nm (Figure 5). Such shift and broadening of the SPR is ascribed to the clustering of the colloids when they are transferred on the glass support. Indeed, by SEM, we observe surface morphologies on the films sprayed on Si (Figure 5) which differ from the colloid morphologies observed by STEM (Figure 2b): The isolated, small spherical NPs detected by STEM evolve into larger agglomerates consisting of mostly spherical particles observed by SEM (Figure 5). Such an agglomeration process induced by spraying is actually a desirable feature when producing substrates for SERS considering that it fosters the formation of hot-spots (Solis, Taboada, Obelleiro, Liz-Marzán, & García de Abajo, 2017).

### 3.4 | SERS measurements

Before addressing the SERS experiments, we measured as a reference the FT-Raman spectrum of a sample consisting of a 6 mg pharmaceutical tablet of Fycompa, denuded of its protective external coating. In such a sample (namely, the core of the tablet), the API perampanel is mixed with the listed excipients (Figure 6). As shown in Figure 6, among all the declared excipients of Fycompa, the FT-Raman spectrum of lactose monohydrate closely matches the measured spectrum of the sample. The well-resolved Raman features (a–d), which by comparison are not due to lactose monohydrate, are assigned to the API, as the most intense Raman peaks of the other excipients cannot be individually observed and just contribute to the background signal. Thus, based on the qualitative assessment of the FT-Raman data, we conclude that the most abundant excipient in the sample is lactose monohydrate that
The FT-Raman spectrum of the Fycompa sample shows four distinct features (a–d) that can be attributed with confidence to the API, as they fall in wavenumber ranges where the excipients do not show any strong Raman line. The position of the observed Raman peaks is also consistent with the chemical structure of perampanel (Figure 6a). Line (a) at 2,216 cm$^{-1}$ is assigned to the stretching of the CN bond. The manifold of Raman lines (b) at (1,622, 1,597, 1,585, 1,569, 1,550 cm$^{-1}$) is assigned to aromatic ring stretching modes, and the line (c) at 989 cm$^{-1}$ can be assigned to the breathing of one of the rings of perampanel. Finally, the position of line (d) at 674 cm$^{-1}$ is consistent with an aromatic ring deformation mode. We notice that, to the best of our knowledge, the FT-Raman features of perampanel in Figure 6b are unprecedented.

The SERS spectrum of the methanol extract of the Fycompa sample is shown in Figure 7. Notably, most of the well-defined SERS features observed in Figure 7 can be traced back to the FT-Raman signals of the above-discussed API. We remark that the difference between the position of the CN stretching line (and other API features, as well) in the SERS spectrum, as compared to the FT-Raman, highlights that such signals originate from drug molecules adsorbed on the Au film, that is, not from perampanel recrystallized from the solution. This indicates the successful SERS measurement of perampanel in the solution extracted from the Fycompa sample even in the presence of excipients. This is a promising result in view of clinical applications, where one expects the interference from organic molecules co-extracted with the API from the patient plasma samples.

4 | CONCLUSIONS

In conclusion, by both ns-PLAL and ps-PLAL, it was possible to synthesize Au NPs with no stabilizing agent. The particles have a narrow size distribution and a remarkable long-term stability. Compared to ns-PLAL, ps-PLAL yields smaller NPs in shorter synthesis time, with reduced tendency to agglomerate. Au NPs were tested, allowing to collect the first FT-Raman and SERS spectra of perampanel, an antiepileptic drug of new generation with clinical relevance.

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