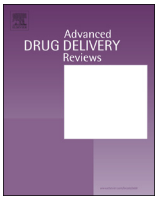
Advanced Drug Delivery Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr



Tip-enhanced Raman scattering—Targeting structure-specific surface characterization for biomedical samples☆

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ARTICLE INFO

Available online xxxx

Keywords:
Optical microscopy
Tip-enhanced Raman
High resolution
Nucleic acids
Lipids
Proteins
TERS applications

ABSTRACT

Tip-enhanced Raman scattering (TERS) has become a powerful tool for nanoscale structural analysis for several branches of organic, inorganic, and biological chemistry. This highly sensitive technique enables molecular characterization with a lateral resolution far beyond Abbe's diffraction limit and correlates structural and topographic information on a nanometer scale. In this review, the current experimental concepts with respect to their strengths and obstacles are introduced and discussed. A further focus was set to biochemistry comprising applications like nucleic acids, proteins, and microorganisms, thus demonstrating the potential use towards the pharmaceutically relevant challenges where nanometer resolution is required.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on “Pharmaceutical applications of Raman spectroscopy—from diagnosis to therapeutics”.

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http://dx.doi.org/10.1016/j.addr.2015.06.007
0169-409X/

Please cite this article as: G. Sharma, et al., Tip-enhanced Raman scattering—Targeting structure-specific surface characterization for biomedical samples, Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.06.007

1. Introduction

Conventional optical microscopy is one of the most commonly used tools for scientist and researchers in natural sciences. For bio-related applications, the challenges are manifold: lateral resolution, contrast, and reproducibility of the measurements are just some of the parameters that have kept on evolving constantly. Of course, the crucial advantage of the technique is the fact that it works non-destructive and label-free. The spatial resolution of optical microscopy is limited by diffraction to half the wavelength of the incident light, giving a range of 200–400 nm as the best working resolution of microscopes (also called Abbe's limit). One of the main targets of this particular review is to address possibilities beyond this diffraction limit, while maintaining at the same time the advantage of being intrinsically molecule specific.

A technique that analyses on the molecular level can provide a wealth of information for chemists, biologists, physicists, and material scientists alike. The advent of near-field optical technologies like scanning near-field optical microscopy (SNOM) enables to surpass the Abbe's limit and probes various material properties at the nanometer scale. A typical SNOM probe is a metal-coated fiber or AFM tip with an aperture size of approx. 30–100 nm limiting the lateral resolution [1]. SNOM has been used for various applications such as fluorescence imaging of single particle, fluorescence lifetime dynamics measurements, and Raman imaging [2,3]. With the invention of scanning tunneling microscopy (STM), imaging of samples down to the atomic level became accessible that allowed the precise positioning of such apertures on a sample surface. Aperture-less or scattering probe systems like metalized tips in atomic force microscope (AFM) or STM provide an even much lower resolution because the dimensions of the used tips can be made smaller (10 nm and below).

A microscopy type that utilizes intrinsic information about a molecular system without the need of labels is Raman spectroscopy. In particular, when only minute amounts of sample are being probed—as in the case of any high spatial resolution microscopy—the usually weak signal must be enhanced by special techniques. Raman signal enhancement of a sample adsorbed on specially structured metal surfaces as defined in surface-enhanced Raman scattering (SERS) is a well-known phenomenon that expanded the capacities of Raman spectroscopy and rendered it extremely sensitive. The very first Raman signal enhancement was realized for pyridine adsorbed on silver (Ag) electrodes in the 1970s [4]. From the experiment, an estimated 10^5-fold increase of the Raman signal (with respect to the standard Raman signal) was reported. In general, SERS is based on an electromagnetic enhancement of Raman signals due to surface plasmons on rough metals. Surface plasmons are localized collective electron oscillations at the metal-dielectric surface excited on irradiation. Due to the surface roughness of the metal layer in SERS substrates, these oscillations can be optically excited e.g. by a laser source. This leads to the generation of strong local electromagnetic fields at spatially narrow regions (so-called hotspots). Noble metals like gold, silver, and copper are suitable metals for SERS analyses in the visible range, and chemical information is obtained of all molecules on the substrate (electrode, colloid, island film) in the laser spot. However, one of the major drawbacks of SERS is the disability to spatially resolve chemical information at the nanometer scale. This changes when a single metal nanoparticle attached to a probe is used for signal enhancement. This principle is known as tip-enhanced Raman scattering (TERS) and combines the abovementioned concept of high-resolution SNOM and SERS to usher new levels of enhanced and highly localized Raman signals.

In this review, important aspects in the development of TERS from the gedanken experiment to current applications are introduced and discussed. Initially, the concept is outlined followed by early experiments and system key parameters such as setup geometry and enhancement factor. In successive sections, high spatial resolution, polarization control, and high vacuum TERS are explained in detail. Finally, the application section discusses TERS experiments on nucleic acids, proteins, lipids, viruses, bacteria, and cells to elucidate future targets in pharmaceutical sciences.

2. TERS concepts

2.1. Wessel's idea

Inspired by the invention of STM [5] in 1985, Wessel [6] proposed an idea that sought to utilize scanning probe's mechanical capability at angstrom resolution. But instead of generating topographic information of the sample, the idea was to probe surface-enhanced non-linear optical properties. He proposed to move a metal particle near the surface. The optical field confinement of surface plasmons in sub-micrometer metal particles should be able to surpass the diffraction limit and the particle will serve as an antenna for the incoming electromagnetic field. This approach was projected to be useful for Raman scattering and two photons or second harmonic generation with a spatial resolution of 1 nm. In other words, it can be seen as SERS experiment turned upside down. The required metal particle can be controlled and will image the topography and enhance the Raman signal simultaneously. However, it was a long time until his idea was realized.

2.2. Early experiments

The first experiment that demonstrated the ability of a metal tip to enhance Raman signals from a sample was presented by Stöckle et al. [7]. With a silver-covered atomic force microscope (AFM) cantilever tip-enhanced Raman spectra of C_{60} and brilliant cresyl blue (BCB) layer were recorded. An excerpt from this measurement is shown in Fig. 1. In the experiment, the incident laser was focused on the BCB dye by the microscope objective and the silver-coated tip was either positioned some micrometers above the sample (Fig. 1a) or directly on the sample (Fig. 1b). It is obvious that no spectra could be recorded when the tip was retracted from the sample. Apparently, the sample volume was too small for conventional Raman spectroscopy and spectra were only obtained from the few molecules underneath the tip. Lowering the tip enabled effective tip–sample interactions resulting in 30-fold enhanced Raman bands. Noteworthy, those signals exclusively originated from molecules in close vicinity to the illuminated tip apex. This result experimentally verified Wessel's idea that surface plasmons generated by laser illumination of a rough metal nanoparticle renders Raman spectroscopy a highly sensitive technique. From the BCB experiment, the

Please cite this article as: G. Sharma, et al., Tip-enhanced Raman scattering—Targeting structure-specific surface characterization for biomedical samples, Adv. Drug Deliv. Rev. (2015), http://dx.doi.org/10.1016/j.addr.2015.06.007