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A label-free detector for liquid chromatography systems using mm-wave technology: First proof of concept

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ABSTRACT

The development of millimeter-wave (mm-wave) technology has enabled the study of bio-molecular interactions by means of electromagnetic waves with frequencies between 30 and 300 GHz. In this study, an attempt has been made to exploit the possibility of mm-wave technology as alternative detection technique for liquid chromatographic (LC) systems. The goal is to design and fabricate a label-free mm-wave detector that is compatible with LC systems. As proof-of-concept experiments, the UV absorbing compounds praziquantel and trans-stilbene-oxide as well as a non-UV absorbing compound sorbitol are injected in an open capillary as well as a capillary with stationary phase and measured by both mm-wave and UV detectors. The in-house developed mm-wave detector is capable of detecting all compounds without the need for labelling. Although the detection limit of such detector still needs to be verified and occasionally improved in the future, it already shows great potential as an additional detection technique for LC systems.

1. Introduction

Throughout the years, various detection techniques have been well established for liquid chromatographic separations. Examples are UV detection, diode array detection (DAD), mass spectrometry (MS), fluorescence detection, evaporative light scattering detection (ELSD) refractive index detection, and electrochemical detection.

UV [1] and DAD [2] are the techniques that are most adopted when it comes to pharmaceutical analysis. One major limit of these techniques is that the compounds must possess chromophoric groups, otherwise labelling is needed to allow detection. Moreover, the sensitivity of such technique can be compromised with compounds possessing low UV absorption.

MS [3] is currently the most sensitive detection technique. However, it requires the mobile phase to be volatile, and is also a destructive detector since the molecules are fragmented during detection. Therefore, it is not always affordable. ELSD [4] suffers from high detection limits. Fluorescence detection [5] is also an alternative technique but often requires fluorescent labelling when the molecules under investigation lack the structural features to emit fluorescence.

It is obvious that each technique has its advantages and drawbacks on different aspects of detection. In this work, for the first time, a new type of detector using millimeter-wave technology has been designed, fabricated and tested in liquid chromatography. The main driver for such novel technology is to enable detection of both UV and non-UV absorbing compounds with the maximum sensitivity.

Millimeter-waves are non-ionizing electromagnetic (EM) waves having a frequency between 30 and 300 GHz. As a matter of fact, many detection techniques (UV, DAD, ELSD and mm-wave) utilise EM waves as signal for detection. Fig. 1 shows the link between mm-waves and other types of EM waves.

The UV and ELSD sensors utilise EM waves with wavelengths of the order of nm. To generate these signals covering the demanded frequency range, photonic technologies such as deuterium lamps and UV Light emitting diodes (LED) [6] are necessary. Due to the bulky nature of photonic devices, there is very little room in terms of cost reduction and miniaturization. On the other hand, as the development of integrated circuits progresses year by year, producing mm-waves with electric circuits integrated on a chip [7,8] has been made possible. This in return provides the possibility to produce compact integrated mm-wave sensor solutions

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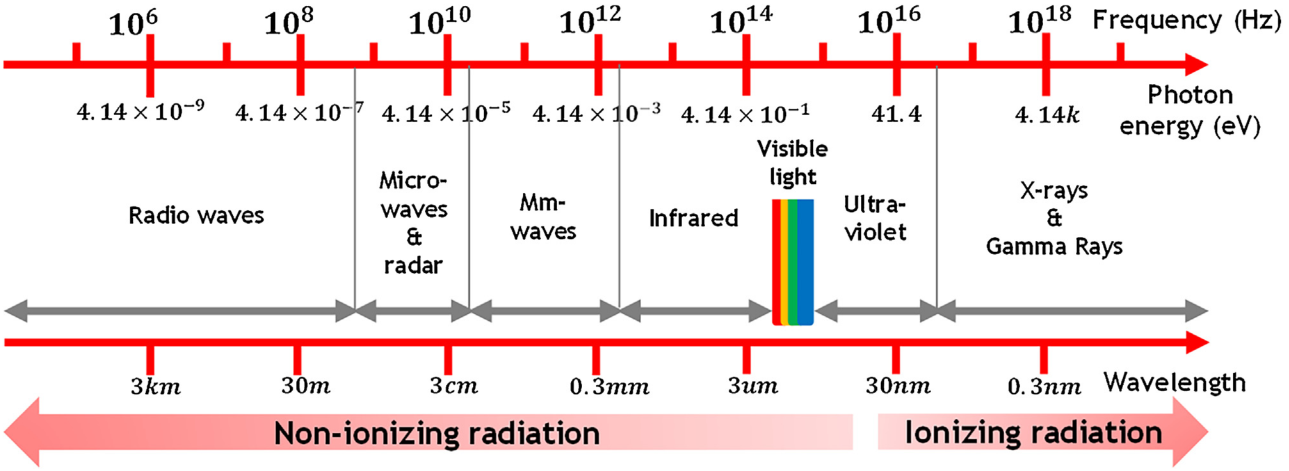

Fig. 1. Different frequency bands of electromagnetic waves.

The interaction of millimeter waves and a tested liquid is governed by the total complex dielectric permittivity of the liquid:

$$\varepsilon = \varepsilon_0 \varepsilon_{\text{total}} \tag{1}$$

with $\varepsilon_0 = 8.8541878176 \times 10^{-12}$ F/m the vacuum permittivity and ε_{total} the relative permittivity of the liquid.

This total complex dielectric permittivity of a given mixture reflects the collective behaviour of all individual molecules under the illumination of mm-waves [9]. As compounds are dissolved in a given solvent, the molecular interactions between solvent and solute involves different forces such as electrostatic, induction and dispersion ones [10]. As a result, modification of the solvent structure takes place in the immediate vicinity of solute molecules, and the modified solvent region is then addressed as "solvation shell". It is expected and has been verified that the molecules of the solvation shell possess a different dielectric permittivity than those of the bulk solvent [11]. As the solute molecules have their own permittivity depending on the molecular structure, the global dielectric permittivity of a solution is given as below [12]:

$$\varepsilon_{total} = \alpha_1\, \varepsilon_{solute} + \alpha_2\, \varepsilon_{solvationshell} + \alpha_3\, \varepsilon_{solvent} \tag{2}$$

With α_1, α_2, α_3 the volume fractions of the corresponding component in the mixture. From this equation, it is clear that with increasing concentration of solute, the total dielectric permittivity of the mixture will deviate away from that of the pure solvent. The changing permittivity then leads to a change in the transmitted and reflected signals of the mm-wave sensor.

2. Material and methods

2.1. Chemicals and reagents

Information about the chemicals and reagents involved in this study is listed as the following:

Praziquantel and trans-stilbene oxide were purchased from Sigma-Aldrich (St. Louis, USA) and dissolved in acetonitrile (ACN) (HPLC grade, VWR, France) at concentrations of 2.5; 5.0; 10.0; 15.0 20.0 and 40.0 mg/ml. Sorbitol (from Fluka Chemicals, Gillingham, UK) was dissolved in ACN at concentrations of 5.0; 10.0; 20.0; 30.0 and 40.0 mg/ml. Thiourea (from Merck KGaA, Darmstadt, Germany) was dissolved in ACN at concentration 20 mg/ml. The used stationary phase was Lichrospher 100 RP 18 endcapped (from Merck KGaA, Darmstadt, Germany) with particle size of 5 μm.

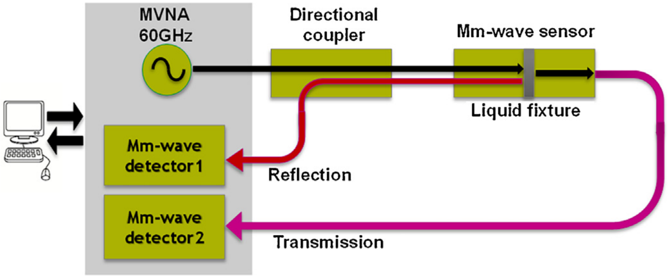

Fig. 2. Millimeter wave measurement set-up.

2.2. Millimeter wave measurement set-up

As shown in Fig. 2, the mm-wave measurement set-up works as follows:

A 60 GHz mm-wave signal is generated by a Millimeter Wave Vector Network Analyzer (MVNA) indicated by the shaded zone in Fig. 2, from AB millimeter [13] (Paris, France) [14]. This machine is capable to generate and detect EM waves with frequencies ranging from 8 to 700 GHz. After generation, the mm-wave signal is sent through a directional coupler (from Mi-wave, Florida, USA) [15]. This device allows the forward propagating wave to travel normally, while it is also responsible for the separation of the reflected wave from the total EM field, making the reflection measurements possible. The mm-wave set-up is developed to monitor the interactions between the mm-waves and the liquid injected into the sensor. The mm-wave sensor is designed as such that very small changes in liquid can be shown on the measurement results. In this study, only the mm-wave sensor is in house developed and is fabricated with 3D printing technology [16]. The rest of the components are commercially available as off the shelf components.

2.3. Liquid chromatography setup

A TriSep-2100 instrument (Unimicro Technologies, Pleasanton, CA, USA) was used to perform the experiments and the TriSepTM Workstation software (2003) operated the instrument. The compounds were injected via a 20 μL loop-injection system in a capillary (fused-silica capillaries from Polymicro Technologies with internal and external diameters of 320 μm and 450 μm, respectively). The UV detection was performed at 254 nm. The pump of the TriSep system provides mobile phase propulsion and a total flow of 0.02 mL/min was set for the analyses. Experiments to measure the