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3D-printed polylactic acid supports for enhanced ionization efficiency in desorption electrospray mass spectrometry analysis of liquid and gel samples

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ABSTRACT

The potential of 3D printing technology was here exploited to prepare tailored polylactic acid (PLA) supports for desorption electrospray ionization (DESI) experiments. PLA rough solid supports presenting wells of different shape (i.e. cylindrical, cubic and hemispherical cavities) were designed to accommodate samples of different physical state.

The potentials of such supports in terms of sample loading capacity, sensitivity, signal stability were tested by analysing a peptide (i.e. insulin) and an aminoglycoside antibiotic (i.e. gentamicin sulphate) from solution and a chitosan-based gel. The results obtained were compared with those obtained by using a traditional polytetrafluoroethylene (PTFE) support and discussed.

By using PLA support on the flat side, signal intensity improved almost twice with respect to PTFE support, whereas with spherical wells a five times improved signal sensitivity and good stability (RSD $< 6\%$) were obtained for the analysis of two model molecules. Limits of detection were in the 3–10 nM range and linearity was demonstrated for both analytes in the 0.05–0.5 μM range for semi-quantitative or quantitative purposes.

The use of a well and the set-up of optimal source parameters allowed the analysis of samples in a gel state with good precision (RSD $< 10\%$) and accuracy (86 ± 6–$102 \pm 9\%$), otherwise difficult to analyse on a flat smooth surface.

These findings are of great interest and stimulus to exploit the advantages of 3D printing technology for the development of devices for a DESI source, presenting different shapes or configuration as a function of the sample types.

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1. Introduction

In the last decade, ambient ionization mass spectrometry (MS) techniques have been widely used in a wide range of applications. Significant advantages in terms of sensitivity, speed, high throughput analysis, minimal sample preparation, imaging analysis were exploited for a number of investigations [1–3]. Among ambient ionization techniques, desorption electrospray ionization (DESI) is the most widespread used source [4–6]. Although it is mainly used for qualitative purposes, DESI-MS technique has been proposed also to obtain semi-quantitative or quantitative information [7–10].

The fundamentals of DESI mechanism and droplet dynamics were well described by Venter et al. [11]. A droplet pickup mechanism, influenced by several factors, such as source geometry, solvent flow-rate, nebulizing gas pressure, is at the basis of the analyte desorption, ionization and transfer phenomena. It is well known that together with the source parameters, the solid support, on which the sample is deposited, could play an important role in the quality of the MS signal observed, in terms of sensitivity, signal stability and repeatability. Different materials, such as polymethylmethacrylate (PMMA), polytetrafluoroethylene (PTFE), and more recently porous silicon, were successfully proposed as support for DESI experiments [12–14]. As described by Schwab et al. [12], usually, hydrophobic, porous surfaces help to improve sensitivity, signal stability and to reduce carry-over effects. Liquid samples can be deposited on a solid support and let to the solvent

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to evaporate before analysis of the solid residues; tissues or pharmaceutical tablets can be promptly analysed by directly flowing the DESI spray on their surfaces [12]. On the other hand, soft matters, like gels or pharmaceutical ointments, are instead difficult to analyse without avoiding sample or solvent splashing.

In the present work we describe the preparation and the use of different tailored DESI supports made with polylactic acid (PLA) by three-dimensional (3D) printing technology.

3D printing technologies are worldwide diffused as extremely powerful manufacturing method. Customized solid objects are created starting from a digital image and laying down materials (i. e. acrylonitrile butadiene styrene, rubber-like polymers, natural polymers) with different modalities [15–17].

Among materials, polylactic acid, an aliphatic thermoplastic polyester, is commonly used for 3D printing. PLA is non-toxic, in its basic form, easy-to-use, strong and mouldable when heated, while it is solid at room temperature. Insoluble in water, PLA presents hydrophobic properties making it an excellent candidate as DESI substrate, as recently proposed by Salentijn et al. [18]. As a matter of fact, hydrophilic and smooth surfaces are not well suitable to obtain stable DESI signals.

Here, a 3D technology was exploited to simply prepare customized PLA rough solid supports. Flat supports and supports presenting wells of different shape (i.e. cylindrical, cubic or hemispherical cavities) capable of accommodating samples of different physical state were printed.

As proof of concept, a peptide hormone (i.e. insulin) and an aminoglycoside antibiotic (i.e. gentamicin sulphate) were analysed from solution and chitosan-based gel samples, to verify the potential of such supports in terms of sample loading capacity, sensitivity and signal stability.

Samples in a gel form, due to their viscous nature, present the tendency to slip along a flat smooth surface when struck by a solvent flow. Taking into account of these difficulties, chitosan gel samples were selected to test the PLA supports for DESI-MS analysis.

Chitosan (CH) is a bio-degradable, bio-compatible polysaccharide widely used, as polymeric matrix, to achieve controlled-drug release by dispersing an active ingredient in several pharmaceutical formulations such as gels, tablets, nanoparticles, hydrogels and/or films [18–21]. In this contest, DESI-MS technique has been recently exploited to add new insights in the drug release behaviour from polysaccharide-based tablets without any sample preparation [22]. In particular, the basic mechanisms regulating the formation of a gel layer and the release of a drug in terms of polymer–solvent and drug–solvent interactions were discussed [22].

The opportunity to dispose of analytical techniques that rapidly provide information on the behaviour of an active ingredient in a formulation is of great value for the rapid pharmaceutical development [23].

Finally, the DESI-MS performances of 3D-printed PLA supports were compared with those obtained by using a traditional PTFE support and the results discussed.

2. Materials and methods

2.1. Materials

Formic acid (purity $>85\%$), LC-grade acetonitrile (AcN) were from Sigma-Aldrich (St. Louis, MO, USA). Purified water was produced with a MILLIQ Gradient system (Millipore, France). Insulin from bovine pancreas (MW 5733) and gentamicin sulphate (MW C1:497; C1a: 449; C2:463) were from Sigma-Aldrich.

2.2. Sample preparation

Insulin stock solution was prepared in 0.1% formic acid aqueous solution (final concentration 1 mM), and gentamicin sulphate stock solution was prepared in deionized water (final concentration 1 mM) and stored at -20 °C. Working solutions were freshly prepared in aqueous solution before analysis and deposited on the PTFE or PLA support, as described below. Linearity was checked in the 0.05–0.5 μM concentration range by analysis 5 concentration levels and by performing triplicate analysis for each level.

Chitosan gels were prepared by mixing chitosan acid solution (0.1% w/v) with insulin or gentamicin sulphate aqueous solution (final concentration 0.1, 0.2 and 0.5 μM) in a 1:1 ratio v/v. The gel (5 μL) was then deposited on the printed PLA-support.

2.3. Preparation of PLA supports

The supports for DESI-MS experiments were printed by using a home-made 3D printer. The PLA 175N1 material used was produced by Velleman Inc. (Legen Heirweg, Gavere, Belgium) without colour pigments [diameter 1.75 mm (1/16′), density 1.25 g/cm^3 (at 21.5 °C), printing temperature 190–225 °C, impact strength 5 kJ/m^2].

The supports were in the parallelepiped form with height (h) 25.40 mm, depth (p) 1.50 mm and length (l) 75.40 mm. The program was set to print alternating layers filled with a raster direction at 90° to one another (Fig. 1A). The base was made up of 7 layers: the first, 0.3 mm high, was used for deposition of the molten PLA, whereas the subsequent 6 layers were 0.2 mm high. In order to obtain a permeable structure with a slight roughness of the filament, the width was set at 0.4 mm and the raster-to-raster air gap set to zero (Fig. 1A).

Customized flat supports and with cavities presenting three different geometries were prepared in order to evaluate the optimal fluidic system (Fig. 1). Cylindrical, cubic and hemispherical cavities (27 for each support) were printed with 4 mm diameter and 1 mm depth at equal distances dx (7 mm) and dy (7 mm) (Fig. 1B and D).

2.4. Surface free energy analysis

The PTFE and PLA surface free energy were measured using a Cahn Dynamic Contact Angle system (DCA-312, Cahn Instruments Inc, Cerritos, USA). Supports were tested three times with water at 25 °C and the surface energy values were calculated using the Wu's equation [24].

2.5. DESI-MS instrumentation

The experiments were performed using an LTQ-Orbitrap XL (Thermo Scientific, San Jose, CA) instrument equipped with a DESI Omni Spray ion source (Prosolia, Indianapolis, IN, USA). The DESI source was equipped with a sample platform and two video cameras to assist in the positioning and monitoring of the spray on the surface. By using the PTFE and flat 3D-printed PLA support (Omni Slide, Prosolia Inc.), the solvent (H_2O/AcN 50/50, v/v) spray nozzle was positioned 2.1 mm from the surface at an incident angle of 57°; the solvent was delivered at the flow rate of 0.5 μL/min.

The configuration was slightly changed by using the 3D-printed PLA supports. The solvent spray nozzle was positioned 0.5 mm from the surface at an incident angle of 55°.

For all the experiments, the surface-to-inlet distance was set to 0.6 mm.

The nebulizing gas (nitrogen, 99.99% purity) pressure was set at 689 kPa (100 psi). Main experimental parameters were as follows:

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