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Characterization of ethylcellulose and hydroxypropyl methylcellulose thin films deposited by matrix-assisted pulsed laser evaporation

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ABSTRACT

In this study is reported the deposition of hydroxypropyl methylcellulose (HPMC) and ethylcellulose (EC) by matrix-assisted pulsed laser evaporation (MAPLE). Both HPMC and EC were deposited on silicon substrates using a Nd:YAG laser (266 nm, 5 ns laser pulse and 10 Hz repetition rate) and then characterized by atomic force microscopy and Fourier transform infrared spectroscopy.

It was found that for laser fluences up to 450 mJ/cm^2 the structure of the deposited HPMC and EC polymer in the thin film resembles to the bulk. Morphological investigations reveal island features on the surface of the EC thin films, and pores onto the HPMC polymer films.

The obtained results indicate that MAPLE may be an alternative technique for the fabrication of new systems with desired drug release profile.

1. Introduction

Transdermal drug delivery systems are alternative methods of drug administration with the potential to change the treatment paradigm for many diseases. The basic design of a transdermal patch is of a polymer multilayer in which a drug is embedded in a polymer film, which is placed between an outer backing film that prevents the loss of drug through the backing surface and an inner polymer film that sticks the films to the skin [1].

Thin films of ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) are widely used in solid pharmaceutical dosage forms to control drug release [2,3]. In order for these thin films to be applied in drug delivery systems they should be uniform in thickness, free from flaws and cracks, adherent, and stable on storage and handling [4].

Although the surface morphology of EC and HPMC films, as well as EC and HPMC blends has been previously investigated, the films were prepared either by dip-coating [5] or spin-coating [2]. The EC and HPMC films investigated in this study were prepared through matrix-assisted pulsed laser evaporation (MAPLE).

In MAPLE, a polymer or a biomolecule is dissolved in a solvent or a binary solvent system (named matrix) in concentrations of 0.1–5%, and the mixture is flash frozen in liquid nitrogen, resulting in a solid target. When the laser beam is focused onto the frozen target the solvent/binary solvent system is evaporated and the dissolved material (the organic material) is collected on a substrate. A successful deposition by MAPLE requires a high absorption of the laser light in the matrix, and as little absorption as possible by the guest (the polymer or the biomolecule) material, and that the matrix must not photochemically interact with the material to be deposited. The advantage of using MAPLE over the more conventional techniques is the good uniformity of the thin films, the well-controlled film thickness, and the fact that MAPLE allows the deposition of multilayers for materials which dissolve in the same or similar solvents [6]. However, simulations reported in [7] have shown that in some cases both solvent as well as target molecules reach together the substrate.

Earlier work with MAPLE has demonstrated that with an appropriate choice of experimental parameters, such as laser wavelength, fluence and pulse duration, type of solvent, target and substrate temperature, and background gas pressure, MAPLE is capable of providing conditions for “soft” ejection and deposition of polymers and biological molecules without significant modifications of the chemical structure and functionality [8–15].

In this study the surface structure of EC and HPMC thin films deposited by MAPLE is investigated to gain information on surface properties of the polymers and help in designing new drug delivery systems.

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2. Materials and methods

The guest materials are ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) both obtained from Sigma-Aldrich. The chemical structure of the polymers is given in Fig. 1.

EC was dissolved in toluene:ethanol (80:20 wt%) (final polymer concentration in the matrix 2 wt%) and HPMC in double distilled water (2 wt%) and then flash frozen in liquid nitrogen resulting in solid targets which were used in the MAPLE experiments.

A "Surelite II" pulsed Nd:YAG laser system (Continuum Company) with an emission wavelength of 266 nm, 6 ns pulse duration and 10 Hz repetition rate was used to irradiate the frozen polymer targets.

The laser spot size was measured to be 0.02 cm^2, as measured by placing thermally sensitive paper in the plane of the target. The number of laser pulses has been varied between 18,000 and 45,000 in order to obtain thin films of similar thicknesses for FTIR investigation. The laser fluence was varied between 120 and 700 mJ/cm^2.

The target was rotated with a motion feedthrough driven by a motor resulting in the laser beam describing a circle onto the sample to achieve uniform evaporation.

In order to control the temperature, two thermocouples were placed at two different positions of the target holder. The background pressures (air) ranging from 7×10^{-3} Pa to 2×10^{-2} Pa, were obtained with a Pfeiffer-Balzers TPU 170 turbomolecular pump. During some depositions the pressure varied probably due to the vaporization caused by the laser pulses, or due to outgassing of the targets under vacuum.

Silicon Si (1 0 0) cut into 1 cm^2 samples polished on both sides, which are transparent in the IR were used as substrates. The Si plates were cleaned prior to any deposition. The Si plates were ultra-sonicated in successive baths of acetone and ethanol, followed by rinsing them three times in the ultrasonic bath with ultrapure water (0.2 μm filtered). They were finally dried in a nitrogen flow.

All substrates were placed at a distance of 4 cm from the frozen target and kept at ambient temperature during the deposition.

Atomic force microscopy (AFM) (XE 100 AFM setup from Park) measurements in non contact mode were carried out to analyze the film surface roughness on several different areas and dimensions (from 5×5 μm^2 to 40×40 μm^2). In addition, AFM measurements were carried out to determine the thickness of the deposited thin films. This was achieved by depositing the polymer thin films with a mask in order to create a sharp edge.

Fourier Transform Infrared (FTIR) spectroscopy was applied to study the characteristic vibrations of functional groups in the deposited thin films. The infrared spectrum of the native molecule was measured and compared with the spectrum obtained from a thin film. The FTIR measurements were carried out with a Jasco FT/IR-6300 type A spectrometer in the range 400–4000 cm^{-1}. All spectra were obtained by transmission measurements, accumulating 128 scans, and CO_2/H_2O correction.

3. Results and discussion

3.1. Morphological investigation

The aim of this study is to produce defect-free thin films by a laser based method that can be used in drug-delivery applications. To achieve this it is important to investigate and optimize the preparation of cellulose thin films i.e. EC and HPMC as these are the most widely used polymers in controlled drug release. Film formation is strongly influenced by solvent quality [16], therefore it is very important to choose the right solvent. EC is a cellulose ether distinguished for its versatility, i.e. flexibility, chemical resistance, and transparency in the UV–VIS region. The toluene:ethanol [80:20 wt%] solvent system has been chosen as solvent for EC to optimize the quality of the deposited thin films. Toluene has a strong absorption peak (at 260 nm) in close proximity of the 4th harmonic of the Nd:YAG laser used for the deposition. Ethanol has been added to the solvent system in order to decrease the viscosity of the EC solution, i.e. EC chains in the binary solvent system being more mobile [4,5,17].

Table 1
Thickness (when applying 18,000 laser pulses) and roughness of HPMC and EC polymer films deposited by MAPLE from 2 wt% polymer solution measured by AFM.

Polymer	Laser fluence [mJ/cm^2]	Thickness range [nm]	RMS [nm]
HPMC	120	~54–62	20
	250	~82–93	15
	450	~120–124	37
	700	~170–181	52
EC	200	~40–50	43
	300	~50–62	64
	450	~100–109	71
	700	~500–522	146

Furthermore, ice water is weakly absorbing in the UV–VIS range (at 266 nm, the wavelength used in this work for thin film deposition) [18]. However, in previous works [9,19] it has been shown that flashfrozen ice water samples absorb light even at short UV wavelengths, the process being non-linear, with plume formation and ion emission.

Therefore, in the case of MAPLE of EC polymer, it can be assumed that the laser energy is mainly absorbed by the matrix, whereas in the case of HPMC polymer the laser light is absorbed by the HPMC molecules, similar to [18,19].

The AFM images of EC thin films deposited at different laser fluences (120 mJ/cm^2, 250 mJ/cm^2, 450 mJ/cm^2, 700 mJ/cm^2) are shown in Fig. 2(a–d). The polymer film covers the entire exposed area of the substrate at laser fluences above 120 mJ/cm^2. Below 120 mJ/cm^2 the deposited thin films are mostly composed of particles and fragments which consist probably of undamaged polymer molecules (see Fig. 2, FTIR investigation).

Above 120 mJ/cm^2 the deposited films have a similar surface morphology with island features. More island structures on the surface of the EC films were observed for the samples deposited at higher laser fluences. The diameter range of the island features on the EC polymer films was estimated using AFM and the measurements were obtained only for isolated island features, similar to [2]. It has been found that for the lowest fluence applied the diameter of the island features was in the range 150–400 nm whereas by increasing the laser fluence to 700 mJ/cm^2 the island diameter increased to 450–1800 nm. Compared to the case of EC deposition by spin coating reported in [2], where the island diameters were found to be in the range 400–760 nm for 100% EC composition, the island features appeared to be smaller in the samples deposited by MAPLE for laser fluences up to 700 mJ/cm^2.

In addition, in Table 1 is given the roughness of the EC and HPMC films deposited by MAPLE, together with the thickness of the films prepared from 2 wt% polymer solutions. The film thickness was also roughly estimated using AFM: the edges of the polymer films were imaged using non-contact mode AFM, and analyses were conducted on the image to estimate the vertical distances between the films and the substrates (film thickness). In Table 1 are shown the estimation results. The thickness range was the results of three measurements at different spots of the same sample. From the thickness of the samples, a rough estimate of the deposition rate can be made. The deposition rate affects the thin film growth and thus the layer properties [20,21]. As it can be seen from Table 1, the HPMC films have much lower thicknesses that the EC films (lower deposition rate), thus leading to differences in surface structure.