Atmospheric pressure plasma deposited silicone-like barrier coatings for drug delivery devices

E. Farsari, K. Giati, T. Argyropoulou, V.E. Vrakatseli, P. Ioannou, E. Amanatides and D. Mataras

Plasma Technology Laboratory, Department of Chemical Engineerimg, University of Patras

Abstract: The deposition of silicone-like coatings through the interaction of HMDSO vapours with atmospheric pressure Ar-O_2 plasma is investigated. The effect of the process parameters (HMDSO mass flow rate and the APPJ position relative to the substrate) on the physicochemical properties of the deposited coatings is examined. Moreover the use of deposited materials as barrier coatings on a two-stage drug delivery system is evaluated.

Keywords: plasma deposited siloxanes, APPJ, controlled drug release

1. Introduction

Time-controlled drug delivery systems have been extensively examined as a sustainable alternative to conventional therapeutic methods. Their ability to carry and deliver pharmaceutical substances in situ, with minimal interference with healthy surrounding tissues, minimizes side effects compared to the diffusion of the substance through tissues and organs in common systemic deliveries. Several approaches have been adopted for the development of drug delivery systems, including liposome-based systems, polymer micro-capsules, porous silicon based nano-particles etc. This work focuses on the fabrication of a two-stage delivery system consisting of a porous silicon matrix loaded with a pharmaceutical substance and a plasma deposited silicone-like barrier coating.

The biocompatibility and the hemocompatibility of plasma deposited silicone-like and SiO_x coatings have been demonstrated in the literature, while several coatings have been used as protective layers on implants, permeation barrier for metallic ions release etc [1,5]. The deposition of such coatings can be carried out either in low pressure plasma reactors or in open air through atmospheric pressure plasma discharges of organosilicon compounds as precursors such as TEOS, PDMS and HMDSO [6,11].

The aim of this work is the deposition of silicone-like coatings from HMDSO vapors using an atmospheric pressure plasma jet and the coatings integration in a two-stage drug delivery system. Precisely, the effect of the process parameters on the materials physicochemical properties, which in turn will affect the coating behavior in physiological fluids are examined. Finally the performance of the deposited films as barriers in drug release process is discussed.

2. Experimental

The experimental set-up used in this work is illustrated in Fig.1. The depositions were carried out in a cylindrical glass reactor. A plasma jet source (described in details in Ref. [12]) is placed at the open edge of the reactor and the angle between the jet and the cylinder axis can be adjusted between 0-45^o. The source is connected with an RF generator (13.56 MHz) via a manual matching network. The Ar-O_2 mixture feeding system consists of two flow-meters and a mixing vessel. The precursor enters the reactor through an opening, placed in the middle of the reactor axis. Before entering the reactor, the HMDSO is evaporated in a KEMSTREAM evaporator system, using synthetic air as carrier gas. The liquid and the carrier gas mass flows can be adjusted using proper software. The depositions were carried out on glass, intrinsic silicon substrates and on porous silicon, adjusting the plasma source position and the liquid mass flow rate.

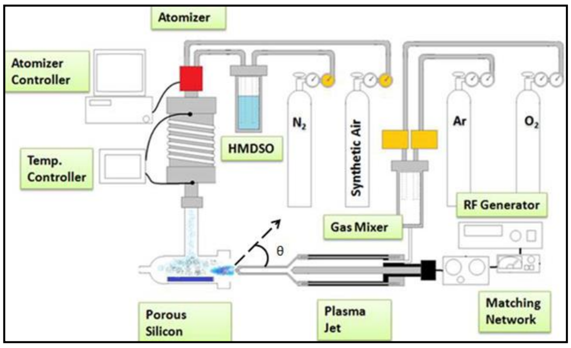

Fig. 1. Experimental set up

The deposited coatings were characterised using FTIR spectroscopy and water contact angle analysis, while the deposition rate was determined ex-situ through contact profilometry measurements.

In order to evaluate whether the coatings can be used as barriers on controlled drug release devices, porous silicon matrices were fabricated by means of constant current anodization. The matrices were loaded with epiroubicin and then they were used as substrates in the deposition process. The matrices were immersed in PBS solutions and the amount of the drug released at different time intervals was estimated using UV-Vis spectrophotometry.

3. Results

In this work several depositions were carried out varying the jet angle as long as the liquid mass flow in order to determine the effect of these parameters on the deposition rate, the chemical composition and the wettability of the coatings. All the other parameters of the process were kept constant: the carrier gas flow was set at 3.3 slm, the flow of Ar-O_2 (0.75% O_2) mixture was 2 slm and the input power was set to 70 W.

Fig. 2 illustrates the deposition rate as a function of the HMDSO mass flow when the plasma source is placed in parallel with the sample and when the angle between the substrate and the source is set at 30^{o}. In both cases the deposition rate reaches a maximum value at intermediate mass flow rates (~0.7g/min). When the mass flow is kept low, the HMDSO vapour density in the reactor is also low, limiting thus the film growth rates. However, when the mass flow exceeds 0.7 g/min, the deposition rate decreases which can be attributed to secondary phase reactions. It is worth noticing that the maximum deposition rate is achieved when the plasma jet is placed at an angle to the substrate and reaches a value up to 75nm/min. In this case, the plasma reactive species are directed to the substrate promoting both the gas phase and surface reactions. When the substrate and the source are placed in parallel, the high gas flow pushes the reactive species away of the substrate region leading to lower deposition rates.

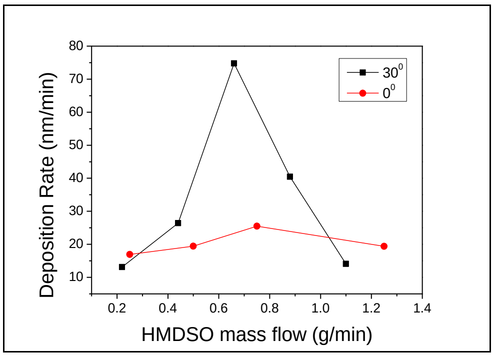

Fig. 2. Deposition rate as a function of the HMDSO mass flow rate

Fig.3 illustrates the water contact angles of the deposited films as a function of the HMDSO mass flow rate, for jet angle equal to 30^{o}. Variation of contact angles is similar to the deposition rate and reach maximum values (~95^{o}) at intermediate HMDSO flow rates. The variation of materials wettability is related to the chemical composition of the coatings.

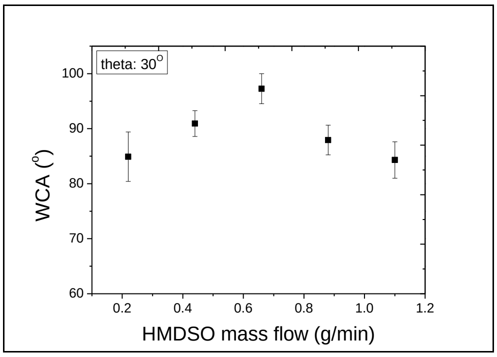

Fig. 3. Water contact angle as a function of the HMDSO mass flow

Fig. 4 illustrates the IR spectra of the samples, presenteded in Fig.3. In all spectra, several bands attributed to silicon-oxygen and silicon-methyl group bond can be distinguished. Among them, the absorbance band between 1000-1100 cm^{-1}, which is attributed to Si-O-Si bonds, and the band at ~1260 cm^{-}, attributed to Si-CH$_3$ bonds can be used for a measure of the organic character of the coating i.e. the ratio (r) of the integrated intensities of the Si-CH$_3$ to Si-O-Si band. Figure 5 illustrates the evolution of the ratio r as a function of the precursor mass flow. The organic component of the coatings is maximal at intermediate flow rates where both the deposition rate and the wetting angles reach their maximum value. When the deposition rate is relatively low, the plasma oxygen species can react with the surface promoting the films oxidation, leading to lower carbon content and thus to lower wetting angles. It is worth noticing that changing the jet angle and the other process parameters, the materials chemical composition can be modified providing wide range of water contact angles (Fig.6).

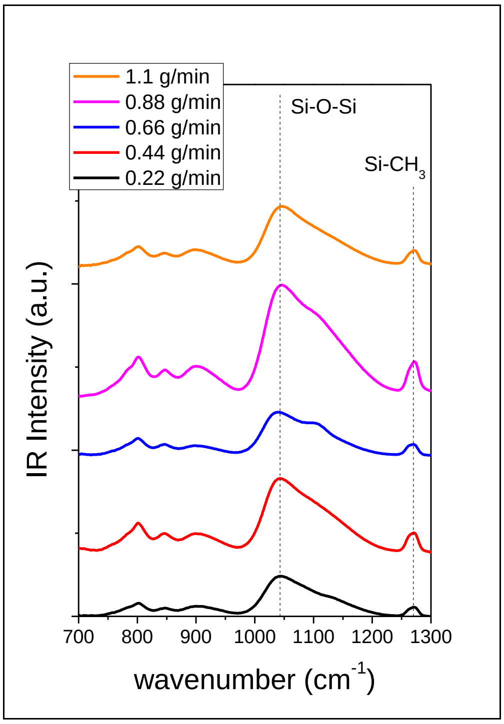

Fig. 4. IR spectra of the samples illustrated in Fig3

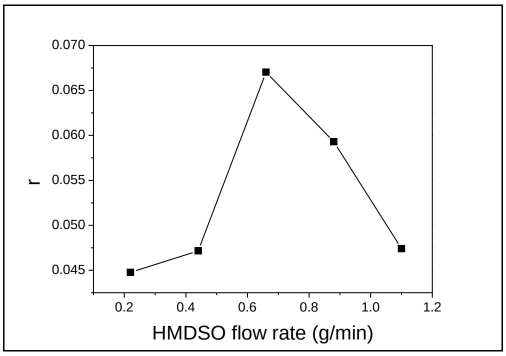

Fig. 5. r as a function of the HMDSO mass flow rate

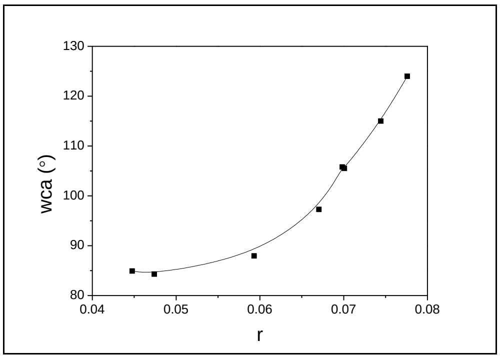

Fig. 6. Water contact angle as a function of organic component of the coatings

Moreover, in order to investigate the stability of the deposited materials in physiological fluids, different coatings on glass substrates were immersed in a PBS solution (pH =7.4) and their water contact angles were measured for 3 days. Fig. 7 illustrates the water contact angles as a function of the immersion time in the PBS solution. The contact angles of the materials, regardless of their initial value, gradually decrease with time indicating materials degradation. However, in all cases the final wca is higher than the substrate wca, indicating that the material is not completely removed from the surface. The gradual degradation of the coatings is an evidence that these coatings could be used as barrier coatings on a controlled drug delivery system.

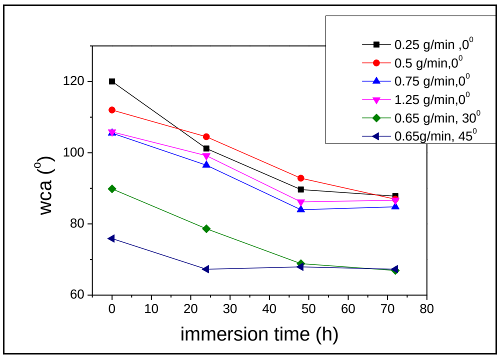

Fig. 7. Water contact angle as a function of the immersion time in PBS solution (pH =7.4)

Several drug delivery systems consisting of porous silicon matrices (thickness 100 μm) loaded with epiroubicin were coated and the amount of the released drug in PBS solutions was determined by means of UV-Vis spectrophotometry. Fig.8 illustrates the dimensionless amount of the drug released at regular time intervals from a silicone-like coated and an uncoated device. The film thickness was adjusted to 150 nm (deposition parameters: jet angle =0°, HMDSO mass flow rate = 0.7 g/min) , the porosity of the matrix was 92% and the diameter of the pores was ~ 40 nm. In both cases the total drug amount is released in a period of 7 days. However, the release profile is different between the coated and the uncoated matrix. In the absence of the coating, the 60% of the drug is released during the first day due to the epiroubicin dilution and diffusion in the pores and then a second non-linear kinetic regime is established attributed to the combination of the drug diffusion from the pores and the dissolution of the porous matrix in the aqueous medium at 7.4pH. The burst release is limited when the silicone-like coating is used as barrier and thus only the 40% of the drug is released the first day. As the coating is gradually degraded and the PBS solution attacks the porous silicon matrix the drug release is accelerated.

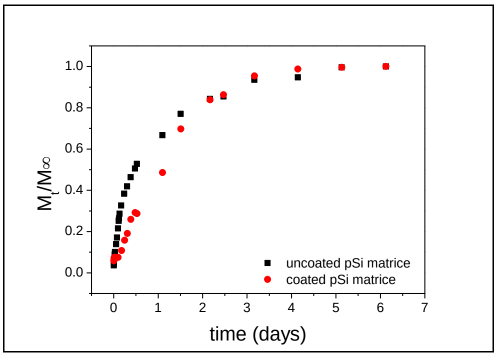

Fig. 8. Dimensionless amount of epiroubicin released using coated and uncoated device.

4. Conclusions

In this work the deposition of silicone-like films using HMDSO vapours as precursor and Ar-O_2 atmospheric plasma was examined. The effect of HMDSO mass flow rate and the experimental set-up on the deposition rate and the physicochemical properties of the coatings was studied.

The deposition rate, the organic component of the films and consequently their wettability are strongly affected by the HMDSO mass flow. When the HMDSO mass flow is kept in the range of 6-7 g/min, the deposition rate and the carbon content of the coating reach their maximum values. Moreover, the position of the plasma source with respect to the substrate affects the deposition rate. When the plasma source is placed at an angle of 30° to the substrate, the plasma species are directed to the substrate promoting both the gas phase and surface reactions.

Finally, when the coatings were deposited on porous silicon matrices loaded with epiroubicin, they acted as a barrier layer, inhibiting the solution attack to the loaded matrix at the early stage of the drug release.

5. Acknowledgements

The authors wish to thank Pr. G. Dinescu, National Institute for Laser, Plasma and Radiation Physics, Bucharest, Romania for providing the APPJ source and As. Prof. N. Spiliopoulos, Laboratory of Solid State Physics, Department of Physics, University of Patras, for providing IR spectroscopic facilities.

6. References

[1] R P. Gandhiraman, M. K. Muniyappa, M. Dudek, C. Coyle, C. Volcke, A. J. Killard, Paul Burham, S. Daniels, N. Barron, M. Clynes, D. C. Cameron, Plasma Processes and Polymers, 7,411(2010)

[2] G. R. Prasad, S. Daniels, D.C. Cameron, B.P. McNamara, Elizabeth Tully, R. O'Kennedy, Surface & Coatings Technology, 200,1031 (2005)

[3] A. Lehmann, S. Rupf, A. Schubert, I. M.Zylla , H. J. Seifert, A. Schindler, T. Arnold, Clinical Plasma Medicine, 3,3 (2015)

[4] L. Zhou, G. H. Lv , C. Ji , S. Z. Yang , Thin Solid Films, 520, 2505 (2012)

[5] J. Schäfer, S. Horn, R. Foest, R. Brandenburg , P.Vašina , K. D. Weltmann, Surface & Coatings Technology, 205,S330 (2011)

[6] J. Schwarz , M. Schmidt, A. Ohl, Surface and Coatings Technology, **98**, 859 (1998)

[7] A. Panou, Ch. Voulgaris, E. Amanatides, D. Mataras, D. Rapakoulias, High Temperature Materials Processes, 9 (2), 279 (2005)

[8] H. Kakiuchi, K. Higashida, T. Shibata , H. Ohmi, T. Yamada a, K. Yasutake, Journal of Non- crystalline solids, **358**, 2462 (2012)

[9] J. Pulpytel, V. Kumar, Pu Peng, V. Micheli, N. Laidani, F. Arefi-Khonsari, Plasma Processes and Polymers, 8,664 (2011)

[10] J. Schäfer ,K. Fricke, F. Mika, Z. Pokorná, L. Zajíčková, R. Foest, Thin Solid Films, 630,71 (2017)

[11] A.S. Meshkova, F.M. Elam, S.A. Starostin, M.C.M. van de Sanden, H.W. de Vries, Surface & Coating Technology, 339, 20 (2018)

[12] E.R. Ionita, M.D. Ionita, E.C. Stancu, M. Teodorescu, G. Dinescu, Applied Surface Science, 255, 5448 (2009)