ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2017, *62*(8-9), 677-685

Dedicated to the memory of
Professor Victor-Emanuel Sahini (1927–2017)

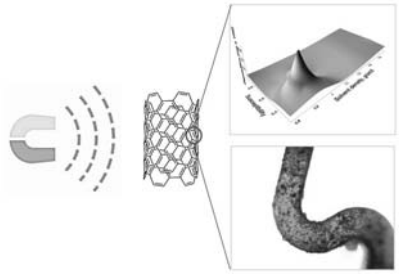
INVESTIGATION CONCERNING THE POSSIBILITIES FOR THE DEPOSITION OF MAGNETIC NANOPARTICLES ONTO A METALLIC STENT

Alina DIACONU, Aurica P. CHIRIAC,* Nita TUDORACHI, Loredana E. NITA and Iordana NEAMTU

"Petru Poni" Institute of Macromolecular Chemistry 41-A Grigore Ghica Voda Alley 700487 Iaşi, Roumania

Received December 21, 2016

The study presents the possibility of depositing magnetic nanocomposite coatings on the surface of a metallic stent by using an alternating magnetic field in relation to the characteristics of the magnetic nano-compound dispersion, such as dielectric constant, dipole moment, electrostatic factor, density, viscosity, surface tension, molar polarization, and magnetic susceptibility. The interdependence between these characteristics and the yield of deposition, as well as the resulted magnetic susceptibility of the stent covered with magnetic nanoparticles, are put into evidence.



INTRODUCTION

Even though coronary stents were on the commercial market in one form or another for several years, the techniques used to create these devices are improving every day.[1] Thus, emerging technology propose novel materials with superior properties, such as fully degradable stents, which can develop and even expand the stent therapy to new patients. Another issue to be considered is that stainless steel endovascular stents are inherently thrombogenic so that thrombus accumulates on these devices. A potential solution to this problem is stent surface modification, which might limit platelet adhesion.

In the context of advancement in the interventional medical device market, the possibilities of obtaining drug–eluting stents, based on core-shell magnetic nanoparticles becomes a major challenge.[2-8] One of the most innovative aspects of stent modification is the use of functionalized magnetic nanoparticles (MNPs) with antioxidant biomolecules coatings to obtain controlled delivery platforms for the release of drugs.[9]

The biomedical applications of magnetic nanoparticles are well-known. Nanoparticles are used for both diagnostic as well as for therapeutic purposes, such as magnetic resonance imaging, hyperthermia, drug and gene delivery, magnetic separation of labelled cells and other biological entities, and so on.[10-13] The clinical use of the magnetic nanoparticles revolves around their broad versatility, chemical stability, and biocompatibility. From the perspective of therapeutic application of superparamagnetic nanoparticles, the site-specific delivery of drugs, via guiding through external

* Corresponding author: achiriac1@yahoo.com

magnetic fields, represents a highly desirable property which also increases the possibility of use in various medical fields. The ability to deliver precise dosages to required sites in the human body is one essential goal of drug delivery research. For magnetic nanocarriers, the essential features are biocompatibility and non-toxicity along with other important characteristics of the nanoparticles like diameter, charge, surface chemistry, their magnetic properties and their ability to carry bioactive agents. These are crucial properties because inappropriate characteristics will strongly affect both blood circulation time and the bioavailability of the particles within the body. Thus, the particles have to be in a size range of 10-100 nm for long circulation times *in vivo* and to enhance their magnetic targeting efficiency.

In our previous studies, the synthesis of poly(maleic anhydride-co-3,9-divinyl-2,4,8,10-tetraoxaspiro [5.5] undecane) (PMAU) an alternant copolymer with precise placement of functional groups along the polymer backbones, was presented. [14- 15] According to the obtained value of the registered lethal dose (as being less than 50) and to the Hodge and Sterner toxicity scale, the copolymer can be included in the group of low toxic compounds. The dual sensitivity of the polymeric structure, to temperature and pH, was also demonstrated. The new structure, owing to the suitable and specific functionalities, is used on the one hand for the preparation of a new magnetic hybrid composite and on the other hand as a reactive polymer to link bioactive compounds via maleic anhydride moiety.[16]

The magnetic composite (MC) was prepared *in situ* during functionalization of PMAU copolymer with erythritol (E) - a strong antioxidant - followed by the incorporation of magnetic nanoparticles into the obtained matrix. The procedure has conferred antioxidant properties to the polymeric structure as well as to the new magnetic nanoparticles owing to the polyol characteristics.[16] Studies made on the new hybrid compounds from the viewpoint of their magnetization attests that the obtained nanocomposites have superparamagnetic properties.

The MC was used as a coating to improve bare metal stents performance and functionalities.[9] Through this strategy, a combination of chemical modifications, by inducing antioxidant properties to the stent surface, and magnetic properties was utilized. The coating process was performed in an alternating magnetic field (AMF). Using the heat generated by the magnetic field and by MC (which occurs due to hysteresis losses and Brownian relaxation in superparamagnetic nanoparticles) during exposure, proper conditions for a uniform deposition were created.

In the present investigation, possibilities of applying magnetic nanocomposite coatings on the surface of a metallic stent were related to the deposition conditions. Thus, the medium characteristics used for the dispersion of the MC, such as dielectric constant, dipole moment, electrostatic factor, density, viscosity, surface tension, molar polarization, and magnetic susceptibility, are correlated with the improvement added to the stent functionality after coupling MNPs. The interdependence between these characteristics, the yield of deposition, and the resulted magnetic susceptibility of the coated stent are put into evidence.

RESULTS AND DISCUSSION

As mentioned, in designing optimal architecture of implanted medical devices like stents, the quality control must be extremely high.[9] The stent configuration, polymer structure, and the bioactive substance formula are important factors to be taken into account when a certain medical decision needs to be made concerning the stent use. The addition of the polymer coating with encapsulated bioactive substance on the metallic substrate must be optimized in order to obtain an appropriate thickness and uniformity of the coating layer, which will ensure a proper drug delivery.[1]

From previous studies made on the synthesis of the polymer matrix based on poly(maleic anhydride-co-3,9-divinyl-2,4,8,10-tetraoxaspiro [5.5] undecane), has resulted that the polymer characteristics, especially thermal properties, dimensional stability, and rheological behaviour, provides suitable conditions for developing core-shell type magnetic composite structures.[14]

The magnetic composite was obtained *in situ* by opening the maleic anhydride (MA) ring with erythritol (E) which ensures the embedding of the magnetic compound into the polymeric shell. This procedure was performed in well-defined ratios between PMAU copolymer, erythritol antioxidant, and magnetic structures.[15] Coating with a suitable polymer endows some important characteristics of the nanoparticles that are essential for their use as drug delivery vehicles. We decided to use poly(maleic anhydride-co-3,9-divinyl-2,4,8,10-

tetraoxaspiro [5.5] undecane) as a polymer matrix because it has a biocompatible character, as it was stated in previous studies.[15] A schematic illustration of the magnetic composite structure based derivative PMAU/E copolymer matrix after MA ring split by erythritol (E) and magnetite encapsulation is presented in Figure 1.

Furthermore, the obtained magnetic composite was deposited onto the metallic stent platform in a process developed in an alternating magnetic field, with the aim of designing an appropriate architecture of the stent with improved functionality. NIR-CI technique reveals the homogeneity of the magnetic nanoparticles, while optical microscopy and magnetic susceptibility values confirm the magnetic composite deposition onto the stent surface.[15] To optimize the conditions needed to cover the stent platform with hybrid magnetic structures, the influence of the solvent nature used for the dispersion of the magnetic nanoparticles during the deposition in an alternating magnetic field, was investigated. In this regard, ten distinct environments differentiated by physical characteristics of the solvents were used and are highlighted in Table 1.

The amount of material applied on the metallic platform depends as well on the number and period of the deposition cycles. The evolution of the deposition of the magnetic nanocomposites onto the stent in conformity with the dispersion medium, the time and the number of cycles are presented in Table 2.

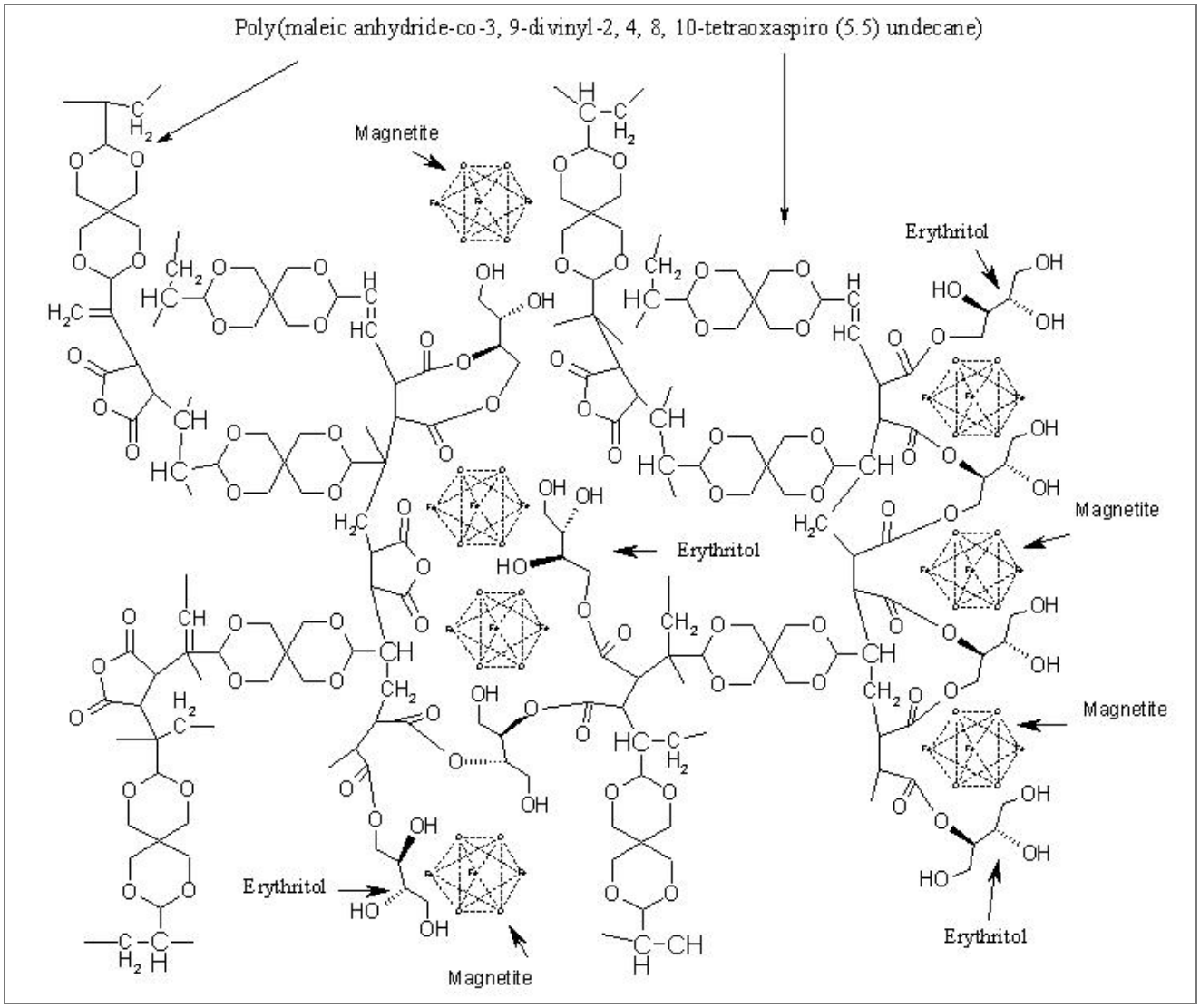


Fig. 1 – Schematic illustration of the magnetic composite structure: derivative PMAU/E copolymer matrix with MA ring split by erythritol and magnetite encapsulation.

Table 1

Physical characteristics of the solvents used for the dispersion of the magnetic nanoparticles

Dispersion medium	Dielectric constant, ε	Dipole moment, (10a-18esu)	Electrostatic factor, EF (ε x μ)	Density, d (g/cm^3)	Viscosity, η (cP)	Surface tension, γ (dyn/cm)	Molar polarization, P	Magnetic Susceptibility, χ x 10^{-6} (cm^3/mol)	Yield , %
Acetone	20.70	2.69	55.68	0.78	0.30	22.01	64.53	-33.86	14.29
Chloroform	4.806	1.15	5.527	1.48	0.514	26.53	44.96	-59.93	27.78
Cyclohexanol	15.00	1.86	27.90	0.97	41.06	33.91	84.90	-70.61	20
Dimethylformamide*	36.71	3.86	141.70	0.94	0.802	35.20	71.64	-43.41	33.33
Dimethylsulfoxide**	46.68	3.90	182.05	1.09	1.99	42.86	67.15	-42.86	66.67
Ethanol	24.55	1.66	40.75	0.79	0.99	21.40	51.65	-34.19	32.55
Ethyl acetate	6.02	1.88	11.32	0.89	0.426	22.55	61.20	-49.11	10
Methylethyl ketone***	18.51	2.76	51.07	0.79	0.36	23.97	77.81	-45.72	19.60
Tetrahydrofuran****	7.58	1.75	13.27	0.89	0.426	26.40	55.57	-39.85	10
Water with surfactant*****	78.39	1.85	145.38	0.99	0.89	71.81	17.41	-12.97	15.79

* - DMF
** - DMSO
*** - MEK
**** - THF
***** - Water and sodium sulfosuccinate tensioactive - W_{NaScc}

Table 2

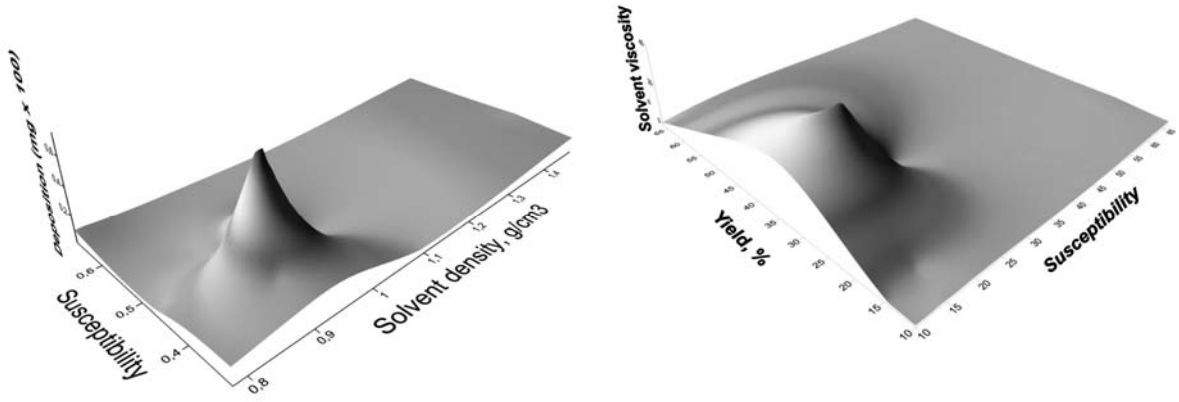
The evolution of the magnetic nanocomposites deposition onto the metallic stent

Dispersion medium	Deposition (mg/min x 10^2)						Deposition		Stent Susceptibility χ	
	3’	3’	3’	3’	3’	3’	mg x 100	%	Volume, e^{-4} V	Masa, e^{-4} M
Acetone	0.45	0.46	0.48	0.48	0.49	0.50	0.06	14.29	0.014	0.495
Ciclohexanol	0.39	0.39	0.40	0.41	0.41	0.42	0.05	20	0.005	0.317
Cloroform	0.43	0.43	0.43	0.45	0.45	0.46	0.8	27.78	0.007	0.453
DMF	0.53	0.58	0.58	0.59	0.60	0.62	0.15	33.33	0.016	0.519
DMSO	0.45	0.56	0.56	0.57	0.60	0.60	0.24	66.67	0.006	0.371
Etanol	0.43	0.43	0.48	0.52	0.56	0.57	0.14	32.55	0.012	0.429
Ethyl acetate	0.50	0.55	0.55	0.56	0.56	0.56	0.05	10	0.016	0.470
MEC	0.54	0.59	0.59	0.59	0.60	0.61	0.10	19.60	0.025	0.668
THF	0.42	0.42	0.43	0.43	0.44	0.44	0.04	10	0.016	0.519
W_{NaScc}	0.41	0.42	0.42	0.42	0.43	0.44	0.04	15.79	0.017	0.453

The coating process can be directly influenced by the physical characteristics of the solvents used as the dispersion medium for the magnetic compound. In the following, this dependence, concretised in the yield of deposition and the resulted magnetic susceptibility, on the layering conditions (6 cycles of 3 minutes each) and the characteristics of the tested solvent, is presented. Among the considered properties taken into the study were the dielectric constant, dipole moment, electrostatic factor, density, viscosity, surface tension, molecular polarization, and the magnetic susceptibility.

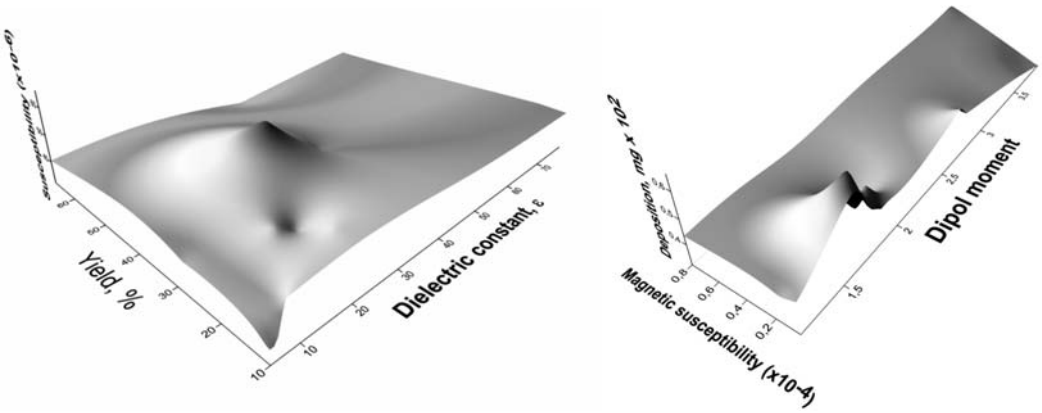
Figure 2a illustrates the dependence of the deposition yield, and the magnetic susceptibility of the resulted stent, relative to the density of the solvent used to disperse the magnetic composite. As it can be observed, at the highest density of the solvents, namely 1.48 g/cm^3 corresponding to chloroform, it was obtained a deposition yield of about 28 % and a magnetic susceptibility of 0.453 e^{-4} for the covered stent (Table 2). The dependence of the deposition efficiency and the values of the magnetic susceptibility for the resulted stent on the solvent viscosity are presented in Figure 2b. Thus, in the case of a viscosity of 41.06 cP, which corresponds to cyclohexanol as the dispersion medium, the obtained yield of deposition was about 20%. Meanwhile, the magnetic susceptibility of the stent was 0.317 e^{-4} M (Table 2).

Figures 3a and b illustrate the influence of the dielectric constant and the dipole moment of the solvents used as dispersant medium in the present study.



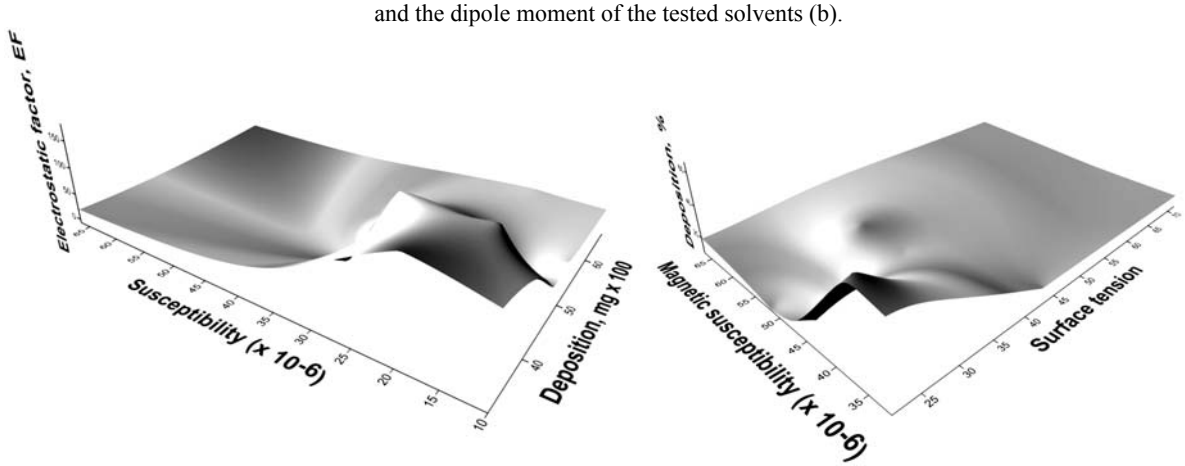
(a) (b)

Fig. 2 – The dependence of deposition yield and magnetic susceptibility of the covered stent on the density (a) and respectively the viscosity of the solvent (b).



(a) (b)

Fig. 3 – The dependence of deposition yield and magnetic susceptibility of the resulted stent on the dielectric constant (a) and the dipole moment of the tested solvents (b).



(a) (b)

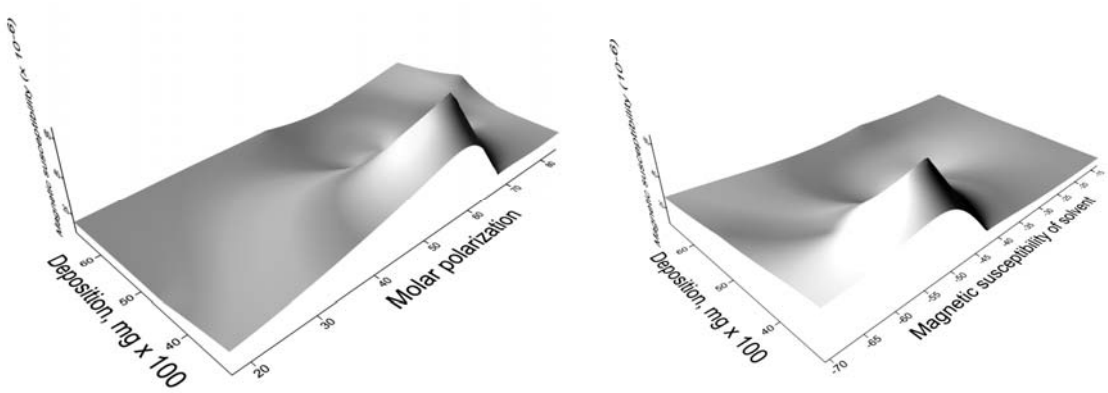
Fig. 4 – The dependence of deposition yield and magnetic susceptibility of the resulted stent on the electrostatic factor (a) and the surface tension of the used solvents (b).

The deposition efficiency of the magnetic composite on the metallic stent, and the magnetic susceptibility values in relation with the dielectric constant of the solvent used as dispersion medium (Fig. 3a) reveals that for the highest value of the dielectric constant of 78.39 (corresponding to water with surfactant medium) a deposition yield of about 16% and a magnetic susceptibility of 0.453 e^{-4}M was obtained (Table 2).

The interdependence between the dipole moment values of the solvents, the deposition capacity, and the magnetic susceptibility obtained for the coated stent, is presented in Figure 3b. Thus, in the case of the highest value of the dipole moment of about 3.90 (corresponding to dimethyl sulfoxide as the dispersion medium), the deposition yield was 67% and the registered magnetic susceptibility of the stent was 0.371 e^{-4}M (Table 2).

The deposition efficiency of the magnetic composite on the metallic stent, and the magnetic susceptibility values in relation with the electrostatic factor of the solvent tested as the dispersion medium (Fig. 3a) shows a yield of 67% and a magnetic susceptibility of 0.371 e^{-4}M, for the highest value (182) corresponding also to dimethyl sulfoxide (Table 2). It must be mentioned as well that at a value of the electrostatic factor of 142 (corresponding to DMF), good yields were obtained, respectively 33.33% (Table 2). Figure 4b evidences a yield of 16% and a magnetic susceptibility of 0.453 e^{-4}M for the covered stent, in the case of the highest value of the surface tension (71.81 dyn/cm), which corresponds to water with surfactant medium (Table 2).

Figures 5a and b illustrate the influence of the molar polarization and the magnetic susceptibility values of the solvent on the deposition efficiency and the magnetic susceptibility of the resulted stent. The molar polarization with the highest value corresponds to cyclohexanol (84.90), and in this case, the yield of deposition was around 20% (Fig. 5a). Meanwhile, the magnetic susceptibility for the covered stent was 0.317 e^{-4} M (Table 2).



(a) (b)

Fig. 5 – The dependence of deposition yield and magnetic susceptibility of the resulted stent on the molar polarization (a) and the magnetic susceptibility of the used solvents (b).

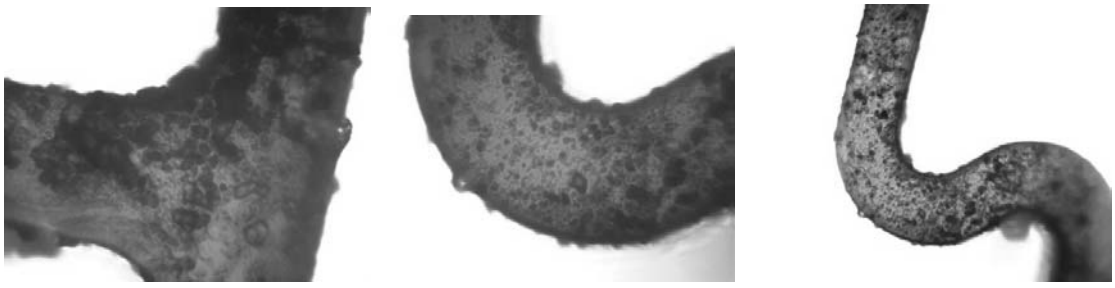
In the case of cyclohexanol, which is the solvent with the highest value of magnetic susceptibility, namely 70.61, a deposition yield of 20% was registered, while the magnetic susceptibility of the covered stent was about 0.317 e^{-4} M (Table 2).

The conducted study has revealed the dependence of the coating process of the magnetic nanocomposite on the stent platform, and this dependence is developing in the following order of the characteristics of the used solvent: density 〉 viscosity 〉 electrostatic factor 〉 magnetic susceptibility 〉 molar polarization 〉 dielectric constant 〉 dipole moment 〉 surface tension. Considering these features, yields of deposition for up to 67% and magnetic susceptibility values of 0.668 e^{-4} M can be obtained, for an initial stent weight of 0.0051 mg.

The strategy regarding the design of a new coating system which involves magnetic nanoparticles applied at the surface of a bare metal stent was based on the behaviour of these hybrid structures as stable colloidal suspensions consisting of monodimensional magnetic nanoparticles dispersed in a suitable solvent in an alternating magnetic field. When nanoparticles are exposed to a high-frequency AMF they are able to generate heat as a result of hysteresis energy loss and Neel or Brown relaxation. At the same time, the magnetic nanocomposites show an affinity for the metal stent platform, which contains micropores and enables the adsorption of MC, creating thus proper conditions for a uniform deposition on the surface of the stent.

By keeping the magnetic compounds in an alternating magnetic field, the system temperature and the agitation of the nanoparticles increases, improving the mobility of the particles in the dispersion medium which enables the coupling to the stent. The dependence of the deposition yield on the solvent characteristics, respectively on high density and viscosity, it is perfectly justifiable. The magnetic particles are subjected to a 'game' called "come-go" generated by the alternant magnetic field based on the dispersion medium properties which restrain the movement of the particles over long distances, and therefore layering the MC on the surface of the stent is easier to achieve.

Optical microscopy images for the coated stents are shown in the following figures which illustrate the achieved deposition of the magnetic nanoparticles in alternating magnetic field by using different solvents as dispersion medium: dimethyl sulfoxide, dimethyl formamide, and water containing a surfactant. The obtained images attest the presence of the magnetic composite on the surface of the stent.



(a) (b) (c)

Fig. 6 – Optical microscopy of stents functionalized with magnetic nanocomposites and deposition performed in dimethyl sulfoxide (a), dimethyl formamide (b), and water with surfactant (c).

EXPERIMENTAL

Materials

All the reagents are of analytical purity and are used without further purification. Maleic anhydride (MA) (purity 95%), 3,9-divinyl-2,4,8,10-tetraoxaspiro[5.5] undecane (U) (purity 98%), 2,20-Azobis(2-methylpropionitrile) (AIBN) (purity 98%), diethyl ether (ACS reagent, anhydrous, purity 99.0%), cyclohexanol (purity 99%), methylethyl ketone (purity 99%) and tetrahydrofuran (purity 99,9%) were purchased from Sigma-Aldrich. 1,4–dioxane (purity 99.5%), dimethylformamide (purity 98%) and dimethylsulfoxide (purity 99.9%) were obtained from Fluka. Chloroform (purity 99.5%), ethanol (purity 99.5%), ethyl acetate (purity 99.5%) and acetone (purity 99.5%) were obtained from Chemical Company. Meso-Erythritol (E) with a purity of 99% was purchased from Alfa Aesar. The water used in the experiments was purified using an Ultra Clear TWF UV System.

The magnetic nanoparticles were synthesized and supplied by R&D National Institute for Technical Physics (Iasi-Romania), dried powder sample with average particle size 220 nm (analyzed with Dynamic Light Scattering method).

The stent platform 316L SS (annealed ASTM F138) was obtained from MEKO Laserstrahl- Material-Bearbeitung – Germany (Closed-cell, slotted-tube, 1.5 cm length, 13.7 mm thickness, 1mm stent strut).

Polymer matrix synthesis

PMAU copolymer was synthesized through radical polymerization in solution of the monomers, with 1:0.5 molar ratio between MA/U comonomers, using a concentration of 2.92 x 10^{-4} M AIBN as initiator, and in 22.5% solution of 1,4-dioxane. The continuous polymerization process was conducted under nitrogen atmosphere, at 75°C, in a constant temperature bath and it was carried out for 24 h. After cooling, the reaction mixture was precipitated and washed several times with diethyl ether, and then filtered and dried under vacuum at room temperature.

Magnetic composite preparation technique

The magnetic composite was prepared *in situ* by reacting 0.2 g PMAU copolymer with 0.6 g E (PMAU/E = 1/3 wt ratio) in 11 ml dioxane in the presence of 5 wt% magnetite against copolymer amount (0.04 g magnetite). The reaction was maintained at 80°C in dioxane for 6 hours with a stirring rate of 200 rpm. Upon completion, the composite has been collected from suspension through magnetic separation, purified by repeated washes with ethanol, and further dried in a vacuum oven at 25°C, for 24 h and 600 mm Hg. During increased functionalization of PMAU with polyol E, the anhydride ring is split and the magnetic compound is embedded and maintained into polymer network through physical bonds.

Covering the metallic stent with MC

An alternant magnetic field (AMF, H = 200 Oe, obtained from the solenoid with the following characteristics: L = 700 μH, V = 125 kHz, I = 2.5 A, U = 1.3 Kv, P = 3 Kvar) was used for the deposition of the MC onto the stent surface. The procedure consists of maintaining the metallic device in the dispersion medium containing magnetic particles in different solvents (1% concentration) under AMF for 3 minutes. This procedure was repeated for six cycles, till no difference in the weight of the covered stent was registered. The stent was weighed after each cycle to determine the yield of deposition.

Methods of characterization

Yield determination (gravimetric %)

The deposition yield was calculated by determining the mass gain of the coated stent with an exact balance. After each cycle of deposition, the stent was removed from de dispersion medium, slightly dabbed on a filter paper to remove the solvent excess and then weighed.

Magnetic susceptibility was determined with Magnetic susceptibility balance MSB – Auto (Geneq Inc.). The reading of volume susceptibility χ_V, or mass susceptibility χ_M, displayed by the balance is proportional to the sample's volume (or mass) present in the measuring region of the balance.

Optical microscopy

Optical microscopy images are acquired on a Reflected light bright field microscope Leica DM 2500 (Leica Microsystems Wetzlar GmbH), magnification across the sample surface: 500x, with a 3.3 Mpix Leica DFC320 R2 digital camera (resolution 2088 x 1550 pixels) mounted on the trinocular head. The photo is later converted into digitized grey scale data for analysis.

CONCLUSIONS

This paper presents an innovative approach to coronary stent design that incorporates biocompatible, magnetic nanocomposite coatings applied in an alternant magnetic field. The surface characteristics of the modified stainless steel stents were investigated by optical microscopy and by magnetic susceptibility estimation in relation to the characteristics of the solvent used as dispersion medium for MC. The results have revealed that the coating process requires specific parameters for the successful deposition. Changing the solvent through the proposed protocol has been shown to increase the deposition yield and magnetic susceptibility, especially when the density and the viscosity of the solvent it's higher. A yield of deposition for up to 67% and a magnetic susceptibility for the covered stent of 0.668 e^{-4} M can be obtained in case of dimethyl-sulfoxide, a solvent with a density of 1.09 g/cm^3, and respectively a viscosity of 1.99cP. The magnetic particles are subjected to an up and down movement generated by the alternant magnetic field, which restrains the movement of the particles over long distances, and therefore layering the MC on the surface of the stent is easier to achieve. The magnetic composite deposition on the stent surface was also confirmed by optical microscopy. The versatility of this approach prompts exploring the

utility of magnetic field-mediated stent coating for combination therapies with enhanced efficiencies and improved safety profiles.

Acknowledgements: The authors thank Dr. Clemens Meyer-Kobbe from MEKO LASERSTRAHL- MATERIAL-BEARBEITUNG – Germany that has kindly provided us with stent samples for the experiments.

REFERENCES

1. I. Neamtu, A.P. Chiriac, A. Diaconu, L.E. Nita, V. Balan and M.T. Nistor, *Mini. Rev. Med. Chem.*, **2014**, *14*, 505-536.
2. D. Diehl, D.G. Adler, J.D. Conway, F.A. Farraye, S.V. Kantsevoy, V. Kaul, S.R. Kethu, R.S. Kwon, P. Mamula, S.A. Rodriguez and W.M. Tierney, *Gastrointest. Endosc.*, **2009**, *69*, 997–1003.
3. S. Kos, R. Huegli, E. Hofmann, H.H. Quick, H. Kuehl, S. Aker, G.M. Kaiser, P.J.A. Borm, A.L. Jacob and D. Bilecen, *Cardio.Vasc. Intervent. Radiol.*, **2009**, *32*, 514–521.
4. B. Gleich, N. Hellwig, H. Bridell, R. Jurgons, C. Seliger, C. Alexiou, B. Wolf and T. Weyh, *IEEE Trans. Nanotechnol.,* **2007**, *6*, 164–170.
5. M.O. Avilésa, H. Chenb, A.D. Ebnera, A.J. Rosengartb, M.D. Kaminskic and J.A. Rittera, *J. Magn. Magn. Mater.*, **2007**, *311*, 306–311.
6. Z.G. Forbes, B.B. Yellen, D.S. Halverson, G. Fridman, K.A. Barbee and G. Friedman*, IEEE Trans. Biomed. Eng*, **2008**, *55*, 643–649.
7. S. Tamaz, *IEEE Trans. Biomed. Eng.*, **2008**, *55*, 854–1863.
8. A. Chanu and S. Martel, *IEEE Eng. Med. Biol. Soc. (EMBS)*, **2007**, 6584–6587.
9. A.P. Chiriac, L.E. Nita, L. Mititelu-Tartau, I. Neamtu, N. Tudorachi and A. Diaconu, *Rev. Roum. Chim.*, **2016**, *61*, 347-355.
10. A.H. Dutton, K.T. Tokuyasu and S.J. Singer, *Proc. Natl. Acad. Sci.*, **1979**, *76*, 3392–3396.
11. B.R. Livesay, *9th Int. Conf. on rare earth magnets and their applications,* 1987.
12. J.G. Treleaven, F.M. Gibson and J. Ugelstand, *The Lancet,* **1984**, *14,* 70–73.
13. J.G. Treleaven, *Adv. Drug. Del. Rev.,* **1988**, *2,* 253–269.
14. A.P. Chiriac, L.E. Nita, N. Tudorachi, I. Neamtu, V. Balan and L. Tartau, *Mater. Sci. Eng. C.*, **2015**, *50*, 48–357.
15. A.P. Chiriac, V. Balan, M. Asandulesa, E. Butnaru, N. Tudorachi, E. Stoleru, L.E. Nita, I. Neamtu and A. Diaconu, *Mater. Chem. Phys.*, **2016**, *180*, 291-300.
16. I. Neamtu, A.P. Chiriac, L.E. Nita, N. Tudorachi and A. Diaconu, *J. Nanopart. Res.*, **2015**, *17*, 254-268.