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POLIMERY

CZASOPISMO POŚWIĘCONE CHEMII, TECHNOLOGII i PRZETWÓRSTWU POLIMERÓW

Od redakcji / Editorial Note

Niniejszy zeszyt „Polimerów" jest poświęcony materiałom polimerowym do zastosowań medycznych. Zespół redakcyjny serdecznie dziękuje Panu prof. dr. hab. Andrzejowi Dworakowi za inicjatywę wydania tego zeszytu oraz cenną pomoc merytoryczną w jego przygotowaniu.

The issue of „Polimery" is devoted to the subject polymeric materials for medical applications. The editorial team expresses cordial thanks to Prof. Dr. Andrzej Dworak for the initiative to publish this issue and his valuable and substantial assistance in its preparation.

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Bioactive polymeric materials in biomedical and pharmaceutical applications — a story ongoing for decades*)

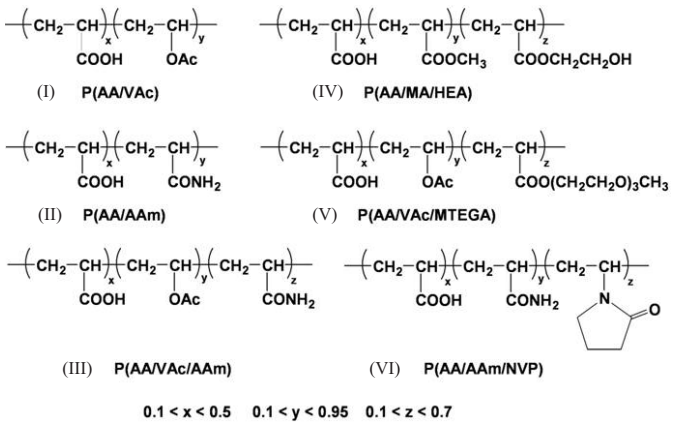
Summary — The article provides an outline of the scientific achievements in polymer science and technology with specific focus on the research activities relevant to the design and selection of bioactive polymeric materials for biomedical and pharmaceutical applications. These have been described by referring to contributions built up in decades and described in selected references.
Keywords: bioactive polymeric materials, nanoparticles, regenerative medicine, tissue engineering, hydrophilic polymeric materials, multiblock amphiphilic copolymers.

BIOAKTYWNE MATERIAŁY POLIMEROWE DO ZASTOSOWAŃ BIOMEDYCZNYCH I FARMACEUTYCZNYCH — OSIĄGNIĘCIA NA PRZESTRZENI DZIESIĘCIOLECI

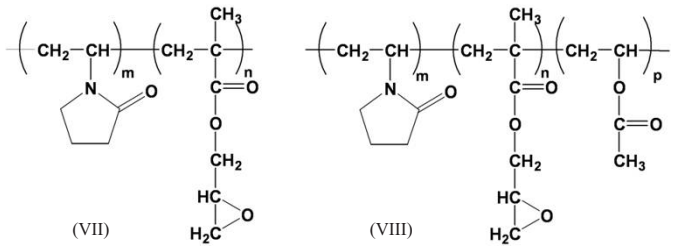
Streszczenie — W artykule opisano zarys osiągnięć naukowych w nauce i technologii polimerów, ze szczególnym uwzględnieniem badań służących projektowaniu i doborowi bioaktywnych materiałów polimerowych do zastosowań biomedycznych i farmaceutycznych. Przegląd ten uwzględnia liczne prace wykonane przez kilka dziesięcioleci przy współudziale autora.
Słowa kluczowe: bioaktywne materiały polimerowe, nanocząstki, medycyna regeneracyjna, inżynieria tkankowa, hydrofilowe materiały polimerowe, multiblokowe kopolimery amfifilowe.

*) The paper stems from a presentation given in the Scientific Station of the Polish Academy of Sciences in Vienna at Training Course „Advances in Biomaterials", March 12—16, 2012.

Mostly hydrophilic and amphiphilic polymeric materials have been designed, prepared, characterized and converted, upon having assayed their biocompatibility, to various devices of biomedical and pharmaceutical interest. In Formulas (I)—(VI) there are collected the general structures of carboxylated hydrophilic polymeric materials that were utilized for the preparation of ocular inserts loaded with pilocarpine for the prolonged therapeutic effect at zero order kinetic release profile [1—5].



In the field of hydrophilic polymers, a series of full carbon backbone copolymers [Formulas (VII) and (VIII)] and a series, prepared according to Scheme A, heteropolymeric materials (polyesters based on glyceric acid) have been obtained [6, 7].

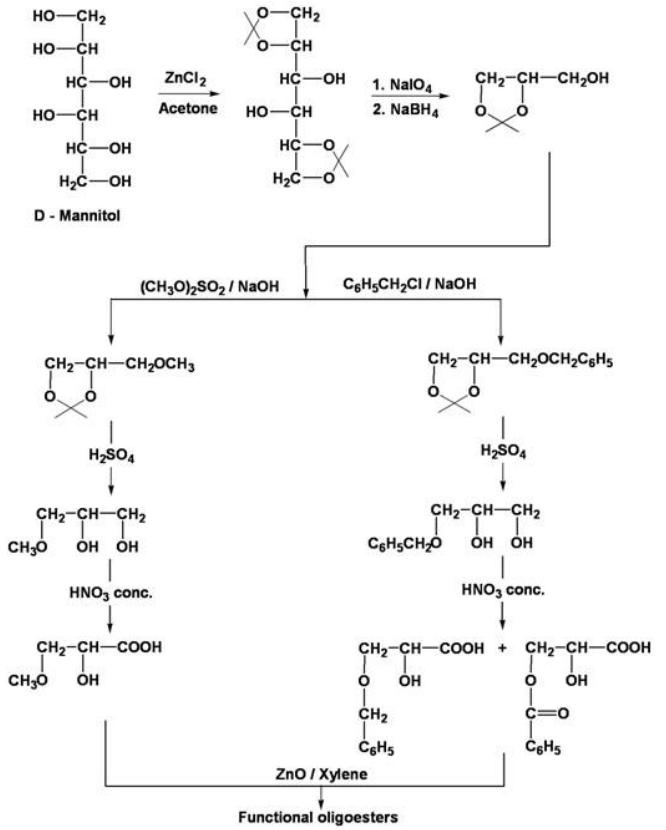


The first series of copolymers was found effective in solving problems in hemodiafiltration and is yet successfully produced and applied on the industrial scale [8].

A series of alternating functional copolymers based on alkylvinyl ethers (AVE) and maleic anhydride (MAn), attainable by charge-transfer complex polymerization mechanism, do offer the opportunity of convenient polymer-analog reactions thanks to the presence of succinoyl moiety in the repeating monomeric units [9, 10].

In Scheme B there is reported preparation of some of the general structures in hemiesterification and imidation reactions of the original alternating copolymers.

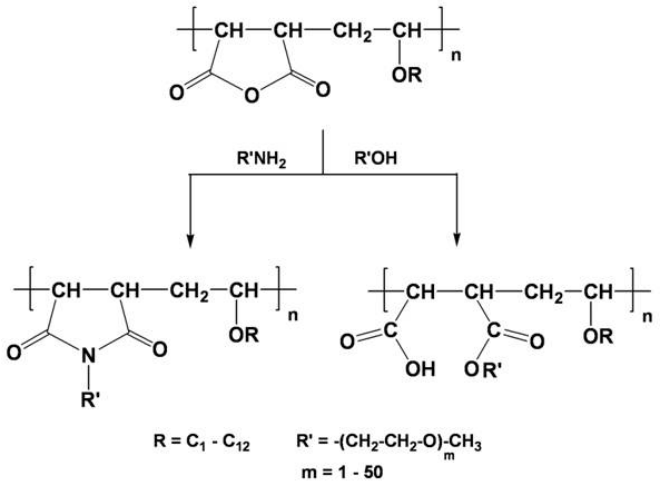
Various batches of hemiesters of alternating MAn/AVE copolymers have been used since mid 1990's in the formulation of nanoparticles (NPs) for the targeted



Scheme A. Preparation and structural representation of polyhydroxylated building blocks for the production of biocompatible/biodegradable hydrophilic polyesters (according to [6, 7])

release of proteic drugs such as α-interferon (IFNα) and later urokinase (UK) [11—13].

In Figure 1 there is sketched the formulation of NPs that have been targeted to the hepatocytes of patient affected by C-hepatitis *via* functional labelling with digalactosyl diacyl glycerol in the first case, where in the second case the NPs were addressed to target fibrin hepi-



Scheme B. Preparation of bioerodible functional polymeric material in reactions of alternating MAn/AVE copolymers (according to [11—13])

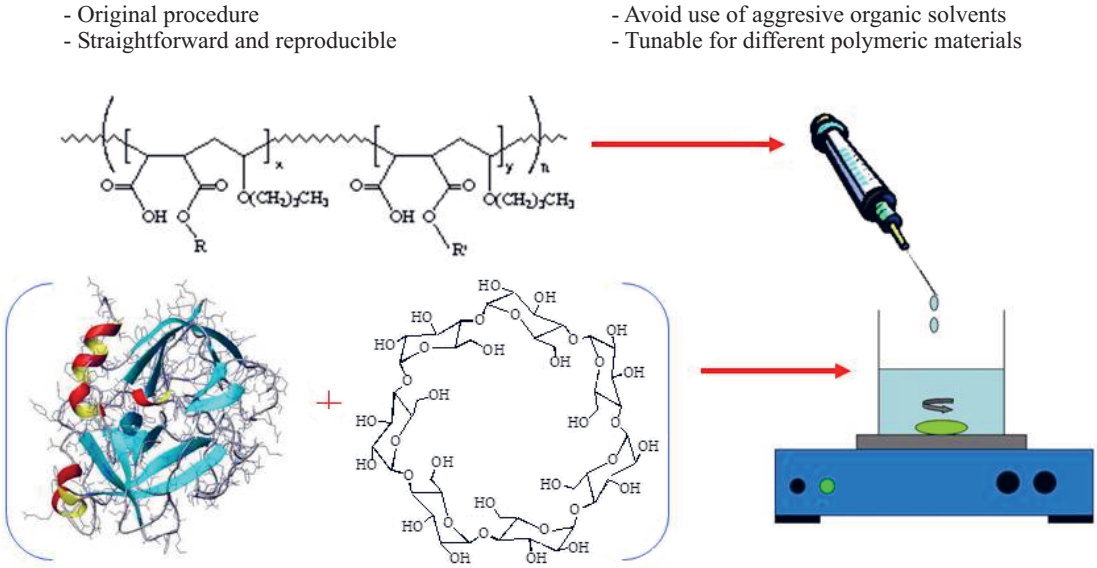
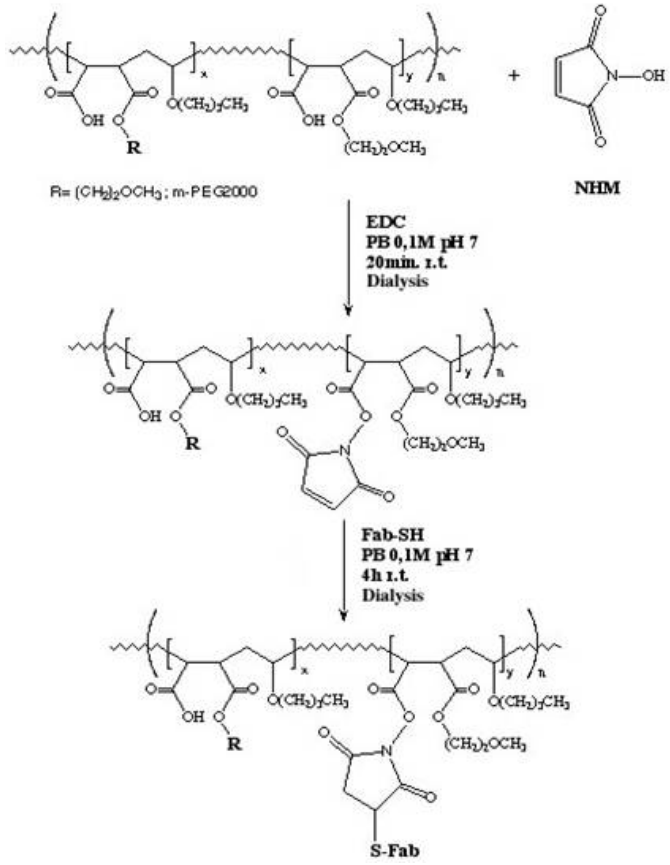


Fig. 1. Representation of the nanoparticle formulation loaded with a proteic drug (according to [14])

tope in patients affected by myocardium infarction by labelling them with a specific antibody fragment (Fab) [14].

In Scheme C there is reported the active labelling *via* a Michael type reaction of a MAn/AVE alternating hemiester with a fragment (Fab-SH) of a monoclonal antibody against fibrin hepitope [15].



Scheme C. Representation of the labelling of alternating MAn/AVE hemiester copolymers by an activated Fab-SH against fibrin hepitope (Reproduction License 3162490537751 by Wiley from Ref. [15])

In Figure 2 there is shown a micrograph of NPs targeted with Fab against fibrin hepitope, loaded with a solution of urokinase (UK) in human serum albumin (HSA) at the HSA/UK ratio = 9 and the relevant NPs size distribution comprising the recorded zeta potential [14].

In Figure 3 there is reported a profile of the UK release from the NPs shown in Figure 2 in comparison with the profile recorded for a direct injection of UK. The release of UK from the NPs follows the zero order kinetic. The NPs can be lyophilized and reconstituted in suspension by saline solution addition as sketched in Figure 3 [14, 15].

Pegylated matrices of MAn/AVE alternating copolymers have been also successfully used for the fabrication of NPs loaded with hemoglobine (Hb). A comparison between Hb-loaded NPs and Hb-loaded microparticles (MPs) based on alginate crosslinked with calcium ions, is sketched in Figure 4 [16, 17].

More recently within the framework of two EU-funded projects, *i.e.* Skintreat and Nanother [18, 19] of the 7th Framework Program, extensive studies have been performed on the preparation of NPs based on multiblock amphiphilic copolymers based on caprolactone and ethylene glycol segments (PCL-*b*-PEG) and commercially available poly(lactic-*co*-glycolic acid) copolymers (PLGA).

In Figure 5 there are represented typical structure and scheme of preparation of the amphiphilic diblock and multiblock polyester/polyether (PCL/PEG) copolymers [20, 21].

In Scheme D there is reported the preparation method of labelling of the PCL/PEG block copolymers by conjugation with folic acid (FA) [21].

In Figure 6 there is shown a comparison between the characteristics of zeta potential and size distribution of

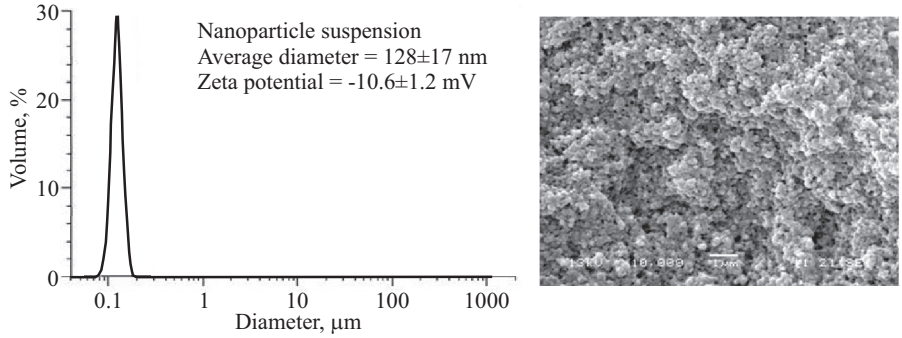


Fig. 2. Diameter size distribution (a) and SEM micrograph (b) of NPs based on MAn/AVE hemiester, loaded with UK (according to [14])

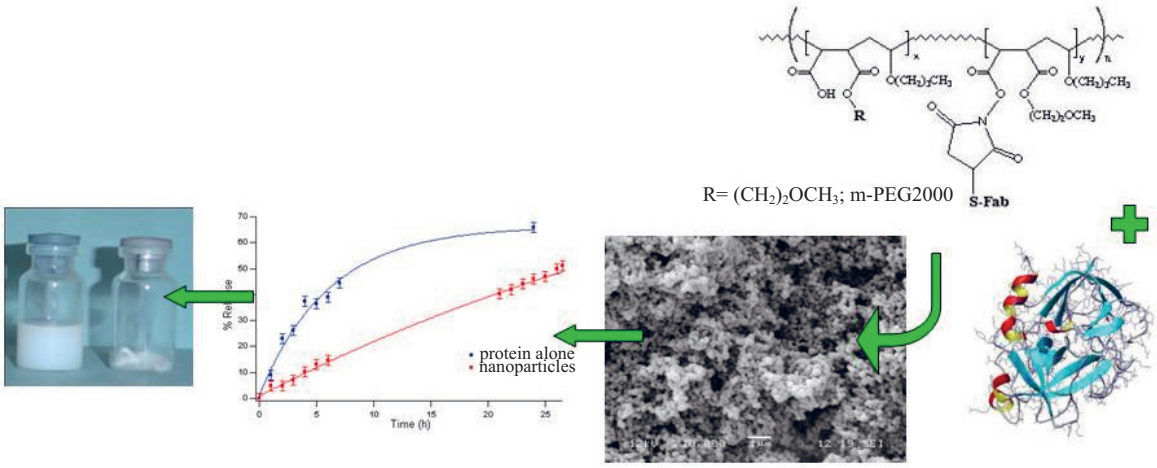


Fig. 3. UK release profile from NPs in comparison with the profile recorded for an UK direct injection (according [14, 15])

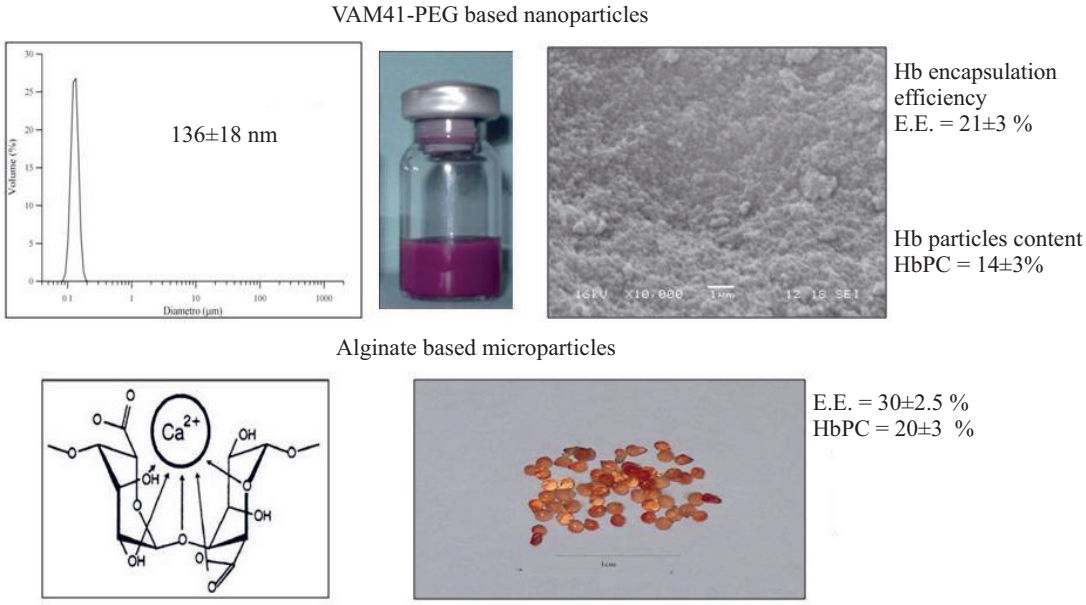


Fig. 4. Representation of: a) Hb-loaded nanoparticles (NPs), b) Hb-loaded microparticles (MPs) (according to [16, 17])

NPs based on PCL-*b*-PEG copolymer as blank unlabelled NPs and NPs labelled with FA [22, 23].

As one can see, while going from the blank to the FA labelled NPs, there is a slight increase in the average size dimension, accompanied by a distortion in the size distribution profile, whereas a substantial increase of the absolute value of zeta potential as a further indication of the FA labelling of NPs is detectable.

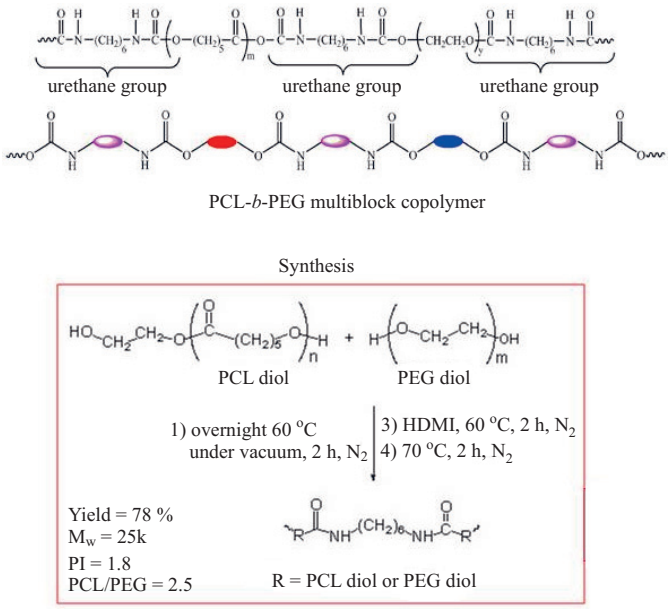


Fig. 5. Structure and the reaction scheme for the preparation of biocompatible amphiphilic PCL/PEG multiblock copolymers (according to [20, 21])

In the implementation of the activities committed in the Nanother project [19] efforts were spent on the preparation and characterization of hybrid NPs (h-NPs) loaded with anticancer drugs and magnetic particles (magnetite and cobalt ferrite) [24]. In Figure 7 there is sketched the procedure adopted for the h-NPs formulation.

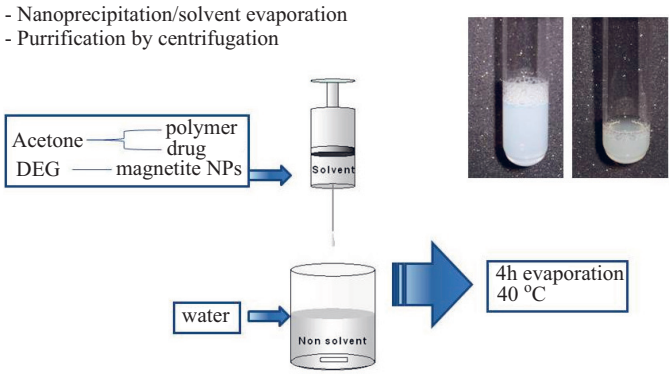


Fig. 7. Steps utilized in the formulation of hybrid nanoparticles (h-NPs) (according to [24])

The presence of a magnetite core in the h-NPs allows for their driving, under magnetic field, to the selected site of action where the hyperthermic effect can be also exploited in a selective way.

h-NPs have been also developed in the implementation of the work plan of the Skintreat Project [18]. In this case the h-NPs do consist of a polymeric continuous matrix loaded eventually with Dead Sea minerals (DSM) in combination or not with drugs utilized for the treatment of contact dermatitis and psoriasis.

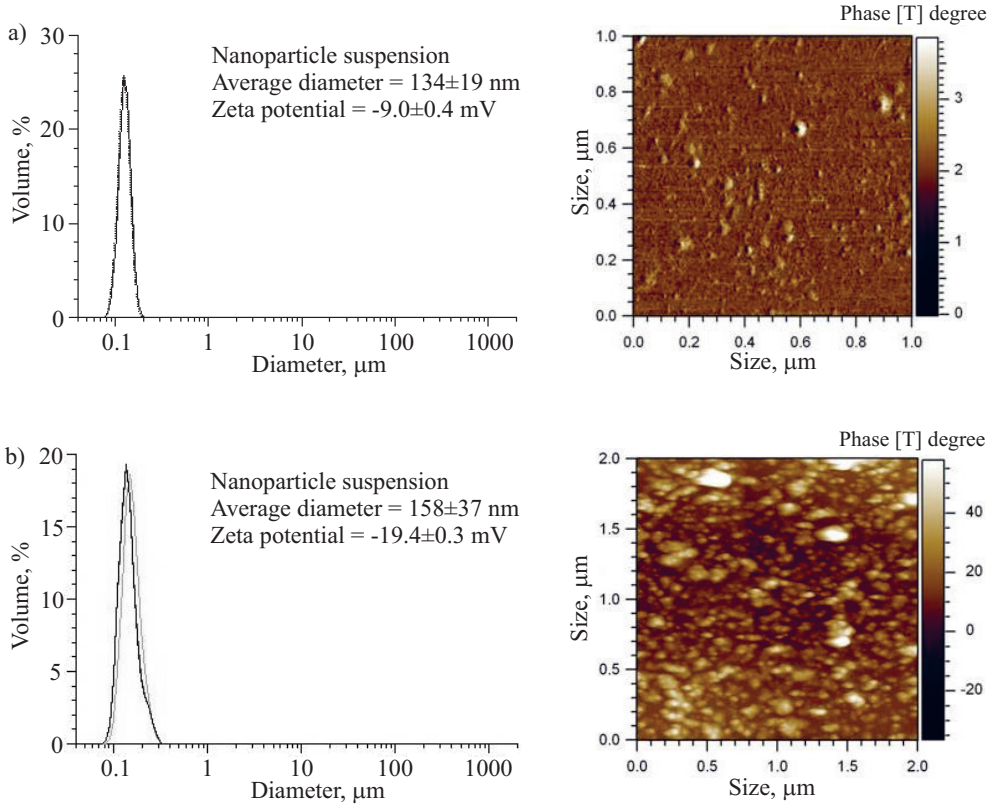
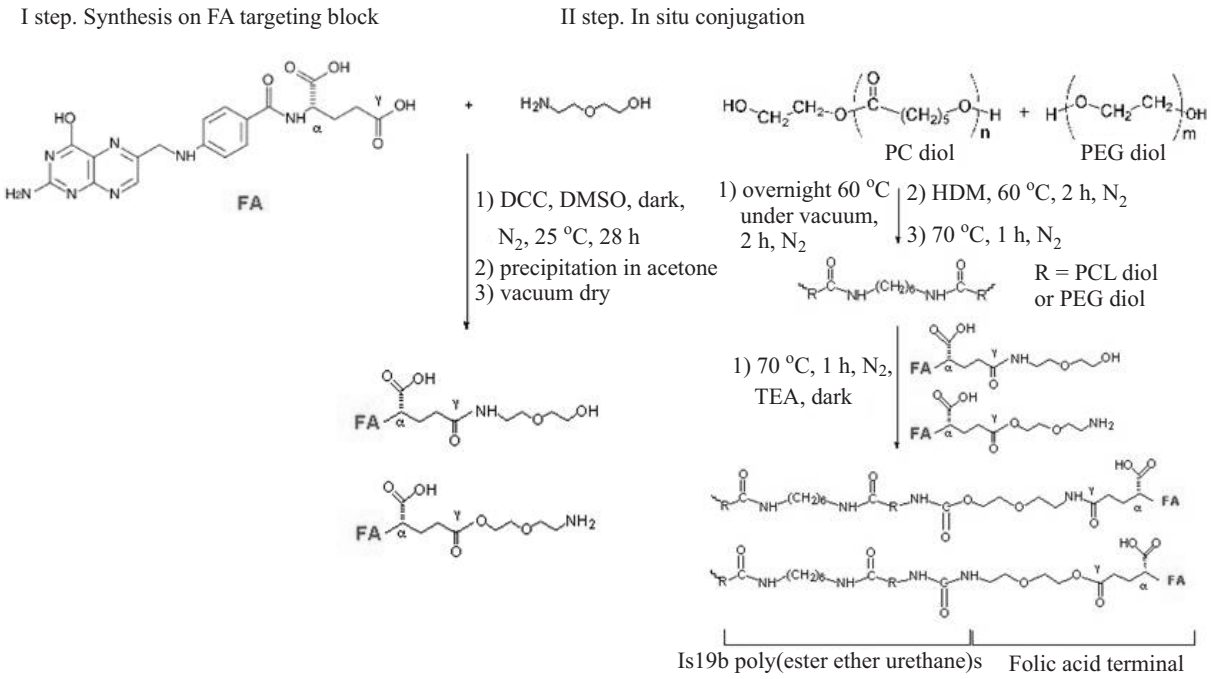


Fig. 6. Comparison of size distribution, zeta potential and AFM micrographs of a) blank (PCL-b-PEG) NPs, b) labelled (PCL-b-PEG)-FA NPs (according to [22, 23])



Scheme D. Bioactivation of biocompatible amphiphilic PCL-b-PEG copolymer with folic acid (FA) (according to [21])

In Figure 8 there is reported a scheme utilized in the preparation of h-NPs containing retinyl palmitate (RP) and DSM. Those h-NPs have been found effective in the treatment of skin affected by contact dermatitis and psoriasis [25, 26].

Parallel to the activities relevant to the preparation of organic NPs and h-NPs for the controlled and targeted administration of conventional and proteic drugs and of bioactive agents, research efforts have been oriented in the last decade to the utilization of bioactive/biocompatible polymers in tissue engineering (TE) and regenerative medicine (RM) applications. The work plan implemented in this area that is in continuous worldwide expansion has been at the basis of two EU funded projects a Network of Excellence (NoE) *i.e.* Expertissues [27] and Hyanji Scaffold [28]. Nanofibers attained by the electrospinning technique of biodegradable-biocompatible polymers have been used for the production of patches and vascular grafts.

In Figure 9 there are reported the SEM micrographs of a nanofiber patch and the picture of a vascular grafts obtained by electrospinning of poly(vinyl alcohol)

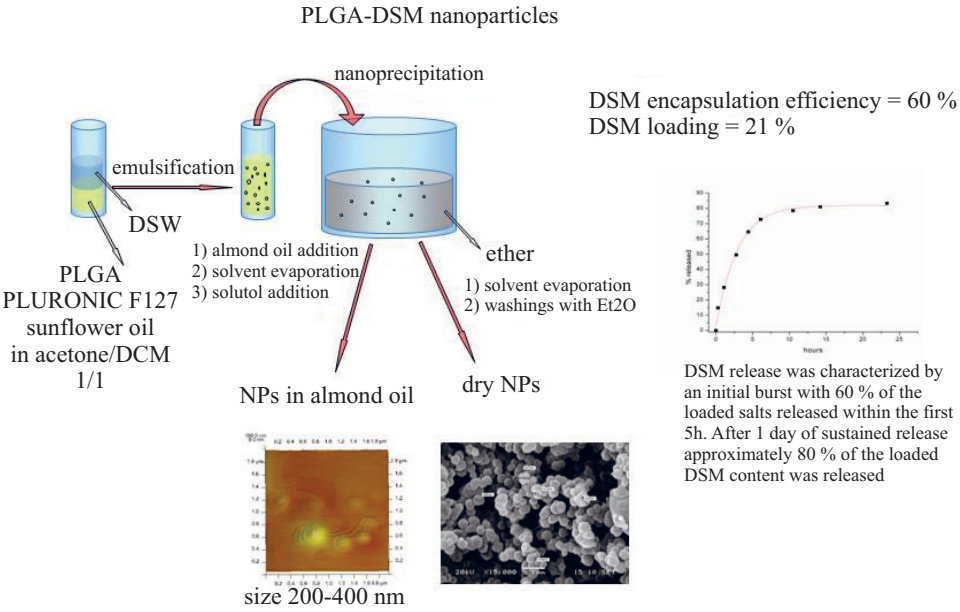


Fig. 8. Hybrid Nanoparticles (h-NPs) loaded with Dead Sea Minerals (DSM) by emulsification/nanoprecipitation process, using PLGA as continuous polymer matrix (according to [25, 26])

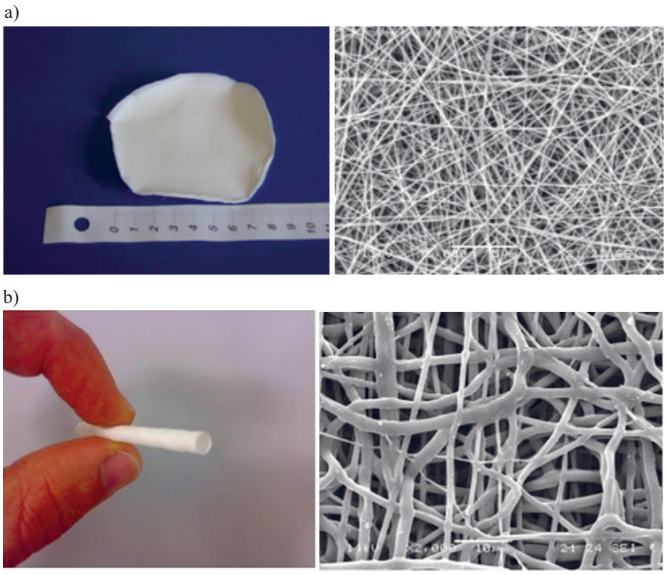


Fig. 9. SEM micrograph of a nanofiber patch based on PVA (a) and photo of a vascular grafts electrospun from Tecoflex® polyurethane (b) (Fig. 9a has been taken from ref. [29] with the permission of Sage publisher, whereas Fig. 9b has been taken from ref. [30] with the granted license n. 3162490218262 by Wiley)

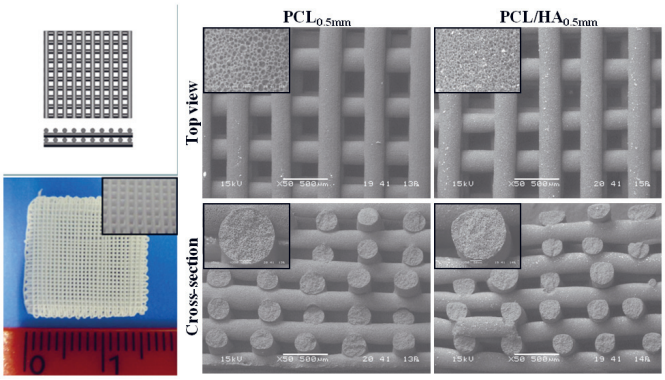


Fig. 10. SEM micrographs of PCL and PCL/HA scaffolds obtained by computer aided wet spinning with aligned fibers assembly (according to [31])

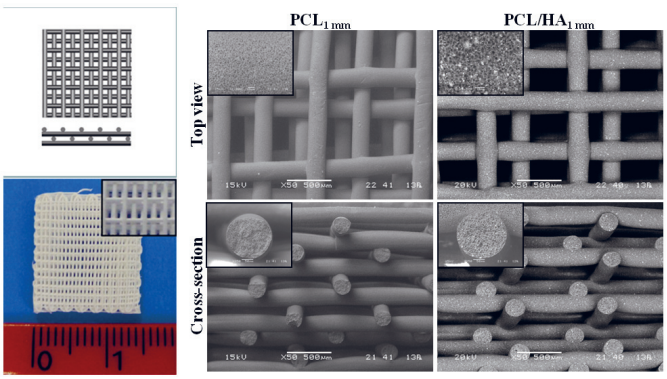


Fig. 11. SEM micrographs of PCL and PCL/HA scaffolds obtained by computer aided wet spinning with staggered fiber assembly (according to [31])

(PVA 8/88) [29] and a commercial polyurethane Tecoflex® [30], respectively.

By a complimentary technique, known as additive manufacturing (AM) consisting in a computer aided wet-spinning, series of differently shaped scaffolds have been prepared by using different biodegradable polymeric matrices [31].

In Figure 10 and 11 there is reported a series of SEM micrographs taken at different magnification of scaffolds based on biocompatible/biodegradable PCL blank and loaded with hydroxyapatite (HA).

CONCLUSIONS

A concise outline of the comprehensive activities in polymer science and technology implemented by Emo Chiellini and co-workers in 50 years of work at the University of Pisa and in a few other universities has been illustrated.

The directions given by Prof. Pero Pieno, one of the major contributors to the Nobel Prize assigned in 1963 to Prof. Giulio Natta for the polypropylene (PP) discovery, had been fundamental to the achievements accomplished in various topics of the polymer science and technology.

The inputs received by research activities oriented to problems solving, as bound to industrial commitments since early 1970's, helped to broaden the field of action and stimulate the scientific curiosity of young researchers, who are the major actors in competitive research challenges.

An integrated striving for innovation in research activities has led to the assembling of a research group endowed with different expertise, ranging from polymer chemistry, materials science, cell and molecular biology, pharmaceutical technology, computer chemistry, chemical engineering, bioengineering and microbiology.

The interdisciplinary structure of the research group, specifically active in topics related to polymer science and technology, may be eventually exploited to the benefit of competitive research in the area of both fundamental and applied science.

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Especially grateful thank to Prof. Roberto Solaro and Prof. Giancarlo Galli, former Laurea Degree Students under the author guidance, who helped to keep a cohesive research group aimed at facing and solving challenging research problems and supervising the work of tens of students involved in Laurea Degree and Doctor Degree Thesis accomplishments.

The scientists who were named in the manuscript deserve a special recognition for their friendship and contributions in collaborative activities and friendly exchange of scientific opinions.

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