BIOCATALYTIC SYNTHESIS OF BLOCK COPOLYESTER AS A POTENTIAL DRUG DELIVERY SYSTEM

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[ENGINEERING OF BIOMATERIALS 163 (2021) 52]

Introduction

Pharmaceutical polymeric nanoparticles (PNP's) are of great interest of nanomedicine due to their broad potential applications including diagnostic devices, gene delivery, vaccine, and drug delivery systems [1]. Depending on the type of potential usage, final physiochemical properties of PNP's can be adjusted to meet the certain requirements especially nanoparticles size which in this field is essential. Considering various methods used in nanoparticles fabrication, precipitation seem to be to most advantageous as it allows an easy control of nanoparticles size by changing organic solvents and polymer concentration. Moreover, fast processing time and low energy consumption is also beneficial [2]. Among a large number of polymeric materials, aliphatic block copolyesters have been commonly used in the manufacturing of drug delivery systems mainly because of their biodegradability that enables controlled drug release, reduced side-effects and improved therapeutic efficiency. However, existing biodegradable polymers that are suitable for biomedical applications are restricted by the crucial requirement of biocompatibility. Driven by those facts, we decided to synthesize a new biodegradable and biocompatible copolyester composed of diethyl adipate (DA), 1,4-butanediol and dilinoleic diol (DLA) as building block monomers to produce polymeric nanocarriers using nanoprecipitation method.

Materials and Methods

The copolyester poly(butylene adipate)-co-(dilinoleic adipate) (PBA-DLA) with 70:30 wt% hard to soft segment ratio was synthesized via two-stage polycondensation method in diphenyl ether using *Candida Antarctica* lipase B as biocatalyst. Briefly, the first step was carried out under inert gas flow at atmospheric pressure and at an initial temperature of 80°C. After 1 hour, when the reaction mixture was homogeneous, the temperature was increased to 95°C and by-product was collected. Further oligomerization was conducted under pressure of 600 Torr for 21 h and after that time the pressure has been gently reduced to 2 Torr and the reaction was performed for the next 72h. Upon completion, the product mixture was dissolved in chloroform, filtered, precipitated into cold methanol, and dried in vacuo at 40°C for 24 h. Different solvents of different Hildebrandt solubility parameters (δ) have been used for nanoprecipitation method for PNP's preparation. Polymer solutions with 0.5 w/v% concentration prepared in different solvents and their mixtures (acetone, acetone/acetonitrile, acetone/dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetone/DMF). The PNP's were produced by pouring 2.0 ml of the polymer solutions into 5.0 ml of pure water. The size of PNP's was further assessed via dynamic light scattering (DLS) measurements. Cytotoxicity of PBA-DLA 70-30 copolyesters was evaluated by indirect contact method according to ISO10993-5 using mouse fibroblasts cell line L929.

Results and Discussion

The expected chemical structure of the obtained copolyester was confirmed using ^{1}H NMR analysis (FIG. 1).

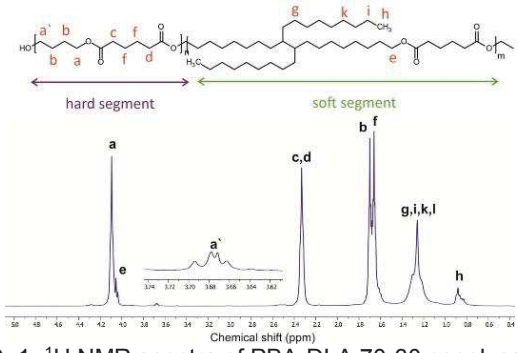

FIG. 1. ^{1}H NMR spectra of PBA-DLA 70-30 copolyester.

According to cytotoxicity studies, PBA-DLA 70-30 copolyester showed a mouse cells viability at 95% (FIG. 2).

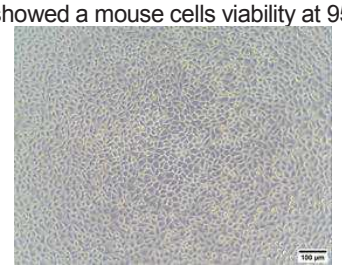

FIG. 2. Confluent mouse fibroblast cells with the presence of extracts from PBA-DLA 70-30 (magnification: 10x)

The nanoprecipitation procedure was performed by using the water miscible solvents of different δ parameter which enabled to obtain PNP's with variable size and low dispersity index similar to standards (<0.1) (FIG. 3).

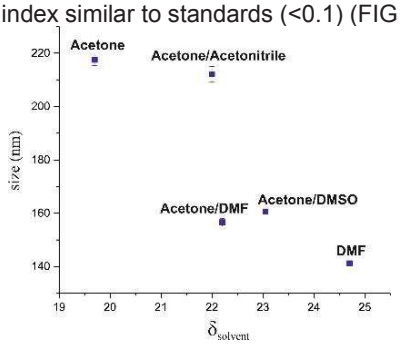

FIG. 3. Influence of the solubility parameter (δ) on the PNP's size.

Conclusions

Biobased PBA-DLA 70-30 copolyester was successfully synthesized via enzymatic polycondensation. Cytotoxicity tests revealed that material is biocompatible and exhibits minimal cytotoxicity to mouse fibroblasts. PNP's with hydrodynamic diameter ranging from 141 to 217 nm were obtained with low dispersity index (<0.1) and through nanoprecipitation. PNP's size was controlled by using different organic solvents and their mixtures.

Acknowledgments

MS acknowledges the financial support from the Dean of Faculty of Chemical Technology and Engineering.

References

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