

Documents

Khodir, W.K.W.A.^{a b}, Ismail, M.W.^a, Hamid, S.A.^{a b}, Daik, R.^c, Susanti, D.^a, Taher, M.^d, Guarino, V.^e

Synthesis and Characterization of Ciprofloxacin Loaded Star-Shaped Polycaprolactone–Polyethylene Glycol Hydrogels for Oral Delivery

(2023) *Micromachines*, 14 (7), art. no. 1382, .

DOI: 10.3390/mi14071382

^a Department of Chemistry, Kulliyah of Science, International Islamic University Malaysia Kuantan Campus, Bandar Indera Mahkota, Pahang, Kuantan, 25200, Malaysia

^b Synthetic and Functional Materials Research Group (SYNTOF), Kulliyah of Science, International Islamic University Malaysia, Kuantan Campus, Bandar Indera Mahkota, Pahang, Kuantan, 25200, Malaysia

^c Department of Chemical Sciences, Faculty of Science & Technology, Universiti Kebangsaan Malaysia, Selangor, Bangi, 43600, Malaysia

^d Department of Pharmaceutical Technology, Kulliyah of Pharmacy, International Islamic University Malaysia, Kuantan Campus, Bandar Indera Mahkota, Pahang, Kuantan, 25200, Malaysia

^e Institute of Polymers, Composites and Biomaterials, National Research Council of Italy, Mostra d'Oltremare Pad.20, V.le J.F.Kennedy 54, Naples, 80125, Italy

Abstract

The administration of poorly water-soluble drugs represents a relevant problem due to the low body fluids transport efficiency through hydrophilic hydrogels. Star-shaped co-polymers, i.e., amphiphilic polymers such as those with a hydrophobic core and a hydrophilic outer shell, can be used to improve weak interactions with drugs, with relevant benefits in terms of administration and controlled delivery. In this work, two different co-polymers, four-arm star-shaped PCL–PEG and six-arm star-shaped PCL–PEG, were synthesized via ring-opening polymerization to be loaded with ciprofloxacin. ¹H-NMR and FTIR analyses confirmed that PCL arms were successfully grafted to the mPEG backbone, while DSC analysis indicated similar crystallinity and melting point, ranging from 56 to 60 °C, independent of the different co-polymer architecture. Therefore, both star-shaped PCL-PEGs were investigated as cargo device for ciprofloxacin. No significant differences were observed in terms of drug entrapment efficiency (>95%) and drug release, characterized by a pronounced burst followed by a slow sustained release, only slightly affected by the co-polymer architecture. This result was also confirmed with curve fitting via the Korsmeyer–Peppas model. Lastly, good antibacterial properties and biocompatibility exhibited in both star-shaped PCL–PEG co-polymers suggest a promising use for oral delivery applications. © 2023 by the authors.

Author Keywords

ciprofloxacin; drug delivery; hydrogels; PCL arms; star co-polymers

Index Keywords

Antibiotics, Biocompatibility, Body fluids, Controlled drug delivery, Crystallinity, Curve fitting, Efficiency, Hydrogels, Hydrophilicity, Polyethylene oxides, Ring opening polymerization, Targeted drug delivery; Ciprofloxacin, Co-polymers, Lower body, Oral delivery, PCL arm, Polymer architecture, Poorly water-soluble drugs, Star co-polymer, Star-shaped, Synthesis and characterizations; Polyethylene glycols

References

- Boyd, B.J., Bergström, C.A., Vinarov, Z., Kuentz, M., Brouwers, J., Augustijns, P., Brandl, M., Pr at, V.
Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems (2019) *Eur. J. Pharm. Sci.*, 137, p. 104967.
- Laffleur, F., Keckeis, V.
Advances in drug delivery systems: Work in progress still needed? (2020) *Int. J. Pharm. X*, 2, p. 100050. 32577616
- Guarino, V., Khodir, W.K.W.A., Ambrosio, L.
Biodegradable Microparticles and Nanoparticles by Electrospraying Techniques (2012) *J. Appl. Biomater. Funct. Mater.*, 10, pp. 191-196. 23258557

- Fasolino, I., Guarino, V., Cirillo, V., Ambrosio, L.
5-Azacytidine-mediated hMSC behavior on electrospun scaffolds for skeletal muscle regeneration
(2017) *J. Biomed. Mater. Res. Part A*, 105, pp. 2551-2561.
- Vinarov, Z., Abrahamsson, B., Artursson, P., Batchelor, H., Berben, P., Bernkop-Schnürch, A., Butler, J., Dupont, D.
Current challenges and future perspectives in oral absorption research: An opinion of the UNGAP network
(2021) *Adv. Drug Deliv. Rev.*, 171, pp. 289-331.
- Uhljar, L., Kan, S.Y., Radacsi, N., Koutsos, V., Szabó-Révész, P., Ambrus, R.
In Vitro Drug Release, Permeability, and Structural Test of Ciprofloxacin-Loaded Nanofibers
(2021) *Pharmaceutics*, 13.
- Muhammad Sarfraz, R., Bashir, S., Mahmood, A., Ahsan, H., Riaz, H., Raza, H., Rashid, Z., Abbas, K.
Application of Various Polymers and Polymers Based Techniques Used to Improve Solubility of Poorly Water Soluble Drugs: A Review
(2017) *Acta Pol. Pharm. Drug Res*, 74, pp. 347-356.
- Alkattan, N.S., Alasmael, N., Ladelta, V., Khashab, N.M., Hadjichristidis, N.
Poly(2-oxazoline)-based core cross-linked star polymers: Synthesis and drug delivery applications
(2023) *Nanoscale Adv*, 5, pp. 2794-2803.
- Lotocki, V., Kakkar, A.
Miktoarm Star Polymers: Branched Architectures in Drug Delivery
(2020) *Pharmaceutics*, 12.
- Somszor, K., Allison-Logan, S., Karimi, F., McKenzie, T., Fu, Q., O'connor, A., Qiao, G., Heath, D.
Amphiphilic Core Cross-Linked Star Polymers for the Delivery of Hydrophilic Drugs from Hydrophobic Matrices
(2021) *Biomacromolecules*, 22, pp. 2554-2562.
- Wakaskar, R.R.
General overview of lipid-polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes
(2018) *J. Drug Target*, 26, pp. 311-318.
28797169
- Bayat, N., McOrist, N., Ariotti, N., Lai, M., Sia, K.C., Li, Y., Grace, J.L., Kavallaris, M.
Thiol-Reactive Star Polymers Functionalized with Short Ethoxy-Containing Moieties Exhibit Enhanced Uptake in Acute Lymphoblastic Leukemia Cells
(2019) *Int. J. Nanomed*, 14, pp. 9795-9808.
31853178
- Somers, K., Wen, V.W., Middlemiss, S.M.C., Osborne, B., Forgham, H., Jung, M., Karsa, M., Gao, J.
A novel small molecule that kills a subset of MLL-rearranged leukemia cells by inducing mitochondrial dysfunction
(2019) *Oncogene*, 38, pp. 3824-3842.
30670779
- Sahranavard, M., Shahriari, M., Abnous, K., Hadizadeh, F., Taghdisi, S.M., Zolfaghari, R., Ramezani, M., Alibolandi, M.
Design and synthesis of targeted star-shaped micelle for guided delivery of camptothecin: In vitro and in vivo evaluation

(2021) *Mater. Sci. Eng. C Mater. Biol. Appl.*, 131, p. 112529.

34857308

- Braunová, A., Chytil, P., Laga, R., Šírová, M., Machová, D., Parnica, J., Říhová, B., Etrych, T.
Polymer nanomedicines based on micelle-forming amphiphilic or water-soluble polymer-doxorubicin conjugates: Comparative study of in vitro and in vivo properties related to the polymer carrier structure, composition, and hydrodynamic properties
(2020) *J. Control Release*, 321, pp. 718-733.
32142741
- Gu, D., Ladewig, K., Klimak, M., Haylock, D., McLean, K.M., O'Connor, A.J., Qiao, G.G.
Amphiphilic core cross-linked star polymers as water-soluble, biocompatible and biodegradable unimolecular carriers for hydrophobic drugs
(2015) *Polym. Chem*, 6, pp. 6475-6487.
- Oliveira, A.S.R., Mendonça, P.V., Simões, S., Serra, A.C., Coelho, J.F.J.
Amphiphilic well-defined degradable star block copolymers by combination of ring-opening polymerization and atom transfer radical polymerization: Synthesis and application as drug delivery carriers
(2021) *J. Polym. Sci*, 59, pp. 211-229.
- Omura, T., Imagawa, K., Kono, K., Suzuki, T., Minami, H.
Encapsulation of Either Hydrophilic or Hydrophobic Substances in Spongy Cellulose Particles
(2017) *ACS Appl. Mater. Interfaces*, 9, pp. 944-949.
- Li, Q., Li, X., Zhao, C.
Strategies to Obtain Encapsulation and Controlled Release of Small Hydrophilic Molecules
(2020) *Front. Bioeng. Biotechnol.*, 8, p. 437.
- Larrañeta, E., Stewart, S., Ervine, M., Al-Kasasbeh, R., Donnelly, R.
Hydrogels for Hydrophobic Drug Delivery. Classification, Synthesis and Applications
(2018) *J. Funct. Biomater.*, 9.
- Mohanty, A.K., Jana, U., Manna, P.K., Mohanta, G.P.
Synthesis and evaluation of MePEG-PCL diblock copolymers: Surface properties and controlled release behavior
(2015) *Prog. Biomater.*, 4, pp. 89-100.
- Bolourchian, N., Mahboobian, M.M., Dadashzadeh, S.
The Effect of PEG Molecular Weights on Dissolution Behavior of Simvastatin in Solid Dispersions
(2013) *Iran. J. Pharm. Res.*, 12, pp. 11-20.
- Guarino, V., Galizia, M., Alvarez-Perez, M., Mensitieri, G., Ambrosio, L.
Improving surface and transport properties of macroporous hydrogels for bone regeneration
(2015) *J. Biomed. Mater. Res. A*, 103, pp. 1095-1105.
- Lust, S.T., Hoogland, D., Norman, M.D.A., Kerins, C., Omar, J., Jowett, G.M., Yu, T.T.L., Marciano, D.
Selectively Cross-Linked Tetra-PEG Hydrogels Provide Control over Mechanical Strength with Minimal Impact on Diffusivity
(2021) *ACS Biomater. Sci. Eng.*, 7, pp. 4293-4304.
- Kumar, A.C., Erothu, H.
Synthetic Polymer Hydrogels

(2016) *Biomedical Applications of Polymeric Materials and Composites*, pp. 141-162. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany

- Heng, P.W.S.
Controlled release drug delivery systems
(2018) *Pharm. Dev. Technol*, 23, p. 833.
- Lei, L., Bai, Y., Qin, X., Liu, J., Huang, W., Lv, Q.
Current Understanding of Hydrogel for Drug Release and Tissue Engineering
(2022) *Gels*, 8.
- Li, J., Mooney, D.J.
Designing hydrogels for controlled drug delivery
(2016) *Nat. Rev. Mater*, 1, p. 16071.
- Brambilla, E., Locarno, S., Gallo, S., Orsini, F., Pini, C., Farronato, M., Thomaz, D.V., Tartaglia, G.
Ploxamer-Based Hydrogel as Drug Delivery System: How Polymeric Excipients Influence the Chemical-Physical Properties
(2022) *Polymers*, 14.
36080699
- Abdul Khodir, W., Abdul Razak, A., Ng, M., Guarino, V., Susanti, D.
Encapsulation and Characterization of Gentamicin Sulfate in the Collagen Added Electrospun Nanofibers for Skin Regeneration
(2018) *J. Funct. Biomater*, 9.
29783681
- Lee, H., Han, S.D., Shin, B.S., Park, J.B.
Development of an in vitro dissolution test method for hydrogel-based drug delivery systems
(2016) *J. Pharm. Investig*, 46, pp. 275-285.
- Ueda, C.T., Shah, V.P., Derdzinski, K., Ewing, G., Flynn, G., Maibach, H., Marques, M., Thakker, K.
Topical and Transdermal Drug Products
(2009) *Pharmacop. Forum*, 35, pp. 750-764.
- Vigata, M., Meinert, C., Hutmacher, D.W., Bock, N.
Hydrogels as Drug Delivery Systems: A Review of Current Characterization and Evaluation Techniques
(2020) *Pharmaceutics*, 12.
- Güney, A., Gardiner, C., McCormack, A., Malda, J., Grijpma, D.W.
Thermoplastic PCL-b-PEG-b-PCL and HDI Polyurethanes for Extrusion-Based 3D-Printing of Tough Hydrogels
(2018) *Bioengineering*, 5.
30441879
- Nabid, M.R., Tabatabaei Rezaei, S.J., Sedghi, R., Niknejad, H., Entezami, A.A., Oskooie, H.A., Heravi, M.M.
Self-assembled micelles of well-defined pentaerythritol-centered amphiphilic A4B8 star-block copolymers based on PCL and PEG for hydrophobic drug delivery
(2011) *Polymer*, 52, pp. 2799-2809.
- Wang, F., Bronich, T.K., Kabanov, A.V., Rauh, R.D., Roovers, J.
Synthesis and Evaluation of a Star Amphiphilic Block Copolymer from Poly(ϵ -caprolactone) and Poly(ethylene glycol) as a Potential Drug Delivery Carrier
(2005) *Bioconjugate Chem*, 16, pp. 397-405.

- Letchford, K., Zastre, J., Liggins, R., Burt, H.
Synthesis and micellar characterization of short block length methoxy poly(ethylene glycol)-block-poly(caprolactone) diblock copolymers
(2004) *Colloids Surf. B Biointerfaces*, 35, pp. 81-91.
15261040
- Faisal, K.S., Clulow, A.J., MacWilliams, S.V., Gillam, T.A., Austin, A., Krasowska, M., Blencowe, A.
Microstructure—Thermal Property Relationships of Poly (Ethylene Glycol-b-Caprolactone) Copolymers and Their Micelles
(2022) *Polymers*, 14.
- Castillo, R.V., Müller, A.J., Raquez, J.-M., Dubois, P.
Crystallization Kinetics and Morphology of Biodegradable Double Crystalline PLLA-b-PCL Diblock Copolymers
(2010) *Macromolecules*, 43, pp. 4149-4160.
- Hua, C., Dong, C.-M.
Synthesis, characterization, effect of architecture on crystallization of biodegradable poly(ϵ -caprolactone)-b-poly(ethylene oxide) copolymers with different arms and nanoparticles thereof
(2007) *J. Biomed. Mater. Res. A*, 82A, pp. 689-700.
- Lombardo, D., Kiselev, M.A., Magazù, S., Calandra, P.
Amphiphiles Self-Assembly: Basic Concepts and Future Perspectives of Supramolecular Approaches
(2015) *Adv. Condens. Matter Phys*, 2015, p. 151683.
- Colinet, I., Dulong, V., Mocanu, G., Picton, L., Le Cerf, D.
New amphiphilic and pH-sensitive hydrogel for controlled release of a model poorly water-soluble drug
(2009) *Eur. J. Pharm. Biopharm*, 73, pp. 345-350.
- Hoare, T.R., Kohane, D.S.
Hydrogels in drug delivery: Progress and challenges
(2008) *Polymer*, 49, pp. 1993-2007.
- Lin, Y.-S., Tsay, R.-Y.
Drug Release from a Spherical Matrix: Theoretical Analysis for a Finite Dissolution Rate Affected by Geometric Shape of Dispersed Drugs
(2020) *Pharmaceutics*, 12.
32585967
- Okugawa, A., Sakaino, M., Yuguchi, Y., Yamane, C.
Relaxation phenomenon and swelling behavior of regenerated cellulose fibers affected by water
(2019) *Carbohydr. Polym*, 231, p. 115663.
- Mishra, G.P., Tamboli, V., Mitra, A.K.
Effect of hydrophobic and hydrophilic additives on sol-gel transition and release behavior of timolol maleate from polycaprolactone-based hydrogel
(2011) *Colloid Polym. Sci*, 289, pp. 1553-1562.
- Paarakh, M.P., Jose, P.A., Setty, C., Peterchristoper, G.
Release Kinetics-Concepts and Applications
(2019) *Int. J. Pharm. Res. Technol*, 8, pp. 12-20.
- Padinjarathil, H., Mudradi, S., Balasubramanian, R., Drago, C., Dattilo, S., Kothurkar, N.K., Ramani, P.
Design of an Antibiotic-Releasing Polymer: Physicochemical Characterization and Drug Release Patterns

(2023) *Membranes*, 13.
36676910

- Wu, J., Zhang, Z., Gu, J., Zhou, W., Liang, X., Zhou, G., Han, C.C., Liu, Y.
Mechanism of a long-term controlled drug release system based on simple blended electrospun fibers
(2020) *J. Control Release*, 320, pp. 337-346.
- Caccavo, D.
An overview on the mathematical modeling of hydrogels' behavior for drug delivery systems
(2019) *Int. J. Pharm*, 560, pp. 175-190.
- Caccavo, D., Cascone, S., Lamberti, G., Barba, A.A.
Hydrogels: Experimental characterization and mathematical modelling of their mechanical and diffusive behaviour
(2018) *Chem. Soc. Rev*, 47, pp. 2357-2373.
- Crovetto, S.I., Moreno, E., Dib, A.L., Espigares, M., Espigares, E.
Bacterial toxicity testing and antibacterial activity of parabens
(2017) *Toxicol. Environ. Chem*, 99, pp. 858-868.
- Rybczyńska-Tkaczyk, K., Grenda, A., Jakubczyk, A., Kiersnowska, K., Bik-Małodzińska, M.
Natural Compounds with Antimicrobial Properties in Cosmetics
(2023) *Pathogens*, 12.
36839592
- Lincho, J., Martins, R.C., Gomes, J.
Paraben Compounds—Part I: An Overview of Their Characteristics, Detection, and Impacts
(2021) *Appl. Sci*, 11.
- Asghar, A.A., Akhlaq, M., Jalil, A., Azad, A.K., Asghar, J., Adeel, M., Albadrani, G.M., Altyar, A.E.
Formulation of ciprofloxacin-loaded oral self-emulsifying drug delivery system to improve the pharmacokinetics and antibacterial activity
(2022) *Front. Pharmacol*, 13, pp. 1-14.
36267282
- Kloskowski, T., Gurtowska, N., Nowak, M., Joachimiak, R., Bajek, A., Olkowska, J., Drewa, T.
The influence of ciprofloxacin on viability of A549, HepG2, A375.S2, B16 and C6 cell lines in vitro
(2011) *Acta Pol. Pharm*, 68, pp. 859-865.

Correspondence Address

Khodir W.K.W.A.; Department of Chemistry, International Islamic University Malaysia Kuantan Campus, Bandar Indera Mahkota, Pahang, Malaysia; email: wkhartini@iiium.edu.my

Daik R.; Department of Chemical Sciences, Selangor, Malaysia; email: rusli.daik@ukm.edu.my

Guarino V.; Institute of Polymers, Mostra d'Oltremare Pad.20, V.le J.F.Kennedy 54, Italy; email: vincenzo.guarino@cnr.it

Publisher: Multidisciplinary Digital Publishing Institute (MDPI)

ISSN: 2072666X

Language of Original Document: English

Abbreviated Source Title: Micromachines

2-s2.0-85166183593

Document Type: Article

Publication Stage: Final

Source: Scopus

ELSEVIER

Copyright © 2024 Elsevier B.V. All rights reserved. Scopus® is a registered trademark of Elsevier B.V.

 **RELX** Group™