



Biocompatible Gelatin Nanofibers as Potential Anticancer Drug Delivery Systems

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ABSTRACT

Abstract: Today, cancer remains a worldwide and severe public health challenge. Cancer is one of the reasons of disease and mortality global; chiefly owing to problems in treatment-associated, recurrence rates, metastasis and late diagnosis. In latest years, with the development of nano-materials, the investigation of drug delivery systems has become a novel field of cancer therapy. Local drug delivery systems are hopeful apparatuses in modern medicine because they can promise the release of drugs with the kinetics necessary; via specific applications and a reduction in unwanted side effects. Drug delivery systems are typically composed of delivery carriers, antitumor drugs, and even target molecules. Over the years, a wide variation of polymeric nano-mats has been explored as implantable single drug delivery systems. Gelatin is a natural polymer with highly biocompatibility and non-toxicity that is manufactured via thermal denaturalization of collagen, which is available in animal skin and bones in the presence of dilute acids. On the other hand, electrospinning is a widely considered method for the progress of drug-delivery nano-mats. 3-D Gelatin electrospun nanofibers (with great porosity and small pore size) can be applied to deliver anti-cancer drugs (like Doxorubicin, Tamoxifen and Curcumin) in cancer therapy. This mini review presents the gelatin nanofibrous anti-cancer drug delivery carriers for clinical application of cancer nanomedicine in the future.

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Introduction

Cancer is described as a wild growth of abnormal cells. It is assessed that there are more than 200 different kinds of cancer, usually named consistent with the tissue wherever the cancer was recognized for the first time. Now, the conservative therapeutic methods for the treatment of cancer are surgery, radiotherapy, and chemotherapy. On the other hand, nanotechnology has been actively combined as drug carriers over the past few years to treat several cancers (1-3). The main objective of nanomedicine in the treatment of oncological illnesses is to selectively carry the drug just to cancer cells. Up to now, numerous anticancer drugs like doxorubicin (DOX), curcumin (CUR), paclitaxel (PTX) and camptothecin (CPT) have been used in drug delivery structures (4).

Gelatin: A Biocompatible macromolecule

Gelatin is a biopolymer that is manufactured via thermal denaturalization of collagen, which is available in animal skin and bones in the presence of dilute acids. Gelatin contains of a great amount of glycine, proline, and 4-hydroxy proline residues (Figure 1) (5). Gelatin is extensively used biopolymer in several industries owing to its outstanding biocompatibility and biodegradability properties (6). Gelatin is a product of collagen hydrolysis, and is a natural, macromolecule that is considered as an perfect biomaterial used to biotechnology applications (7). In the next paragraphs, the various studies and researches based on *Gelatin nano-mats* in cancer treatment field will be highlighted and stated in detail.

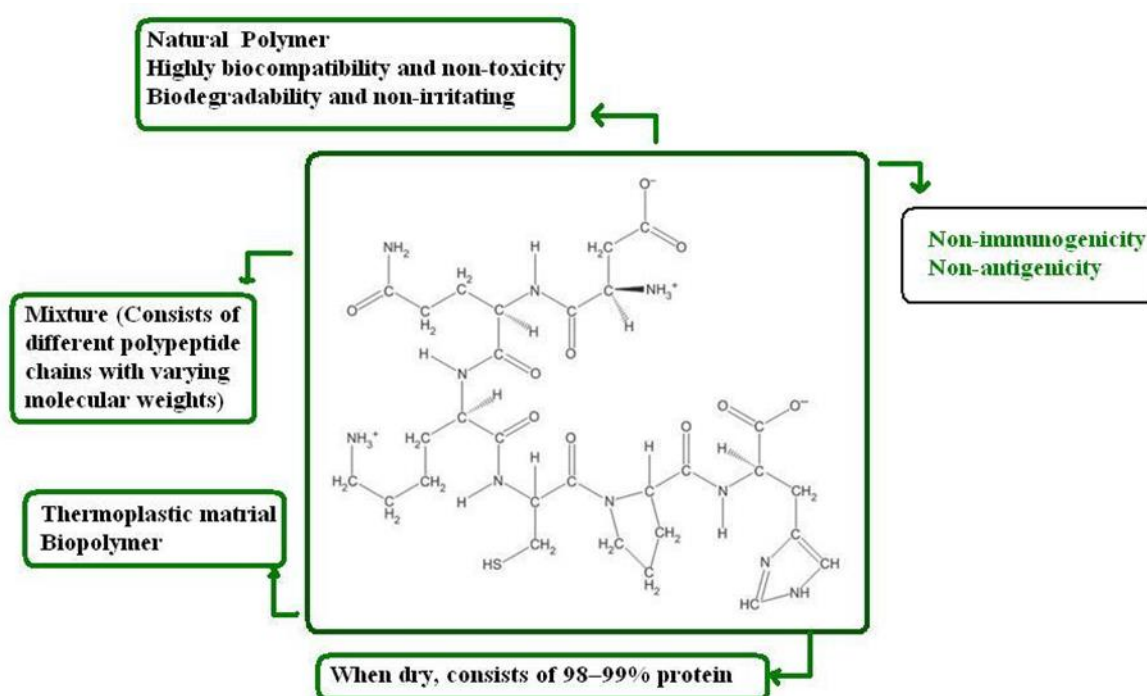


Figure 1. Gelatin. A natural polymer

Electro-spun Gelatin Nano-mats

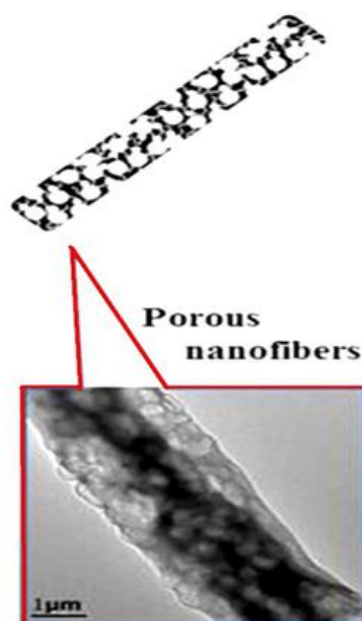
Nano-fibrous meshes refer to the structures made of ultra-fine polymeric fibers (8-10). The diameter of such fibers varieties from several micrometers down to few nano-meters, therefore are mentioned among nanotechnology and micron size world (11, 12). Such very small diameter results in a relatively high surface area to volume ratio (Approximately 100 m²/g for a 100 nm diameter nano-fibrous mat) (13, 14). Such increase in surface area can significantly affect the physio-chemical and morphological properties of the nanofibers (15, 16).

➤ High porosity and small pore size

The technique that nanofibers are synthesized allow self-assembled nanofibers to align themselves into a characteristic 3D pattern, such as a honey comb meshes (17-19). Because of the small fiber diameter and high surface area to volume ratio, tiny pores in the range of 0.5 nm are formed within the nanofiber mesh, resulting in highly porous 3D structure (Scheme 1) (20, 21). Numerous synthetic, semisynthetic and natural polymers have been utilized to produce nanofibers (22, 23). Electrospun nanofibers offer several necessary structures as drug delivery systems (25,26).

1. The electro-spinning procedure can be used to manufacture nano-fibers from an extensive variety of solutions of both natural Polymers (27-29).
2. Nanofibers have high surface-layer area to volume ratios which provide efficient delivery of both hydrophilic and hydrophobic drug molecules (30, 31).
3. The drug release profile can be tuned to meet the specific clinical usage by modulating a variety of parameters, for instance the drug to polymer ratio, fiber diameter, morphology, and-or porosity (32-34).

Electro-spinning of gelatin delivers a hopeful approach to integrate the great presentations of gelatin with the perfect morphology and structure of electrospun nanofibers (35). As a water-soluble polymer, water is used as a solvent to dissolve gelatin for electrospinning use (36, 37).

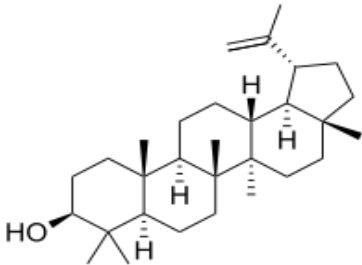
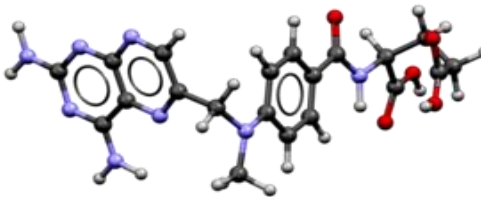
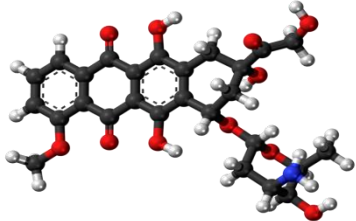
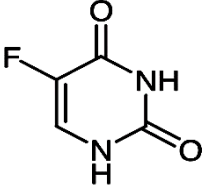


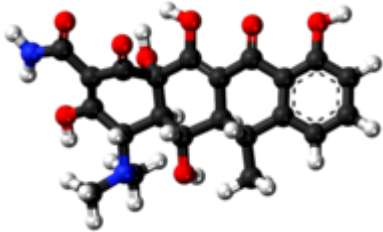
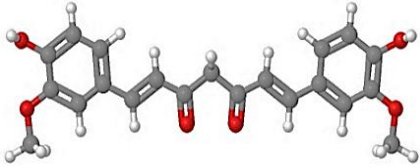
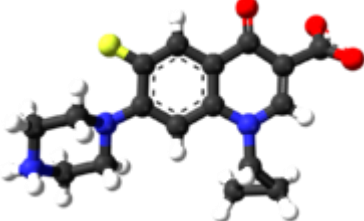
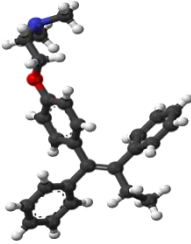

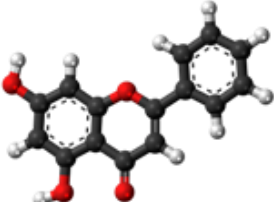
Scheme 1. Electrospun nanofibers with high porosity and small pore size (24)

Gelatin nanofibers as potential anti-cancer drug delivery structures

In latest years, anticancer nanomedicines have mainly been progressed for chemotherapy and combination therapy in which the chief contributing anticancer drugs (Synthetic anti-cancer drugs like Curcumin (1, 38-40) and Herbal anti-cancer drugs like Doxorubicin (41, 42) are delivered by deliberately designed nano drug delivery systems (43-45). Table 1 presents the application of gelatin nano-mats as novel anti-cancer delivery systems.

Table 1. Novel gelatin nano-fibrous structure as anti-cancer delivery systems

Gelatin Nanomat			
Chemical Formulation	Physical Structure	Drug	Ref.
Gelatin+Polycaprolactone	Nanofibrous Mat	Lupeol (C ₃₀ H ₅₀ O)	(46)
			
Gelatin+Poly(3-hydroxybutyric acid)	Nanofibrous Scaffold	Methotrexate (C ₂₀ H ₂₂ N ₈ O ₅)	(47)
			
Gelatin+Poly(l-lactide-co-ε-caprolactone)	Core-shell Nanofibers	Doxorubicin (C ₂₇ H ₂₉ NO ₁₁)	(48, 49)
			
Gelatin	<u>Forcespun Nanofibers</u>	Isorhamnetin (C ₁₆ H ₁₂ O ₇)	(50)
Gelatin+Poly(caprolactone)	Nanofibers	5-Fluorouracil(C ₄ H ₃ FN ₂ O ₂)	(51)
			

Gelatin+Poly-caprolactone+ Hydroxyapatite nanoparticles	Hybrid Nanofibers	Doxycycline($C_{22}H_{24}N_2O_8$) (52)	
Gelatin	Electrospun nanofibers	Curcumin($C_{21}H_{20}O_6$) (53), (54-	
Gelatin+poly(lactide-co-ε- caprolactone)	Electrospun nanofibers	Ciprofloxacin($C_{17}H_{18}FN_3O_3$) (51)	
Gelatin	Nanofibers	Tamoxifen($C_{26}H_{29}NO$) (56, 62)	
Gelatin+Poly (vinyl alcohol)	Multilayer Nanofibers	Fluconazole ($C_{13}H_{12}F_2N_6O$) (63)	
Gelatin+Poly(caprolactone)	Nanofibers	Chrysin($C_{15}H_{10}O_4$) (64)	

Conclusion

Gelatin has been shown to be a prospective biopolymer to be applied in drug delivery uses owing to its biocompatibility and bio degradability nature. In contrast nanofibers can be applied to deliver anti-cancer drugs, so as Gelatin nanofibers are the novel biomaterials which are capable as drug carriers in human body for numerous applications like cancer therapy. This mini-review gives detailed information about the recent developments and uses of gelatin nanofibers as anti-cancer drug delivery vehicles for cancer treatment.

Future aspects

The author proposes an alternative strategy “Ultraviolet/O3 surface treatment” on gelatin nanofibers (for reduction of hydrophobicity). This strategy is expected to increase the success of anticancer drug solution in the gelatin nano-mats.

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Competing Interests

The author declares no conflict of interest.

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References

1. Chavda VP, Patel AB, Mistry KJ, Suthar SF, Wu Z-X, Chen Z-S, et al. Nano-Drug Delivery Systems Entrapping Natural Bioactive Compounds for Cancer: Recent Progress and Future Challenges. *Front Oncol.* 2022;12:1-18.
2. Arun A, Malrautu P, Laha A, Ramakrishna S. Gelatin Nanofibers in Drug Delivery Systems and Tissue Engineering. *Eng Sci.* 2021;16:71-81.
3. Fattahi F, Zamani T. Poly (Lactic Acid) Nanoparticles: A Promising Hope to Overcome the Cancers. *J Fasa Univ Med Sci.* 2021;11(2):3791-814.
4. Fattahi FS, Zamani T. Synthesis of Polylactic Acid Nanoparticles for the Novel Biomedical Applications: A Scientific Perspective. *Nanochem Res.* 2020;5(1):1-13.
5. Chopra V, Thomas J, Chauhan G, Kaushik S, Rajput S, Guha R, et al. Gelatin Nanofibers Loaded with Zinc-Doped Hydroxyapatite for Osteogenic Differentiation of Mesenchymal Stem Cells. *ACS Appl Nano Mater.* 2022;5(2):2414-28.
6. Li A, Li L, Li X, Liang W, Lang M, Cheng B, et al. Antibacterial, antioxidant and anti-inflammatory PLCL/gelatin nanofiber membranes to promote wound healing. *Inter J Biol Macromol.* 2022;194:914-23.
7. Lin M, Liu Y, Gao J, Wang D, Xia D, Liang C, et al. Synergistic effect of co-delivering ciprofloxacin and tetracycline hydrochloride for promoted wound healing by utilizing coaxial PCL/gelatin nanofiber membrane. *Inter J Mol Sci.* 2022;23(3):1895-1899.
8. Abu Owida H, Al-Nabulsi JI, Alnaimat F, Al Sharah A, Al-Ayyad M, Turab NM, et al. Advancement of Nanofibrous Mats and Common Useful Drug Delivery Applications. *Adv Pharmacol Pharm Sci.* 2022;12: 9073837-49.
9. Fattahi F, Zamani T. Investigation into the Effects of Nano-fibrous Wound Dressings on Wound Healing Process in Animal Models. *J Text Sci Technol.* 2020;8(4):29-48.
10. Fattahi F-s, Khoddami A, Avinc O. Poly (lactic acid)(PLA) nanofibers for bone tissue engineering. *J Text Polym.* 2019;7(2):47-64.

11. Naz M, Jabeen S, Gull N, Ghaffar A, Islam A, Rizwan M, et al. Novel Silane Crosslinked Chitosan Based Electrospun Nanofiber for Controlled Release of Benzocaine. *Front Mater.* 2022;9:1-9.
12. Fattahi F, Khoddami A, Avinc O. Poly (Lactic Acid) Nanofibres as Drug Delivery Systems: Opportunities and Challenges. *Nanomed Res J.* 2019;4(3):130-40.
13. Fattahi F-S, Zamani T. Release mechanisms for profen-loaded nanofibers: Challenges and opportunities. *J Adv BioMed. Pharm Sci.* 2021;4(4):195-213.
14. Ataollahi H, Larypoor M. Fabrication and investigation potential effect of lentinan and docetaxel nanofibers for synergistic treatment of breast cancer in vitro. *Polym Adv Technol.* 2022;33(5):1468-80.
15. Mitra S, Mateti T, Ramakrishna S, Laha A. A Review on Curcumin-Loaded Electrospun Nanofibers and their Application in Modern Medicine. *JOM.* 2022;24:14-35.
16. Golestannejad Z, Khozeimeh F, Mehrasa M, Mirzaeei S, Sarfaraz D. A novel drug delivery system using acyclovir nanofiber patch for topical treatment of recurrent herpes labialis: A randomized clinical trial. *Clin Exp Dent Res.* 2022;8(1):184-90.
17. Abu Owida H, Al-Nabulsi JI, Alnaimat F, Al Sharah A, Al-Ayyad M, Turab NM, et al. Advancement of Nanofibrous Mats and Common Useful Drug Delivery Applications. *Adv Pharmacol Pharm Sci.* 2022;12: 9073837-47.
18. Elsadek NE, Nagah A, Ibrahim TM, Chopra H, Ghonaim GA, Emam SE, et al. Electrospun Nanofibers Revisited: An Update on the Emerging Applications in Nanomedicine. *Mater.* 2022;15(5):35-51.
19. Fattahi FS, Khoddami A, Avinc O. Potansiyel Yara Pansuman Malzemesi Olarak Poli (Laktik Asit)(PLA) Nano Yapı Matları. *Pamukkale Üni Mühendis Bilimleri Dergisi.* 26(7):1193-203.
20. Gelb MB, Punia A, Sellers S, Kadakia P, Ormes JD, Khawaja NN, et al. Effect of drug incorporation and polymer properties on the characteristics of electrospun nanofibers for drug delivery. *J Drug Deliv Sci Technol.* 2022;68:103112-21.
21. Mozaffari S, Seyedabadi S, Alemzadeh E. Anticancer efficiency of doxorubicin and berberine-loaded PCL nanofibers in preventing local breast cancer recurrence. *J Drug Deliv Sci Technol.* 2022;67:102984-91.
22. Poláková L, Širc J, Hobzová R, Cocârță A-I, Heřmánková E. Electrospun nanofibers for local anticancer therapy: Review of in vivo activity. *Inter J Pharm.* 2019;558:268-83.
23. Fattahi F-S. *Poly (Lactic Acid) Nano-fibers as Novel Drug Delivery Systems: A Bird's Eye View: LAP LAMBERT Academic Publishing; 2020.*
24. Fattahi F-S, Zamani T. Release mechanisms for profen-loaded nanofibers: Challenges and opportunities. *J adv BioMed Pharm Sci.* 2021;4(4):195-213.
25. Behere I, Ingavle G. In vitro and in vivo advancement of multifunctional electrospun nanofiber scaffolds in wound healing applications: Innovative nanofiber designs, stem cell approaches, and future perspectives. *J Biomed Mater Res A.* 2022;110(2):443-61.
26. Fattahi F-S. Nanoscience and nanotechnology in fabrication of scaffolds for tissue regeneration. *Inter Nano Lett.* 2021;11(1):1-23.
27. Xu L, Li W, Sadeghi-Soureh S, Amirsaadat S, Pourpirali R, Alijani S. Dual drug release mechanisms through mesoporous silica nanoparticle/electrospun nanofiber for enhanced anticancer efficiency of curcumin. *J BioMed Mater Res A.* 2022;110(2):316-30.
28. Rahmani Del Bakhshayesh A, Babaie S, Niknafs B, Abedelahi A, Mehdipour A, Ghahremani-Nasab M. High efficiency biomimetic electrospun fibers for use in regenerative medicine and drug delivery: A review. *Mater Chem Phys.* 2022; 279:125785-91.
29. Fattahi FS, Khoddami A, Avinc OO. Poly (Lactic Acid) Nano structure mats as potential wound dressings. *Pamukkale Univ J Eng Sci.* 2020;26(7):14-25.
30. Eren Boncu T, Ozdemir N. Electrospinning of ampicillin trihydrate loaded electrospun PLA nanofibers I: effect of polymer concentration and PCL addition on its morphology, drug delivery and mechanical properties. *Inter J Polym Mater Polym Biomater.* 2022;71(9):669-76.

31. He H, Wu M, Zhu J, Yang Y, Ge R, Yu D-G. Engineered Spindles of Little Molecules Around Electrospun Nanofibers for Biphasic Drug Release. *Adv Fiber Mater.* 2022;4(2):305-17.
32. Khandaker M, Alkadhem N, Progrid H, Nikfarjam S, Jeon J, Kotturi H, et al. Glutathione Immobilized Polycaprolactone Nanofiber Mesh as a Dermal Drug Delivery Mechanism for Wound Healing in a Diabetic Patient. *Process.* 2022;10(3):12-19.
33. Gao L, Xu M, Zhao W, Zou T, Wang F, Da J, et al. Ultrathin, elastic, and self-adhesive nanofiber bio-tape: An intraoperative drug-loading module for ureteral stents with localized and controlled drug delivery properties for customized therapy. *Bioact Mater.* 2022;18:128-37.
34. Fattahi FS, Khoddami A, Avinc O. Sustainable, renewable, and biodegradable poly (lactic acid) fibers and their latest developments in the last decade. *Sustainability in the Textile and Apparel Industries*, Springer; 2020. 173-94.
35. Fattahi F-s, Zamani T. Release of profens from nanofibers: Challenges and opportunities. *Trends Pharmacol Sci.* 2021;7(3):201-218.
36. Li T, Sun M, Wu S. State-of-the-Art Review of Electrospun Gelatin-Based Nanofiber Dressings for Wound Healing Applications. *Nanomater.* 2022;12(5):127-132.
37. Laha A, Sharma CS, Majumdar S. Electrospun gelatin nanofibers as drug carrier: effect of crosslinking on sustained release. *Mater Today Proc.* 2016;3(10):3484-91.
38. Fan J, Wang S, Sun W, Guo S, Kang Y, Du J, et al. Anticancer drug delivery systems based on inorganic nanocarriers with fluorescent tracers. *AIChE J.* 2018;64(3):835-59.
39. Hossen S, Hossain MK, Basher MK, Mia MNH, Rahman MT, Uddin MJ. Smart nanocarrier-based drug delivery systems for cancer therapy and toxicity studies: A review. *J Adv Res.* 2019;15:1-18.
40. Fattahi FS, Khoddami A, Avinc O. Nano-fibrous and tubular poly (lactic acid) scaffolds for vascular tissue engineering. *Nanomed Res J.* 2019;4(3):141-56.
41. Siddiqui AJ, Jahan S, Singh R, Saxena J, Ashraf SA, Khan A, et al. Plants in Anticancer Drug Discovery: From Molecular Mechanism to Chemoprevention. *BioMed Res Inter.* 2022;14:5425485-96.
42. Patra JK, Das G, Fraceto LF, Campos EVR, Rodriguez-Torres MdP, Acosta-Torres LS, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobio Technol.* 2018;16(1):71-77.
43. Ravichandran S, Radhakrishnan J Anticancer efficacy of lupeol incorporated electrospun Polycaprolactone/gelatin nanocomposite nanofibrous mats. *Nanotechnol.* 2022;33(29):14-34.
44. Ding J, Guo Y. Recent Advances in Chitosan and its Derivatives in Cancer Treatment. *Front. Pharmacol.* 2022;13.
45. Cui W, Aouidate A, Wang S, Yu Q, Li Y, Yuan S. Discovering Anti-Cancer Drugs via Computational Methods. *Front Pharmacol.* 2020;11:1-8.
46. Ravichandran S, Radhakrishnan J Anticancer efficacy of lupeol incorporated electrospun Polycaprolactone/gelatin nanocomposite nanofibrous mats. *Nano Technol.* 2022;33(29):295104-109.
47. Ramanathan G, Thangavelu M, Jeyakumar Grace Felciya S, Tiruchirapalli Sivagnanam U. Dual drug loaded polyhydroxy butyric acid/gelatin nanofibrous scaffold for possible post-surgery cancer treatment. *Mater Lett.* 2022;323:132597-604.
48. Darbasizadeh B, Mortazavi SA, Kobarfard F, Jaafari MR, Hashemi A, Farhadnejad H, et al. Electrospun Doxorubicin-loaded PEO/PCL core/sheath nanofibers for chemopreventive action against breast cancer cells. *J Drug Deliv Sci Technol.* 2021;64:102576-94.
49. Wang L, Huang Y, Xin B, Li T. Doxorubicin hydrochloride-loaded electrospun poly(1-lactide-co-ε-caprolactone)/gelatin core-shell nanofibers for controlled drug release. *Polym Inter.* 2021;70(12):1717-24.
50. García-Valderrama EJ, Mamidi N, Antunes-Ricardo M, Gutiérrez-Urbe JA, Angel-Sanchez D, Elías-Zúñiga A. Engineering and Evaluation of Forcespun Gelatin Nanofibers as an Isorhamnetin Glycosides Delivery System. *Pharm.* 2022;14(6):1116-21.
51. Ghahreman F, Semnani D, Khorasani SN, Varshosaz J, Khalili S, Mohammadi S, et al. Polycaprolactone-Gelatin Membranes in Controlled Drug Delivery of 5-Fluorouracil. *Polym Sci A.* 2020;62(6):636-47.

52. Ramírez-Agudelo R, Scheuermann K, Gala-García A, Monteiro APF, Pinzón-García AD, Cortés ME, et al. Hybrid nanofibers based on poly-caprolactone/gelatin/hydroxyapatite nanoparticles-loaded Doxycycline: Effective anti-tumoral and antibacterial activity. *Mater Sci Eng. C.* 2018;83:25-34.
53. Gulsun T, Inal M, Akdag Y, Izat N, Oner L, Sahin S. The development and characterization of electrospun gelatin nanofibers containing indomethacin and curcumin for accelerated wound healing. *J Drug Deliv Sci Technol.* 2022;67:103000-014.
54. Moradkhannejhad L, Abdouss M, Nikfarjam N, Shahriari MH, Heidary V. The effect of molecular weight and content of PEG on in vitro drug release of electrospun curcumin loaded PLA/PEG nanofibers. *J Drug Deliv Sci Technol.* 2020;56:101554-59.
55. Farghadani R, Naidu R. Curcumin as an Enhancer of Therapeutic Efficiency of Chemotherapy Drugs in Breast Cancer. *Inter. J Mol Sci.* 2022;23(4):41-49.
56. Faramarzi N, Mohammadnejad J, Jafary H, Narmani A, Koosha M, Motlagh B. Synthesis and in vitro Evaluation of Tamoxifen-Loaded Gelatin as Effective Nanocomplex in Drug Delivery Systems. *Inter J Nanosci.* 2020;19(05):2050002-012.
57. Ariamoghaddam Ar, Ebrahimi-Hosseinzadeh B, Hatamian-Zarmi A, Sahraeian R. In vivo anti-obesity efficacy of curcumin loaded nanofibers transdermal patches in high-fat diet induced obese rats. *Mater Sci Eng C.* 2018;92:161-71.
58. Alehosseini A, Gómez-Mascaraque LG, Martínez-Sanz M, López-Rubio A. Electrospun curcumin-loaded protein nanofiber mats as active/bioactive coatings for food packaging applications. *Food Hydrocoll.* 2019;87:758-71.
59. Sharifi S, Zaheri Khosroshahi A, Maleki Dizaj S, Rezaei Y. Preparation, Physicochemical Assessment and the Antimicrobial Action of Hydroxyapatite–Gelatin/Curcumin Nanofibrous Composites as a Dental Biomaterial. *Biomimetics.* 2022;7(1):19-35.
60. Saadipour M, Karkhaneh A, Haghbin Nazarpak M. An investigation into curcumin release from PLA particles loaded in PCL-GELATIN fibers for skin application. *Inter J Polym Mater Polym Biomater.* 2022;71(5):386-94.
61. Sundhari D, Dhineshbabu NR, Sutha S, Raja Saravanan ME. Encapsulation of bioactive agent (Curcumin, Moringa) in electrospun nanofibers – Some insights into recent research trends. *Mater Today Proc.* 2021;46:2682-5.
62. Tsoi H, You C-P, Leung M-H, Man EPS, Khoo U-S. Targeting Ribosome Biogenesis to Combat Tamoxifen Resistance in ER+ve Breast Cancer. *Cancer.* 2022;14(5):19-23.
63. Ilhan E, Cesur S, Sulutas RB, Pilavci E, Dalbayrak B, Kaya E, et al. The role of multilayer electrospun poly (vinyl alcohol)/gelatin nanofibers loaded with fluconazole and cinnamaldehyde in the potential treatment of fungal keratitis. *Eur Polym J.* 2022;176:111390-99.
64. Sadeghi-Soureh S, Jafari R, Gholikhani-Darbroud R, Pilehvar-Soltanahmadi Y. Potential of Chrysin-loaded PCL/gelatin nanofibers for modulation of macrophage functional polarity towards anti-inflammatory/pro-regenerative phenotype. *J Drug Deliv Sci Technol.* 2020;58:101802-815.