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Experimental study of processing of PCL (polycaprolactone)-peptides nanoparticles and its biodistribution analysis for drug delivery system

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Abstract

Two types of cells targeting Peptides, TAMS-1 (CSPGAKVRCY {Lys (Biotin)}) and MDSC-peptide (Biotin {PEG4}-MEWSLE-KGYTIK), were synthesized for targeting CD206 M2 macrophage and myeloid-derived suppressor cells (MDSC), respectively. Each peptide was coaxially electro sprayed where PCL (Polycaprolactone) is the core, and the peptide is the sheath to create a PCL nanoparticle with peptides. Electro spraying parameters included applying a voltage of 44 kV, humidity between 35–44%, tip to collector distance at 160 mm, core flow rate of 0.5 ml/hr, and a sheath flow rate of 0.7 ml/hr. UV–VIS (Ultraviolet–Visible) spectrometry, SEM (Scanning Electron Microscopy) imaging, and in vivo biodistribution techniques were used to study the morphology and performance of the PCL-peptide nanoparticles. Peak absorbance values for PCL were found at around 275 nm. Peptides absorbance value was observed between 230 and 250 nm. Scanning Electron Microscope image shows nanoparticles as small as 100 nm and agglomerates as large as 1 µm. In-vivo biodistribution of PCL and CD206 M2 macrophage targeting peptide (TAMS-1) nanoparticles after intravenous injection in the tumor mice model showed uptake to the tumors. On the other hand, MDSC peptide did not show any uptake to the site of tumors. Most activity is shown in the intestine indicating excretion of the agents through the hepato-biliary system.

Introduction

Cancer is the second most common cause of mortality worldwide. A safer and more efficient approach to targeted cancer treatment is emerging from the expanding field of nanomedicine. Combining a biodegradable core, a polymer envelope, and a membrane recognition ligand is the main goal of the majority of current nano delivery systems research initiatives. The drugs are carried inside the body in water-soluble vehicles such as a polymer, microcapsule, lipoprotein, micelle, vesicle, or micro particles that comprise of biodegradable synthetic polymers. The carriers can be adjusted to allow for slow degradation, stimuli-reactive responses, and targeted delivery to a specific recipient such as a cancer cells or tumor associated cells. Successful drug targeting and delivery are dependent on controlled drug release and successive biodegradation [1, 2].

The drugs delivery system's ability to function effectively at a particular site of interest is referred to as drug targeting. This type of targeted therapy is more advantageous over conventional cancer treatment where healthy cell get damage along with the deceased one [3]. Two basic mechanisms comprise site-directed drug release systems: passive targeting and active targeting [1]. Nano carrier based drugs rely on passive targeting through

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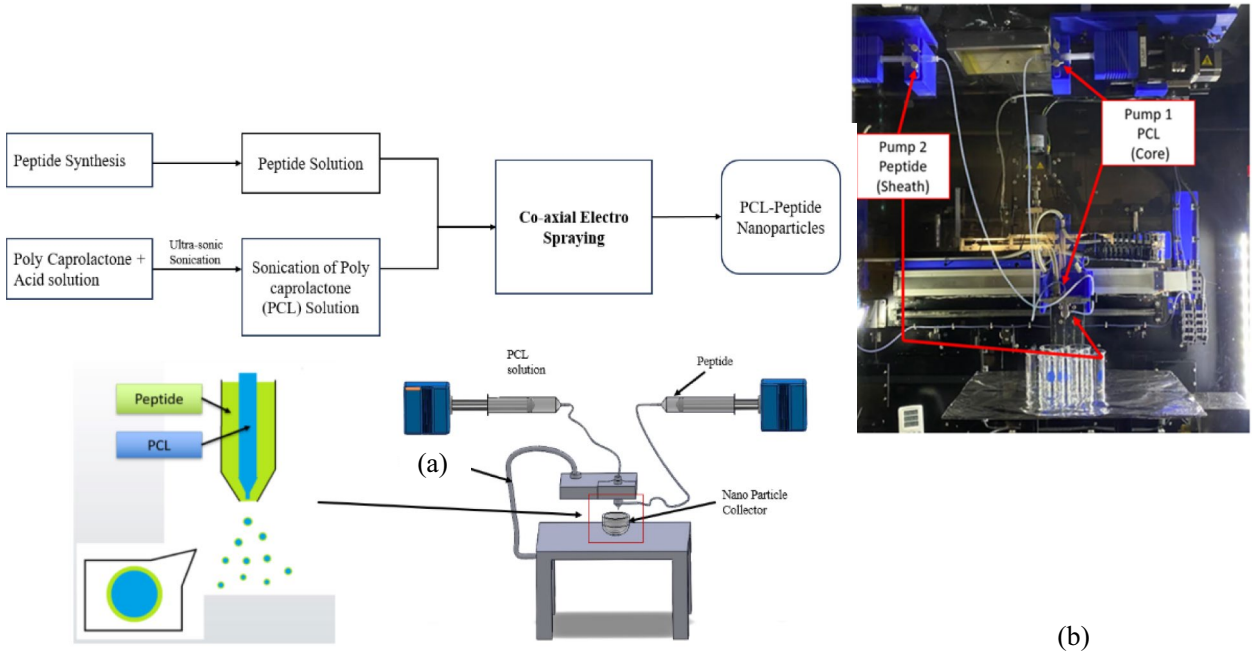

Fig. 1 **a** Flow chart and the schematic of the fabrication process of nanoparticles **b** Experimental set up of coaxial electro spraying with PCL as core and Peptide as sheath

processes known as enhanced permeability and retention (EPR) [4]. Since nanoparticles are smaller and have a higher subsurface-to-volume ratio, nanoparticles can escape through deceased porous blood vessel walls into the targeted cells [5].

Electro spraying is one of the effective methods of nanoencapsulation. Previous research on synthesis of submicron-sized colloidal particles that have a therapeutic agent (such as paclitaxel or GW2580) encapsulated within Polycaprolactone by electro spraying methods are a basis of this research [6]. The controlling parameters of co-axial electro spraying can be divided as solution variables, process variables and environmental variables [7]. These include solution properties like viscosity [8], conductivity [9], and surface tension [10]. Variables on the machinery such as voltage [11], hydrostatic pressure in the capillary tube, flow rate [11], the electric potential at the capillary tip, tip to collector distance [12], and collector type. Lastly, ambient, and environmental conditions such as solution temperature, humidity [13].

In this study, a manufacturing method, known as electro spraying, is used to produce injectable biocompatible nano particles. Previous research in electro spraying has proven the development of injectable drug-encapsulated nano capsules. Our previous research has demonstrated a scalable synthesis and fabrication process where chemotherapeutic drugs are nanonized first and then encapsulated with carrier polymers (PCL) for sustained and prolonged release [6, 14]. Such drug delivery systems, which is biocompatible, and biodegradable are in the size range compatible to the EPR effect (10 -100 nm). These nanoparticles are loaded with nanonized therapeutics (drug nanocrystals) and can deliver them to tumors through the enhanced permeability and retention (EPR) effect and/or by targeting receptor [15–17]. PCL is a semi-crystalline biodegradable polymer which is FDA approved and commonly used in medical applications [18]. PCL has well-known degradation and hydrophobic properties, which makes it suitable to control/tune drug release pattern (prolonged and sustained delivery) with having less to no toxicity due to its complete biocompatibility. PCL nanoparticles are generally prepared by nanoprecipitation, solvent displacement, and solvent evaporation [19]. In cases of drug delivery, accumulations of the drug combined with peptides will increase the efficacy of the drug and decrease its negative side effects [20]. Peptides offer high specificity that allows active concentrations as low as the nano-molar range. Targeting sequences for peptides can be developed and determined through different techniques, including the development of derivatives inspired by the natural protein sequence [16]. Coaxially electro spraying the biocompatible polymer, PCL, and the tumor-targeting peptides together (where PCL is the core and peptide is the sheath) shows potential to produce an active tumor targeting polymer.

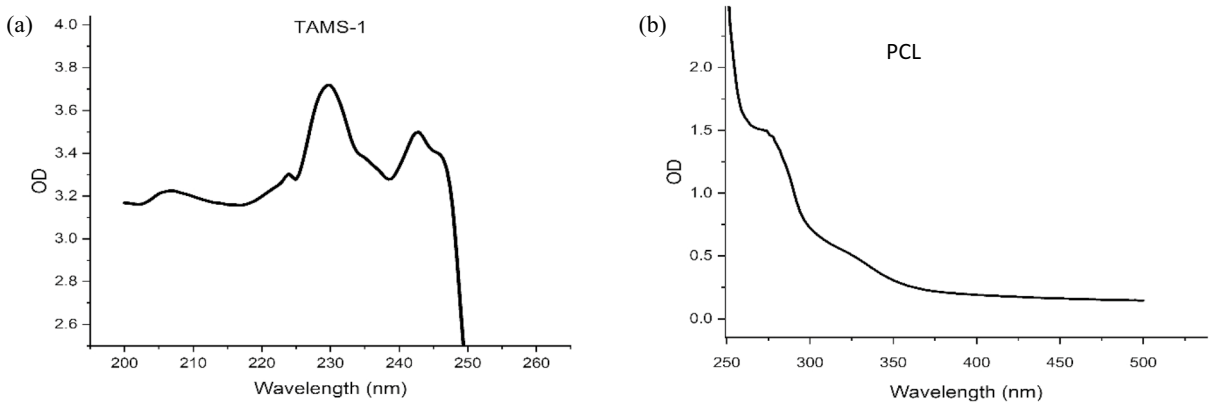

Fig. 2 Characteristic peaks of the **a** TAMS-1 U3012DA110-1CSPGAKVRCY{Lys (Biotin)} peptide (around 230, 245 nm) and **b** PCL (around 275 nm)

Materials and methods

Synthesis and fabrication methods

Polycaprolactone (PCL) with an average molecular weight of 14,000 g/mol was purchased from Sigma-Aldrich. The CD206 M2 macrophage targeting peptide CSPGAKVRC was custom synthesized from the GenScript (Piscataway, NJ). CSPGAKVRC {Lys} was made, and Biotin was added at the N terminal of the peptide. Similarly, utilizing normal peptide synthesis, a custom peptide synthesis from GenScript (Piscataway, NJ) was used to create the myeloid derived suppressor cells (MDSC) targeting peptide MEWSLEKGYTIK. After creating the MEWSLEKGYTIK-(PEG-4) MDSC targeting peptide, biotin was added to its C terminal. Finally, TAMS-1 CSPGAKVRCY {Lys (Biotin)} and Biotin {PEG4}-MEWSLEKGYTIK were the two peptide forms that were produced. All other solvents including dimethyl sulfoxide (DMSO), acetic acid (AA), formic acid (FA), and trifluoroethanol (TFE) were purchased from Sigma Aldrich.

CD206 M2 macrophage targeting peptides were dissolved in dimethyl sulfoxide (DMSO) with a concentration of 0.04 mg/ml. A homogenous solution was prepared using a magnetic stirrer. The biocompatible polymer, PCL, was dissolved in a combination of three solvents consisting of formic acid (FA), acetic acid (AA) and trifluoroethanol (TFE) with a volume ration of 9:9:1 ratio, with a concentration of 32.86 mg/mL using a magnetic stirrer. The three-solvent system was used to lower the conductivity and volatility of the sheath solution when compared to the core solution [6]. After the PCL was completely dissolved into the solution, the PCL solution was sonicated for 24–30 h non-continuously using a Vibracell ultrasonic materials processing unit and a 13 mm probe (750W with 20 kHz). The sonication parameters included: amplitude 30%, pulse frequency of 50 s ON and 10 s OFF; cut-off temperature 47 °C.

A NF-500 Electrospinning Unit (MECC, Japan) was used for electro spraying the PCL nanoparticles with conjugated CD206 M2 macrophage targeting peptides. Figure 1 shows the flow diagram and the experimental process of fabricating the nanoparticles. A special concentric nozzle, the ultra-coaxial spinneret, is used to produce a core and sheath coaxial stream. The ultrafine coaxial spinneret was used for creating a coaxial stream of biocompatible polymer solution in the core and CD206 M2 macrophage targeting peptide solution at the sheath. A 27-gauge blunt tip dispensing fill needle with an outer diameter of 0.413 mm and length of 25.4 mm, or 1 inch, acted as the core nozzle. This needle was placed concentrically into the shell, which had an outer diameter of 0.8 mm. Solutions were pumped to the coaxial spinneret using two separate high-precision syringe pumps and 5 mL NORM-JECT latex-free syringes. The electro spraying machine was equipped with two feed pumps. The relative humidity was maintained at approximately 43% throughout the electro spraying process. The total flow rate, the summation of the core flow rate and the sheath flow rate) were controlled to achieve a continuous and stable electrospray. The system processing parameters included a voltage of 44 kV, tip to collector distance 160 mm, mass flow rate for the biocompatible polymer solution: 4.56 μg/s, mass flow rate for the CD206 M2 macrophage targeting peptide solution: 0.0077 μg/s were kept constant throughout the manufacturing of the nanoparticles. The nanoparticles were collected in a glass beakers kept on the grounded collector surface of the electro spraying machine. The nanoparticles manufactured from this method were injected directly into the mice for performance analysis on uptake to the site of tumor microenvironment.

UV–VIS spectrometry

An Epoch 2 Microplate Spectrophotometer (Agilent FKA Biotek, CA) was used to observe the UV–Vis absorbance measurements. 100 µL of each solution were dispensed into multiple wells on a 96-well clear and flat bottom UV-transparent microplate manufactured by Corning (Corning, NY). The 96-well plates have a well volume of 205 µL and working volumes of 25–100 µL. Absorbance values between 200 and 350 nm were measured for each solution. DMSO was used to prepare the peptide solution. UV–VIS absorbance was recorded for Peptide-DMSO solution and for only DMSO solution. Characteristic peaks of the peptides were found by performing the subtraction of wavelength absorbance values of the pure DMSO solvent from the absorbance values of the Peptide -DMSO solution. Similarly, characteristic peaks for PCL were found from PCL solution prepared with combination (9:9:1volumetric ratio) of Formic Acid (FA), Acetic Acid (AA), and Tetrafluoroethylene (TFE). As seen in Fig. 2**,** peak absorbance values for the TAMS-1 CSPGAKVRCY{Lys(Biotin)} peptide are found around 230 nm, 245 nm, at optical densities (OD) around 0.035, while peak absorbance values for PCL are found around 275 nm at optical densities (OD) around 0.45.

Ethics statement

All the experiments were performed according to the National Institutes of Health (NIH) guidelines and regulations. The Institutional Animal Care and Use Committee (IACUC) of Augusta University (protocol #2014–0625) approved all the experimental procedures. All animals were kept under regular barrier conditions at room temperature with exposure to light for 12 h and dark for 12 h. Food and water were offered ad libitum. All efforts were made to ameliorate the suffering of animals. CO2 with a secondary method was used to euthanize animals for tissue collection.

Mice model and cell line

For in vivo biodistribution studies of CD206 Peptide, Balb/C (Jackson Laboratory, Main USA) female mice were used. Mice were between 5 and 6 weeks of age and weighing 18–20 g. From American Type Tissue Culture Collection (ATCC), murine mammary carcinoma cell line from a BALB/cfC3H mouse 4T1 was obtained. To express reporter gene, luciferase 4T1 cell was modified at Augusta University. For in vivo specificity studies of MDSC Peptide, C57BL/6 (Jackson Laboratory, Main USA) female mice were used. Mice were between 5 and 6 weeks of age and weighing 18–20 g. Luciferase positive syngeneic GL261 glioma cells were implanted subcutaneously.

Cell culture

For CD206 Peptide, Roswell Park Memorial Institute 1640 medium (RPMI) (Thermo Scientific), supplemented with 10% fetal bovine serum (FBS) (Nalgene-GIBCO), 2 mM glutamine (GIBCO, Grand Island, NY, USA), and 100 U mL^{-1} penicillin and streptomycin (GIBCO, Grand Island, NY, USA) was used to culture the modified 4T1 cell in 5% CO2 and 37 °C in a humidified incubator. For MDSC, Dulbecco's Modified Eagle Medium (DMEM) (Corning, NY, USA) supplemented with 10% fetal bovine serum (FBS) (Nalgene-GIBCO), 2 mM glutamine (GIBCO, Grand Island, NY, USA), and 100 U mL^{-1} penicillin and streptomycin (GIBCO, Grand Island, NY, USA) was used to culture the modified GL261 cell in 5% CO2 and 37 °C in a humidified incubator.

Cell preparation and tumor implantation

For CD206 Peptide samples, Modified 4T1 cell were collected in 50% RPMI media and 50% matrigel matrix (Corning, Arizona, USA) and 50,000 cells were used in 50 µl volume for each mouse. We injected in Balb/C mice

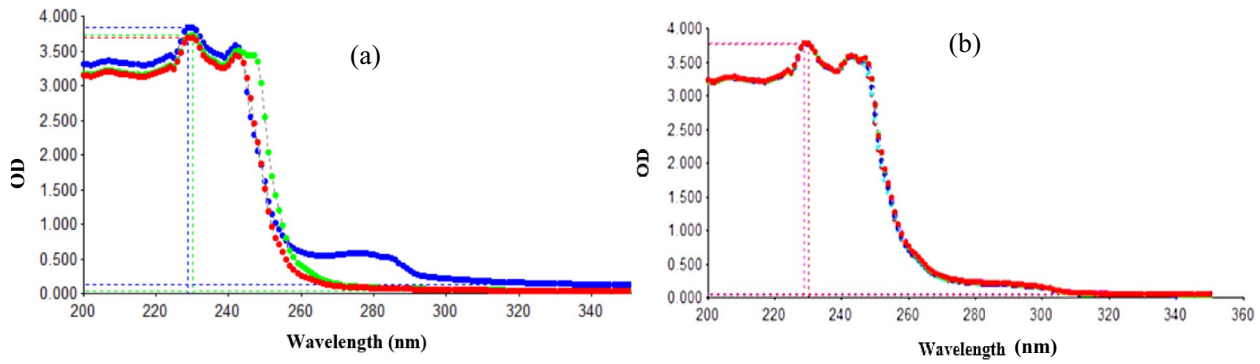

Fig. 3 **a** UV–VIS of Peptide, PCL before electro spraying **b** UV–VIS of Peptide- PCL Nanoparticle Solution Electro sprayed at 44 kV collected with DMSO (DMSO was used as media and the absorbance value was subtracted)

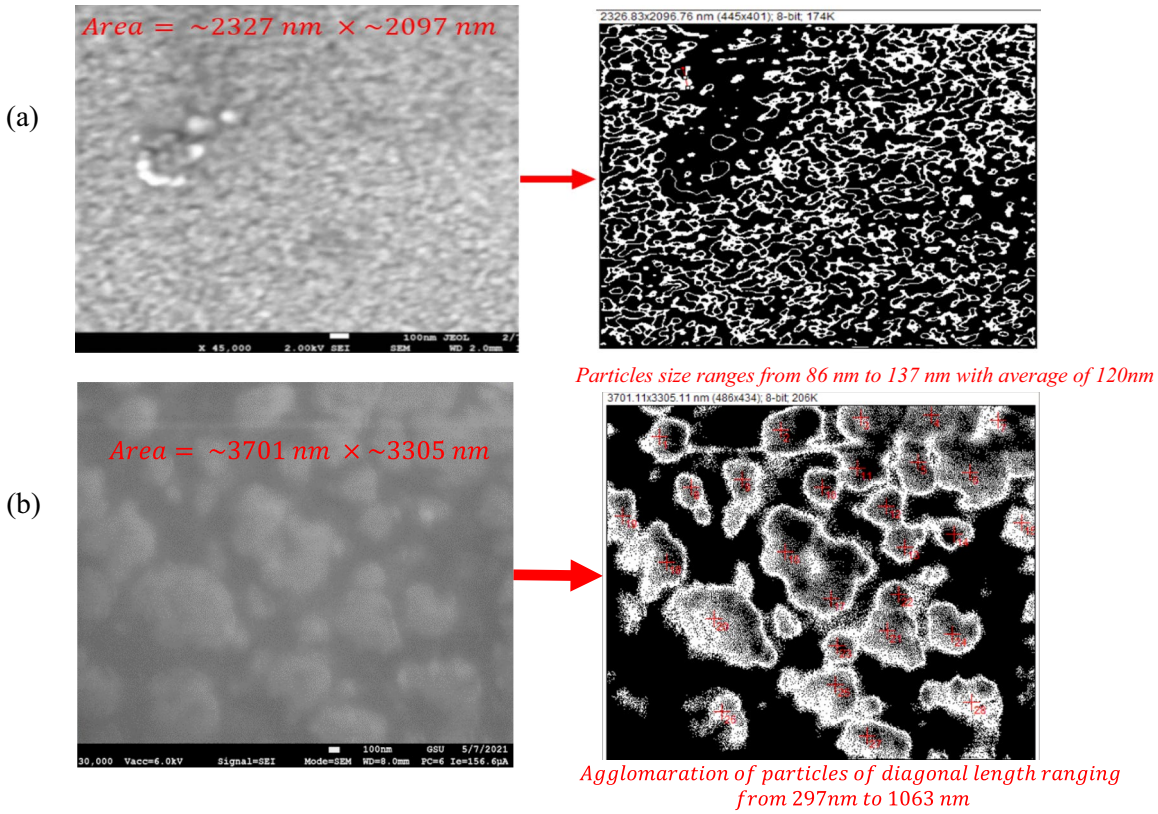

Fig. 4 SEM Image of **a** PCL-Peptide Nanoparticles as low as 100 nm **b** Agglomeration of particles during the electrospraying

subcutaneously in the flank. For MDSC samples, Modified GL261 cell were collected in 50% DMEM media and 50% matrigel matrix (Corning, Arizona, USA) and 50,000 cells were used in 50 µl volume for each mouse. We injected in C57BL/6 mice subcutaneously at the flank.

Bioluminescence imaging of mice

The injection site was monitored each week to observe the tumor growth. After 15 days, optical bioluminescence imaging was performed to determine the tumor growth and metastases. An intraperitoneal injection of 100 µL of luciferin (150 mg kg^{-1}) was administered. Bioluminescence signal was acquired by spectral Amix optical imaging system. LLC photon intensity per millimeter per sec was measured using Spectral Instruments Imaging's Aura imaging software. The animals were kept under anesthesia (2% with oxygen) during the procedure and were anesthetized with 2.5% isoflurane (2 ± 1 L min^{-1} O2).

In-vivo biodistribution procedure

The PCL-Peptide (CSPGAKVRCY{Lys(Biotin)} nanoparticles were produced on glass petri dishes, and was collected using a cell scraper. The nanoparticles were taken in through a 1 ml Eppendorf tube and 500 µl Hyclone DPBS/Modified (GE Life Science, USA) was added. A Branson 3510 Ultrasonic homogenizer is used to sonicate the samples to make the nanoparticle dispersed and suspended for 30 min. Rhodamine-tagged streptavidin were added to the solution to label biotinylated peptide with rhodamine. This process is completed using standard protocol for labeling supplied by the vendor (Thermo Fisher Scientific). The solution is passed through the 0.22 µm filter. Extra DPBS was added and injected in 2 mice intravenous by tail vein injection (200 µl solution for each mouse).

For the PCL- Peptide (Biotin{PEG4}-MEWSLEKGYTIK), nanoparticles, the procedures were the same. Extra DPBS was added and injected into two tumor bearing mice and two control mice (which did not have any tumors). The solution is administered by intravenous tail vein injection where 200 µl solution was used for each mouse. One more tumor bearing mice had rhodamine-tagged streptavidin (only) added in sterile PBS and injected 200 µl solution by intravenous tail vein injection.

Incubation and collection of organs

Three hours following IV administration of the agent, animals were euthanized, and the lung, spleen, heart,

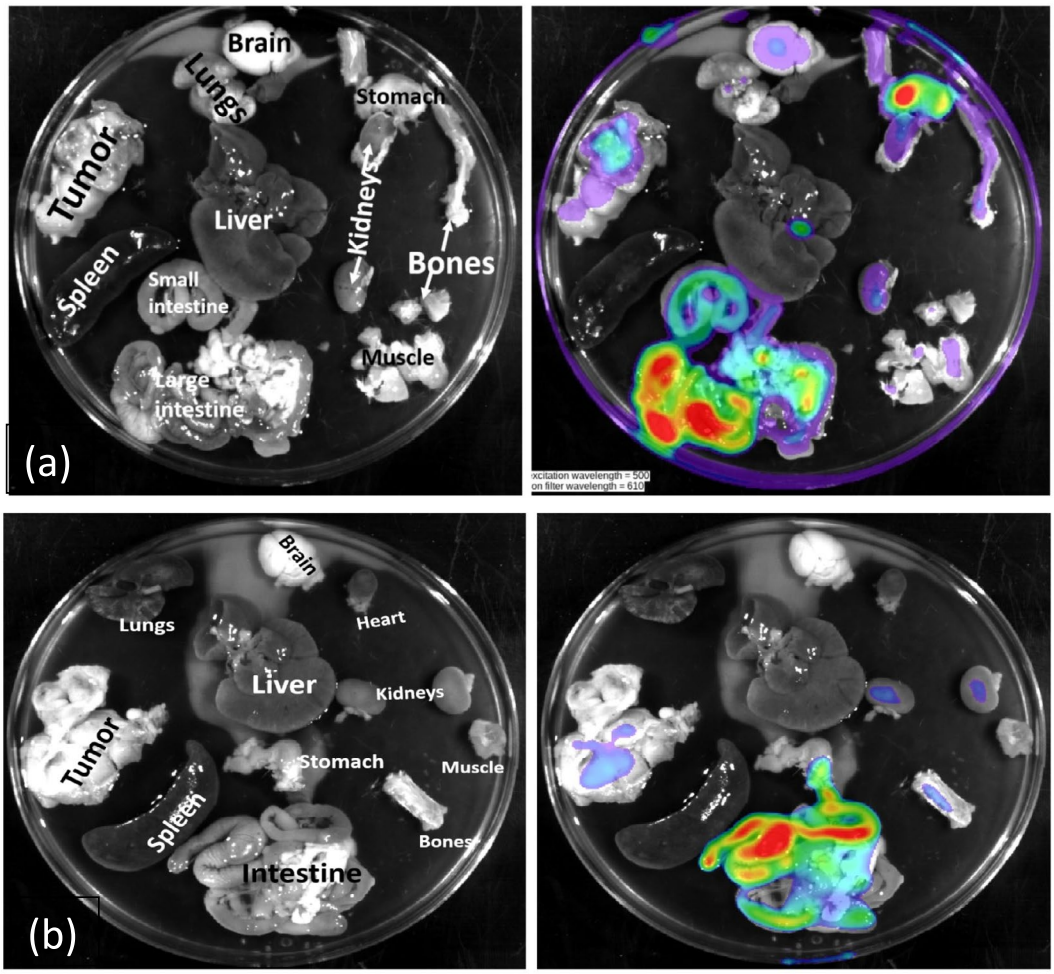

Fig. 5 Animals organs collected after 3 h after IV injection. **a** On the left side, Balb/C mouse 1 labelled organs (lung, spleen, heart, liver, kidney, brain, muscle, intestine, stomach, bone, and tumor); On the right-side fluorescent image obtained using excitation at 500 nm and emission at 610 nm showing the accumulation of PCL-conjugated TAMS1 peptide in brain, tumor, stomach, bone, kidney, small intestine, and large intestine. **b** On the left side, Balb/C mouse 2 labelled organs; On the right-side fluorescent image obtained using excitation at 500 nm and emission at 610 nm showing the accumulation of PCL-conjugated TAMS1 peptide in brain, tumor, stomach, bone, kidney, small intestine, and large intestine as well

liver, kidney, brain, muscle, Intestine, stomach, bone, and tumor were collected. We placed those organs on petri dish and took normal camera picture and acquire fluorescent image at excitation 500 nm and at emission 610 nm.

Results and discussions

UV–Vis spectroscopy

UV–Vis Spectroscopy measurements are shown in Fig. 3. As can be seen in Fig. 3 an absorbance wavelength of the Peptide and PCL were found at around 230, 245 and 275 nm before electro spraying. Then PCL -Peptide nanoparticles were electrosprayed in DMSO solution at a voltage range between 36 and 44 kV. The absorbance values of DMSO are subtracted. Figure 3b shows the absorbance values of the PCL-peptide nanoparticles. In accordance with the characteristic peaks' absorbance values were measured between 200 and 350 nm. The UV–VIS Spectrometry as shown in Fig. 3b indicates peptides absorbance peaks similar to the calibration curves are present. Absorbance peaks around 230 nm and 245 nm are observed. This observation indicates that the exposure of the peptide biomolecules at as high as 44 kV did not disintegrate the chemical or physical structure of the molecules.

Scanning electron microscopy

Scanning electron microscope (SEM) images of the manufactured nanoparticles were completed using a JEOL JSM- 7600F Field Emission SEM. The PCL-peptide nanoparticles are observed in Fig. 4. Sizes of individual nanoparticles (Fig. 5a) ranges from 86 to 137 nm with an average of 120 nm, however agglomeration was also

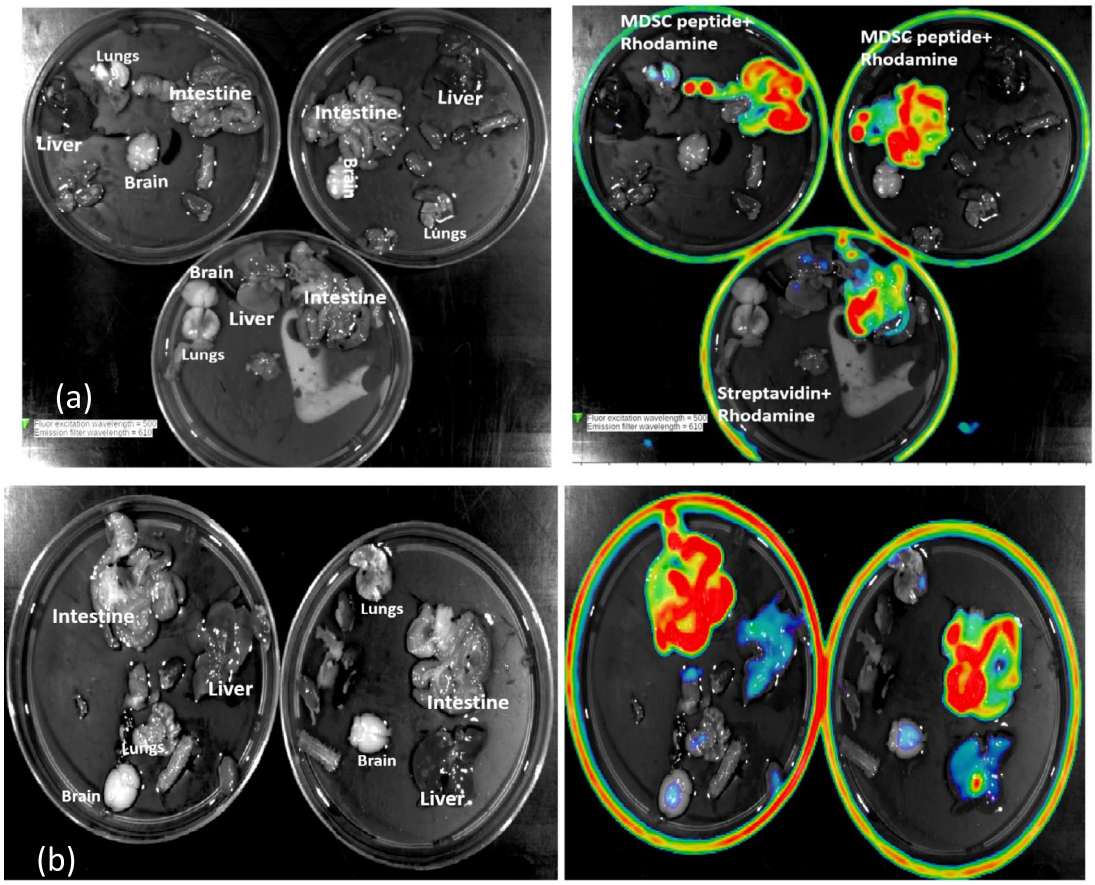

Fig. 6 Animals organs collected after 3 h after IV injection. **a** On the left side, Tumor bearing C57BL/6 mice labelled organs (intestine, liver, lungs, and brain; only major organs are shown); On the right-side fluorescent image at excitation at 500 nm and emission at 610 nm showing the accumulation of PCL-conjugated MDSC targeting peptide in mostly in the intestine similar to that of rhodamine dye only. **b** On the left side, control C57BL/6 mice (non-tumor bearing) labelled organs; On the right-side fluorescent image at excitation at 500 nm and emission at 6100 nm showing PCL-conjugated MDSC targeting peptide in brain, liver, and intestine

observed at different places (Fig. 5b). Agglomerations of nanoparticles can be as large as 1 µm.

CD206 M2 macrophage targeting peptide bind to CD206 M2 macrophage in vivo

After intravenous injection, the PCL-peptide was distributed in vivo to target CD206 M2 macrophages in the Balb/C tumor bearing (4T1 tumor) mouse model. The objective was to determine whether the peptide might accumulate by binding with CD206 M2 macrophage cells in areas where CD206 M2 macrophages are common. Figure 5 shows the accumulation of PCL-conjugated peptide in brain, tumor, stomach, bone, kidney, small intestine, and large intestine. The majority of the activities are displayed in the intestines, suggesting that the agents are excreted through the hepato-biliary system. Images reveal uptake to the tumors where it is expected to bind due to the presence of CD206 M2 macrophages. There is no issue with leftover excretion because the kidneys are not showing much activity. The most unexpected finding was that the spleen showed no activity. Images of the biodistribution can be seen below in Fig. 5. Figure 5B shows Balb/C mouse #2 organs similar to mouse #1. On the left side, normal photograph of the organs. On the right-side fluorescent image at excitation at 500 nm and emission at 600 nm. It shows the accumulation of PCL-conjugated peptide in brain, tumor, stomach, bone, kidney, small intestine, and large intestine. It seems the agents are passing through hepato-biliary system although showed activity in the tumors.

MDSC targeting peptide binding to MDSC in vivo

We further investigate *in-vivo* distribution of PCL-Peptide nanoparticles to target MDSC after intravenous injection in C57BL/6 tumor mice model to observe whether our peptide could accumulate by binding with MDSC cell in those area where CD206 M2 macrophage is prevalent. Images show most of the activities are in the intestine indicating excretion of the agents through the

hepato-biliary system. Very little activity is seen in the brain and liver. No activity was seen in the spleen, Intestine, stomach, bone, and tumor. As can be seen in Fig. 6, in mouse 1 and mouse 2, we injected PCL-peptide nanoparticles which are labelled with rhodamine-streptavidin and mouse 3 only rhodamine-streptavidin in PBS. On the left side, it shows photograph of organs. On the right-side fluorescent image excitation at 500 nm and emission at 610 nm. It shows the accumulation of PCL-conjugated peptide in mostly in the intestine. In Fig. 6B shows control C57BL/6 mice organs. Same organs were collected from mouse 1, 2, and 3. On the left side, normal camera picture and organs are shown. On the right-side fluorescent image excitation at 500 nm and emission at 610 nm. It shows PCL-conjugated peptide in brain, liver, and intestine.

Conclusion

This study was to synthesize biocompatible and biodegradable FDA approved polymer, polycaprolactone, by coaxial electro spraying with NGR Peptide (individual nanoparticles diameter $\leq$ 100 nm). The nanoparticles were analyzed by UV–VIS Spectrometry to support the ability of peptides to resist disintegration after being introduced to high voltages, 36–44 kV, due to the electro spraying process. The size and form of the nanoparticles were displayed in a scanning electron microscope image. Upon examining the in-vivo biodistribution assays, the CD206 + M2-macrophage targeting peptide TAMS-1 U3012DA110-1CSPGAKVRCY {Lys (Biotin)} was found to be taken up by tumors.

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Author contributions
Dr. Mujibur Khan is the Principal Investigator. Dr. Khan has planned, designed, prepared, and supervised the manuscript. He and his team are working on Nanonization of drugs and Nanoencapsulation of targeting agents for last several years. Dr. Arbab is the main collaborator and Co-Investigator for the study. Dr. Arbab and his team has designed facilitated and supervise in-vivo studies and interpreted the results. Mr. Anthony Yamasta and Jannatul Ferdaus were the graduate students who were working on the research project under the supervision of Dr. Khan. Mr. Anthony Yamasta has conducted the experiments of the processing the nanoparticles and characterizing them. Ms. Jannatul Ferdaus has contributed to literature study and prepare and edit the manuscript. Mahrima Parvin, is the graduate student of Dr. Arbab who, acquire the in-vivo experimental bio distribution study and record the findings. Dr. Ahmed has contributed to the electro spraying voltage of the processing methodology and data collection. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this submitted article. Data/Experimental results are presented in the manuscript and if appropriate, datasets/experimental results used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent for publication
We would like to mention that this manuscript has not been published and or not submitted elsewhere for publication while being considered by the journal Nanomaterials.

Competing interests
The authors do not have any competing interests. The authors declare that they have no competing interests.

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