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COUMARIN-BASED POLY(ε-CAPROLACTONE)-*BLOCK*-POLY(ETHYLENE GLYCOL) COPOLYMERS FOR LIGHT-SENSITIVE DRUG DELIVERY SYSTEM

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Introduction

Drug treatment of tumors is often hindered by the rapid elimination and degradation of the drug. To overcome these problems, there are targeted therapies that allow the control of drug distribution by suppressing side effects. Drug delivery systems (DDSs) are supramolecular assemblies that incorporate drugs intended to treat a disease.[1] DDSs are made of nanoparticles, liposomes, or natural or synthetic polymers. Among the polymers used for DDS, PCL (polycaprolactone) and PEG (polyethylenglycol) are of considerable importance due to their biocompatibility.[2]

Polymeric nanocarriers responding to external or internal stimuli have received great interest for controlled drug release. In particular, by introducing in the DDSs photochromic groups, the light may be used as external stimulus to ensure that the drug arrives at the specific site and at the right time. The irradiation could be carried out by ultraviolet (UV), visible or near infrared light (NIR).[3] The NIR spectrum is considered an ideal light source for monitoring drug release due its safety and strengthened tissue penetration. Coumarin has a high two-photon absorption cross section, suitable for NIR triggered drug release.[4]

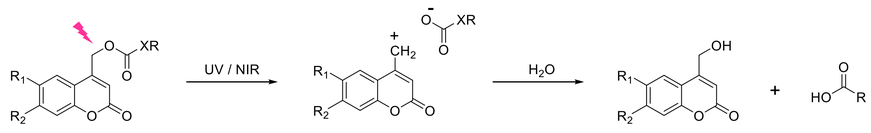


Figure 1. *Photo-cleavage mechanism of coumarin derivative*.

Results and discussion

SYNTHESIS OF COUMARIN-BASED POLY(ε-CAPROLACTONE)-BLOCK--POLY(ETHYLENE GLYCOL) COPOLYMERS

We have designed DDSs made of biocompatible poly(ε-caprolactone)-*block*-poly(ethylene glycol) copolymer,[2] acting as light sensitive polymeric materials due to the presence of coumarin on the polymer backbone.

The coumarin-terminated block copolymer (Fig.2) was obtained by Steglich's esterification between coumarin alcohol and COOH-terminated poly(ε-caprolactone)-poly(ethylene glycol) copolymer.

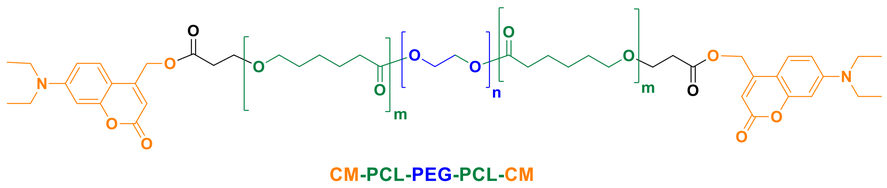


Figure 2. *Structure of coumarin-functionalized telechelic PCL-PEG-PCL copolymer.*

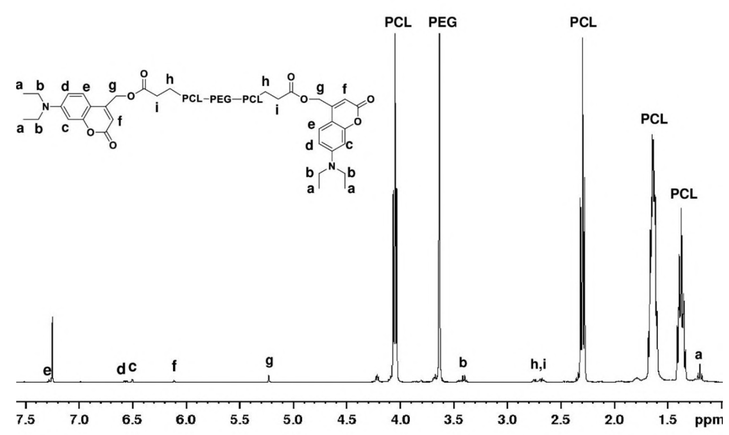
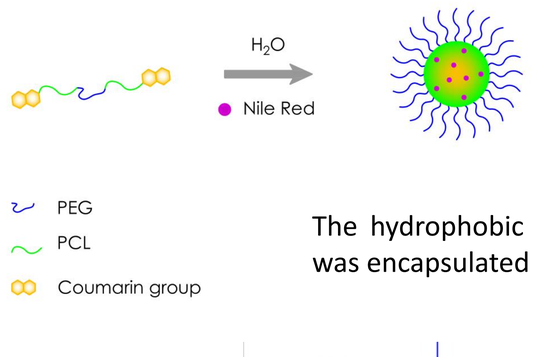


Figure 3. *^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of copolymer end-capped with coumarin.*

SELF-ASSEMBLY OF NANOPARTICLES IN WATER



When dialyzed against water, coumarin-functionalized telechelic PCL-PEG-PCL copolymer assembled into nanoparticles having a hydrophobic core and a hydrophilic shell.

The hydrophobic Nile Red, used as a model guest molecule, was encapsulated in the nanoparticles.

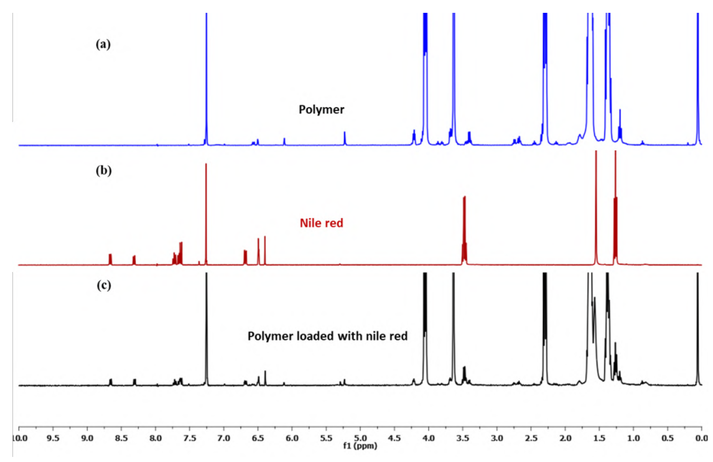


Figure 4. *^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of:* ***(a)*** *unloaded polymer;* ***(b)*** *Nile Red;* ***(c)*** *polymer loaded with Nile Red.*

LIGHT RESPONSIVE BEHAVIOR STUDIES

Coumarin-functionalized poly(ε-caprolactone)-*block*-poly(ethylene glycol) nanoparticles were loaded with Nile Red and its release was studied by using UV and NIR irradiation and assessed by SEM and DLS analyses. Then, drug release was confirmed by fluorescence studies.

UV irradiation

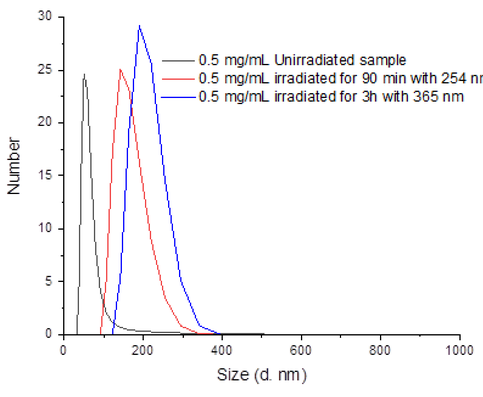


Figure 5. *Dynamic light scattering (DLS) measurement of micelles in aqueous solution before and after irradiation.*

After irradiation with UV light at a wavelength of 254 nm and at a wavelength of 365 nm, the mean size of the diameter of the polymeric nanoparticles was increased due to disruption of the polymeric micelles and aggregation phenomena.

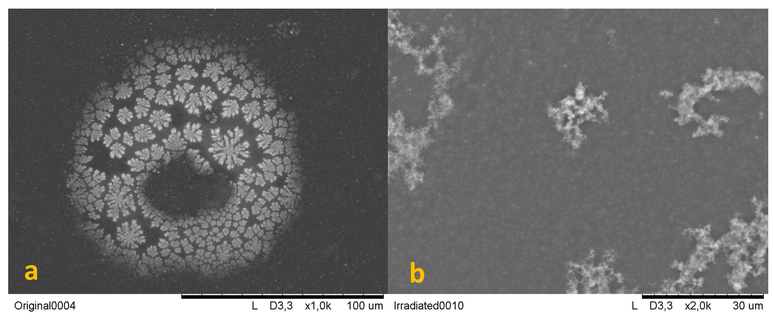


Figure 6. *Scanning electron microscopy (SEM) images of polymer micellar solutions before (**a**) and after (**b**) UV irradiation.*

The disruption of the polymeric micelle was further confirmed by the SEM analysis as shown in Fig.6.
Before irradiation, nice spherulite was observed, while after irradiation the nanoparticles lost their morphological integrity and formed aggregates.

NIR irradiation

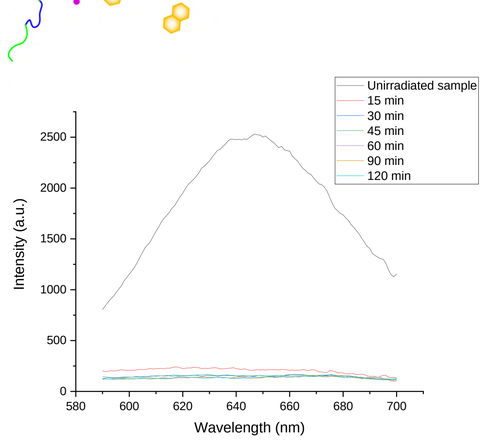


Figure 7. *Fluorescence emission spectrum of a polymeric micellar solution (0.5 mg/mL) loaded with Nile Red under NIR irradiation*

After irradiation with NIR light at a wavelength of 800 nm, release of the drug (Nile Red) has occurred rapidly within a few minutes (less than 15 minutes).

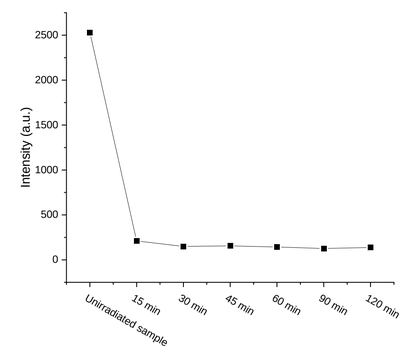


Figure 8. *The switch-on and switch-off method is used for radiation using NIR lamp.*

A sharp drop in the intensity is observed indicating the release of Nile Red within minutes.

Conclusions

These novel coumarin-functionalized poly(ε-caprolactone)-*block*-poly(ethylene glycol) based nanoparticles are promising smart DDSs; due to the light-sensitive portion, a spatio-temporal controlled drug release could be assured.

References

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4. Sana B., Finne-Wistrand A., Pappalardo D. Recent development in near infrared light-responsive polymeric materials for smart drug-delivery systems. Materials Today Chemistry 25 (2022) 100963.