POLITECNICO DI TORINO
Repository ISTITUZIONALE

Multi stimuli-responsive drug delivery systems obtained by green chemistries

Original
Multi stimuli-responsive drug delivery systems obtained by green chemistries / Laurano, R., Boffito, M., Ciardelli, G.. - ELETTRONICO. - (2025). (GreenChemCo Pisa 16-18 Giugno 2025).

Availability:
This version is available at: 11583/3004120 since: 2025-10-16T13:11:00Z

Publisher:
/

Published
DOI:

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

19 November 2026

Multi stimuli-responsive drug delivery systems obtained by green chemistries

Rossella Laurano[1], Monica Boffito[1], Gianluca Ciardelli[1]

[1]*Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Corso Duca degli Abruzzi 24, Turin, Italy*

Corresponding author: Rossella Laurano, +393405561248, rossella.laurano@polito.it

Keywords (Max 5): plasma treatment, carbodiimide chemistry, drug delivery systems, smart hydrogels, sustainable devices

Introduction

The development of multi-stimuli-responsive hydrogels has garnered significant attention among scientists working on the engineering of active formulations, owing to the ability to tune and control their features in response to stimuli coming from the surrounding environment (e.g., temperature, pH, UV/Vis light). For example, thermo-responsive hydrogels exhibit temperature-controlled viscosity changes and sol-to-gel transition; pH-sensitive formulations display increased or decreased capability to absorb fluids as a function of their pH value; UV/Vis light-sensitive formulations demonstrate tunable network strength based on light intensity and exposure time. Regardless of the specific external stimulus, imparting such responsiveness often necessitates the engineering of very complex formulations and/or the functionalization of their polymeric components through chemistries requiring the use of organic solvents and highly toxic reagents. In this work, we explored the potential to confer multi-stimuli-responsiveness to amphiphilic poly(ether urethane)s (PEUs), differing for their building block composition, by employing various environmentally friendly approaches, finally leading to polymers with suitable features for their exploitation as smart drug delivery (SDD) systems and biomaterial inks.

Experimental

Amphiphilic PEUs were synthesized via a two-step reaction using Poloxamer® 407 and 1,6-diisocyanatohexane, followed by chain extension with either 1,4-cyclohexane dimethanol (CHP407) or N-Boc diethanolamine (DHP407). CHP407 powder was plasma-treated in the presence of Ar gas and acrylic acid vapors to expose alkaline pH-sensitive -COOH groups. Differently, DHP407 was subjected to Boc removal and functionalized via water-based carbodiimide chemistry to expose light-sensitive (i.e., thioglycolic acid, 2-carboxyethyl acrylate and 5-norbornene-2-carboxylic acid) and glucose-responsive (i.e., 3-phenylboronic acid) moieties. The success of the synthesis and functionalization was confirmed by Infrared (IR) and Nuclear Magnetic Resonance (NMR) spectroscopies and chromatographic analyses, while colorimetric assays quantified the number of grafted molecules. Thermo/photo-rheology and swelling/stability tests in physiological mimicking conditions were conducted to study hydrogel responsiveness to temperature and light irradiation and to alkaline-pH and glucose, respectively. Hydrogel cytocompatibility was assessed according to the ISO 10993:5 regulation, while their suitability as smart delivery carriers and biomaterial inks was investigated through *in vitro* pH- and glucose-controlled drug release tests and by extruding 3D constructs with different geometries.

Results and Discussion

Both CHP407 and DHP407 showed high Number Average Molecular Weight ($\overline{M_n}$ = 30kDa), low Polydispersity Index (D=1.4) and the characteristic IR peaks at 1720, 1635 and 1534 cm^{-1} ascribed to the C=O, N-H and C-N vibrations belonging to the urethane bonds, thus proving the success of the synthesis. Moreover, the NMR and colorimetric quantification of -COOH groups confirmed the feasible functionalization of water-soluble powder through plasma-treatment while preserving the chemical integrity of the PEU backbone. Specifically, by varying the Argon gas flow rate during the treatment it was possible to tune the exposure of -COOH groups, with the highest -COOH unit/$g_{polymer}$ quantified to be $5.3\times10^{18}\pm0.6\times10^{18}$ by setting Ar flow at 10 sccm. On the other hand, water-based carbodiimide chemistry was exploited to expose light-sensitive groups (i.e., thiols, acrylates and norbornene double bonds) and glucose molecules to deprotected DHP407 through the formation of amide bonds between PEU secondary amines and the carboxylic acid groups of the grafting molecules. Specifically, by properly tuning the pH of the grafting step (range: 5-9) it was possible to maximize the functionalization yield (approx. 100% for all considered molecules as assessed through NMR and colorimetric assays) while preserving the functional groups. Irrespective of adopted functionalization technique, temperature ramp tests performed on PEU hydrogels showed a temperature-dependent viscosity increase up to 37 °C ascribed to Poloxamer® 407 building block. Specifically, the temperature marking the beginning of the gelation transition was measured to be approx. 14 °C, while at physiological temperature all systems were in the gel state. Moreover, photo-rheology confirmed the increased network capability to withstand applied deformation upon light exposure compared to not-irradiated samples. An additional control over hydrogel mechanical strength was obtained by properly reacting grafted functional groups (i.e., thiol/norbornene gave higher mechanical features compared to thiol/acrylate). Swelling/stability tests evidenced higher hydrogel capability to absorb alkaline fluids and glucose-enriched media for systems prepared by using plasma-treated and glucose-functionalized PEUs, respectively, compared to their corresponding control conditions (i.e., hydrogels based on not-functionalized PEUs). Furthermore, all systems were cytocompatible (i.e., cell viability higher than 90%) according to the ISO regulation. Lastly, multi stimuli-responsive hydrogel suitability as smart carriers was demonstrated through *in vitro* drug release tests. Specifically, temperature changes were exploited for drug encapsulation (i.e., lactoferrin and insulin) in the hydrogels. Then, plasma-treated formulations showed increased lactoferrin release by increasing the releasing medium pH from 5 to 11, while glucose-responsive hydrogels were able to trigger insulin release in response to glucose levels. On the other hand, thermo- and light-responsive systems showed suitability as biomaterial inks as a consequence of temperature and light changes which ensured extrudability under mild conditions and construct stability over time.

Conclusions

Green chemistries are powerful tools to design multi-stimuli responsive biomaterials as SDD system- and biomaterial ink-components showing a high degree of tunability of their properties.

Acknowledgments

Study carried out within the HERO project (CUP E53D23003120006) – funded by European Union – Next Generation EU Mission 4, Component 1 within PRIN 2022 program (D.D. 104 - 02/02/2022 MUR). R.L. acknowledges financial support from the FSE REACT-EU - PON Ricerca e Innovazione 2014-2020. This abstract reflects only the authors' views and opinions and the Ministry cannot be considered responsible for them.