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境外生研究獎學金

Research Scholarship for International Graduate Students

Non-Anticoagulant Heparin Prodrug Loaded Biodegradable and Injectable Thermoresponsive Hydrogels for Enhanced Anti-Metastasis Therapy

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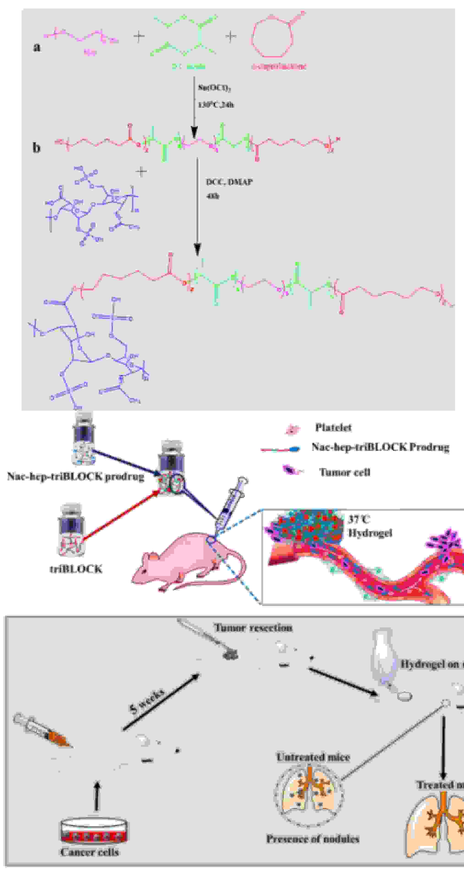
ABSTRACT

In this study, a non-anti-coagulate heparin prodrug was developed for metastasis treatment with a localized treatment system using temperature-sensitive (poly-(ε-caprolactone-co-lactide)-b-poly (ethylene glycol)-b-poly (ε-caprolactone-co-lactide) polymeric hydrogel. The drug molecule (heparin) was conjugated with the polymer via esterification, and its sustained release was ensured by hydrolysis and polymeric biodegradation. An aqueous solution of the polymer could be used as an injectable solution at below 25 ℃ and it achieved gel formation at 37 °C. The anti-metastasis effect of the hydrogels was investigated both in vitro and in vivo. The results demonstrated that local administration of injectable heparin-loaded hydrogels effectively promotes an inhibitory effect on cancer metastasis.

EXPERIMENT



Scheme 1. Synthesis and *in vivo* application

RESULT

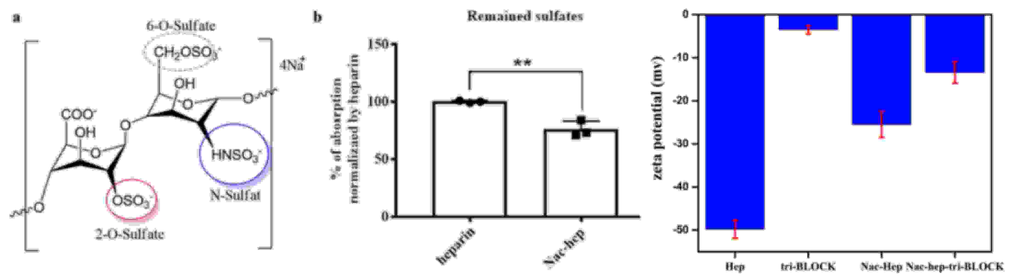


Fig. 1. Modified heparins compared to native heparin as measured by absorbance of DMMB and zeta potential

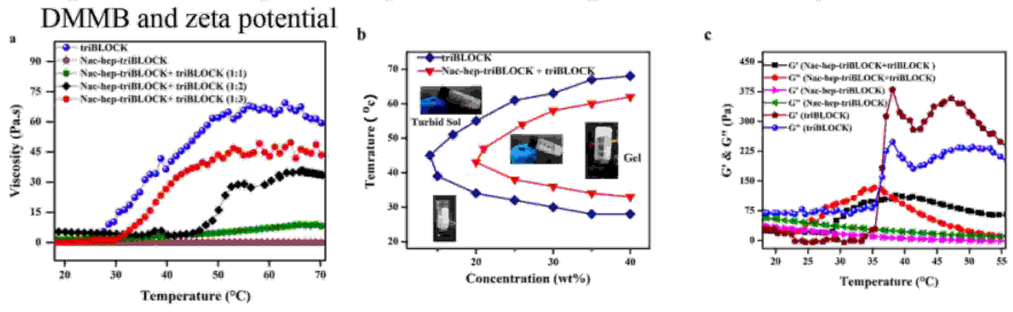


Fig. 2. Viscosity, Sol-gel phase transition diagram and Storage modulus (G′) and loss modulus (G″) of triBLOCK, Nac-hep-triBLOCK, and Nac-hep- triBLOCK+triBLOCK

Table 1. Molecular weight of PEG, PCLA, and Nac-hep-triBLOCK, determined by GPC.

Sample	Mn (g mol^{-1})	PDI
PEG	10511	1.10
triBLOCK	14714	1.07
Nac-hep-triBLOCK	35140	1.13

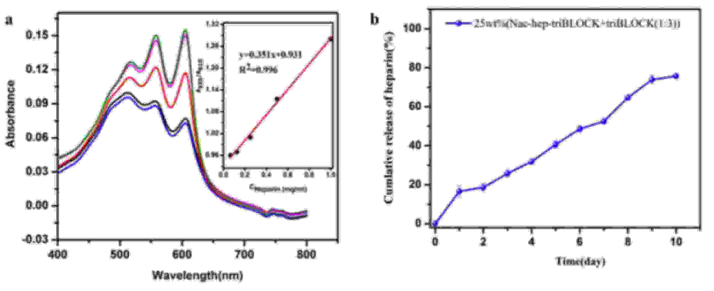


Fig.3. Release profiles of heparin from 25 wt% Nac-hep-triBLOCK prodrug loaded triBLOCK hydrogel

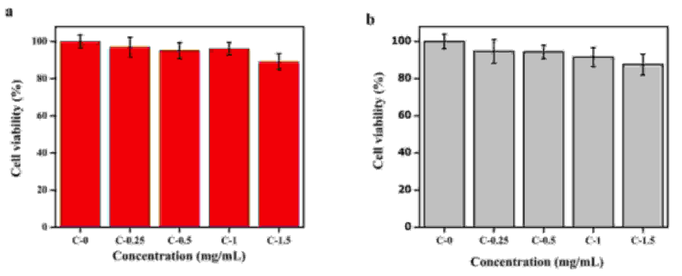


Fig.4. *In vitro* cytotoxicity assay against HeLa cells and HaCaT cells

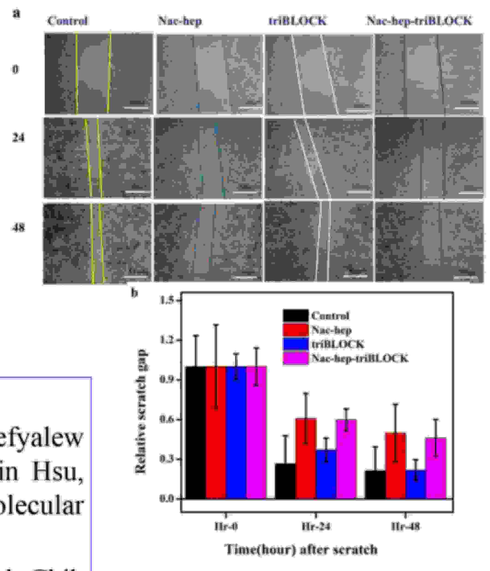


Fig.5. Microscopic images from *in vitro* scratch wound healing assay of HeLa cell cultures treated

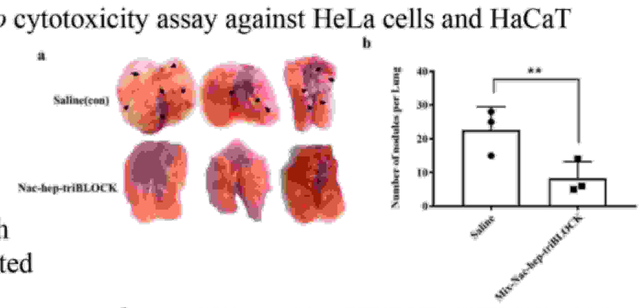


Fig.6. *In vivo* anti-metastatic effects of Nac-hep tri-BLOCK hydrogel

JOURNAL PUBLICATIONS

1. **Abegaz Tizazu Andrgie**, Shewaye Lakew Mekuria, Kefyalew Dagnew Addisu, Balkew Zewge Hailemeskel, Wei-Hsin Hsu, Hsieh-Chih Tsai, and Juin-Yih Lai (**2019**). Macromolecular Bioscience. 19, 1800409.
2. **Abegaz Tizazu Andrgie[1],** Haile Fentahun Darge[1], Hsieh-Chih Tsai, and Juin-Yih Lai. (**July 2019**),International Journal of Biological Macromolecules. V. 133, P. 545-563.([1]Equal contribution to this work)
3. Yihenew Simegniew Birhan, Balkew Zewge Hailemeskel, Tefera Worku Mekonnen, Endiries Yibru Hanurry, Haile Fentahun Darge, **Abegaz Tizazu Andrgie,** Hsiao-Ying Chou, Juin-Yih Lai, and Hsieh-Chih Tsai. (**August, 2019**).International Journal of Pharmaceutics V.567, 15 p. 118486.
4. Balkew Zewge Hailemeskel, Wei-Hsin Hsu, Kefyalew Dagnew Addisu, **Abegaz Tizazu Andrgie**, Hsiao-Ying Chou, Juin-Yih Lai, Hsieh-Chih Tsai. (**October 2019**).Materials Science and Engineering: C. V. 103, p.109803.
5. Kefyalew Dagnew Addisu, Balkew Zewge Hailemeskel, Shewaye Lakew Mekuria, **Abegaz Tizazu Andrgie**, Yu-Chun Lin, Hsieh-Chih Tsai (**2018**) ACS Applied Materials & Interfaces. 10, 5147−5160.

CONCULSION

- Nac-hep-triBLOCK prodrugs were synthesized and carefully tuned with triBLOCK hydrogel as an injectable anti-metastasis implant after tumor resection.
- The in vitro metabolism tests confirmed the biocompatibility of the hydrogels with HeLa cells and HaCaT cells.
- Nac-hep-triBLOCK treatment can efficiently inhibit cell migration in vitro and reduce tumor metastasis to the vulnerable lungs in nude mice.

ACKNOWLEDGMENTS

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