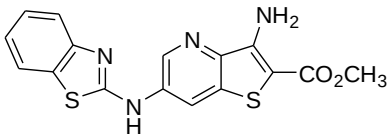
Biocompatible peptide-based hydrogels as nanocarriers for a new antitumoral drug

Ana C. L. Hortelão[1], Bruno F. C. Hermenegildo[1], Helena Vilaça[2], Goreti Pereira[2], Bing Xu[3], Maria-João R. P. Queiroz[2], José A. Martins[2], Paula M. T. Ferreira[2], Elisabete M. S. Castanheira[1]

[1]Centro de Física (CFUM), Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[2]Centro de Química (CQ/UM), Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[3]Department of Chemistry, Brandeis University, Waltham, MA, 02454 USA
alchortelao@gmail.com

The biocompatibility of peptide-based hydrogels make them ideal for biomedical applications such as drug delivery, biosensing, tissue engineering and wound healing [1-3]. However, the enzymatic hydrolysis of these materials can be regarded as a serious disadvantage. One way to increase the biostability of this type of hydrogels consists in using non-proteinogenic amino acids. In this work, several new hydrogelators were developed, containing a Naproxen or a Naphthalene group (Table 1), and their critical aggregation concentrations were determined by fluorescence. The influence of pH in the aggregation of these molecules was also investigated. TEM images revealed that these hydrogels contain entangled nanofibers with width ranging from 9 nm to 18 nm (Figure 1).

The ability of these hydrogels to act as nanocarriers for an antitumoral drug was investigated. For that purpose, FRET (Förster Resonance Energy Transfer) assays were performed between the several hydrogels (acting as energy donors) and the new antitumoral fluorescent thieno[3,2-*b*]pyridine derivative **1** [4] (acting as energy acceptor). Donor-acceptor distances between 2.5nm and 3.5nm were determined.



Antitumoral thieno[3,2-*b*]pyridine derivative **1**

The interaction between the new hydrogels and models of biological membranes was also confirmed by FRET. Lipid vesicles composed of egg lecithin/cholesterol 7:3 were used as membrane models, containing both the antitumoral compound **1** (as energy donor) and the lipid probe Nile Red (as energy acceptor). In this system, efficient energy transfer is observed. Upon interaction with the several hydrogelators, FRET vanishes, indicating a strong increase of the donor-acceptor distance.

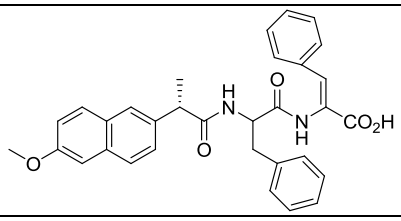
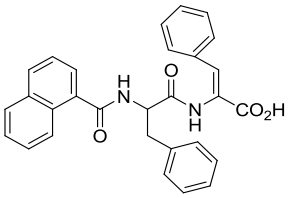
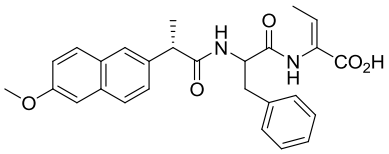
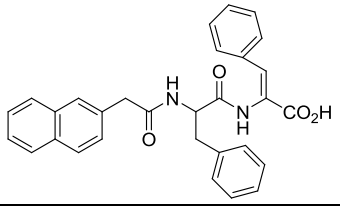
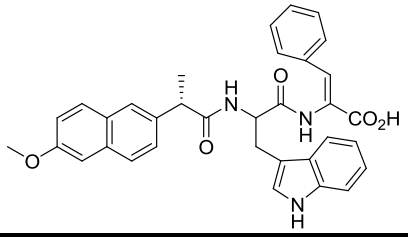
As the antitumoral compound tested here is especially active against human melanoma cell lines (GI_{50}= =3.5 μM) [4], the results obtained here confirm the ability of these hydrogels to act as drug nanocarriers, being promising to the development of formulations for topical application.

Acknowledgements: Foundation for the Science and Technology (FCT, Portugal), FEDER and QREN for financial support to the Research Centers, CFUM [Strategic Project PEst-C/FIS/UI0607/2013 (FCOMP-01-0124-FEDER-037291)] and CQ/UM [Strategic Project PEst-C/QUI/UI0686/2013 (FCOMP-01-0124-FEDER-037302)]. FCT is also acknowledged for the PhD grant of H. Vilaça (SFRH/BD/7265/2010).

References

[1] F. Zhao, M. L. Ma, B. Xu, Chem. Soc. Rev., **38** (2009) 883.
[2] X. Zhao, F. Pan, H. Xu, M. Yaseen, H. Shan, C. A. E. Hauser, S. Zhang, J. R. Lu, Chem. Soc. Rev., **39** (2010) 3840.
[3] Y. Zhang, Y, Kuang, Y. A. Gao, B. Xu, Langmuir, **27** (2011) 529.
[4] M.-J. R. P. Queiroz, R. C. Calhelha, L. Vale-Silva, E. Pinto, M. S.-J. Nascimento, Eur. J. Med. Chem., **45** (2010) 5732.

Table 1. Structure of the several hydrogelators

Hydrogelator	Structure	Hydrogelator	Structure
Npx-Phe-ΔPhe-OH		1-Naph-Phe-ΔPhe-OH	
Npx-Phe-ΔAbu-OH		2-Naph-Phe-ΔPhe-OH	
Npx-Trp-ΔPhe-OH		Npx: Naproxen Phe: Phenylalanine Abu: Aminobutyric acid Trp: Tryptophan Naph: Naphthalene	

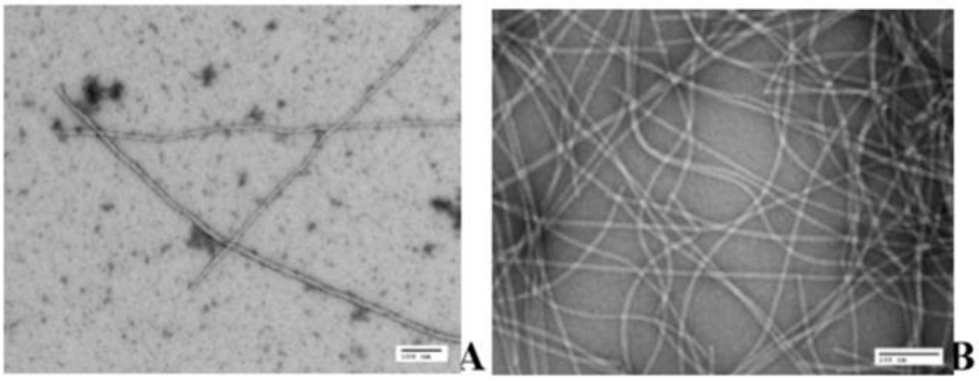


Figure 1. TEM images of Npx-Phe-ΔPhe-OH (**A**) and Npx-Phe-ΔAbu-OH (**B**).

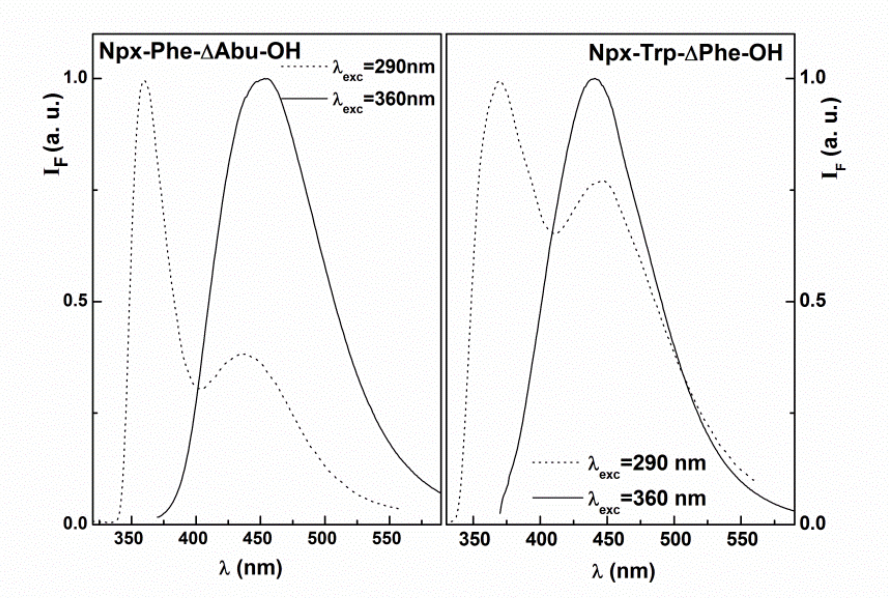


Figure 2. Normalized emission spectra of Naproxen hydrogels in the presence of compound **1**, exciting the hydrogels (λ_{exc}=290 nm) and exciting only compound **1** (λ_{exc}=360nm).