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Novel Atorvastatin loaded peptide amphiphiles for corneal neovascularization

Chaired by Dr. Alfredo Berzal-Herranz and Prof. Dr. Maria Emília Sousa

pharmaceuticals MDPI

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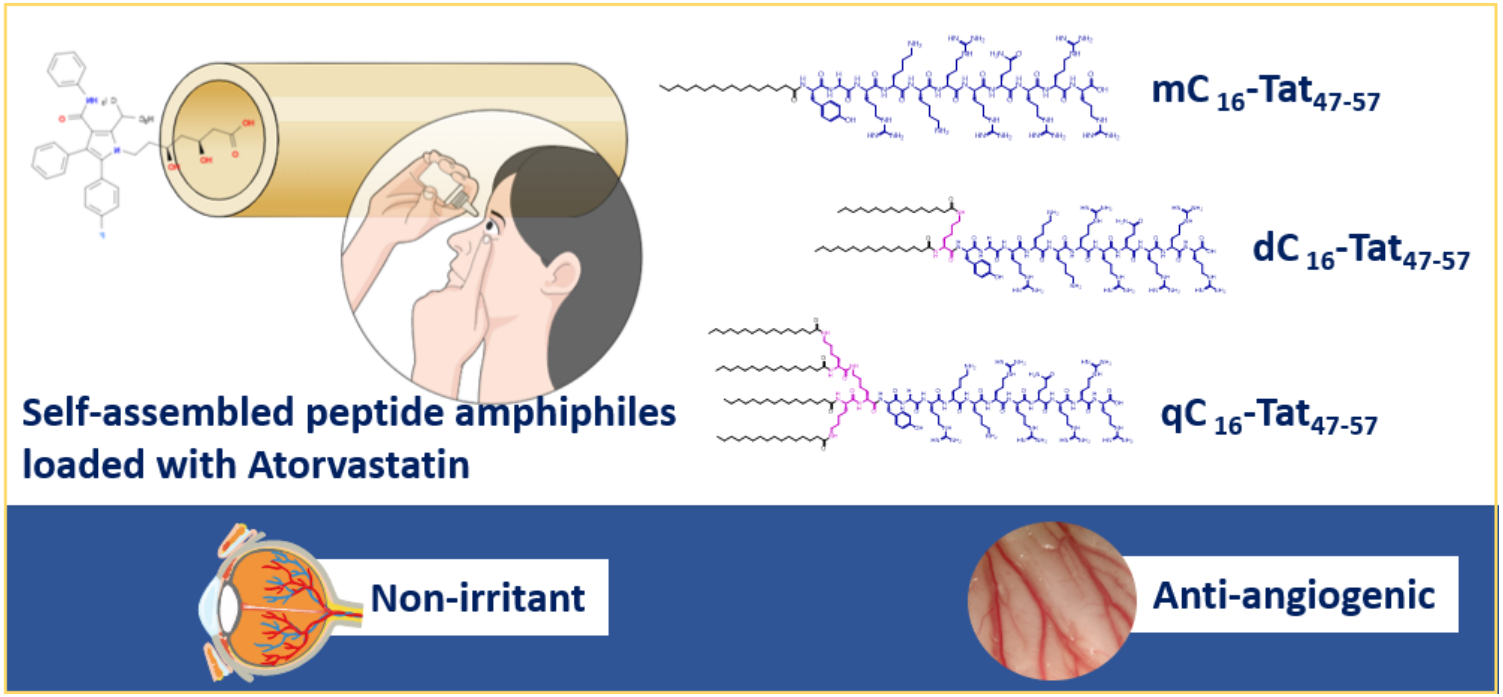
Novel Atorvastatin loaded peptide amphiphiles for corneal neovascularization



Abstract: Corneal neovascularization constitutes a serious sight-threatening disease. This pathology can be treated using antiangiogenic and anti-inflammatory compounds. Therefore, in this area, atorvastatin (ATV) constitutes a suitable candidate to be administered topically to the eyes due to its pharmacological properties. However, ATV possess low water solubility and it is rapidly eliminated in traditional formulations. Therefore, to attain suitable efficacy, ATV has been encapsulated into custom-developed peptide amphiphiles.

In this study, three peptide amphiphiles bearing one, two or four C_{16}-alkyl groups (mC_{16}-Tat_{47-57}, dC_{16}-Tat_{47-57} and qC_{16}-Tat_{47-57}) were synthesized using solid-phase synthesis, characterized physically and morphologically and loaded with ATV. From them, ATV-qC_{16}-Tat_{47-57} showed higher encapsulation efficiency than mC_{16}-Tat_{47-57} and dC_{16}-Tat_{47-57} and more defined nanostructures with a tubular shape. Moreover, in vitro ATV release was also assessed confirming that ATV-qC_{16}-Tat_{47-57} showed ATV prolonged release. In vitro (HEM-CAM and CAM-TBS) and in vivo ocular tolerance (Draize test in New Zealand rabbits) of ATV-qC_{16}-Tat_{47-57} confirmed that ATV-qC_{16}-Tat_{47-57} were not irritant. Moreover, ATV-qC_{16}-Tat_{47-57} demonstrated to be antiangiogenic in an *in ovo* model and was able to prevented ocular inflammation *in vivo*.

Therefore, ATV-qC_{16}-Tat_{47-57} constitutes a promising topical medication against corneal neovascularization.

Keywords: atorvastatin; angiogenesis; drug delivery; ocular inflammation; peptide amphiphiles.

Introduction

Corneal neovascularitzation

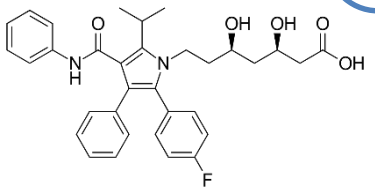
Corneal neovascularization is a major cause of blindness worldwide affecting 1.4 million people/year

Ocular inflammation
May trigger CNV

Angiogenesis
Growth of blood vessels in the cornea

Introduction

ATORVASTATIN

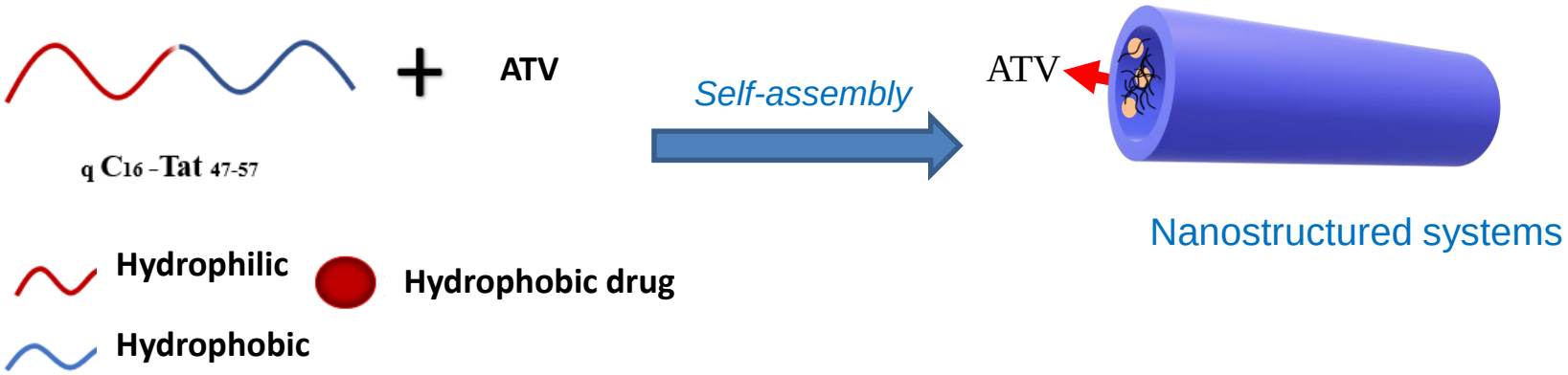


- Anti/pro-angiogenic
- Anti-inflammatory
- Low water solubility

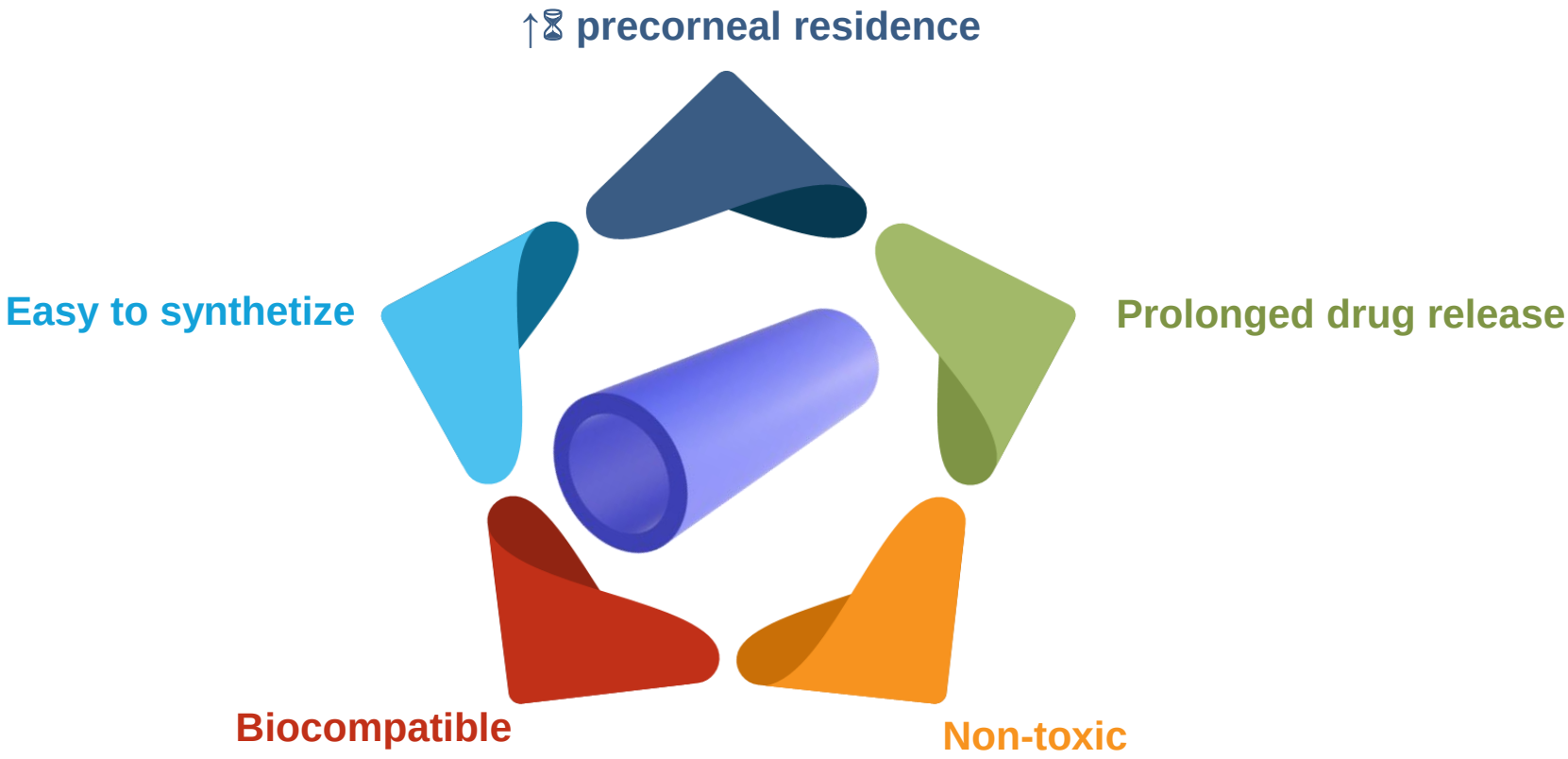
<5 % is able to arrive to ocular tissues

Introduction

PEPTIDE AMPHIPHILES

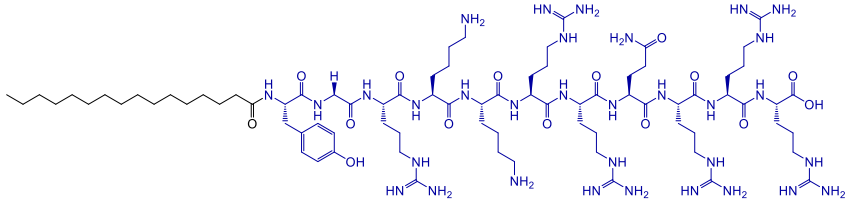


Introduction

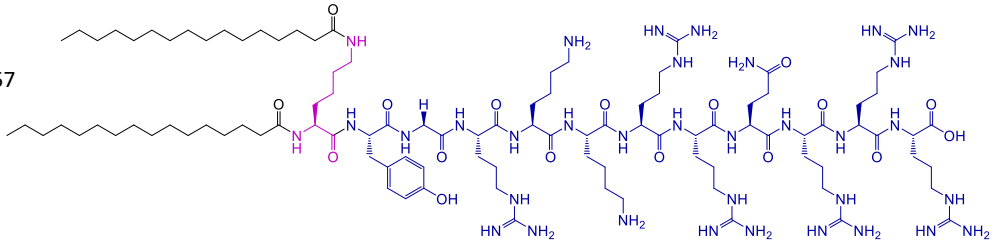


Results and discussion

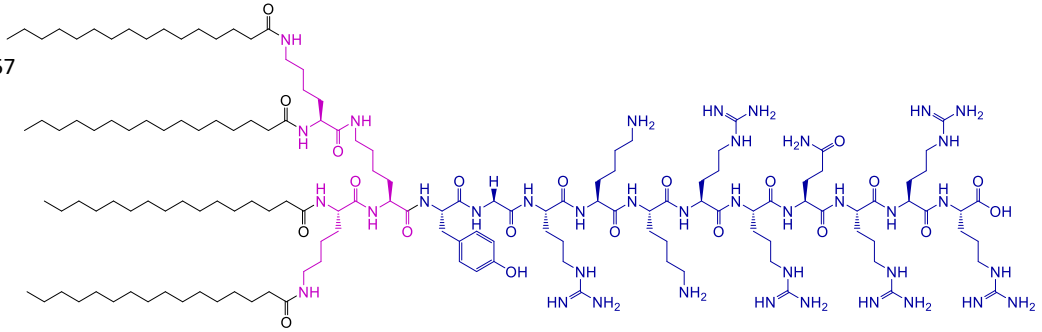
mC_{16}-Tat_{47-57}



dC_{16}-Tat_{47-57}

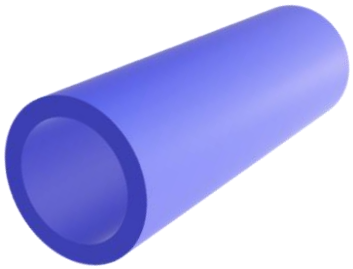


qC_{16}-Tat_{47-57}



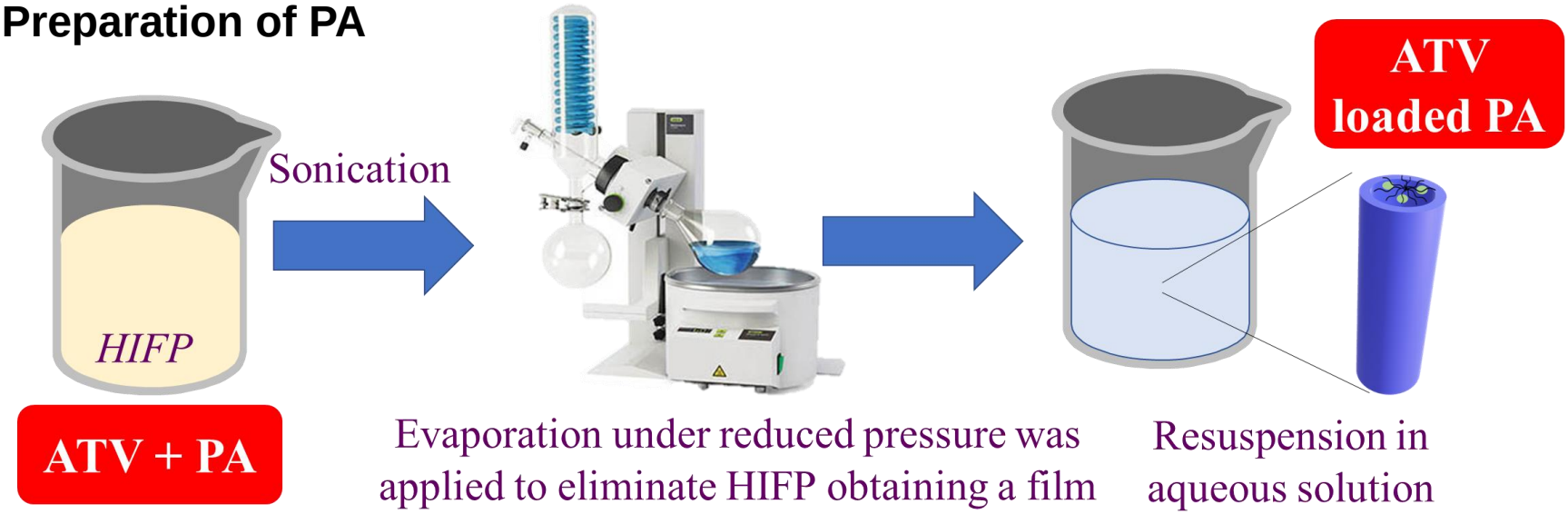
Solid-phase synthesis

3 Peptide amphiphiles (PA)



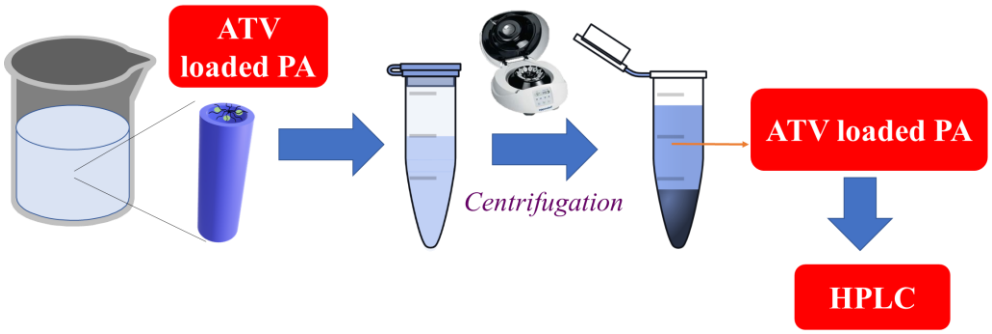
Results and discussion

Preparation of PA



Results and discussion

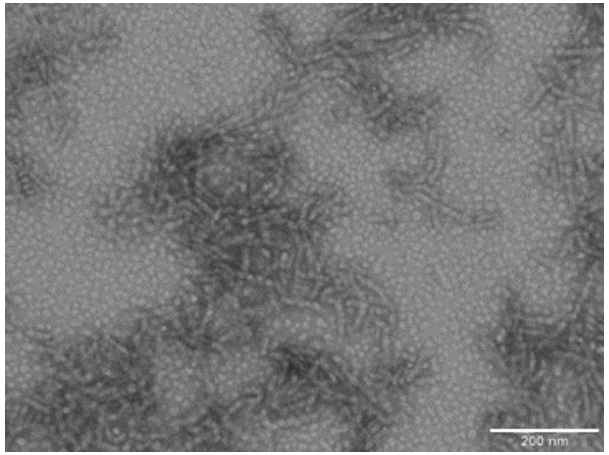
PA ATORVASTATIN LOADING



PA	EE (%)	ATV encapsulated (mg/ml)	Zeta potential (mV)
mC_{16}-Tat_{47-57}	5.0	0.011	+ 14.4 ± 1.5
dC_{16}-Tat_{47-57}	35.0	0.086	+ 25.4 ± 1.4
qC_{16}-Tat_{47-57}	40.8	0.098	+ 17.5 ± 0.2

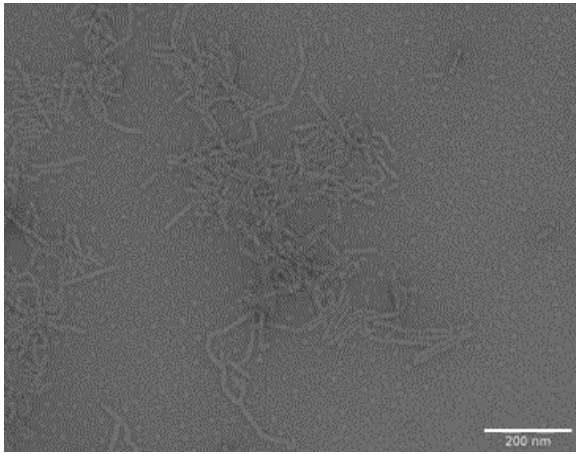
Results and discussion

qC_{16}-Tat_{47-57}



11.49 ± 1.78 nm
94.76 ± 28.45

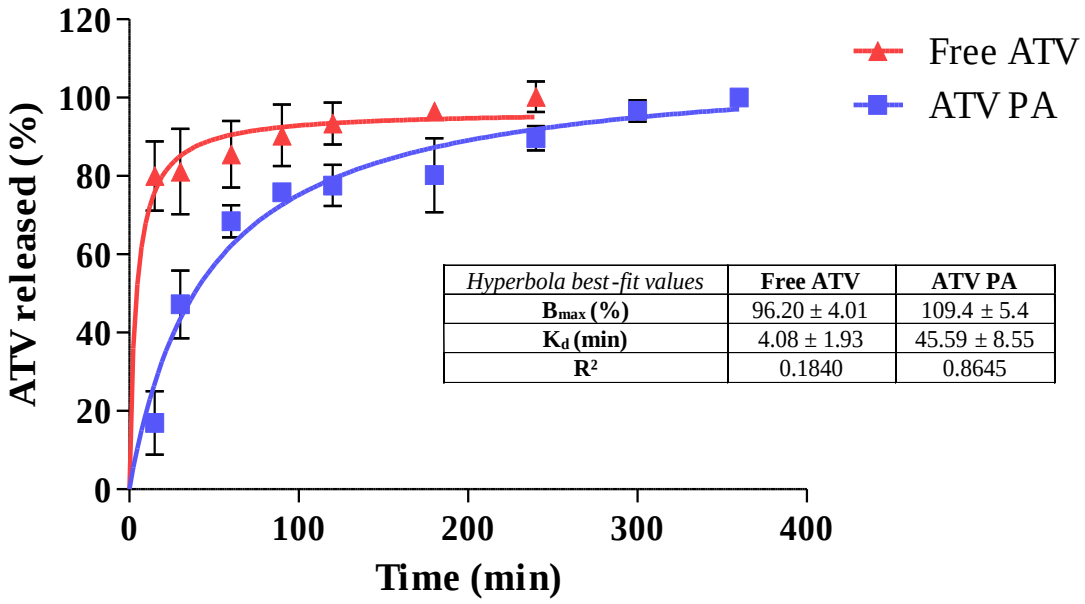
ATV-qC_{16}-Tat_{47-57}



11.70 ± 2.03 nm
142.22 ± 24.63 nm

TRANSMISSION ELECTRON MICROSCOPE

Results and discussion

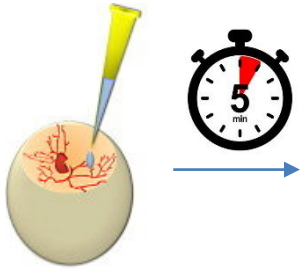


Hyperbola best-fit values	**Free ATV**	**ATV PA**
B_{max} (%)	96.20 ± 4.01	109.4 ± 5.4
K_d (min)	4.08 ± 1.93	45.59 ± 8.55
R^2	0.1840	0.8645

IN VITRO ATORVASTATIN RELEASE

Results and discussion

HET-CAM test

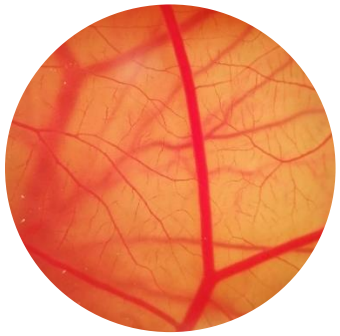


Hemorrage

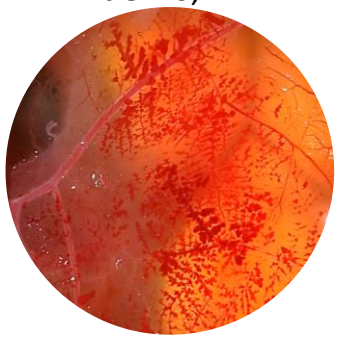
Coagulation

Vasoconstriction

ATV-qC$_{16}$-Tat$_{47-57}$



NaOH 0,1 M



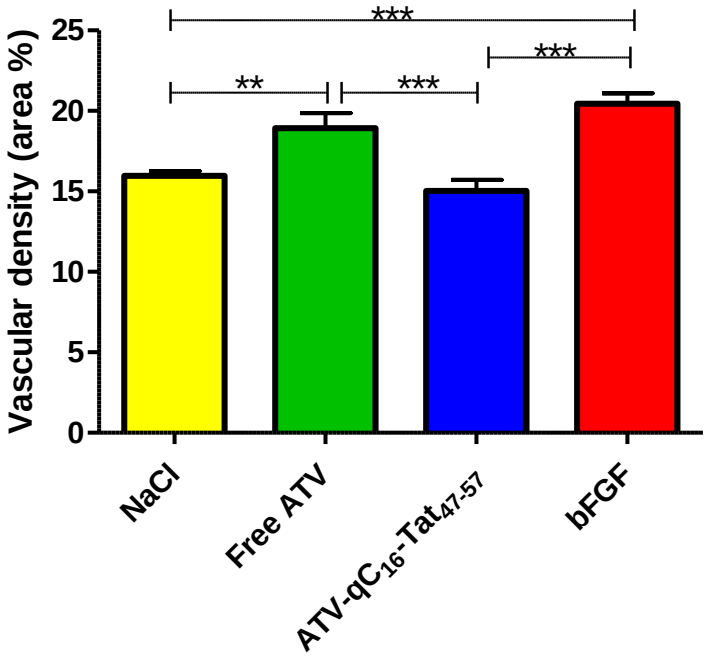
Draize test

OII = 0

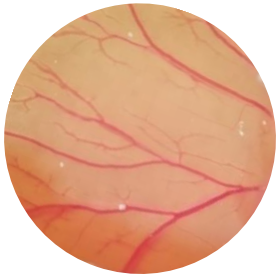
OCULAR TOLERANCE

Results and discussion

48 h → CAM evaluation



ATV



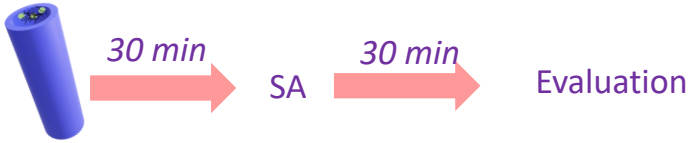
ATV-qC$_{16}$-Tat$_{47-57}$

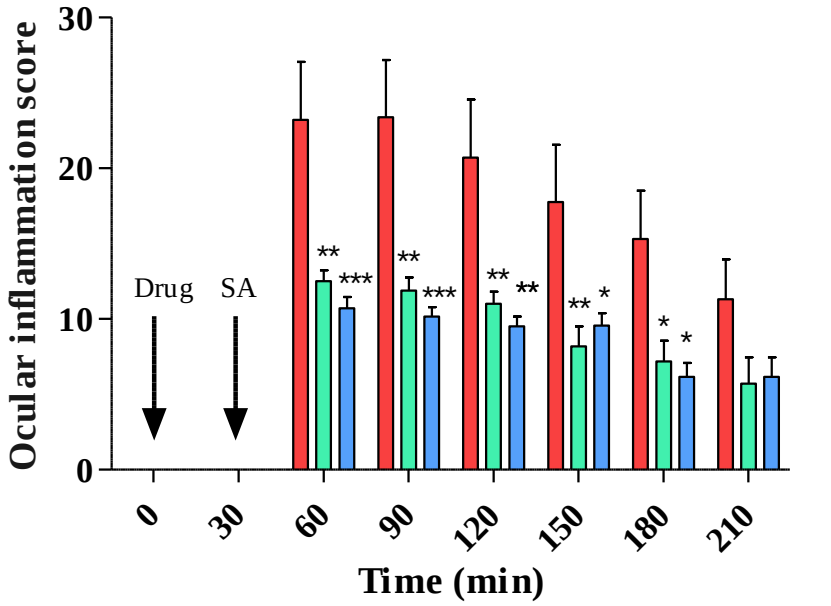
NaCl 0,9 %

bFGF

OCULAR ANGIOGENESIS

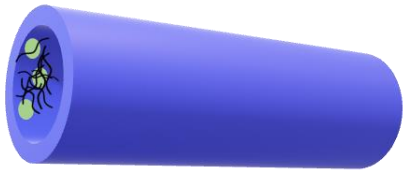
Results and discussion





OCULAR INFLAMMATION

Conclusions



Atorvastatin PAs

- Prolongued ATV release
- Suitable ocular tolerance
- Anti-angiogenic
- Anti-inflammatory

Acknowledgments

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