Release kinetic model and antimicrobial activity of an innovative minocycline and voriconazole co-delivery system

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Introduction

✱ **Co-encapsulating** of drugs as an advantageous means for administration [1]

✱ Co-delivery of two antimicrobials at the infection site

✱ **Minocycline** and **voriconazole** were the assayed drugs

✱ **Osteomyelitis** treatment

Aim & Strategy

✱ Development of a new local drug-delivery system aiming bone infection and the modulation of the polimicrobial activity

✱ Simultaneous delivery of **minocycline** and **voriconazole**, antibacterial and antifungal agents, respectively

✱ Polylactide (PDLLA) scaffolds functionalized with collagen and bioglass, osteogenic enhancers

Methodology

✱ Polylactide (PDLLA) scaffolds prepared by methodology previously optimized [2]

✱ *In vitro* release assays used HEPES buffer, at 37ºC

✱ Aliquots of the supernatant collected and analyzed in triplicate

✱ Minocycline quantified by UV spectroscopy

✱ Voriconazole quantified by HPLC

✱ Antimicrobial activity against *S. aureus* (ATCC 25923) and *C. albicans* (ATCC 10231) evaluated using the agar diffusion method

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References

Vitorino, C.; Almeida, J.; Gonçalves, L.; Ameida, A.; Sousa, J.; Pais, A. *J Control Release* 2013, 167(3), 301-314

Martin, V.; Anjos, I.; Saraiva, A.; Zuza, E.; Gonçalves, L.; Alves, M.; Santos, C.; Ribeiro, I.; Bettencourt, A.; 2019 IEEE 6th Portuguese Meeting on Bioengineering (ENBENG) 2019, pp. 1-4 and PDLLA scaffold for rabbit femur defect regeneration. *Biomed Mater*. 2019;14, :65007.

Results

1– Release kinetic model

Table 1 - The parameters of adjustement of kinetic models of drug release

Data		Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
		K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K	n	R^2
Single delivery	MH	5,788	0,537	0,147	0,394	11,869	0,625	1,143	0,465	24,132	0,374	**0,738**
	Vor	5,788	0,915	0,151	0,816	17,911	0,982	1,929	0,915	33,297	0,309	**0,992**
Co-delivery	MH	1,405	0,914	0,031	0,904	4,567	**0,946**	0,468	0,914	43,291	0,070	0,916
	Vor	4,847	0,500	0,068	0,450	16,554	0,654	1,616	0,500	71,812	0,168	**0,783**

✱ The **Korsmeyer-Peppas** kinetic model presents the best fitted of the release assays

✱ All the drug releases appear to be driven by diffusion mechanisms (*n* values lower than 0.5)

✱ A Fickian behavior is suggested

Results highlight a release mechanism driven by diffusion, over dissolution of the polymeric system and even over transport through the polymer

2– Antimicrobial activity of scaffolds

Table 2 - Results of drug inhibition of growth of *S. aureus* and *C. albicans* assays. Average ± SD

MH - minocycline, Vor- voriconazole, FCZ—fluconazole

		Inhibition zone diameter (mm)				
Organisms		MH-Vor scaffold	MH-Vor disk	MH disk	Vor disk	FCZ disk
S. aureus	24 h	27.5 ± 2.8	34.6 ± 0.7	33.1 ± 1.5	-	-
C. albicans	24 h	21.3 ± 2.1	32.6 ± 1.9	15.4 ± 1.5	25.0 ± 4.1	27.1 ± 1.6
	48 h	17.0 ± 2.6	29.4 ± 3.7	-	-	-

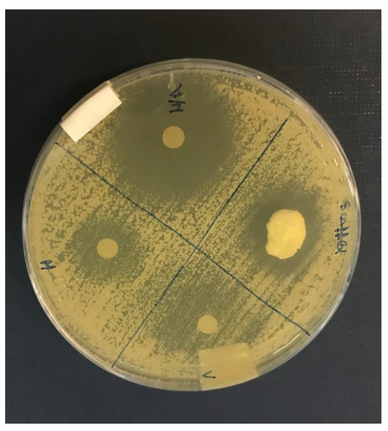

Fig. 1. Results of drug inhibition of growth of *S. aureus* and *C. albicans* for 48h

✱ The scaffold combining minocycline and voriconazole has activity against *C. albicans* for 48h, in comparison with the controls of minocycline disk and voriconazole disk (activity for 24h)

✱ In the assays to both microorganisms, the scaffold studied and the disk combining the two therapeutic agents, presented antimicrobial activity

Results suggest that the scaffold combining both antimicrobials has activity against *C. albicans* and *S. aureus*

Conclusions

The release kinetic model and microbiological results propose this structure as a promising co-delivery system for local antimicrobial therapy in osteomyelitis.