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Composite Biodegradable Systems for Localized Treatment of Osteomyelitis

A thesis submitted in the partial fulfillment of the requirements for the Master Degree in Pharmaceutical Sciences (Pharmaceutics)

By

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List of Abbreviations

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide	MTT
50% inhibitory concentration	IC50
Alkaline phosphatase	ALP
Alpha-tricalcium phosphate	α-TCP
Antibody	Ab
Antigen	Ag
Avidin-Horeradish Peroxidase	HRP
Beta-tricalcium phosphate	ß-TCP
Biopharmaceutical classification system	BCS
Bone-marrow-derived mesenchymal stem	BMSCs
Bulk density	ρb
Calcium phosphate	CaP
Calcium phosphate cements	CPCs
Calcium phosphates	CaPs
Chitosan	Cs
Ciprofloxacin	CIP
Colony forming unit	CFU
Commercial beta-tricalcium phosphate	C-ß-TCP
Commercial dicalcium hydrogen phosphate	C-Di-CP
Commercial hydroxyapatite	C-HAp
Computed tomography	CT
Crystallization temperature	T_c
Dicalcium phosphate dihydrate	DCDP
Dichloromethane	DCM
Differential scanning calorimeter	DSC
Ethylene diamine tetra-acetic acid	EDTA
Extracellular matrix	ECM
Fourier transform infrared	FTIR
Gram negative	G -ve
Gram positive	G +ve
Heat of crystallization	ΔH_c
Heat of melting	ΔH_m
Human bone marrow stem cell	hBMSCs
Human fetal osteoblast cells	hFOB
Human lactoferrin 1-11	hLF1-11
Hydroxyapatite	HAp
Kilogray	KGy

Magnesium phosphate cement	MPC
Magnetic resonance imaging	MRI
Melting temperatures	T_m
Methicillin-resistant Staphylococcus aureus	MRSA
Modified Eagle Minimum Essential Medium	MEME
Molecular weight	Mw
Monocalcium phosphate	MCP
Moxifloxacin hydrochloride	MOX
Optical density	OD
Orthopedic device-related infections	ODRI
Osteomyelitis	OM
Phosphate buffered saline	PBS
Platelet-rich fibrin	PRF
Polycaprolactone	PCL
Poly-lactide	PLA
Poly-lactide-co-glycolic	PLGA
Poly-lactide-co-ε-caprolactone	PLC
Polymethyl methacrylate	PMMA
Polyurethane	PU
Polyvinyl alcohol	PVA
Porosity	ϕ
Quaternized chitosan	HACC
Rifampin	RF
scanning electron microscopy	SEM
Silver	Ag
Skeletal density	ρs
Standard deviation	SD
Staphylococcus aureus	*S. aureus*
Tetracalcium phosphate	TTCP
Tetramethylbenzidine	TMB
Tissue culture flasks	TCF
Titanium	Ti
Titanium aluminum niobium	TAN
True partition coefficient	Log P
US Food and Drug Administration	FDA
Vancomycin	VAN
Wavelength t the maximum absorbance	λ_{max}
X-ray powder diffraction	XRPD

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Abstract

Scaffold-based application carries a tremendous hope for bone defect diseases. When a bone fragment is lost due to bone degenerative diseases or infections; the defect should be replaced with a functional osseous filler. Coupling calcium phosphate (CaP) compounds with biodegradable polymers to fabricate composite scaffolds loaded with antibiotics were intensively studied for treatment of osteomyelitis (OM). Moxifloxacin hydrochloride (MOX) efficiency is reported in the treatment of OM with a higher tendency to invade bone cells.

Hence, the aim of this thesis was to formulate and *in vitro* characterize CaP-based composite scaffolds loaded with MOX for prevention and treatment of OM. This was accomplished through the *in-situ* preparation of CaP within either chitosan (Cs) or poly-lactide-co-caprolactone (PLC) matrices, followed by their mixing with MOX and compression into medicated composite scaffolds.

Cs-based CaP composites were successfully synthesized through *in situ* precipitation approach. The synthetic biodegradable co-polymer, Polylactide-co-ε-caprolactone (PLC), was used for the fabrication of CaP composites through *in situ* one-pot technique. For comparative purposes, different commercially available preformed-CaP powders, namely hydroxyapatite (C-HAp), dicalcium hydrogen phosphate (C-Di-CP) and beta-tricalcium phosphate (C-ß-TCP); were used to prepare preformed-CaP composites using the selected PLC polymer grade with the same polymer weight ratio as that extracted from the selected *in situ*-prepared composite.