Accepted Manuscript

Gentamicin Loaded Thermosetting Hydrogel and Moldable Composite Scaffold: Formulation Study and Biologic Evaluation

Rossella Dorati, Antonella De Trizio, Ida Genta, Alessia Merelli, Tiziana Modena, Bice Conti

PII: S0022-3549(17)30147-8

DOI: 10.1016/j.xphs.2017.02.031

Reference: XPHS 673

To appear in: *Journal of Pharmaceutical Sciences*

Received Date: 10 January 2017

Revised Date: 16 February 2017

Accepted Date: 27 February 2017

GENTAMICIN LOADED THERMOSETTING HYDROGEL AND MOLDABLE COMPOSITE SCAFFOLD: FORMULATION STUDY AND BIOLOGIC EVALUATION.

[1,3]Rossella Dorati, [1]Antonella De Trizio, [1,3]Ida Genta, [2]Alessia Merelli, [1]Tiziana Modena, [1,3]*Bice Conti

Department of Drug Sciences, [1]Pharmaceutcial Chemistry section, [2]Pharmacology section, University of Pavia, Viale Taramelli 12, [3]Center for Health Technology (CHT), University of Pavia, Via A. Ferrata 1, 27100 Pavia, Italy.

***Corresponding author: bice.conti@unipv.it**

ABSTRACT

The aim was to design biodegradable drug delivery systems for gentamicin local delivery, meanwhile acting as scaffold for bone regeneration. Gentamicin loaded thermosetting composite hydrogels (TCHG) were prepared combining chitosan with bovine bone substitutes (BBS Orthoss® granules), beta-glycerophosphate as crosslinker, and lyophilized to obtain composite moldable scaffolds (mCSG). Diverse techniques for gentamicin loading into mCS were investigated by drug incorporation during hydrogel preparation, or drug absorption on preformed mCS. Rheologic hydrogel characterization was performed. MCSG were characterized for porosity, stability (water retention, water uptake) gentamicin release, cell seeding and proliferation, antimicrobial effect on *E.Coli ATCC 10356*. Results show suitable gentamicin loadings were 4 mg in 1 ml TCH starting solution, irreversible hydrogel thermosetting behavior, and cosolute effect of gentamicin on sol/gel transition. Positive results in terms of porosity (80-86%), scaffold water uptake and retention capability were obtained. Antibiotic *in vitro* release was completed in 4 hours. Good cell seeding results were observed for mCSG1-5. MCSG3; mCSG5 resulted the best as cell proliferation results. MCSG exerted bactericidal effect for 24 hours, with superimposition of chitosan bacteriostatic effect in the first 4 hours. The results lead to consider the drug delivery for reducing infection risk during bone open surgeries.

1. INTRODUCTION

Osteomyelitis is an inflammatory bone disease which leads to bone destruction (osteolysis). It can arise by direct contamination (e.g. open fractures and ulcers) or by spreading from blood stream (hematogenous source) or from contiguous site or implant. Surgical interventions for treating bone defects or bone fusion, such as open surgery, involve air exposure times and potential for surgical injury that can easily lead to infection. Bacteria causing infection often originate from patient's skin as well from operating personals. Moreover, orthopedic implants can be a nidus for infection, and infection can spread easily and faster after an orthopedic general surgery. Serious infections can be induced around the graft site because the damaged tissue has not blood supply and bacteria can live and spread.,