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In Vitro Silver Sulfadiazine Controlled Release from Chitosan Cross-linked Films

M. G. N. Campos[(1)*], N. Satsangi[(2)], H. R. Rawls[(2)] and L. H. I. Mei[(3)]

(1) Department of Science and Technology, Federal University of Alfenas, Rua Corumbá, n° 71, 37701-100, Poços de Caldas-MG, Brazil, e-mail: mgabriela@unifal-mg.edu.br
(2) Department of Restorative Dentistry, Biomaterials Division, Dental School, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229-3900, USA
(3) Department of Polymer Technology, School of Chemical Engineering, State University of Campinas, UNICAMP, P.O. Box 6066, 13083-970, Campinas-SP, Brazil
* Corresponding author.

Abstract – In this work, a novel wound dressing was developed to controlled delivery silver sulfadiazine while covering and protecting the wound, as well, reducing the drug dosage and dosing times. Chitosan, a biocompatible and biodegradable biopolymer with attractive biological characteristics, was used to prepare the antibiotic loaded films. Hexamethylene 1,6-Di(aminocarboxysulfonate), a water soluble and blocked diisocyanate, was used as cross-linker agent. *In vitro* sulfadiazine release was observed for 2 weeks. The effects of silver sulfadiazine initial concentration, cross-linking ratio and neutralization time on the kinetics of sulfadiazine release were evaluated.

Silver sulfadiazine - SS - has been a standard topical treatment for burns, ulcers and infected wounds due to its broad spectrum of activity against both Gram positive and negative bacteria. Absorption of silver ions has been a major concerned during usage of SS cream in deep burns that may be cytotoxic for treated tissues. In this work, a novel SS loaded wound dressing was developed, in order to protect the wound, while releases antibiotic to treat or avoid bacterial infection.

Chitosan has found wide application in biomedical area, such as: implants, drug delivery matrix, scaffolds for tissue engineering, skin substitutes and wound dressings. In order to prepare an efficient drug delivery matrix, chitosan was cross-linked with 1,6-Hexa Methylene Diisocyanate - HMDI, previously blocked with sodium bisulfite to protect reactivity and to increase water solubility before be reacted with chitosan. The product of block reaction, Hexamethylene 1,6-Di (aminocarboxysulfonate) - HDACS, is stable in acidic aqueous solutions and readily reacts with amines. The effects of cross-linking ratio, silver sulfadiazine initial concentration and neutralization time on the *in vitro* release of SS were evaluated. The release was followed for 2 weeks and sulfadiazine concentration was determined by UV Spectrophotometry (236 nn).

SS is poorly water soluble and after dissociation, releases silver as well as sulfadiazine ions. Thus, SS release can be divided in two steps: sulfadiazine and silver releases. Because there is no interaction between sulfadiazine and chitosan, sulfadiazine release depends on the solubility of silver sulfadiazine in the dissolution medium. However, chitosan contains amino groups which are capable of binding silver and hence, silver release depends also on the chemical interactions between silver ions and chitosan. Moreover, both releases depend on the mass transport resistance caused by chitosan films. All samples displayed a burst release in the first days. This initial release is very important to fast control bacterial infection in wounds treatment. According to Figure 1, samples 2, 5 and 8 showed similar behavior and have released around 30% of theirs initial concentration after 14 days, while samples 3, 6 and 9 have released about 15%.

In conclusion, chitosan films mass transport resistance did not control sulfadiazine release, but SS solubility did. Samples 3, 6 and 9 which contained twice of the SS initial concentration of samples 2, 5 and 8, released approximately half of the percentage of SS released by these samples.

Table 1: Experimental Design.

Sample	[HDACS], %*	[SS], %**	Neutralization time, min.
1	0	0	0
2	0	5	30
3	0	10	60
4	30	0	30
5	30	5	60
6	30	10	0
7	50	0	60
8	50	5	0
9	50	10	30

*based on NH_2 availability on chitosan.
** based on chitosan concentration in the cross-linked films.

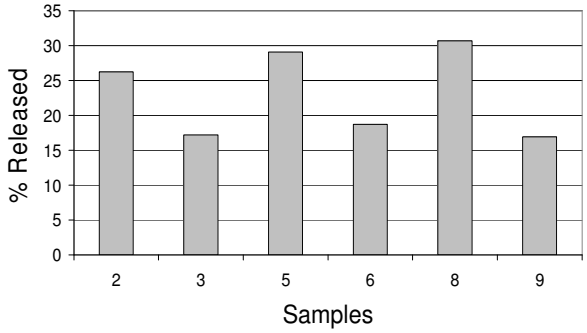

Figure 1: SS Cumulative Release.