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HEMOSTATIC ACTIVITY OF CHITOSAN IN WOUND MANGEMENT

Technical Progress Report No. 3
for the Period July 1, 1989 to September 30, 1989

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Although research has continued on the preparation of a hemostatic agent in the form of a lyophilized sponge composed of chitosan glutamate and collagen, results obtained this quarter have not met expectations. 3M has not yet been able to identify a sponge composition which satisfies all the proposal guidelines and has therefore not successfully completed Milestone 1 of the contract according to the published timeline. Work on other tasks of the contract has not been initiated since these tasks depend on a satisfactory sponge product as input material. 3M will expand the research to include other methods in addition to the lyophilized sponge for delivery of chitosan glutamate to the wound site.

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1.0 INTRODUCTION

This report covers progress during the third three months of the Office of Naval Research Contract N00014-89-C-0024. The various sections of the report are numbered and titled using the format of the original proposal.

2.0 PROGRESS REPORT

2.1 Task 2: Formulation and Optimization

During the past quarter, 3M has evaluated two compositions and two fabrication processes from Semex Medical. The lyophilized sponges were made of collagen and up to 40 weight% chitosan glutamate. The two processes yielded sponges of different bulk density. Lyophilized sponges made only from chitosan glutamate solution were also tested. The testing this quarter has been conducted in dog models. Wounds have been made in dog spleens, and the various experimental sponges have been evaluated for hemostatic activity. A dog model has also been utilized to evaluate sponges in animals in which the normal clotting cascade sequence was either hindered by platelet deactivation or inactivated by treatment with heparin. Platelet deactivation was accomplished by administration of aspirin for 7-10 days prior to surgery. Heparin was given after the spleen had been isolated.

The results obtained thus far have not met expectations. Although all compositions showed hemostatic activity in dogs without a compromised clotting system, hemostatic activity has not been observed with any of the experimental samples in the dogs treated either with aspirin or heparin. Since chitosan glutamate has been shown previously by 3M to form stable coagula in both aspirin treated and heparinized blood in vitro, it appears that the same mechanisms are not operative with current lyophilized chitosan salts tested in vivo. Based on the work thus far, it would seem that an aqueous solution of chitosan salt is necessary to achieve a stable coagulum of red blood cells. Exposure of the lyophilized forms of chitosan salts tested thus far to blood in the in vivo models must not result in appreciable solution formation of the salt and therefore hemostasis is not observed.

Milestone 1 of the proposal was for 3M to identify a final product form for the sponge product; the results of experiments conducted this quarter indicate that this milestone has not been met since all performance characteristics of the sponge product have not been met. Since solution forms of chitosan glutamate continue to show promising hemostatic activity in both in vivo and in vitro experiments, 3M will redirect the research efforts to include product formulations in which sufficient chitosan glutamate solution is delivered to the bleeding site. This concept could include simply a sterile aqueous solution which could be delivered with any sterile carrier, a sterile sponge fully soaked with aqueous chitosan glutamate, or a lyophilized chitosan glutamate/collagen sponge which readily releases the chitosan salt when exposed to water or saline.

3.0 **CONCLUSIONS**

Since all tasks identified in the proposal except Task 1 (Raw Material Characterization) depend on the successful completion of Milestone 1, further work on other tasks of the proposal has not been completed this quarter. Samples tested this quarter did not exhibit acceptable hemostatic activity in the compromised dog model described. Based on the experimental results obtained thus far, it appears that delivery of chitosan salt solution is critical for hemostatic activity. The research at 3M will be expanded to include this product concept.