

CELLULOSIC SYSTEMS FOR DRUG DELIVERY

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Thesis submitted to the Indian Institute of Technology, Delhi
for the award of the degree of
DOCTOR OF PHILOSOPHY

Department of Chemical Engineering
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1979

CERTIFICATE

This is to certify that the thesis entitled "CELLULOSIC SYSTEMS FOR DRUG DELIVERY" being submitted by Mr. Maninder Singh to the Indian Institute of Technology, Delhi for the award of the Degree of Doctor of Philosophy of the Indian Institute of Technology, New Delhi, is a record of bonafide research work carried out by him under our supervision and guidance and to our knowledge it has reached the standard fulfilling the requirement of the regulations relating to the degree.

The results contained in this thesis have not been submitted in part or in full to any other University or Institute for the award of any degree or diploma.


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ACKNOWLEDGEMENTS

I am deeply indebted to Dr. Padma Vasudevan for her inspiring, ever-available and invaluable help, advice and guidance during this entire work. Needless to say that without her involvement in this project, it would have made little headway. Equal credit must go to Dr. A.R. Ray who was also instrumental in giving shape to this work. I would like to thank Prof. S.K. Guha for taking a keen interest throughout this work and for his valuable suggestions and criticisms. I am grateful to Prof. R.D. Dua, ^Head, Centre for Biomedical Engineering, and the Directors, IIT and AIIMS for extending the necessary facilities.

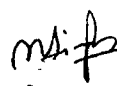
Invaluable guidance of Prof. Kusum Verma, Department of Pathology, A.I.I.M.S., New Delhi in carrying out experiments on biocompatibility is gratefully acknowledged. The help of Prof. P. Mohanty, School of Life Sciences, J.N.U., New Delhi was not less significant in carrying out the radioactivity experiments. The technical assistance of Mr. Alexander and Mr. Avais Ahmed is also appreciated in this connection. I am extremely indebted to Prof. A.S. Chawla, McGill University for gifting some chemicals for the research work.

It is my pleasure to acknowledge the contribution of Dr. Kiran Bala in microencapsulation experiments, of Mr. Man Mohan Misro, in experiments on rabbits and of Miss Kanchan Ralhan and Mr. Ranjit Singh Chauhan in other animal experiments. The ready co-operation of M/s. Bala Dutt, L.C. Sharma and Durga Singh of the Instruments Lab, Chemistry Department was a great help in the spectroscopic measurements.

The critical suggestions given by Mr. V. Vasudevan during the writing of the thesis were extremely useful. Dr. N.C. Srivastava, Dr. P.K. Sharma, Mr. N.D. Arora, Mr. J.M.L. Sinha and Miss Veena Narang helped immensely in the arduous task of the preparation of the thesis and their efforts are appreciated. Mr. G. Vasudev, Mr. Arun Agarwal and Mr. R. Kumar also deserve a mention for their help during many phases of this work. I also thank all other members of the Centre for Biomedical Engineering for their ready co-operation and help.

A special word of praise and appreciation is due to members of my family and all friends.

Finally, the enthusiasm, patience and spirit displayed by Mr. N.D. Arora in typing the thesis and promptness with which Mr. N.L. Arora produced neat drawings are gratefully acknowledged.


(Maninder Singh)

ABSTRACT

Alternatives to the conventional methods of drug delivery were analysed and modes of delivery using biodegradable and non-biodegradable polymers identified. Systems, based on cellulosic materials were chosen for the study because these are abundantly occurring natural polymers made up of glucose units joined by β -1,4 linkages. Cellulose itself does not degrade enzymatically in the body. But it was proposed that on oxidizing it with periodate, formation of aldehyde groups at the 2- and 3 positions may facilitate a hydrolytic cleavage of the β -glucosidic bonds, thus making the matrix biodegradable. Further, the aldehyde groups would act as sites for anchoring drugs which may subsequently be released in the biological environment.

The in vitro degradation of the matrix was studied in solutions simulating the body fluids, using spectrophotometric as well as radio-labelling techniques. The biocompatibility and biodegradability of the matrix was assessed by subcutaneous implantation in rats over a period of ~~six months~~ and conducting histopathological studies ^{over a period of six months}. Toxicological tests on the products of

degradation were carried out in mice. It was found that the biocompatibility of oxidized cellulose was comparable to that of silastic, a well known non-irritant widely used as a control. The oxidised cellulose matrix degrades slowly, the rate of degradation increasing with increase in the degree of oxidation.

Feasibility of formulating a drug depot for sustained delivery using the oxidized cellulose matrix was examined by taking α -chymotrypsin as the model. The enzyme was immobilized by Schiff's base formation and the elution pattern was studied in Ringer's solution. The release of the enzyme sustained upto 10 days while retaining its activity. The period of release could be prolonged by reducing the Schiff's base with sodium borohydride. The possibility of using oxidized cellulose-based depots for therapeutic applications was examined with insulin as an example. Insulin depots were injected intraperitoneally into rabbits and the resulting hypoglycemic effect was studied. Further, the delivery of insulin from such depots to rabbits diabetized with alloxan was taken up. The results indicated that sustained insulin delivery to diabetic subjects over a period of a few weeks could be achieved.

Drug delivery by diffusion from microcapsules was considered as an alternative mode for sustained release.

Among the cellulose derivatives, cellulose acetate was chosen as the wall material since it has good film forming properties. Conditions of microencapsulation with this polymer were examined. Good microcapsules with hydrocortisone as the core material were obtained. The release profile of the drug in vitro was determined indicating the possibility of using such a system for sustained delivery of drugs.

The overall results are summarized and critically analyzed. The limitations of the present systems and possible improvements are discussed and the scope for further work is outlined.

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