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Biomedical Materials— Drug Delivery, Implants and Tissue Engineering

EDITORS

Thomas Neenan
Michele Marcolongo
Robert F. Valentini

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Biomedical Materials— Drug Delivery, Implants and Tissue Engineering

Symposium held November 30–December 1, 1998, Boston, Massachusetts, U.S.A.



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*Invited Paper

PREFACE

The continual growth and increasing sophistication of biomaterials industries has been driven in large part by advances in the basic sciences of the materials involved. Indeed, advances in understanding biological systems at the molecular level have quickly been exploited by materials scientists to develop more sophisticated approaches to therapeutics and diagnostics. The interdisciplinarity and breadth of the biomaterials field necessitates the close cooperation of scientists in many different fields, including materials science, chemistry, biology, engineering, and medicine.

The 1998 MRS Fall Meeting brought together researchers in many of these converging fields in the form of three symposia: "Polymeric Materials—Drugs, Delivery, and Devices," "Tissue Engineering," and "Advanced Materials, Coatings and Biological Cues for Medical Implants." Over 100 papers and posters from 20 countries were presented.

This proceedings volume brings together many of the oral and poster presentations that were given at these symposia, and is divided into six sections that approximate the symposia sessions. Lively discussions after each paper and during the poster sessions helped in the process of stimulating dialogue between participants from various disciplines. The only regret voiced frequently during the two days was frustration on the part of audience members who were forced, because of concurrent scheduling, to choose between talks of equal interest.

We hope that this volume provides a snapshot of the vigor and diversity of the biomaterials field at this time, and trust that the papers presented here stimulate further discussion and research in what will continue to be a vital area of discovery and development.

Thomas Neenan
Michele Marcolongo
Robert F. Valentini

February 1999

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Part I

Polymeric Drugs and Delivery

THREE GENERATIONS OF BILE ACID SEQUESTRANTS

W. HARRY MANDEVILLE, WILLIAM BRAUNLIN, PRADEEP DHAL, AMY GUO, CHAD HUVAL, KAREN MILLER, JOHN PETERSEN, STEVEN POLOMOSCANIK, DAVID ROSENBAUM, ROBERT SACCHIERO, JAMES WARD AND S. RANDALL HOLMES-FARLEY, GelTex Pharmaceuticals, 9 Fourth Ave., Waltham, MA 02451

ABSTRACT

Cholestyramine, the first bile acid sequestrant to be marketed, has been in use for over 20 years. Despite its low potency, requiring 16-24 g of polymer to achieve 20% LDL cholesterol reduction in hypercholesterolemic individuals, only one other sequestrant, colestipol, has come to market in the ensuing period. GelTex Pharmaceuticals has been involved for over six years in the discovery and development of new, more potent polymeric sequestrants. Two binding mechanisms are presented – one that operates via an aggregate binding structure and one that is effective via a defined site binding structure. These two binding mechanisms are compared and contrasted through bile acid binding isotherms. The best of these new sequestrants bind bile acids through a combination of hydrophobicity and ion exchange. Optimization and balancing of each of these interactions led us to more potent materials. The first of these, colesevelam hydrochloride is expected to be three to four times more potent than cholestyramine. A third generation product is still in research at GelTex. With another twofold increase in potency possible, single tablet therapy may become a reality.

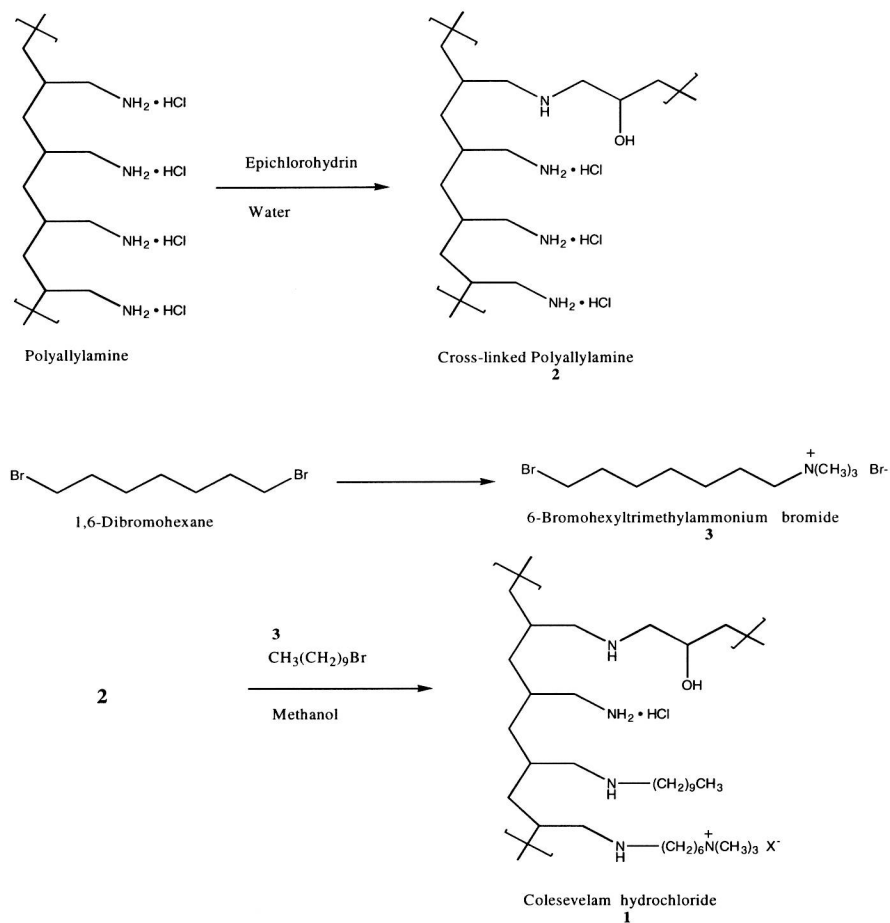
INTRODUCTION

Elevated plasma total and LDL cholesterol (LDL_c) levels, hypertriglyceridemia, and a low HDL cholesterol (HDL_c) level are major risk factors for coronary artery disease (CAD). However, the majority of the individuals at risk require only a modest (20-30%) reduction in LDL_c to reach levels recommended by the National Cholesterol Education Program (NCEP) [1]. The reduction of elevated cholesterol levels is one of the most common therapeutic treatments for patients worldwide. The treatment regime of first choice is invariably dietary modification, but it has been shown to be of limited efficacy in the majority of patients [2]. One of the mechanisms for cholesterol reduction in hypercholesterolemic individuals is sequestration of bile acids. The sequestrants have a good safety record over a 30-year period, but large doses make compliance problematic. A more potent sequestrant, one that will reduce cholesterol with small doses such that tablet formulations are feasible, has been the object of many quests by several companies.

The concept of control of cholesterol through removal of bile acids was brought to reality by the introduction of cholestyramine, sold under the brand name Questran[®] by Bristol Laboratories (now Bristol Myers Squibb). Cholestyramine, first used in the treatment of hypercholesterolemia in 1959[1] was introduced in the early 1970's and since then the search for a better bile acid sequestrant has continued unabated. This search is documented in a review by Stedronsky[2]. The literature, both open and patent, describing "new" bile acid sequestrants is voluminous. Invariably, these new sequestrants have shown very high *in vitro* activity, and many have also claimed very high *in vivo* activity, but none have emerged as the replacement to cholestyramine.

This paper will compare the two commercial sequestrants, cholestyramine and colestipol with a new sequesterant currently in phase III human clinical trials, colessevelam hydrochloride, and two experimental sequestrants that are candidates for human clinical development.

Experimental Section.



Scheme 1. Synthesis of colessevelam hydrochloride

Materials. - Cholestyramine, cholyl glycine, sodium salt and glycochenodeoxy-cholic acid, sodium salt were purchased from Sigma Chemical Co. Polyallylamine was purchased from Nitto Boseki, Ltd., Japan. Epichlorohydrin, 1-bromodecane, 1,6-dibromohexane and trimethylamine were purchased from Aldrich Chemical Co.

Synthesis of cross-linked polyallylamine hydrochloride, 2. Poly(allylamine hydrochloride) (2136.1 g of 50% aqueous solution, 11.42 equiv.) was dissolved in 3200 mL of deionized water