# Polysaccharide Applications



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# Polysaccharide Applications

## Cosmetics and Pharmaceuticals

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# Foreword

THE ACS SYMPOSIUM SERIES was first published in 1974 to provide a mechanism for publishing symposia quickly in book form. The purpose of the series is to publish timely, comprehensive books developed from ACS sponsored symposia based on current scientific research. Occasionally, books are developed from symposia sponsored by other organizations when the topic is of keen interest to the chemistry audience.

Before agreeing to publish a book, the proposed table of contents is reviewed for appropriate and comprehensive coverage and for interest to the audience. Some papers may be excluded in order to better focus the book; others may be added to provide comprehensiveness. When appropriate, overview or introductory chapters are added. Drafts of chapters are peer-reviewed prior to final acceptance or rejection, and manuscripts are prepared in camera-ready format.

As a rule, only original research papers and original review papers are included in the volumes. Verbatim reproductions of previously published papers are not accepted.

ACS BOOKS DEPARTMENT

# Preface

Polysaccharides are very important and much neglected ingredients in Nature. Proteins and biopolymers, from DNA to collagen, and presently even lipids, have had much positive publicity. But polysaccharides, and their special capacities for self organization, have remained by and large in *terra incognita*. They are very important molecules in cell adhesion as well as in the glycolipids of the brain and in plants. They are contained in most of the foods we eat, such as whole grains and vegetables. Although much recent academic interest has been shown, most research has resided in the hands of the formulators of industry. Research on products applications and performance are still very much an art form. The work, not less interesting because of that, is mainly unpublished. Polysaccharides are mostly biodegradable, derived from renewable resources, and commonly used in most cosmetics and pharmaceutical products, where they are the work horse molecules of the thickeners, fillers, gellants, delivery systems, film formers, and so on. The specialized researches on these materials (theoretical, chemical, physical, biological, and technological) have often been conducted in almost complete isolation of each other.

The purpose of the volume is to consolidate some current work in the subject of polysaccharide chemistry to bring synergism and interaction between researchers in the fields of cosmetic and pharmaceutical applications. We hope that by doing so, other researchers such as those in foods and pesticides will also derive some benefits.

International authors representing academia, industry, and governmental research centers have provided a balanced perspective in their presentations on the diverse facets of polysaccharides pertaining to their applications.

Several chapters cover modification of polysaccharides to optimize their performance, for example, in drug and vaccine delivery. The field is in its infancy. Immunologists have only recently begun to realize that adsorption of proteins on adjuvants such as aluminum hydroxide particles are essential to vaccine effectiveness. Presentation of proteins and antigens at the cell surface in the right structural form and environment is clearly the key to recognition, which must be through the polysaccharide coating of all surfaces. Hence presentation of agents within cell surface compatible polysaccharide vehicles must be a promising area of some importance. Chapter 1 presents information on an alginate microparticles for vaccine delivery, whereas Chapter 2 covers gene delivery via quaternary chitosan. Cyclodextrin-drug complexation in the presence of soluble polymers and their performance in percutaneous transport is discussed in Chapter 3. Some remarkable new molecular tubes and other peculiar structures that can be tailored at will for host–guest systems are presented in Chapter 4. Chapter 5 introduces research on cyclodextrin-linked chitosan technologies, whereas Chapter 6 covers chitin–PEG systems for drug





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delivery. Silicified microcrystalline cellulose as a novel pharmaceutical material is discussed in Chapter 7 and thermoreversible sucrose hydrogel in Chapter 8.

These chapters present the state of the art in this obviously important area. Another group of chapters form a nice complement to Chapters 1–8. They are concerned with a fundamental question related to the first—What is the microstructure of surfactant-polysaccharide, or polysaccharide–other polymer self-assembled aggregates? Chapters here span a diversity of mixed systems—chitosan–pluronic networks and protein transport within them in Chapter 12. Those systems form the basis of emerging bacterial-resistant membrane technologies, an area of much activity, which has not been publicized previously. Chapters 13–15 deal with the physical chemistry and microstructure of polysaccharide-surfactant gels. Chapters 16 and 17 address the rheology of emulsions, and the wide range of properties that can be accessed with polysaccharide polymers. Then to complement these, in turn, we have a further group of contributions showing new usable analytical techniques for characterization of these systems. These include ultrasonic techniques (Chapter 18) for concentrated polymer dispersions, fluorescence microscopic studies of polysaccharide adsorption (Chapter 19), small-angle neutron scattering (Chapter 20), gel-permeation chromatography combined with multi-angle light scattering applied to characterization of polysaccharides (Chapter 21), and finally, capillary electrophoresis in starch analysis (Chapter 22). The final group of chapters (Chapters 18–22) deals with some new explorations of polysaccharide hydration (a core issue, hardly researched so far). Therefore, any progress toward understanding the recognition specificity of carbohydrate isomers is important. The novel work of Chapters 9 and 10 and the major review in Chapter 11 on cellulosic liquid crystals contribute to the issue as well.

We believe, the chapters provide a nice complementary balance, which will be of value not only to experts but also to workers who wish to enter this field. In spanning so wide a range of applications the contributions provide a ready access to a scattered literature that is very difficult for even specialists to locate.

Although the editors worked hard to present a comprehensive view of the field, the resulting collection reflects the fact that most application studies have not been published. We hope this volume will stimulate more exchange, dialogue, and learning between academia and industry.



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Chapter 1

# Alginate Microparticles for Vaccine Delivery

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Many pathogens initially establish infection on the mucosal surfaces lining the respiratory and gastrointestinal tracts in both man and animals. Although immunization against infectious pathogens is frequently effective, efficacy could be enhanced if directed specifically to the mucosal surfaces. Oral immunization in particular would be advantageous, since large numbers of individuals could be quickly and easily immunized, possibly through the feed or drinking water. Efforts at oral immunization are hampered by dilution and destruction of antigens within the harsh environment of the gastrointestinal tract. Encapsulation of antigen in alginate microparticles was examined as a means to orally immunize rabbits against the important bacterial pathogen, *Pasteurella* multocida. Initial studies in mice showed that the bacterial load of microparticles could be reduced by a factor of $10^3$ by boiling, but that this process diminished the immunogenicity of a potassium thiocyanate extract of *P. multocida* (PTE) incorporated into the microparticles. Studies in rabbits showed that incorporation of PTE into alginate microparticles allowed effective immunization through the drinking water. Alginate microparticles can be used for immunization against infectious disease; however, alternative methods for sterilization will need to be pursued.





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Infectious disease related to viruses, bacteria, fungi, and parasites is a major cause of morbidity and mortality in animals and humans worldwide. An example in an animal model is *Pasteurella multocida*, which is the most common bacterial pathogen of domestic rabbits. Although infection may be subclinical, disease characterized by rhinitis, pneumonia, abscessation of viscera and subcutaneous sites, metritis, orchitis, septicemia, and otitis interna may occur (1). Losses due to *P. multocida*-related disease pose a serious problem for those using rabbits in research and for production of food and fiber.

Although efficacious therapeutic measures have been developed for many such diseases, including lapine Pasteurellosis (2,3), specific treatment is hampered by expense, limited supply of some antimicrobial compounds, and noncompliance by patients with respect to scheduled self-medication. Rather, vaccination is widely viewed as a means to induce lasting immunity to large numbers of individuals at relatively little expense and without the need for self-medication.

Standard vaccination methods have typically relied on parenteral immunization, usually by intramuscular injection of the vaccine. Such methods stimulate the humoral arm of the immune system to produce antibody, a glycoprotein which is created in response to immunogenic stimulation and which may interact with specific antigens. If the antigen represents a key epitope of the infectious agent, the interaction with antibody can facilitate inactivation of the agent. A number of antigenic preparations have been examined as potential vaccine candidates for immunization of rabbits against Pasteurellosis, including lipopolysaccharide (4), outer membrane proteins (5), and potassium thiocyanate extracts (6,7) by intramuscular or subcutaneous routes of administration.

Although spectacularly successful for protection against some infectious agents, parenteral immunizations has several limitations. First, injection site reactions may occur. In the case of feline leukemia virus vaccination, injection site reactions have been associated with eventual development of sarcoma (8,9). Second, injection of vaccine can be painful for some individuals, leading many to avoid participation in vaccination programs. Third, parenteral immunization typically stimulates elaboration of serum antibody by plasma cells, particularly IgG. In contrast, many infectious agents, including *P. multocida*, initially access the body at mucosal surfaces, such as those lining the gastrointestinal, respiratory, and genitourinary tracts.

Immunization by delivery of vaccine directly at mucosal surfaces has been shown to be a promising alternative to parenteral vaccination. At mucosal sites, secretory IgA (sIgA) is the predominant antibody isotype present. Elaboration of sIgA at mucosal surfaces represents, then, a first-line immunological defense against many infectious agents. For example, presence of sIgA specific to epitopes on influenza virus on surfaces of the upper respiratory tract following

vaccination strongly correlate with resistance of individuals to challenge with infectious influenza (10,11).

There are many examples of the use of locally administered vaccines that stimulate a protective immune response to bacterial pathogens. These include use of a temperature-sensitive mutant of *Bordetella* bronchiseptica administered intranasally to dogs to induce protection against the bacterial component of kennel cough (12); aerosolization of *P. multocida* to chickens (and inhalation of the inhaled vaccine) is a practical as well as effective method of vaccinating a large number of birds against that pathogen (13); and an attenuated *Salmonella cholerasuis* var. *kunzendorf* vaccine used to prevent disease in swine when administered either orally or intranasally (14).

Induction of immunity at mucosal surfaces requires administration of antigen directly to a mucosal site. Interestingly, the mucosal immune system is linked, such that exposure to an immunogen at one mucosal surface can result in secretion of sIgA onto other mucosal surfaces. This phenomenon is due to stimulated antigen-specific B lymphocytes (plasma cell precursors) entering the lymphatic and general circulation from the stimulated mucosal site and dispersing to distant mucosal sites. In transit, these cells enter local draining lymph nodes, such as the mesenteric lymph nodes that drain the gastrointestinal tract, where they undergo further differentiation and maturation. Most of the differentiated plasma cells preferentially home back to the originating mucosal tissue; however a significant number also migrate to the other mucosal sites. Although the homing of lymphocytes to mucosal sites is not fully understood, special receptors on endothelial venule cells and lymphocytes (selectins and integrins) are thought to interact to allow extravasation of lymphocytes selectively into the lamina propria of mucosal sites (15). The lamina propria is the effector site of the mucosal immune system where plasma cells produce primarily IgA, and T cell-mediated response occur.

Mucosal immunization by oral administration of vaccines is a particularly appealing potential method for stimulating protective immunity. Theoretically, vaccines could be administered in the feed or drinking water by this means. Oral vaccination has the advantages of limited possibility of reaction to the vaccine, high acceptability by patients, ease of administration, and low cost. In the case of rabbits, a vaccine delivered in the drinking water would allow quick immunization of a large number of animals and with little stress or risk of handling-related injury to both animals and handlers. Despite these advantages, development of oral vaccines has been slow. Primary among the limitations to development is the degradation of important vaccine components by bacteria, enzymes, and low pH within the gastrointestinal tract. Furthermore, dilution and loss of antigen in ingesta as well as poor diffusion through the mucus layer on intestinal villi prevent antigen from being taken up by the lymphoid tissue.

Microencapsulation is a unique way to protect antigens and stimulate their