# Biotechnological Polymers

## MEDICAL PHARMACEUTICAL and INDUSTRIAL APPLICATIONS

*A CONFERENCE IN PRINT*

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**PART III: BIODEGRADABILITY AND APPLICATIONS**

# APPLICATIONS OF HYALURONAN AND ITS DERIVATIVES

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## INTRODUCTION

During the past two decades hyaluronan (HA, hyaluronic acid) and its derivatives have become important therapeutic agents in medicine. This development was triggered by the recognition in the late 1960's that the highly purified form of hyaluronan (the non-inflammatory fraction of Na-hyaluronan - NIFNaHA) prepared from animal tissues, is extremely biocompatible when applied to such sensitive tissue compartments as the vitreus of the eye and the synovial space in joints {1, 2}. A few years later this discovery led to the medical application of NIF-NaHA in ophthalmic surgery and for the treatment of arthritis in humans and in horses {3, 4}.

In the mid 1980's, the field of crosslinked hyaluronan derivatives began to develop. Two crosslinked forms of hyaluronan, hylan fluid and hylan gel, were invented and their biological activity and medical usefulness were widely explored {5}. They proved to be just as biocompatible as the native hyaluronan, but had enhanced rheological properties and longer residence time in the tissues than hyaluronan. The therapeutic application of the hylans in a broad spectrum of medical specialties is now in progress. These include: viscosurgery, arthritis therapy, adhesion management, topical administration, drug delivery and soft tissue augmentation (e.g. dermal, urological and reconstructive applications). This important development stimulated broad interest in new forms of crosslinked or otherwise modified forms of hyaluronan.

This paper will review the chemistry of the various hylans and other crosslinked hyaluronans, focusing on their current usage and proposed medical applications.

## HYALURONAN

This ubiquitous polysaccharide molecule is located in the intercellular space and fills the space between the collagen and elastin fibers, cell membranes and basal laminae. It is produced by many cell types in the cell membrane and is, therefore, never stored inside the cell. After synthesis it is extruded directly into the extracellular space. It is considered as a space filling, structure stabilizing, cell coating and cell protective polysaccharide. Its primary biological role is to stabilize the intercellular structure of fibrous and membranous proteins. It forms a structurally integrated system with the fibrous proteins of the intercellular space, creating the elastoviscous, protective, lubricating and stabilizing matrix in which cells are embedded. Hyaluronan solutions are extremely elastoviscous and pseudoplastic. Their exceptionally high rheological properties are present even in highly hydrated polymer systems (water content more than 99%). This combination of high elastoviscosity and low solids content permits unhindered diffusion of metabolites to and from the cells embedded in or separated by the viscoelastic hyaluronan molecular network.

The unusual rheological properties of hyaluronan are based on a relatively simple structure. It is a linear, unbranched (not crosslinked) polyanionic molecular chain consisting of repeating glucuronic acid-N-acetyl glucosamine dimers with a large mass (4-5 million). In aqueous solution, the hyaluronan molecule behaves as a highly hydrated random coil with very large molecular volume, forcing the molecules to become entangled and interpenetrate at relatively low

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