

**HYALURONICS ACID FRACTIONS, METHODS
FOR THE PREPARATION THEREOF, AND
PHARMACEUTICAL COMPOSITIONS
CONTAINING SAME**

This application is a continuation of co-pending application Ser. No. 756,824, filed on Jul. 19, 1985 and now abandoned, which is a continuation-in-part application of U.S. application Ser. No. 719,113, filed on Apr. 2, 1985, now abandoned, and application Ser. No. 669,431 filed on Nov. 8, 1984, now abandoned, which are hereby incorporated by reference.

**BACKGROUND AND FIELD OF THE
INVENTION**

This invention relates to specific molecular weight fractions of hyaluronic acid (hereinafter referred to as "HA" or HY) which have therapeutic applications and which are non-inflammatory when utilized. One of the HA fractions of this invention is particularly useful for facilitating wound healing, while the second HA fraction is particularly useful for intraocular use to substitute for endobulbar fluids or for intraarticular injection for use in treating damaged bone joints.

The invention further relates to the use of the HA fractions as vehicles for ophthalmic drugs. The use of HA as a vehicle provides a formulation compatible with the corneal epithelium and enhances the activity of some ophthalmic drugs.

Furthermore, the invention relates to new medications for topical use and more precisely to medications containing:

1. an active pharmacological substance or an association of pharmacological substances, either active or suitable for topical administration and
2. a vehicle made of hyaluronic acid or a molecular weight fraction of the same or a salt thereof with an alkaline metal, an alkaline earth metal, with magnesium, aluminum, ammonium or ammonium substitute, and optionally additional ordinary excipients used in pharmaceutical preparations for topical use, therapeutic use or preventive purposes.

Hyaluronic acid is a naturally occurring heteropolysaccharide consisting of alternating residues of D-glucuronic acid and N-acetyl-D-glucosamine. HA is a linear polymer of high molecular weight, generally up to about 8 to 13 million, and has been found in cell coats, pericellular gels, the extracellular ground substance of connective tissues of vertebrates, in the synovial fluid in joints, in the endobulbar fluids or vitreous humor of the eye, in human umbilical cord tissue, in rooster combs and in some bacteria.

Previous investigations on HA include the work of Balazs, U.S. Pat. No. 4,141,973, directed to a fraction of HA useful for replacing endobulbar fluids, as well as other therapeutic applications. This patent, however, is specifically directed to an HA fraction having an average molecular weight greater than about 750,000, and preferably greater than about 1,200,000. Balazs specifically teaches that fractions of HA having an average molecular weight of less than 750,000 are not therapeutically useful because of their inflammatory activity. These lower molecular weight fractions of HA are discarded by Balazs. However, this results in discarding about 90% of the total amount of available HA obtainable from the source tissues, resulting in a use of only a small amount (about 10%) of the available HA.

In addition, hyaluronic acid has been widely useful in medicine and a cosmetic use is also being considered (see for example the article by Balazs et al. in "Cosmetics & Toiletries" Italian edition No. 5/84 with relative references). It has especially been used as a therapeutic agent in therapies for arthropathies, such as in the veterinary field to cure arthritis in horses (see Acta Vet. Scand. 167, 379 (1976)). Hyaluronic acid and fractions thereof have been used in ophthalmic surgery as therapeutic, auxiliary and substitutive agents for natural organs and tissues (see for example E. A. Balazs et al. "Modern Problems in Ophthalmology, 10, 3 (1970), E. B. Strieff, S. Karger, eds. Basel and Balazs et al. "Viscosurgery and the Use of Sodium Hyaluronic During Intraocular Lens Implantation", Paper presented at the International Congress and First Film Festival on Intraocular Implantation, Cannes, 1979).

There is also at present particular interest in obtaining ophthalmic vehicles which do not cause sensitization phenomena in the cornea and which guarantee perfect tolerability, thereby forming efficient vehicles for drugs. In this context much attention has been placed on the use of natural biological molecules as possible vehicles for ophthalmic drugs as they ensure a high level of tolerability and compatibility with the corneal epithelium.

Contrary to the teachings of Balazs, the present inventors have discovered that lower molecular weight fractions of HA do indeed have useful pharmaceutical activity. Thus, according to the present invention, about 80% of the HA obtainable from various sources is utilized. In particular, the present inventors have discovered one fraction of HA which is useful for stimulating wound healing, and a second fraction of HA which is useful for intraocular injections to substitute for the endobulbar liquids in the eye and for intraarticular injections as a treatment for damaged joints. Moreover, the inventors have discovered that hyaluronic acid and the molecular weight fractions of HA are useful as a vehicle for drugs, particularly ophthalmic and topically administered drugs.

**OBJECTS AND SUMMARY OF THE
INVENTION**

It is, therefore, one object of the present invention to provide specific well defined fractions of hyaluronic acid having pharmaceutical applications and without inflammatory activity.

It is another object of the present invention to provide a fraction of HA which is useful for stimulating wound healing.

It is another object of the invention to provide a fraction of HA which is useful for intraocular and intraarticular injections for replacing the endobulbar liquids in the eye and for treating damaged bone joints, respectively.

It is a further object of the present invention to provide fractions of HA which are therapeutically useful and which permit the use of a high percentage of the available HA that can be obtained from source tissues.

It is still a further object of the present invention to provide a method for obtaining specific fractions of HA depending upon the average molecular weight for differing therapeutic applications.

It is another object of the present invention to provide ophthalmic solutions having excellent toleration to the cornea.