Equiprovet Canada Inc.
Innovating Equine Performance

HYALURONIC ACID:

To cross-link or not to cross-link? That is the question.

We at Equiprovet Canada Inc, as a specialized wholesaler in orthopedic veterinary formulations, receive a vast number of questions about hyaluronic acid.

The most common question that pops up is: "*Should I, as a veterinarian, choose a linear or a cross-linked hyaluronic acid?*"

To answer this question, we will provide 1.) a short introduction of the molecule of hyaluronic acid followed by 2.) an explanation of the different properties and applications of the different formulations:

1.) Introduction to the HA Molecule:

Glycosaminoglycans (GAGs) are linear polysaccharides formed from repetitions of a disaccharide unit composed of one aminosugar and one uronic acid residue. Among these, hyaluronic acid (HA) is a biopolymer of broad scientific interest and primarily applied in different biomedical fields.

This macromolecule is most frequently referred to as hyaluronan, because of the many different forms the molecule can assume under physiological conditions (i.e. the acid form, HA, and the salts, such as sodium hyaluronate) (Balazs & Gibbs, 1970).

The HA biopolymer is widespread and has been identified in vertebrate soft tissues (e.g. joints, synovial fluid, skin, vitreous humour of the eye, etc.)

HA in commercial formulations can be:
1. linear
2. derivatised
3. crosslinked

In some fields of application, HA is used in its natural occurring linear form. However, for many purposes, HA requires chemical modifications and is often subjected to derivatization processes (modifications of the linear chain) or crosslinking processes (formation of covalent bonds between HA chains resulting in three-dimensional HA networks).

Modifications allow for overcoming the high rate of HA in vivo turnover that is required in particular applications. For instance, if linear HA was used for intra-dermal injections, it would too rapidly degrade to provide advantageous effects over a significant period of time. Modified HA, on the contrary, being less susceptible to chemical and enzymatic hydrolysis,shows a prolonged in vivo persistence thus performs better (Brown and Jones, 2005). Modification processes, especially crosslinking ones, also enhance specific mechanical properties of the material (Brown & Jones, 2005).

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2.) Properties & Applications:

Linear Hyaluronic acid properties:

- fast degradation mainly due to the action of hyaluronidases
- short residence time: 24h (in the skin); few weeks (in cartilage).
- poor mechanical properties

Crosslinked Hyaluronic acid properties:

- less susceptible to enzymatic degradation
- prolonged in vivo residence time: from months to years.
- enhancement of mechanical properties

In the last decade, many strategies have been developed for the production of crosslinked HA, some of them commonly employed in marketed formulations. All processes mentioned above involve the carboxyl groups of the HA chains. Other strategies involving the HA hydroxyl groups include divinyl sulfone crosslinking (Larsen et al., 1993, Ibrahim et al., 2010) and di-epoxide crosslinking (Agerup, 1998; Segura et al., 2005).

Equiprovet sells two cross-linked formulations: one based on a patent that is held by our mother company, based on dvs cross-linking; and one that rests on a di-epoxide cross-link acquired from a European based producer.

Linear HA applications:

Linear HA finds application mainly in cosmetics, ophthalmology and wound healing. Almost all main cosmetic brands present a line of hyaluronan-based creams.

Preparations based on linear HA are: used to favour healing in the general treatment of skin irritations and injuries; intended for the coating of acute and chronic wounds (abrasions, areas of skin grafts, post-surgical incisions, first and second-degree burns, metabolic and vascular ulcers, pressure sores); some osteoarthritis treatment.

In ophthalmologic surgery, linear HA physiological solutions are used to protect the delicate eye tissues and to provide space during surgical manipulations (Brown & Jones, 2005; Arshinoff et al., 2002; Neumayer et al.,)

Crosslinked HA applications:

Crosslinked HA derivatives find application especially in aesthetic medicine and in the treatment of osteoarthritis and tissue engineering. The use of crosslinked HA in aesthetic medicine has considerably increased in the last decade. (Lupo, 2006; Andre, 2004). In fact, HA-based dermal fillers have become the most successful response to the current massive demand for non-surgical soft tissue augmentation. HA fillers are made of micrometric differently crosslinked HA particles suspended in physiological solution. Often, they also contain linear un-crosslinked HA to facilitate injectability.

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HA & Osteoarthritis: HA is a physiological component of synovial fluid but its concentration is reduced in osteoarthritic joints (Mathieu et al., 2009).
Intra-articular injections of crosslinked and linear HA are found to have therapeutic effects on osteoarthritic pathologies. Several studies have been performed investigating such effects, revealing that HA can suppress cartilage degeneration, protect the soft tissue surfaces of joints, normalize the rheological properties of the synovial fluid, and to reduce pain perception (Altman, 2000; Uthman et al. 2003; Girish & Kemparaju, 2007).

In summary, at Equiprovet we take our role very seriously. For this reason we offer 2 cross-linked formulations, a variety of linear formulations, AND formulas combining hyaluronic acid with other Gags enabling you, as a veterinarian, to choose the formulations best suited to your clients!