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Short communication

Influence of Sodium hyaluronate molecular weight on critical quality attributes and filterability of solutions

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Introduction

Hyaluronan (HA) is a glycosaminoglycan composed of disaccharide repeats of N-acetylglucosamine and glucuronic acid (Bartosikova et al., 2008). It can be present in various molecular weight (MW) forms, each of them having different biological activities (Morozkina et al., 2020). Sodium salt of hyaluronate is a widely used agent in pharmaceutical preparations such as injectables, eye drops and nasal solutions. Due to its thermal liability (Kalina et al., 2015), sterile drug products containing HA cannot be terminally sterilized and filtration trough 0.2 µm sterilizing grade filter is sterilization method of choice. Nevertheless, these solutions are often highly viscous and can be challenging to filter. Furthermore, HA concentration, as well as its molecular weight are directly related to final product critical quality attributes (CQA).

Materials and methods

Sodium hyaluronate (pharmacopoeial quality) was obtained from Contipro a.s. (Czech Republic). In present work different molecular weight forms were used (MW range 7 - 1000 kDa). Standard pharmacopoeial excipients were used for solutions preparation.

Critical quality attributes were measured using following equipment: viscosimeter Brookfield DVII; spindle ULY, pH meter Mettler Toledo SevenExcellence, osmometer Gonotec 3000 D, SprayVIEW NOSP measuring system, and Spraytec system.

Filtration was performed using sterilizing grade laboratory disk filters of material polyether sulfone (PES), manufactured by Pall.

During development of nasal spray solution, different molecular weight and concentrations of HA were tested to evaluate influence on product CQA (viscosity, osmolality, pH, spray appearance and droplet size distribution (DSD)) and critical process parameters (filterability). All solutions were filtered through sterilizing 0.2 µm PES filters and filled in 10 ml high density polyethylene (HDPE) bottles with 3K spray pump system, provided by Aero Pump GmbH. The study was conducted in two stages. Initially, formulations were prepared using high molecular weight (HMW) HA (550-1000 kDa) in concentrations 0.3%, 0.6% and 1.0% respectively. In the second stage, formulations were prepared using low molecular weight (LMW) HA (7-15 kDa and 150-250 kDa) in concentration 0.3%. All formulations were tested on CQA and filterability.

Results and discussion

Target of the study was to have a solution that results with adequate spray appearance and complies with values for DSD: Dv (10) >10 µm; Dv (50) 20-90 µm and Dv(90) < 200 µm, which are average values of DSD obtained on commercially available nasal sprays. Additionally, prepared solution should pass through 0.2 µm sterilizing grade filter without filter clogging which results in filtration stoppage. Results of CQA in first study stage are presented in Table 1 and Figure 1. Due to higher viscosity, formulations were hardly filterable, except for lower tested concentration (0.3%). Spray performance including spray pattern geometry and droplet size distribution was not matching target values for none of the formulations. The application of the solution must result in visible spray, not a jet. For formulations with 0.6% and 1.0% HA, DSD was not measurable, and application of spray resulted as a jet, not a spray, therefore noncomplying to requirement.

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Table 1. Influence of HMW HA in increasing on filterability and CQA

Parameter	0.3% HA	0.6% HA	1% HA
MW HA	550-1000 kDa		
Filterability	Normal filtration	Very slow, filter clogging	Very slow, filter clogging
pH	5.90	5.90	5.95
Viscosity (mPas)	6.89	74.83	413.35
Osmolality (Osmol/kg)	0.305	0.316	0.329
Dv(10) (µm)	106.05	Not measurable	Not measurable
Dv(50) (µm)	225.50	Not measurable	Not measurable
Dv(90) (µm)	447.08	Not measurable	Not measurable
Span	1.52	Not measurable	Not measurable

Fig.1 Spray performance of HMW HA

Study was continued using LMW HA (7-15 kDa and 150-250 kDa, respectively) in concentration 0.3%. Results are presented in Table 2 and Figure 2. Both formulations were filterable and have similar, comparable results of physical parameters, except for viscosity which is expected as MW of HA is directly related to final product viscosity. DSD of both formulations is within target limits. Formulation with HA of MW 150-250 kDa, has more spherical spray shape in respect to more irregular shape of spray in formulation with HA of MW 7-15 kDa.

Table 2. Influence of LMW HA (different MW ranges) on filterability and CQA

Parameter	0.3% HA (7-15 kDa)	0.3% HA (150-250 kDa)
Filterability	Normal filtration	Normal filtration
pH	4.89	4.90
Viscosity (mPas)	6.89	74.83
Osmolality (Osmol/kg)	0.305	0.316
Dv(10) (µm)	16.6	19.8
Dv(50)(µm)	35.8	45.8
Dv(90) (µm)	78.8	109.8
Span	1.7	2.0

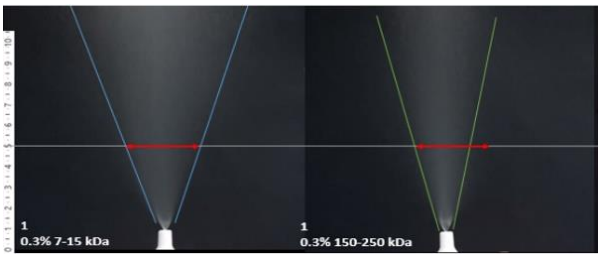

Fig. 2 Spray pattern geometry of LMW HA

Conclusion

MW and concentration of HA has considerable effect on tested quality parameters. When developing sterile nasal sprays these factors must be carefully evaluated to meet desired quality product profile. For nasal spray products, LMW HA (<250 kDa) should be used to obtain adequate spray characteristics and viscosity.

References

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