In response to several deaths and severe side effects associated with the parenteral use of heparins reported in the USA beginning of 2008, an intense activity was devoted by regulators and industry to identify and better characterise causative impurities eventually present in heparin preparations.

The discovery of a link between the presence of over-sulphated chondroitin in heparin and the occurrence of serious hypotensive and allergic reactions in patients triggered a co-ordinated action among regulators. The outcome was an immediate revision and implementation of the relevant monographs of the European Pharmacopoeia to control the presence of this adulterant. As an emergency measure, the techniques of nuclear magnetic resonance spectrometry and capillary electrophoresis applying appropriate procedures were prescribed to test for the presence of over-sulphated chondroitin sulphate (OSCS) in the Production section. Although these methods were not ideal, they were thought to be the best at that time and further method development was considered essential.

The Laboratory of the European Directorate for the Quality of Medicines and HealthCare has recently implemented the method proposed by Somsen G[#]. (personnal communication) and analysed several heparin samples of various origin. The method successfully separated OSCS from heparin but also heparin from chondroïtin and dermatan. Selectivity was significantly improved resulting in baseline separation between OSCS and heparin.

The method which is described below will enable users of the revised monographs "*Heparin calcium*, 0332" and "*Heparin sodium*, 0333" to apply capillary electrophoresis as prescribed under the Production section for the detection of OSCS where necessary.

Method: Evaluation of impurities in Heparin Sodium by Capillary Electrophoresis

Capillary Electrophoresis Equipment:

Capillary : bared fused-silica, internal diameter 20 μm, 60 cm total length, 50 cm effective length.

Electrolyte buffer : 850 mM Tris phosphate, pH 3.0

Capillary temp :	35°C
Sample temp :	5°C
Detection wavelength :	200 nm
Injection :	2.0 psi for 48 sec
Polarity:	negative
Voltage :	30 kV
Separation time :	about 20 min
Rinse between runs:	flush at 50 psi, *water R* for 5 min, buffer for 2 min

Sample preparation: heparin solutions containing 50 mg/ml were prepared with *water R.*

The example electropherograms presented have been recorded with heparin samples spiked with OSCS in a range between 0.5 % to 4.5 %.

For any further questions please contact Dr. G. Rautmann, EDQM DLAB.
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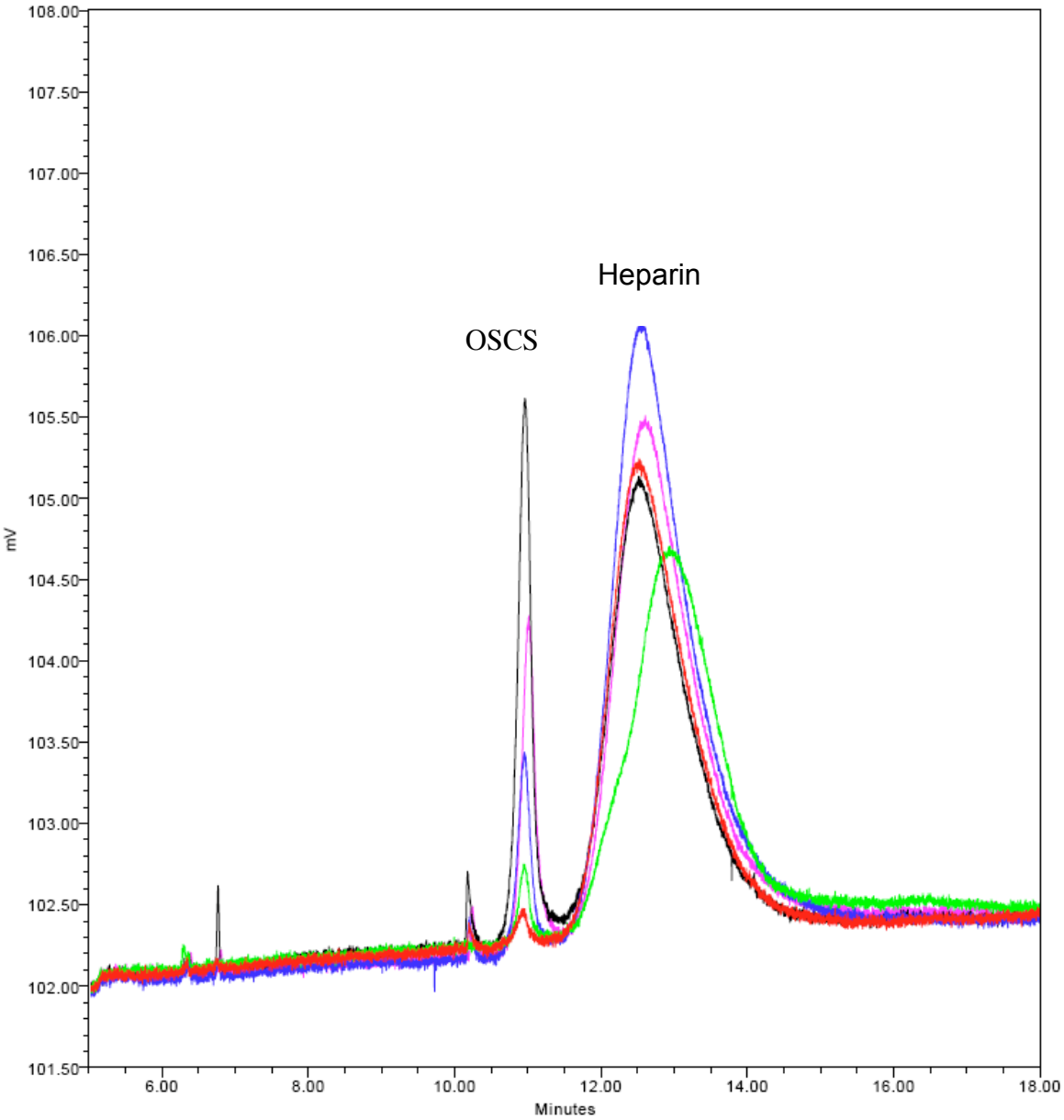

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