

Evaluating storage condition and handling procedure of polyoxyl castor oil as source for potential critical material attributes relevant for Quality by Design considerations



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INTRODUCTION

Polyoxyl castor oil (PEG-40 Hydrogenated Castor Oil) is a non-ionic solubiliser and emulsifying agent obtained by reacting 1 mole of hydrogenated castor oil with 40 moles of ethylene oxide. The main constituents of the excipient are glycerol polyethylene glycol hydroxy-stearate, which, together with fatty acid glycerol polyglycol esters, forms the hydrophobic part of the product. The hydrophilic part consists of polyethylene glycols and glycerol ethoxylate.

The excipient is described in all major pharmacopoeias, e.g.:

BP: Hydrogenated Polyoxyl Castor Oil
 Ph.Eur.: Macroglyglycerol Hydroxystearate
 USP-NF: Polyoxyl 40 Hydrogenated Castor Oil

The main application of polyoxyl castor oil is to act as a solubiliser and/or emulsifier in oral and topical liquid and semi-solid dosage forms (e.g. LBDDS, SEDDS). Due to its inherent nature to contain a mixture of various chemical substances, polyoxyl castor oil has no distinct melting point, yet melts in a rather broad range of -16 to +26 °C.

The aim of this study was to investigate the potential requirement of melting and homogenising the product prior to use. Respectively, it is discussed whether a Critical Material Attribute (CMA) arises, if the product is not homogenised before taking sub-quantities.

MATERIALS AND METHODS

Polyoxyl castor oil (Kolliphor® RH 40, BASF) was tested in original commercial drums of 60 kg each. Each drum was treated differently according to the following description:

Drum A: frozen, not homogenised
 The whole drum was frozen at -18 °C and stored at this temperature for one week. Then the whole drum was cut into three pieces allowing the individual analytical investigation of the upper, middle, and lower section of the fill to evaluate its homogeneity.

Drum B: molten, not homogenised
 The whole drum was molten at 40 °C and stored at this temperature for one week. Then the drum was opened and samples of the fill representing upper, middle, and lower section were carefully taken to prevent any cross mixing or homogenisation.

Drum C: molten, and homogenised
 The whole drum was molten at 40 °C and then opened. The whole fill was intensively homogenised (stirring). Then a sample was taken and presented to an analytical investigation as reference.

In addition, samples (n=3) were passed through a swing test. The polyoxyl castor oil was molten at 65 °C, and kept at 60 °C for 5 days. After that, the product was cooled down for solidification at ambient temperatures, and stored under this condition for 24 hours. The whole cycle was repeated 20-times. After that, samples were presented to an analytical investigation and the results compared with the initial values.

According to the monographs in the current pharmacopoeias, polyoxyl castor oil is specified by: congealing temperature, acid value, hydroxy value, iodine value, saponification value, water content, as well as sulphated ash. All these tests were conducted applying compendial methods.

Differential scanning calorimetry (DSC)
 A DSC Q2000 V24.4 Build 116 was used with a sample weight of 8 to 9 mg. After fast cooling to -80 °C, the melting temperatures (T_m) were determined with a heating rate of 20 K/min (n=2) in the temperature range of -80 °C up to +85 °C. Two cycles were conducted, the values of the second cycle (T_{m2}) were evaluated.

Size exclusion chromatography (SEC)
 SEC separations were performed on an Agilent 1200 HPLC system, consisting of a solvent degasser, a quaternary UPLC pump, autosampler, heated column compartment, a refractive index and a variable wavelength UV-detector. Calibration was obtained using polyethylene glycol standards of low polydispersity (Polymer Labs).

Table 1. SEC parameters and set-up.

| Parameter | Description |
|------------------|---|
| Columns | 1 SDV pre-column (8 x 50 mm, PSS GmbH) 3 SDV columns (1'000 Å, 100'000 Å and 1'000'000 Å, each 8x300 mm, PSS GmbH) |
| Solvent | Tetrahydrofuran (THF, Merck Chromasolv) |
| Flow rate | 1 mL/min |
| Temperature | 60 °C |
| Concentration | 2 mg/mL |
| Injection volume | 100 µL |

Samples were dissolved in the SEC eluent and the resulting solutions were filtered through a syringe filter (Chromafil Xtra PTFE, 0.20 µm) prior to injection.

MALDI-TOF

Spectra were obtained in the positive reflector mode on a Bruker ultraflexXtreme MALDI mass spectrometer. Samples were prepared by the dissolution/grinding-method, as this technique tends to provide more reproducible spectral data than liquid droplet preparation. A tip of a spatula of matrix (trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile, DCTB) was added to a small agate mortar, together with approx. 10 µL of a solution of NaCl (0.1 mol/L in H₂O).

The matrix and salt solution were ground to a fine paste. Subsequently, approx. 10 µL of a solution of the sample (10 mg/mL in THF) was added and the mixture was ground for a few more seconds. The paste was applied as a very fine film onto a ground steel target using a plastic spatula.

RESULTS AND DISCUSSION

Polyoxyl castor oil is a natural based product obtained by the chemical reaction of hydrogenated castor oil with ethylene oxide (Figure 1). The final excipient inherently consists of several different components. This variety of product-components has been described to support the products superior functionality to act as a solubiliser. In terms of QbD considerations, Critical Material Attributes could arise by variations in the products integrity or homogeneity.

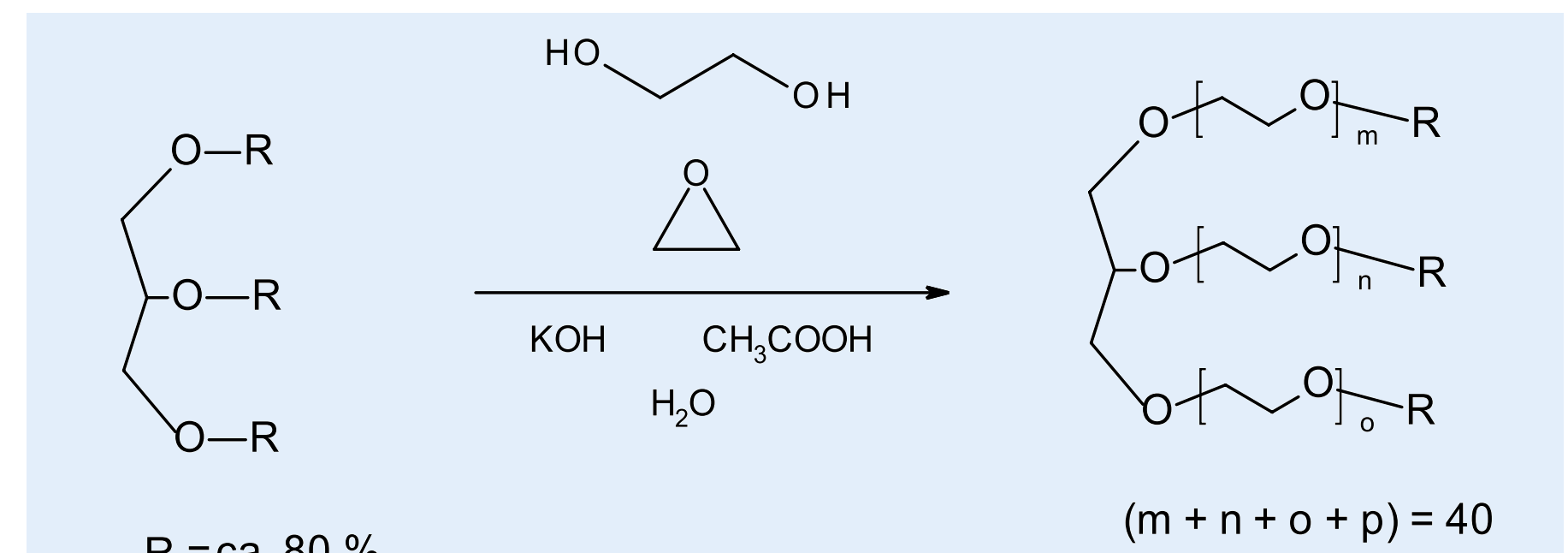


Figure 1. Synthesis scheme of polyoxyl castor oil.

The presence of multiple product components consequently results in a broad melting range of the product of -16 °C up to +26 °C, indicated in DSC analysis (Figure 2). The melting point of one component at a temperature of about -16 °C is the main-course for the semi-solid appearance of the product at ambient conditions. At a temperature of about +26 °C the main-fraction melts/solidifies representing the upper end melting range reported in literature. The product appears as consistently liquid when stored at temperatures higher than +26 °C. However, the DSC analysis reveals that there are higher melting components contained as well, which melt in a temperature range of about +33 °C to +38 °C.

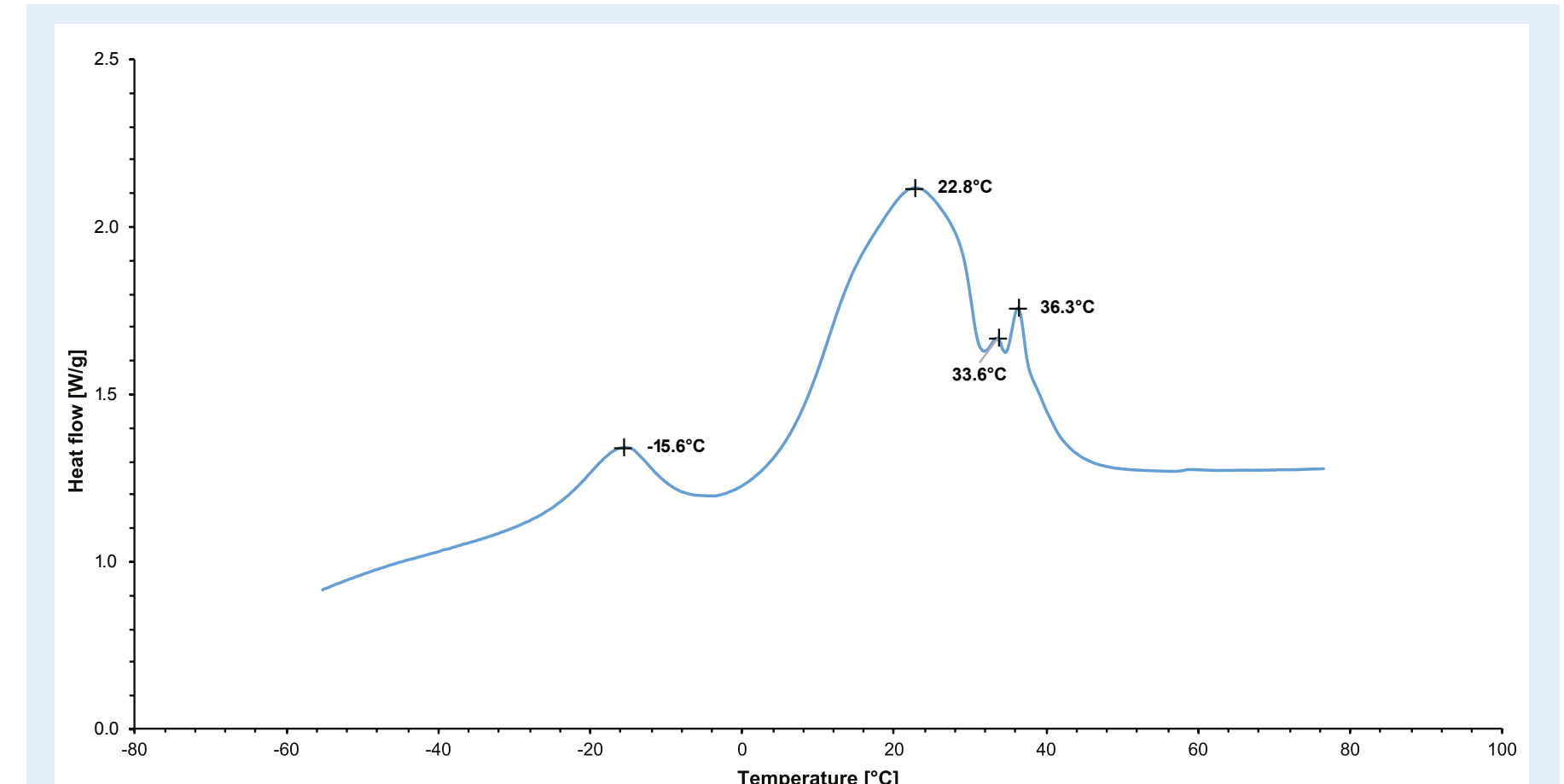


Figure 2. DSC analysis of a homogenised polyoxyl castor oil sample, indicating the various melting points of the main component.

Assuming, that the different melting temperatures represent different main components of the product, homogeneity can be evaluated by means of DSC analysis. Therefore, samples of different sections of the drums were taken and presented to DSC testing (Table 2). Both aspects, the absence of a melting peak or a less pronounced onset would indicate that the respective component is either not contained or merely present in a lower concentration.

Table 2. Melting temperatures (T_m-values) determined for the different samples.

| Sample | Melting temperatures (T _m) [°C] | | | | |
|--------------------|---|-------|-------|-------|-------|
| Homogenised sample | -15.6 | +22.8 | +33.6 | +36.6 | |
| Drum A | upper section | -15.8 | +18.3 | | |
| | middle section | -15.9 | +12.1 | +20.8 | |
| | lower section | -15.8 | +12.5 | +33.2 | +36.4 |
| Drum B | upper section | -16.2 | +19.2 | | |
| | middle section | -16.3 | +11.8 | +18.2 | |
| | lower section | -15.9 | +12.8 | +31.6 | +37.8 |
| Drum C | homogenised | -16.2 | +19.9 | +33.5 | +38.5 |

The results found for the homogenised Drum C were in-line with the melting temperatures found for the reference sample (Figure 2), suggesting a proper homogeneity of the product.

Differently, the results for Drum A and Drum B. During the freezing process, fractions holding a higher melting temperature solidify first and start to settle in the remaining liquid product. This can be visualised when filling polyoxyl castor oil into a glass flask at a temperature level of 40 °C, and then leaving it to cool down (Figure 3).

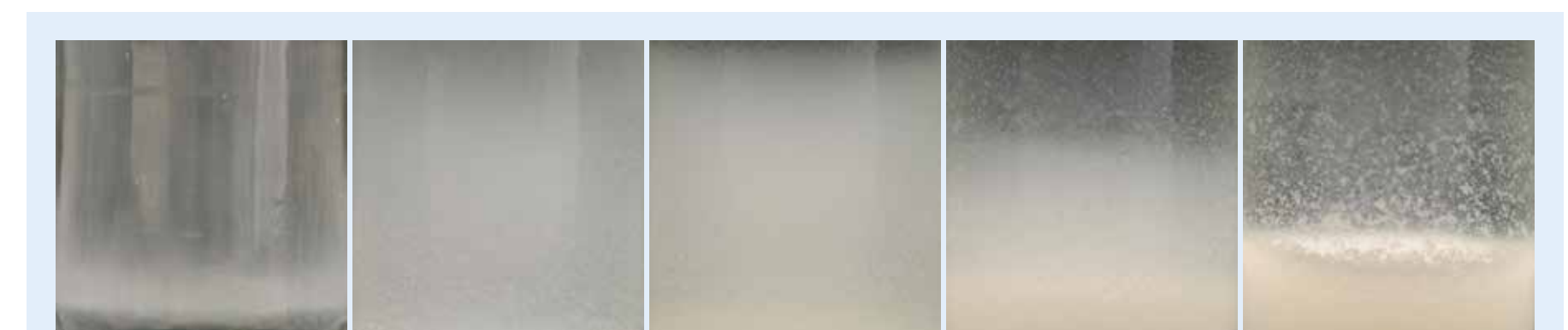


Figure 3. Solidification of polyoxyl castor oil during cool down from 40 °C to ambient temperature (decreasing temperature from left to right).

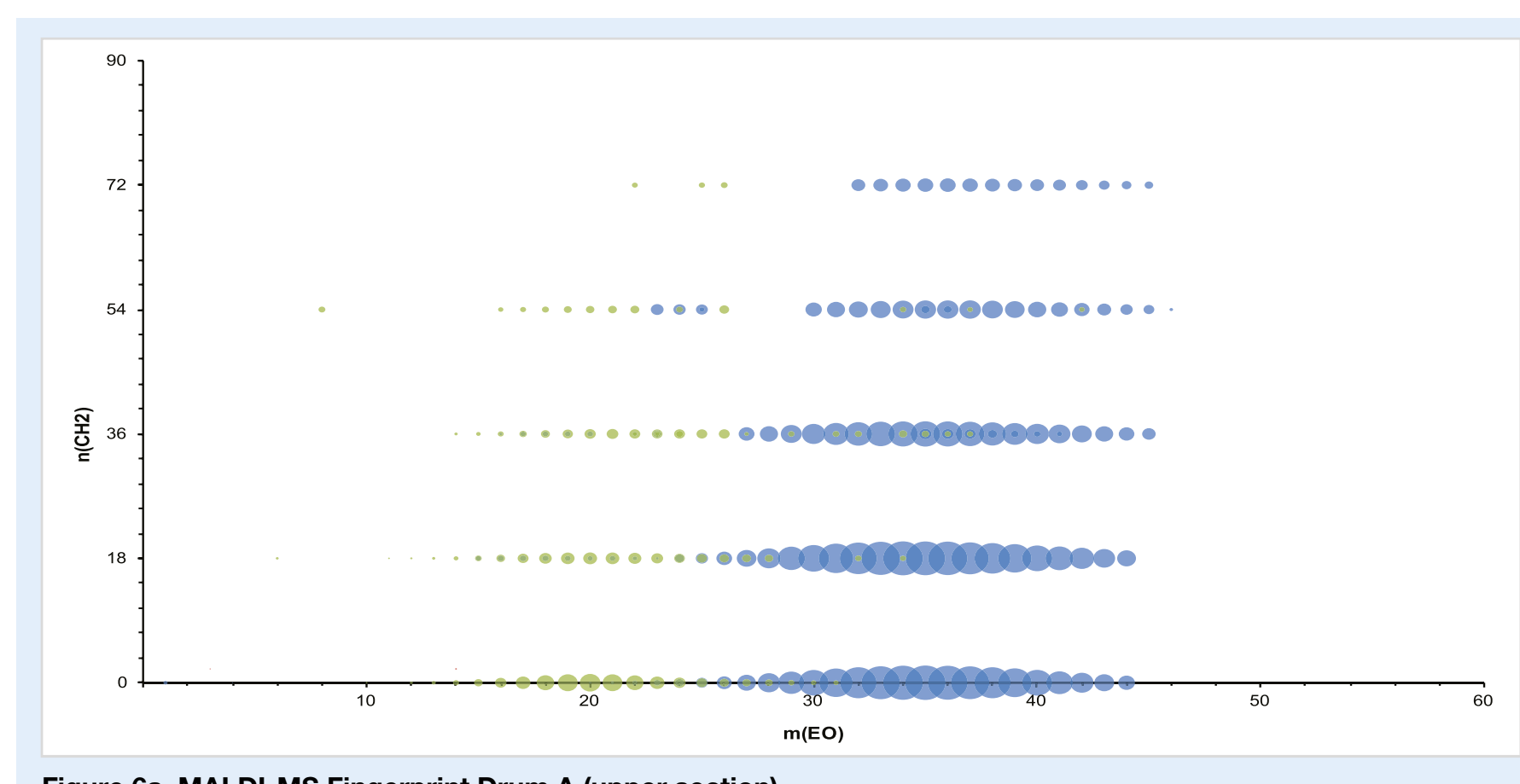


Figure 6a. MALDI-MS Fingerprint Drum A (upper section)

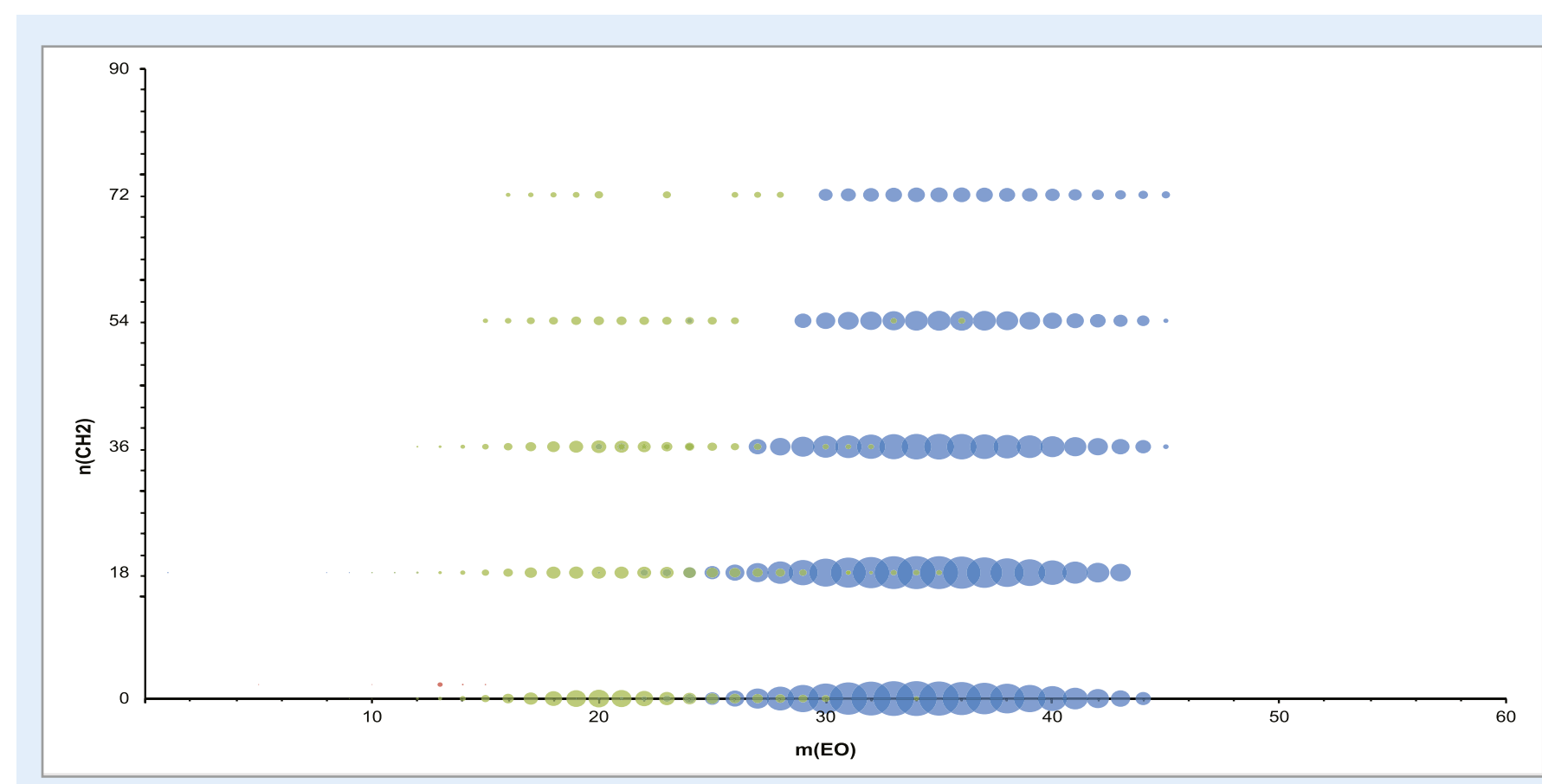


Figure 6b. MALDI-MS Fingerprint Drum A (middle section)

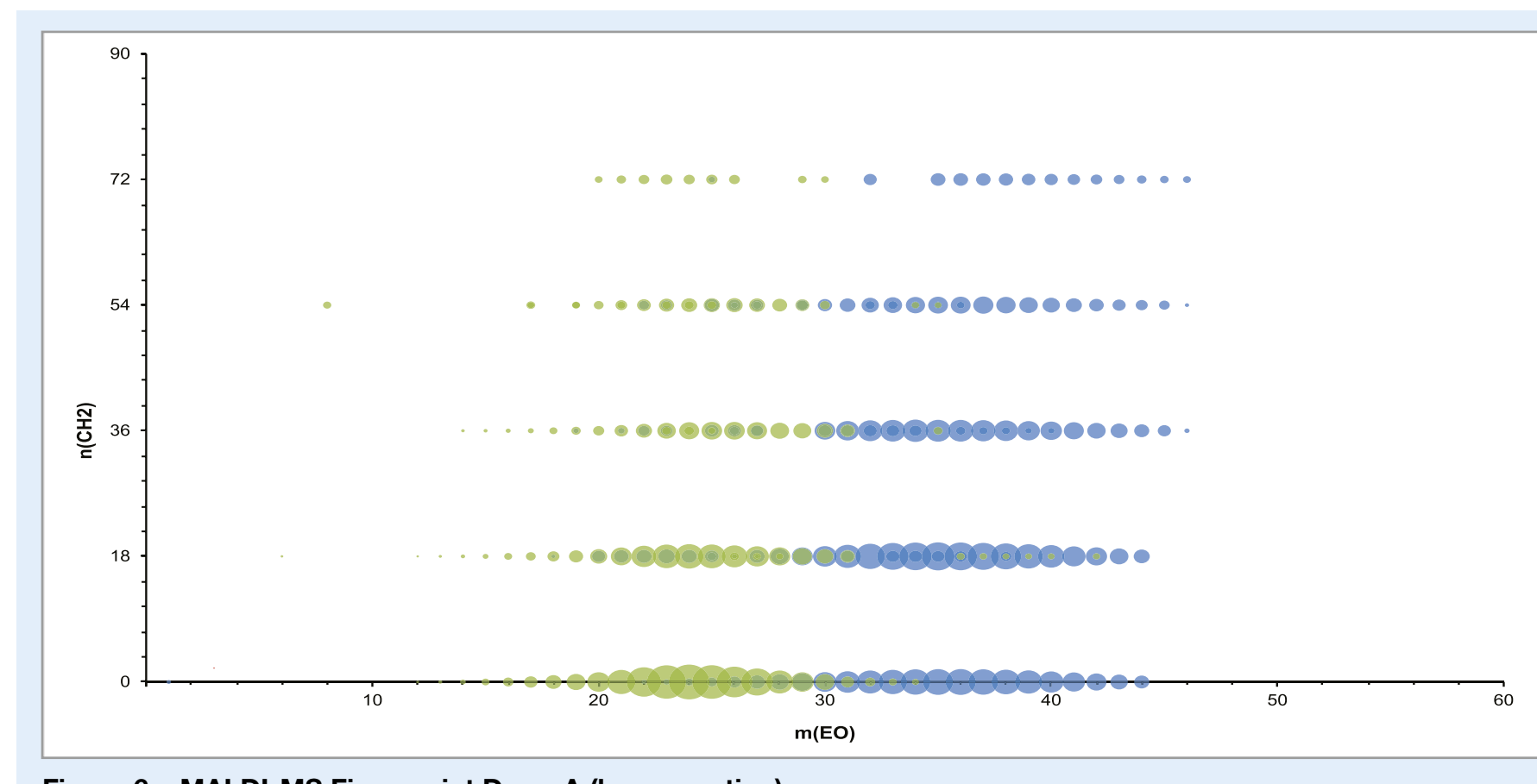


Figure 6c. MALDI-MS Fingerprint Drum A (lower section)

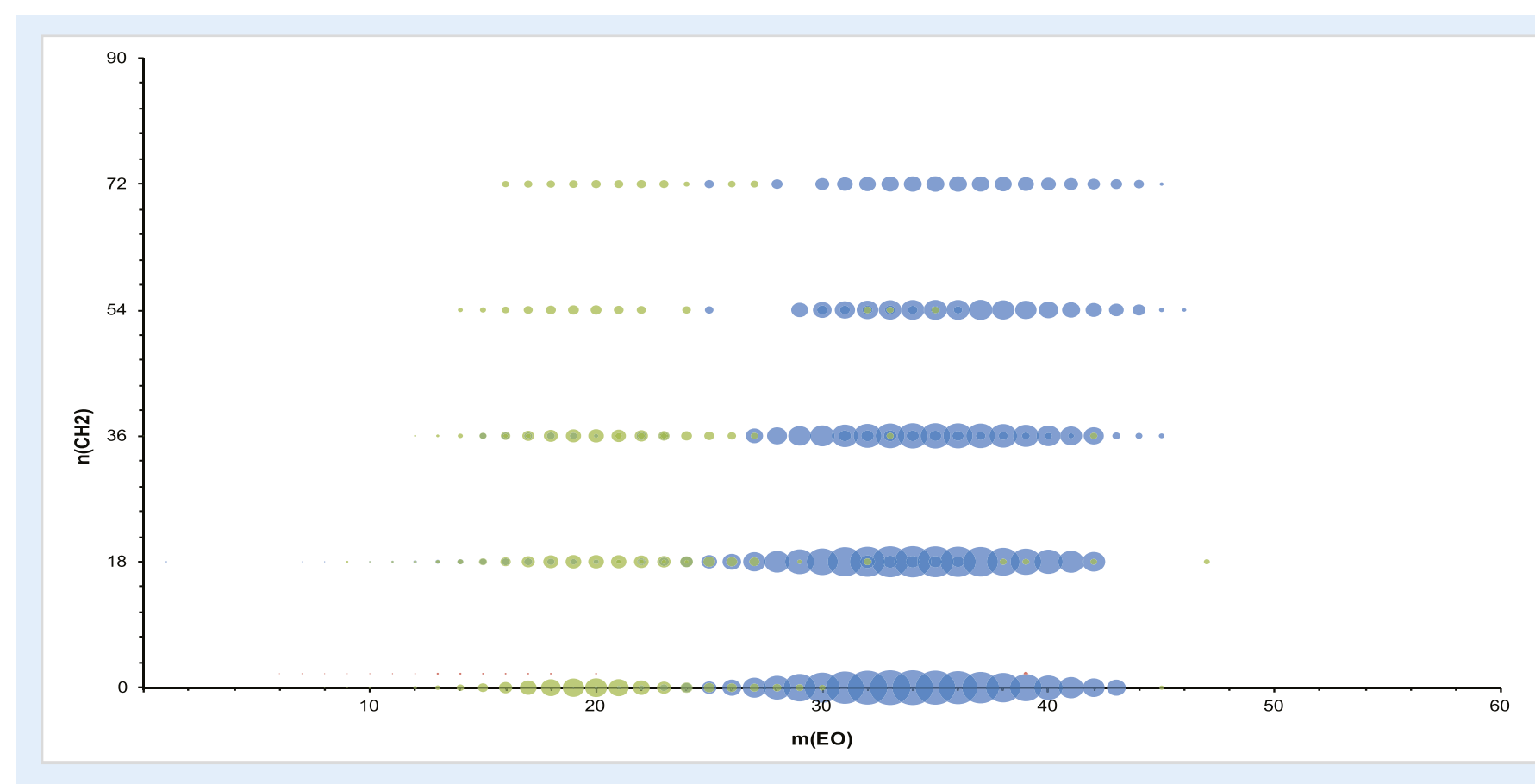


Figure 7a. MALDI-MS Fingerprint Drum B (upper section)

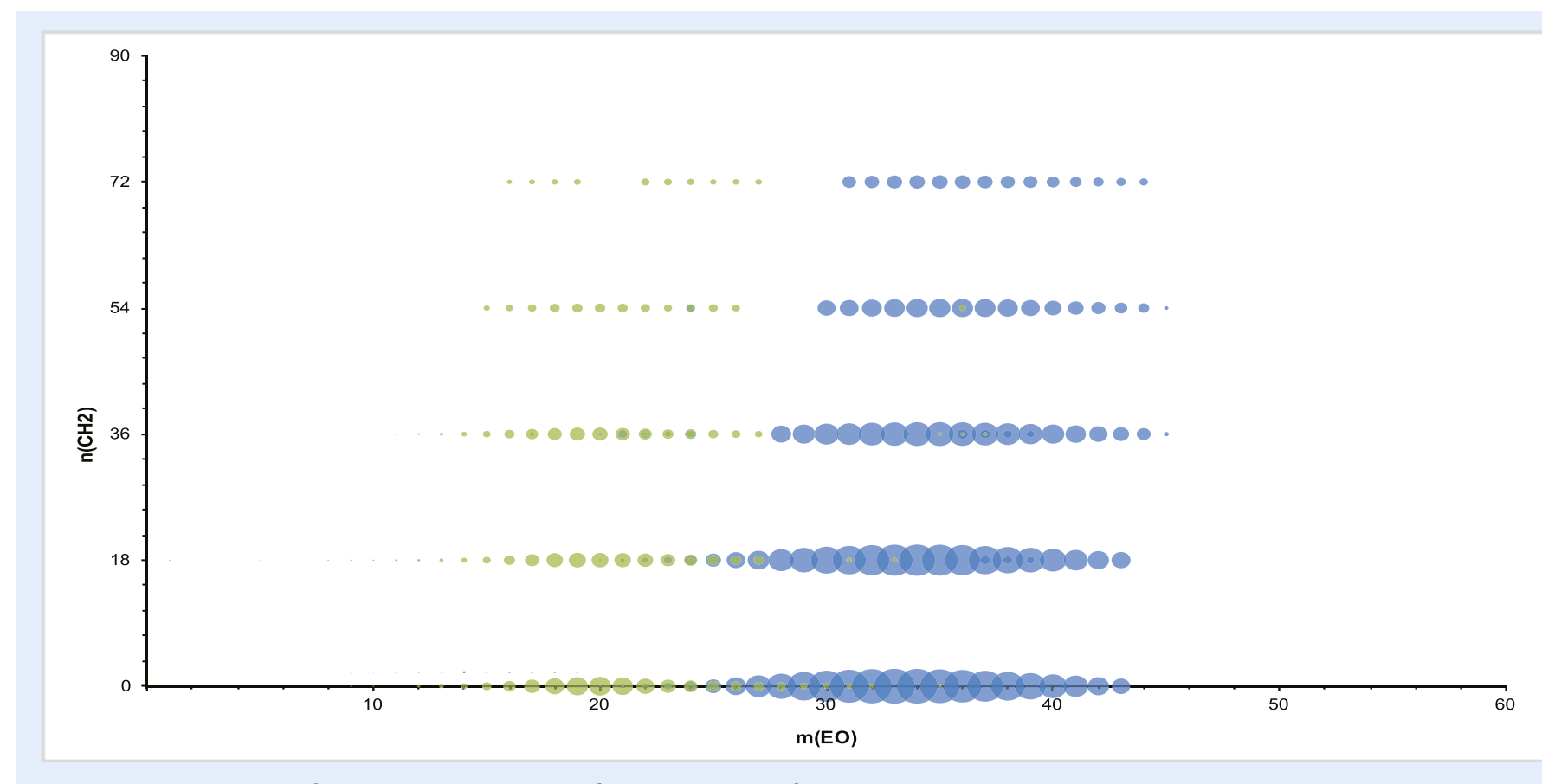


Figure 7b. MALDI-MS Fingerprint Drum B (middle section)

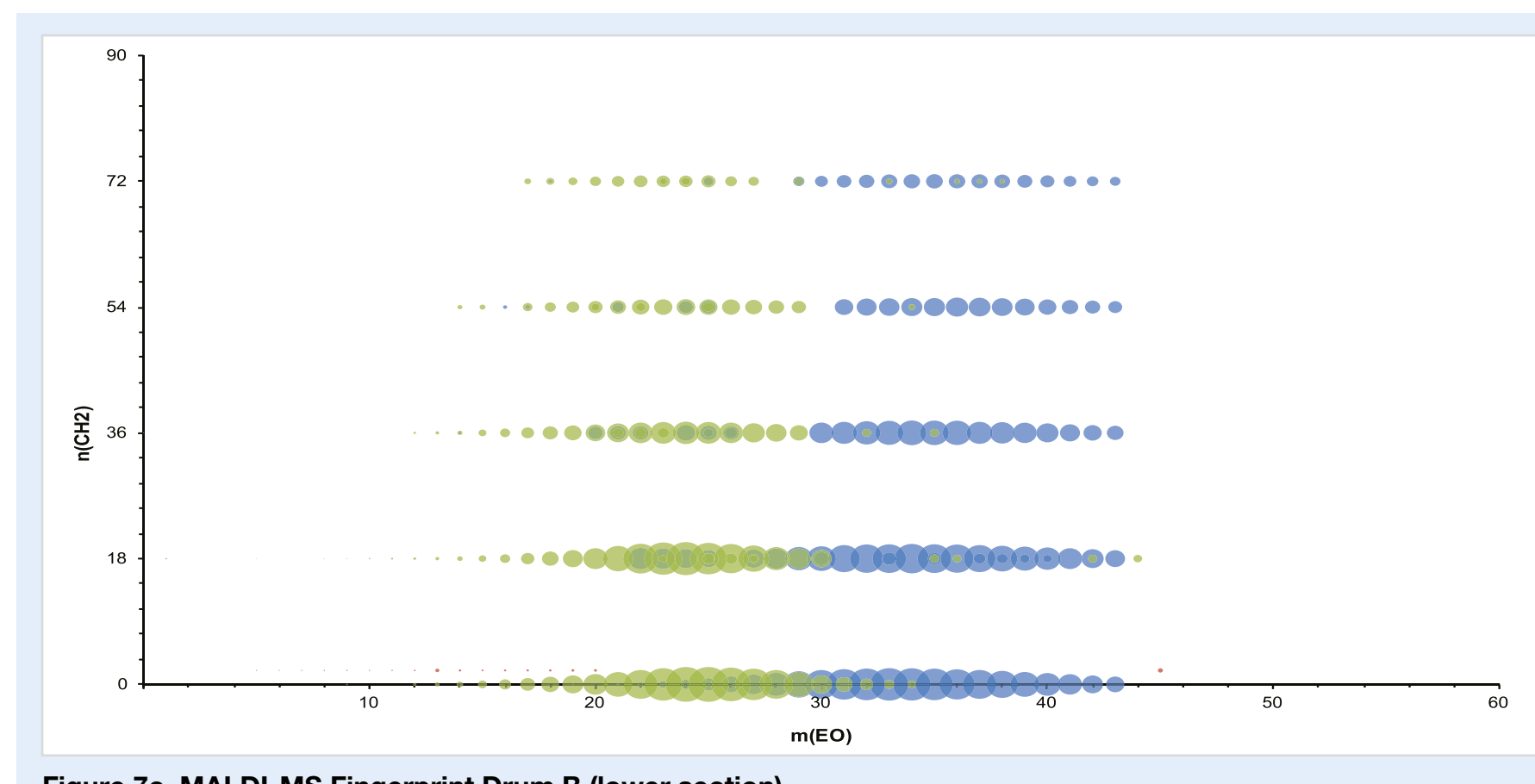


Figure 7c. MALDI-MS Fingerprint Drum B (lower section)

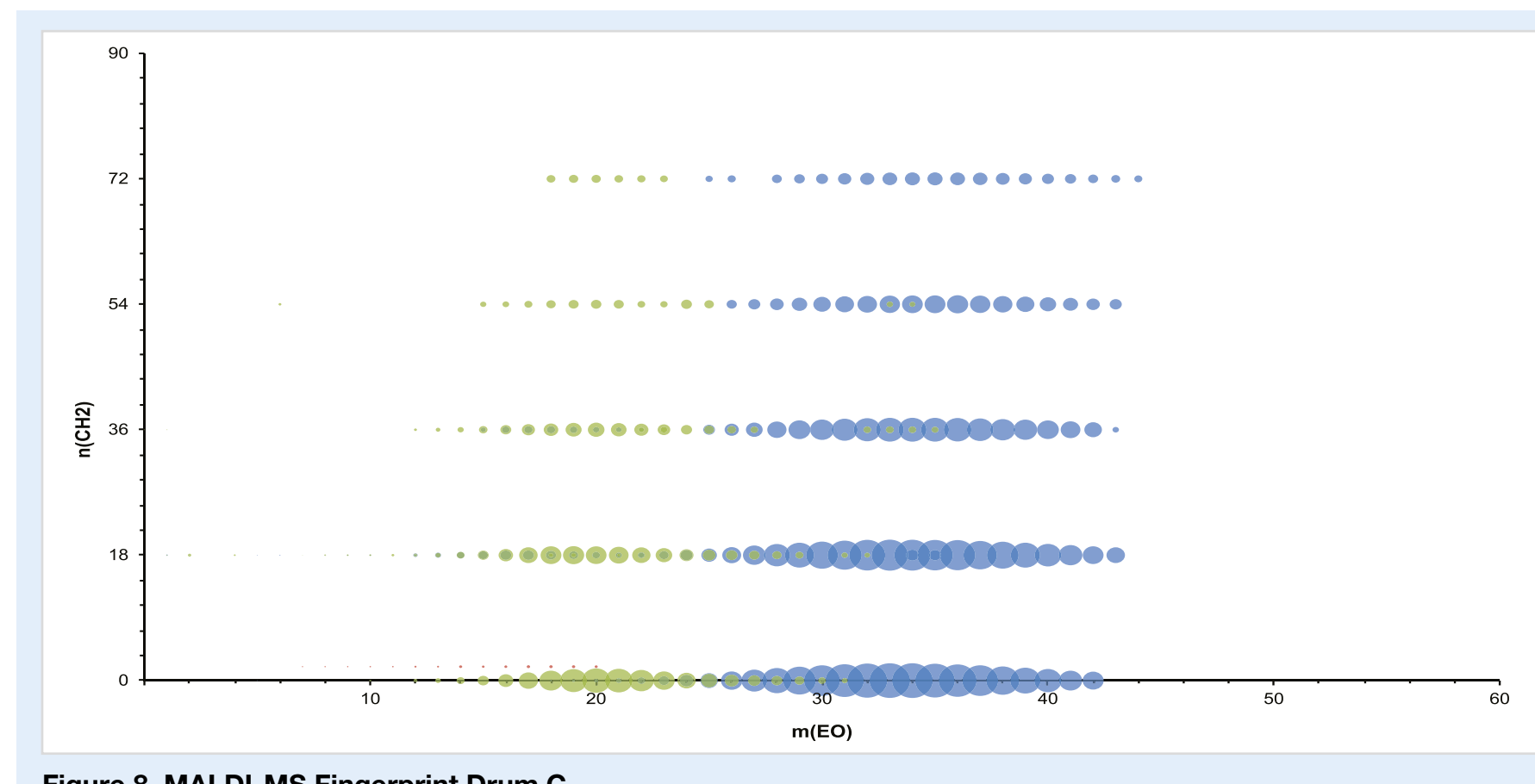


Figure 8. MALDI-MS Fingerprint Drum C

Because of this sedimentation, components of higher melting temperature consolidate in the lower section of the drum. Consequently, the product needs to be regarded as inhomogeneous when stored at ambient temperatures.

The results for Drum B demonstrate that the separation of the components remained upon melting. Merely melting, without mixing the product does not result in a homogeneous product.

SEC analysis can be employed to prove that the separation is based on a variation in molecular weight of the product components. In the range of about 1,000 g/mol relative molecular mass a variation depending on the drum section where the sample was taken, could be found (Figure 4).

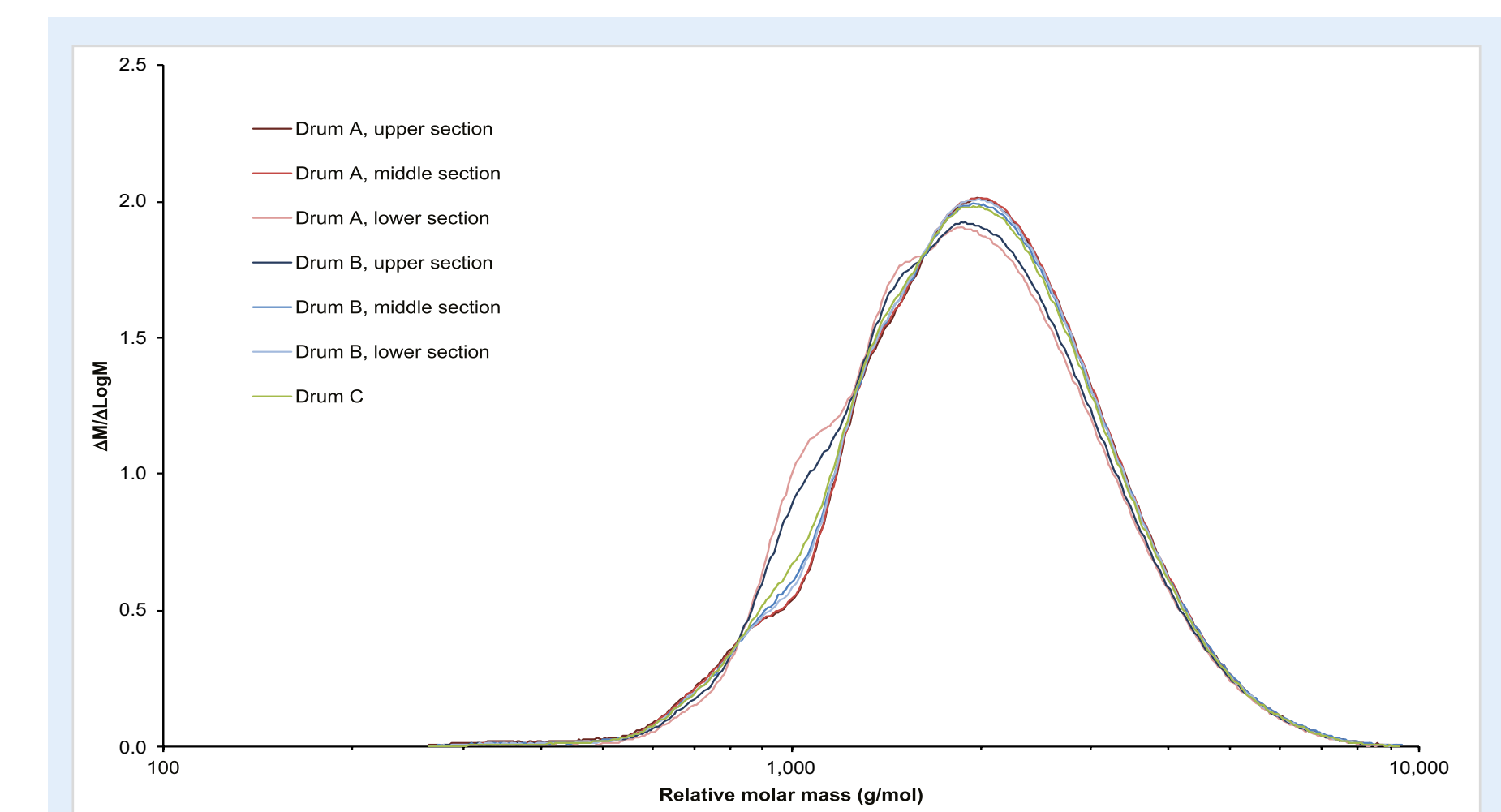


Figure 4. SEC analysis indicating the variation of product components in a relative molar mass of about 1,000 g/mol.

These results could be confirmed by MALDI-MS data. The variation of the different samples clearly indicated the varying composition of the product fractions (Figure 5). MALDI-TOF data can help to understand the chemical nature in these fractions (Figure 6, Figure 7, Figure 8). Products listed in Table 3 are the most likely components.

Table 3. MALDI-TOF analysis results.

| Compound | Content [%] |
|---|-------------|
| Glycerol - Mono-(PEG - 12 - Hydroxystearate)* | ca. 20 |
| Glycerol - Di-(PEG - 12 - Hydroxystearate)* | ca. 12 |
| Glycerol - Tri-(PEG - 12 - Hydroxystearate) | ca. 6 |
| PEG - 12 - Hydroxystearate | ca. 7 |
| PEG | ca. 18 |
| Glycerol - PEG | ca. 35 |

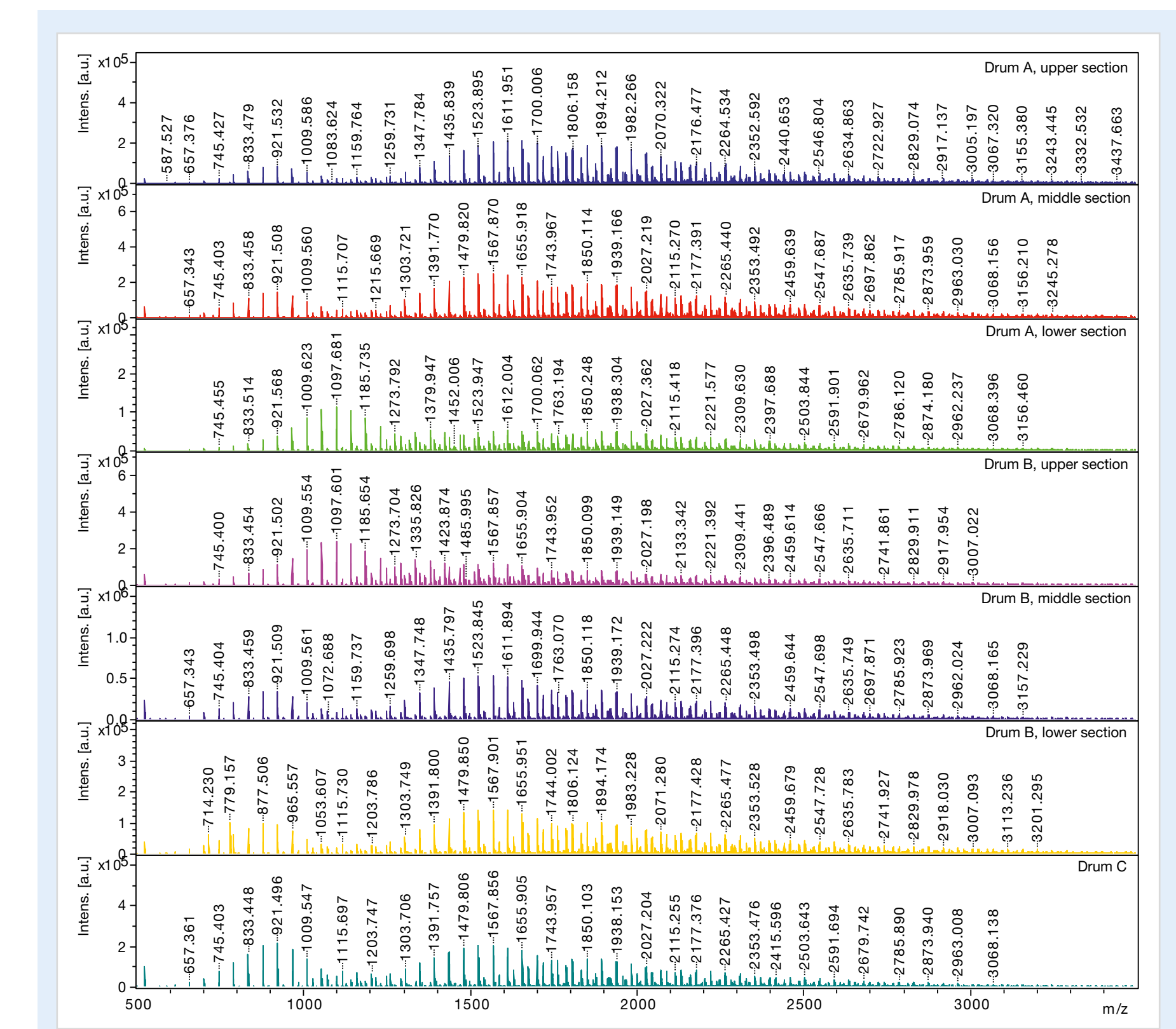


Figure 5. MALDI-MS (+) Spektrum (m/z = 500-3500).

In a MALDI-MS fingerprint, the mass spectral intensities are plotted as a function of chain-length and functional group rather than mass-to-charge ratio. While the MALDI-MS fingerprint is not an absolute quantitative representation of the sample composition, it allows a semi-quantitative comparison of batch-to-batch changes in the complex multidimensional homologue distributions governing these types of product.

The diagrams visualise the composition of the different samples. The blue dots represent species consisting of glycerol, PEG, and hydroxy stearic acid whereas the green dots represent species consisting of PEG and hydroxy stearic acid, only. The y-axis indicates the number of stearic acid units present in one molecule (molecules: non-esterified, mono-, di-, tri, and tetra-esters, indicated by an increasing y-scale value). It can clearly be seen that species containing up to four hydroxy stearic acid moieties are present in the product mixture.

A comparison of the different MALDI-MS fingerprint diagrams, clearly visualise the differences in the various samples analysed. These differences can most clearly be seen when comparing the upper and the lower section of Drum A. The lower fraction shows a noticeable higher amount of free PEG (green dots on the x-axis with no hydroxy stearic acid present). This enrichment of free PEG can neither be seen in the upper fractions nor in the samples of the homogenised drum.

Thus, the PEG fraction evidently indicates the inhomogeneity which arises during solidification. Moreover, the melting point of free PEG matches with the DSC findings of melting temperatures above 30 °C.

All the analytical results discussed so far guide to the strong recommendation that it is essentially required to melt and homogenise the product every time, before sub-quantities are taken.

Regarding a multiple melting of the product, it is important to understand whether this repeated procedure of melting and solidification has any impact on the products quality. Therefore, homogenised samples were presented to a swing test of 20 melting and freezing cycles, subsequently followed by testing against product specification. The results clearly indicated that this handling procedure does not affect product's quality/stability (Table 4).

Table 4. Swing test results in comparison to average commercial batches (n=30, average value (±SD)).

| Test | Average* | Start | Sample 1 | Sample 2 | Sample 3 |
|---------------------------------|------------|-------|----------|----------|----------|
| Congealing temperature [°C] | 24 (±1) | 24 | 25 | 25 | 25 |
| Acid value [mg KOH/g] | 0.1 (±0.1) | 0.1 | 0.3 | 0.3 | 0.3 |
| Hydroxy value [mg KOH/g] | 71 (±1) | 71 | 72 | 72 | 72 |
| Iodine value [g I/100 g] | 0.3 (±0.1) | 0.3 | 0.3 | 0.3 | 0.3 |
| Saponification value [mg KOH/g] | 54 (±1) | 54 | 54 | 54 | 54 |
| Water [g/100g] | 1.0 | 0.8 | 0.8 | 0.8 | 0.8 |
| Sulphated ash [g/100g] | | 0.18 | 0.19 | 0.18 | 0.18 |

CONCLUSION

Polyoxyl castor oil contains a mixture of various chemical substances resulting in a rather broad melting range of the product of -16 to 26 °C. When elevating the product's temperature in that range, all chemical components transfer from a solid into a liquid state as function of their chemical nature (e.g. molecular weight). However, merely melting does not provide a homogeneous product.

Homogeneity can only be achieved when stirring the whole product melt intensively. Since the product is frequently used as a solubiliser (e.g. LBDDS, SEDDS), the reliable incorporation of all product components in precisely the same ratio is essentially required. Merely a proper proceeding prevents the creation of a Critical Material Attribute caused.

Consequently, before taking sub-quantities of a drum, the whole amount of material needs to be molten and homogenised with a suitable stirrer. The repeated melting has no impact on the products quality and can therefore be conducted without any concern. Though, to simplify handling, required quantities can be taken from a molten and homogenised drum and dosed into precisely the quantities required for the subsequent process. Following the latter approach, melting is not required, if the handling procedure guarantees that the whole quantity of material is transferred into the process subsequently applied.

It must be avoided to take sub-quantities of solid material. The solidified product cannot be homogenised and does not solidify in a homogeneous manner.