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APPLICATION NOTE

Accelerate Your Cetuximab Biosimilar Development

with Maurice

Stability studies of biotherapeutics require several orthogonal analytical techniques to ensure product quality. As the competition among drug manufacturers is growing, so is the demand for more robust and efficient analytical tools that accelerate various processes during development. Maurice, a fully integrated capillary electrophoresis (CE) instrument, enables rapid charge (icIEF) and size (CE-SDS) analysis of biotherapeutics. This application note discusses the use of Maurice in assessing the stability of Cetuximab (Erbitux®) under different stress conditions. Cetuximab is a chimeric monoclonal antibody (mAb) used to treat head, neck, and metastatic colorectal cancer. With its patents having expired in Europe and the US in 2014 and 2016 respectively, there are several biosimilars that are in development and require robust analytical tools for stability studies and comparability assessments. The goal of this study is to demonstrate how protein charge and size heterogeneity analysis from a single instrument for stability studies can be used as guidance in biosimilar stability design.

In this study, both charge and molecular weight heterogeneity of Cetuximab were evaluated under eight different conditions – high temperature (accelerated and stress condition), freeze-thaw cycles, agitation, low pH, high pH, exposure to light (photostability), oxidation, and glycation.

Materials and Methods

The following materials were obtained from ProteinSimple: Maurice cIEF Method Development Kit (PN PS-MDK01-C), Maurice cIEF System Suitability Kit (PN 046-044), iCE Electrolyte Kit (PN 102506), 1% Methyl Cellulose Solution (PN 101876), Maurice cIEF pI Marker 7.05 (PN 046-032), Maurice cIEF pI Marker 10.17 (PN 046-035), Maurice cIEF pI Marker 6.14 (PN 046-031), Maurice cIEF pI Marker 9.50 (PN 046-047), CE-SDS PLUS Cartridge (PN PS-MC02-SP), CE-SDS PLUS Sample Buffer (PN 046-567), CE-SDS Wash Solution, 20 mL (PN 046-569), Maurice CE-SDS Running Buffer – Top (PN 046-384), Maurice CE-SDS Orange Pressure Caps (PN 046-572), Separation Matrix, 15 mL (PN 046-386), Running Buffer – Top, 10/pack (PN 046-384), Running Buffer – Bottom, 12 mL (PN 046-385), Conditioning Solution 1, 20 mL (PN 046-014), Conditioning Solution 2, 20 mL (PN 046-015), 2 mL Glass Reagent Vials (PN 046-017), 96-well Plates, 10/pk (PN 046-021), Clear Screw Caps for Sample Vials (PN 046-138), CE-SDS Internal Standard, 2/pk (PN 046-144), CE-SDS Cartridge Cleaning Vial (PN 046-125). The following materials were obtained from Millipore Sigma: 2-Mercaptoethanol (PN M3148), Iodoacetamide (PN I1149), Hydrochloric Acid (PN H1758), Hydrogen Peroxide, 35% (PN 7722-84-1) and D-Glucose (PN NIST917C). Sodium Hydroxide Pellets (PN 1310-73-2) were obtained from Thermo Fisher Scientific.

Sample Preparation

For icIEF experiments, Cetuximab (0.4 mg/mL final) was mixed with 3–10 Pharmalyte (1%), 8–10.5 Pharmalyte (3%), Maurice cIEF pI markers 6.14 (1%) and 9.5 (1%), arginine (10 mM), urea (2 M), and methyl cellulose (0.35%). The samples were separated in a Maurice cIEF cartridge (PN PS-MC02-C) for 10 minutes at 3,000 V. Absorbance images were captured and analyzed with the Compass for iCE software, version 2.2.0.

For CE-SDS experiments under reduced conditions, Cetuximab (1 mg/mL final) was diluted separately in the CE-SDS Plus Sample Buffer (1X) and prepared to a final sample containing the 25X CE-SDS Internal Standard (4%) and 2-Mercaptoethanol (650 mM). For non-reduced conditions, Cetuximab (1 mg/mL final) was diluted separately in the CE-SDS Plus Sample Buffer (1X) and prepared to a final sample containing the 25X CE-SDS Internal Standard (4%) and iodoacetamide (11.5 mM). The samples were then denatured at 70 °C for 10 minutes and stored on ice. The reduced samples were electrokinetically injected for 20 seconds at 4,600 V and separated for 25 minutes at 5,750 V. The non-reduced samples were also electrokinetically injected for 20 seconds at 4,600 V, but were separated for 35 minutes at 5,750 V. All samples were analyzed using the Compass for iCE software, version 2.2.0.

Results

Accelerated Study: Temperature Stress at 25°C

Various degradation pathways are activated when mAbs are exposed to high temperatures. Fragmentation due to the cleavage of peptide bonds, deamidation, and the formation of soluble and insoluble aggregates—both covalent and non-covalent—are typical consequences of temperature-induced mAb degradation[1,2]. These degraded variants impact the safety and stability of the biotherapeutic and must therefore be evaluated. In this accelerated study, Cetuximab was stored at 25 °C for 21 days, and icIEF and CE-SDS analyses conducted on the 1st, 7th, 14th, and 21st days. With icIEF analysis, a decrease in the peak areas of all eight isoforms was observed on Day 21, indicating sample degradation. A decrease in the acidic variants was also seen from the 1st to the 21st day (**FIGURE 1A**). However, with reduced CE-SDS analysis, the Cetuximab sample appeared to be stable at 25 °C even on the 21st day, having shown no major changes as the days progressed (**FIGURE 1B**). In contrast, non-reduced CE-SDS analysis (**FIGURE 1C**) showed an increase in the 2-heavy-1-light (2H1L) peak from Day 1 to Day 21, indicating aggregate formation.

High Temperature Stress Study at 40°C

icIEF and CE-SDS analyses were next conducted on Cetuximab samples incubated at 40 °C for 7 days. The analyses were conducted on the 1st, 3rd, and 7th days. As the days progressed, a significant decrease in the peak areas of acidic and basic variants was observed with icIEF analysis (**FIGURE 2A**). Degradation of the antibody was clearly visible on Day 7. Reduced CE-SDS analysis showed a decrease in the peak areas of both the heavy chain and the light chain on the 7th day, as seen in **FIGURE 2B**. Expansion of the same data revealed the presence of species running faster than the heavy chain as the days progressed. An increase in fragmentation, as expected from high temperature stress exposure, was observed in non-reduced CE-SDS analysis along with a decrease in the main peak area (**FIGURES 2C**). A summary of the non-reduced CE-SDS results is presented in **TABLES 1A and 1B.**

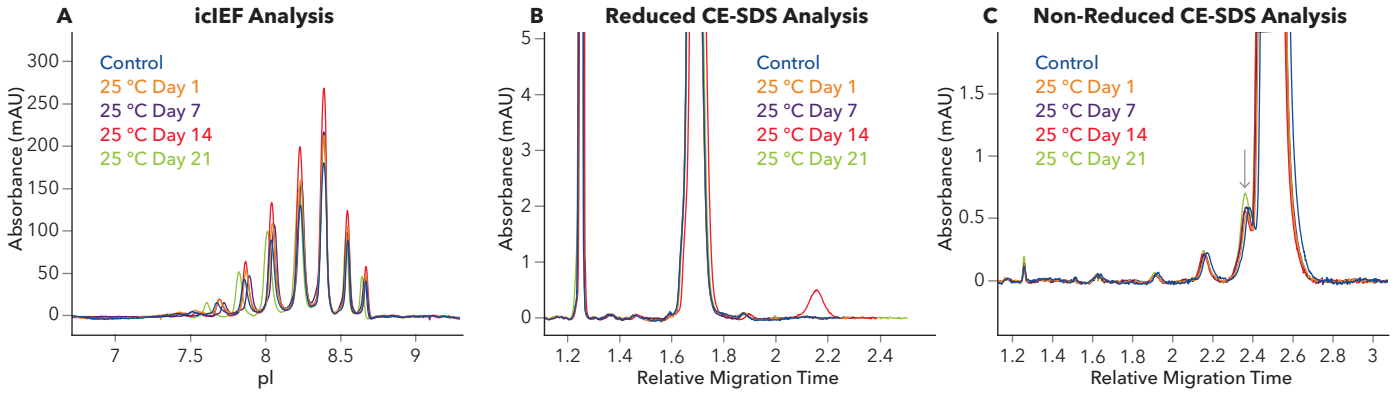

FIGURE 1. Impact of accelerated temperature stress (25 °C) on Cetuximab. Cetuximab was incubated for 21 days at 25 °C. (**A**) Degradation of the sample was observed by day 21 with icIEF analysis. (**B**) Reduced CE-SDS analysis did not show any major changes to the molecule. (**C**). Non-reduced CE-SDS analysis indicated an increase in the 2H1L species as the days progressed, likely due to aggregate formation.

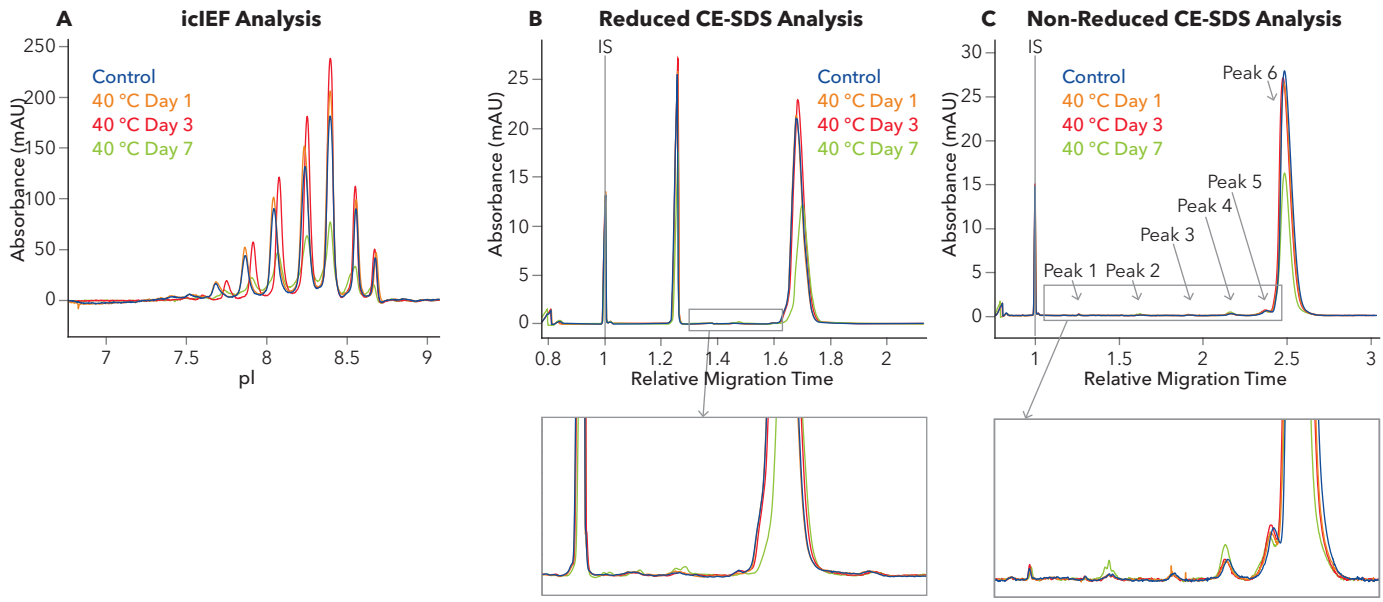

FIGURE 2. Effects of high temperature (40 °C) on Cetuximab. The samples were incubated for 7 days. (**A**) icIEF detected a decrease in the peak areas of acidic and basic variants, with sample degradation clearly visible on day 7. (**B**) Likewise, a decrease in the heavy chain and light chain peak areas was seen on day 7 with reduced CE-SDS analysis. The inset shows an increase in low molecular weight species. (**C**) Non-reduced CE-SDS analysis showed a decrease in the main peak area on day 7, along with increased fragmentation as seen in the inset. IS: Internal Standard.

A

STRESS SAMPLE	PEAK 1			PEAK 2			PEAK 3		
CETUXIMAB (NR)	RMT	AREA	% AREA	RMT	AREA	% AREA	RMT	AREA	% AREA
Control	1.3	2.6	0.1	1.6	2.8	0.2	1.9	2.2	0.1
Day-1	1.3	2.3	0.1	1.6	3.3	0.2	1.9	1.7	0.1
Day-3	1.3	3.1	0.2	1.6	1.9	0.1	1.9	1.5	0.1
Day-7	1.2	2.9	0.3	1.6	9.9	1	1.9	2	0.2

B

STRESS SAMPLE	PEAK 4			PEAK 5			PEAK 6		
CETUXIMAB (NR)	RMT	AREA	% AREA	RMT	AREA	% AREA	RMT	AREA	% AREA
Control	2.2	12	0.7	2.4	29.2	1.6	2.5	1785	97.3
Day-1	2.2	11.6	0.7	2.4	28.6	1.7	2.5	1623.6	97.2
Day-3	2.2	10.5	0.6	2.4	30.2	1.7	2.6	1682.1	97.3
Day-7	2.1	18.5	1.9	2.3	28	2.8	2.5	925.6	93.8

TABLE 1. Summary of results from non-reduced CE-SDS analysis of Cetuximab incubated at 40 °C for 7 days. The relative migration time (RMT), peak area, and percent peak area are reported for (**A**) peaks 1–3 and (**B**) 4–6.

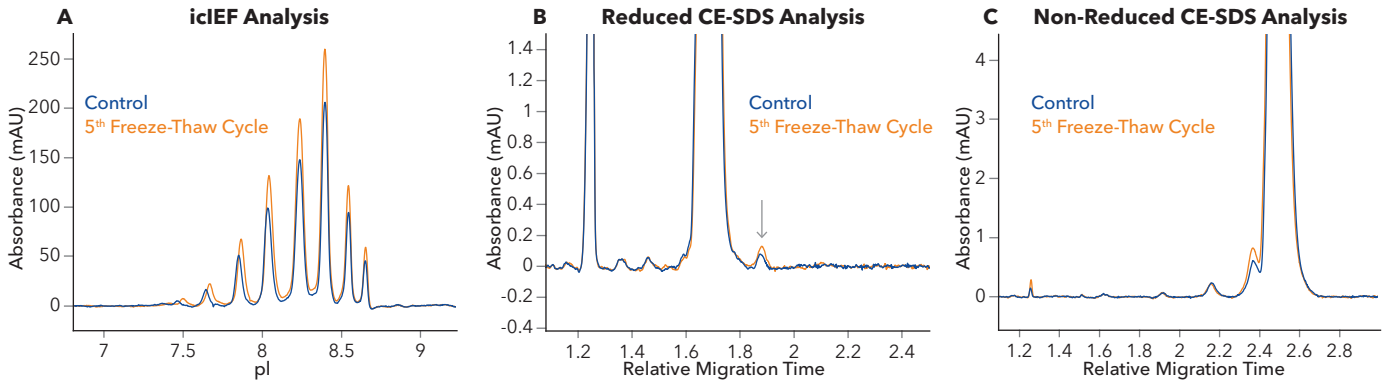

FIGURE 3. Effects of 5 freeze-thaw cycles on Cetuximab. The samples were analyzed after the 5th cycle. (A) All 8 isoforms showed a slight increase in the peak areas with icIEF. (B) Apart from a slight increase in high molecular weight species, Cetuximab was found to be stable even after the 5th freeze-thaw cycle with reduced CE-SDS. (C) Small amounts of impurities were detected with non-reduced CE-SDS, although the sample appeared to be stable overall.

Freeze-Thaw Study

mAbs are routinely subjected to freezing and thawing during manufacturing. Effects of such freeze-thaw conditions include the formation of non-covalent protein aggregates[3], which could increase the risk of immunogenicity in patients[4]. Therefore, freeze-thaw studies are typically included in the stability assessment of mAbs.

Cetuximab was subjected to 5 freeze-thaw cycles and CE analyses were conducted on the 5th cycle. With icIEF, all 8 isoforms showed an increase in the peak area (FIGURE 3A). This was expected, as freeze-thaw cycles can induce aggregation, oxidation, hydrolysis, and pH changes that directly impact mAb stability. With reduced CE-SDS analysis, Cetuximab appeared to be relatively stable even after the 5th freeze-thaw cycle, showing only a slight increase in species weighing more than the heavy chain. (FIGURE 3B). Non-reduced CE-SDS analysis did not indicate any major changes to the sample either, although small amounts of impurities were detected (FIGURE 3C).

Agitation Study

A common physical stress affecting mAbs is agitation, which is caused by activities such as stirring, shaking, etc. during manufacturing processes, formulation development, and transportation. Because agitation can result in the formation protein aggregates[5], mAbs are deliberately agitated and evaluated during stability studies.

To induce agitation, Cetuximab was vortexed at 400 rpm for 3 days. Samples were analyzed on the 1st and 3rd days and compared with a control. FIGURE 4A shows the results from icIEF analysis, where a decrease in peak area and percent peak area of the acidic variants was observed. Reduced CE-SDS analysis showed a decrease in peak areas of the heavy chain and light chain on Day 3 (FIGURE 4B). Similarly, non-reduced CE-SDS analysis showed a significant decrease of the main peak area (FIGURE 4C).

pH Study

Different processes involved in the production of mAbs have their own unique pH requirements. For example,

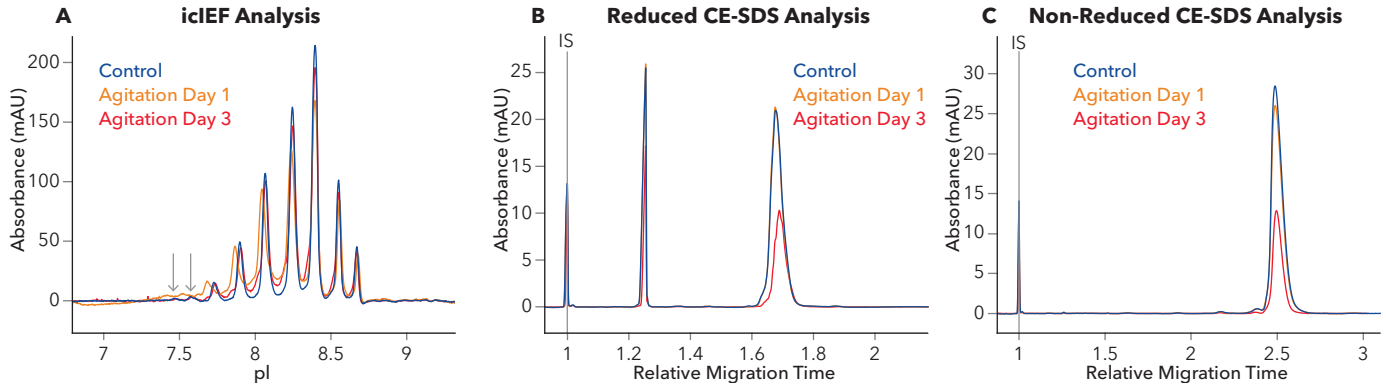

FIGURE 4. Effects of agitation (vortexted at 400 rpm for 3 days). (A) The acidic variants showed a decrease in peak area and percent peak area with icIEF analysis. (B) The heavy chain and light chains also showed a decrease in peak areas with reduced CE-SDS analysis on Day 3, and (C) non-reduced CE-SDS analysis demonstrated a decrease in main peak area.

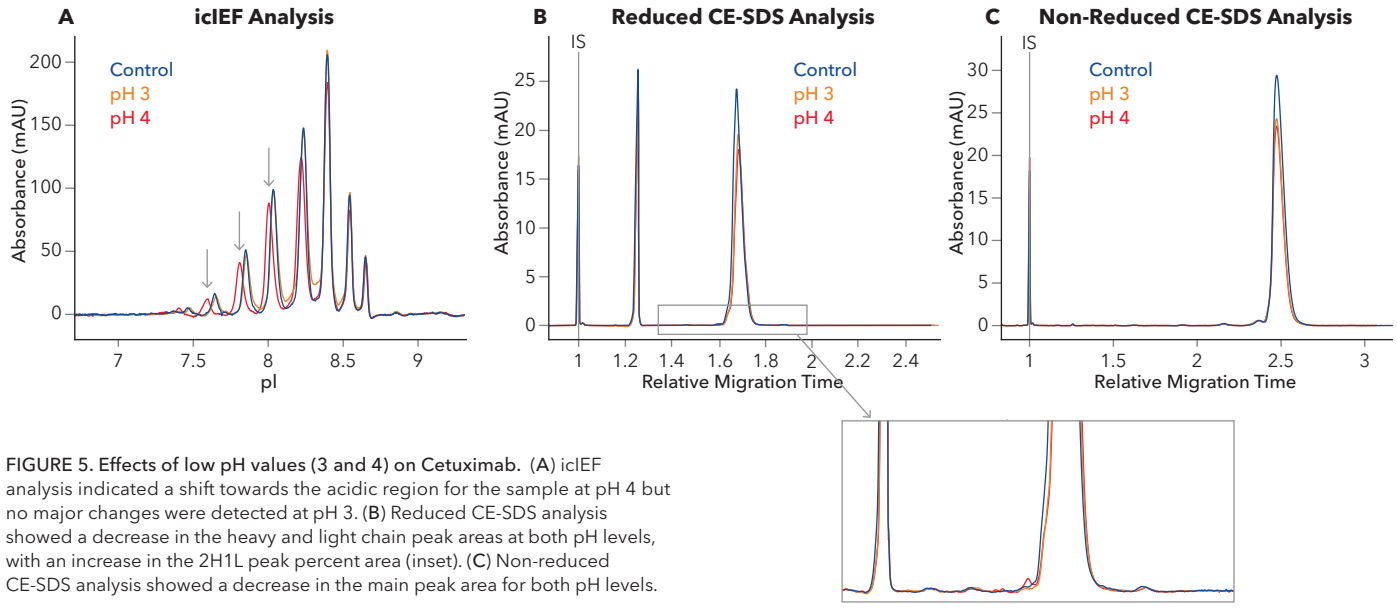

FIGURE 5. Effects of low pH values (3 and 4) on Cetuximab. (**A**) icIEF analysis indicated a shift towards the acidic region for the sample at pH 4 but no major changes were detected at pH 3. (**B**) Reduced CE-SDS analysis showed a decrease in the heavy and light chain peak areas at both pH levels, with an increase in the 2H1L peak percent area (inset). (**C**) Non-reduced CE-SDS analysis showed a decrease in the main peak area for both pH levels.

during protein A chromatography, acidic solutions (low pH) are used for elution. Conversely, a high pH buffer is required for the neutralization step following protein A chromatography. Exposure to extreme pH conditions, both low and high, leads to the formation of aggregates and can accelerate antibody fragmentation[6,7].

The pH of the Cetuximab formulation buffer lies between 7 and 7.4. To study the effects of various pH levels on this sample, the pH was first adjusted to 3 and 4 by using 1M HCl. For the sample at pH 4, icIEF analysis indicated a shift towards the acidic region, while the sample at pH 3 didn't show any major changes (**FIGURE 5A**). At low pH levels, reduced CE-SDS analysis showed a decrease in the peak areas of the heavy and light chains, along with an increase in the 2H1L peak percent area (**FIGURE 5B**, inset). A significant change observed with non-reduced CE-SDS analysis was a decrease in the main peak areas of the samples at pH 3 and 4. (**FIGURE 5C**).

Next, to evaluate Cetuximab at high pH levels, 1M NaOH was used to increase the formulation buffer pH to 8 and 9. The sample was found to be stable with icIEF analysis, as seen in **FIGURE 6A**. However, a decrease in peak areas of the heavy and light chain was clearly visible with reduced CE-SDS analysis, indicating degradation of the sample (**FIGURE 6B**). Similarly, a decrease in the main peak area and percent peak areas of the low molecular weight (LMW) and 2H1L species, likely due to fragmentation, was seen with non-reduced CE-SDS experiments (**FIGURE 6C**, inset).

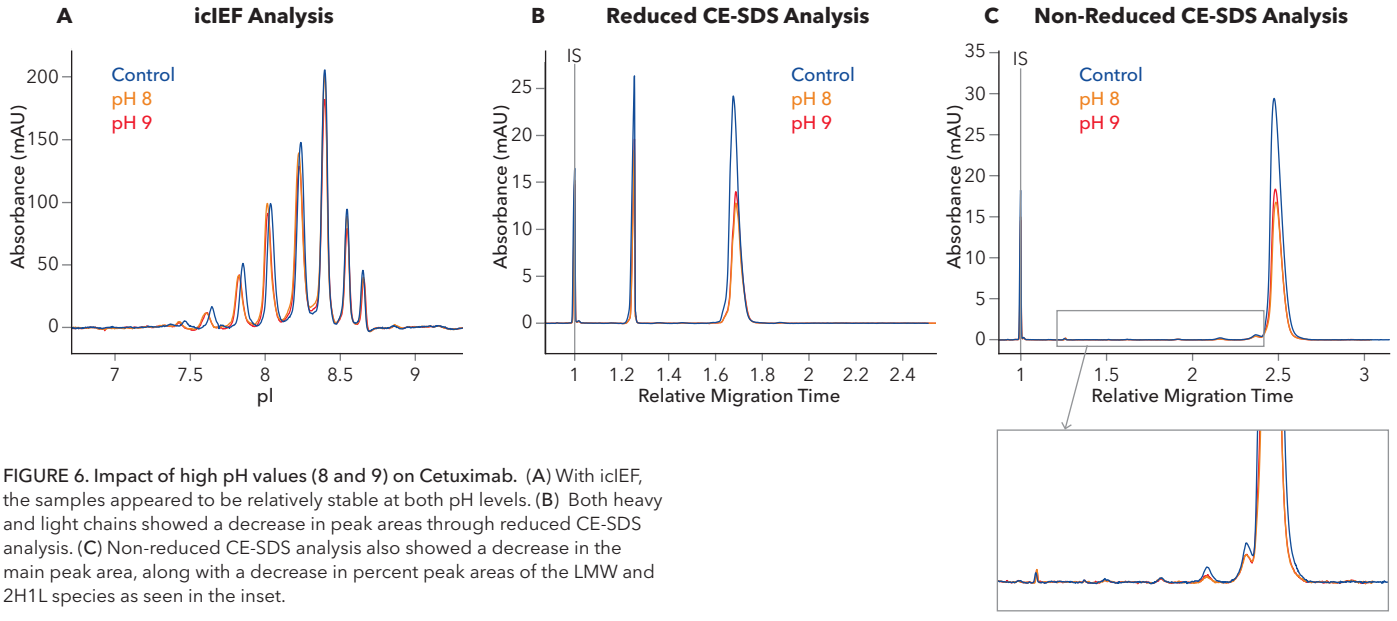

FIGURE 6. Impact of high pH values (8 and 9) on Cetuximab. (**A**) With icIEF, the samples appeared to be relatively stable at both pH levels. (**B**) Both heavy and light chains showed a decrease in peak areas through reduced CE-SDS analysis. (**C**) Non-reduced CE-SDS analysis also showed a decrease in the main peak area, along with a decrease in percent peak areas of the LMW and 2H1L species as seen in the inset.

Photostability Study

Light is yet another environmental factor that impacts the structure of proteins. Specific amino acids such as tryptophan, tyrosine, phenylalanine, and cysteine are typically affected by light, causing protein degradation[8]. In mAbs, photo-induced degradation takes the form of covalent aggregates and can induce fragmentation near the hinge region[9].

In this study, one vial of the Cetuximab sample was directly exposed to UV light, while another vial of sample, serving as an intermediate control, was wrapped in aluminum foil, and subjected to UV light. After three days of incubation, no major changes in the samples were detected with either icIEF or reduced CE-SDS analysis (FIGURES 7A and 7B). Apart from a slight increase of the 2H1L peak area observed with non-reduced CE-SDS analysis, no other changes were observed in the samples (FIGURE 7C, inset). Results from the non-reduced analysis are summarized in TABLES 2A and 2B.

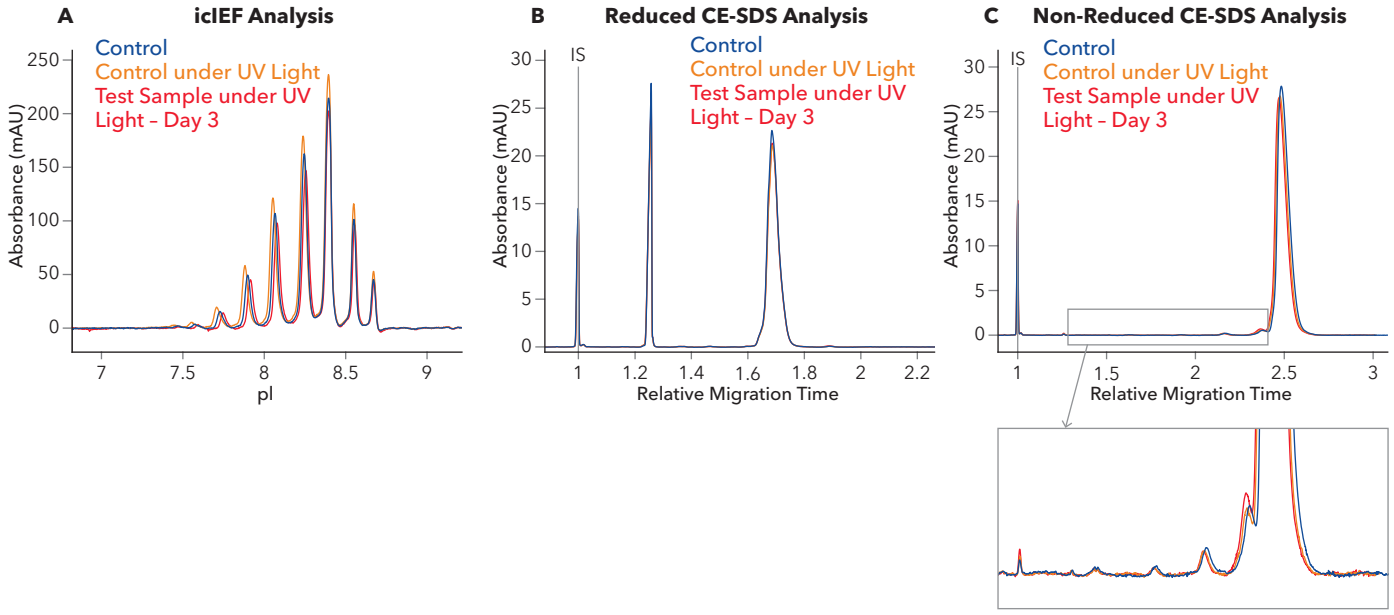

FIGURE 7. Photostability of Cetuximab after exposure to UV light. After three days of light exposure, no major changes were observed in the samples with (A) icIEF detection and (B) reduced CE-SDS analysis. (C) Non-reduced CE-SDS analysis did not indicate major changes to the samples apart from a slight increase of the LC and 2H1L peak area (inset).

A

PHOTOSTABILITY	PEAK 1			PEAK 2			PEAK 3		
CETUXIMAB (NR)	RMT	AREA	% AREA	RMT	AREA	% AREA	RMT	AREA	% AREA
Control (Real Time)	1.3	2.6	0.1	1.6	2.8	0.2	1.9	2.2	0.1
Control (UV light)	1.3	3	0.2	NA	NA	NA	1.9	1.5	0.1
Day 3	1.3	4.4	0.3	1.6	1.7	0.1	1.9	1.5	0.1

B

PHOTOSTABILITY	PEAK 4			PEAK 5			PEAK 6		
CETUXIMAB (NR)	RMT	AREA	% AREA	RMT	AREA	% AREA	RMT	AREA	% AREA
Control (Real Time)	2.2	12	0.7	2.4	29.2	1.6	2.5	1785	97.3
Control (UV light)	2.2	8.8	0.5	2.4	27.1	1.6	2.5	1652.3	97.6
Day 3	2.2	8.3	0.5	2.4	33.5	2	2.5	1634.5	97.1

TABLE 2. Results from non-reduced CE-SDS analysis of Cetuximab subjected to UV light. The relative migration time (RMT), peak area, and percent peak area are reported for (A) peaks 1–3 and (B) 4–6.

Oxidation Study

Air, dissolved oxygen, free radicals from metals, and impurities from raw materials are different oxidizing conditions that mAbs are exposed to. When these antibodies are treated with oxidizing agents like hydrogen peroxide (H_2O_2), methionine sulfoxide is formed because of oxidation of methionine residues. Oxidation of mAbs can also cause fragmentation and formation of insoluble and soluble aggregates[10,11].

Three different concentrations of H_2O_2 (0.5%, 1%, and 2%) were added to Cetuximab and the samples were left at room temperature for 3 days. Analyzed on the 1st and 3rd day, icIEF detection showed a decrease in the peak areas and percent peak areas of both acidic and basic variants by the 3rd day. Results from icIEF analysis on the 1st day are summarized in **TABLES 3A and 3B**. At 2% H_2O_2, degradation of the sample was clearly visible by Day 3 (**FIGURE 8A**). With reduced CE-SDS analysis, no major changes were observed for samples treated with 0.5% and 1% H_2O_2 even on the 3rd day. However, at 2% H_2O_2, the peak area of the high molecular weight variant increased by the 3rd day (**FIGURE 8B**). Interestingly, with non-reduced CE-SDS analysis, an increase in the percent peak area of species with lower molecular weights than the main peak was observed on the 3rd day at all three concentrations of H_2O_2 (**FIGURE 8C**).

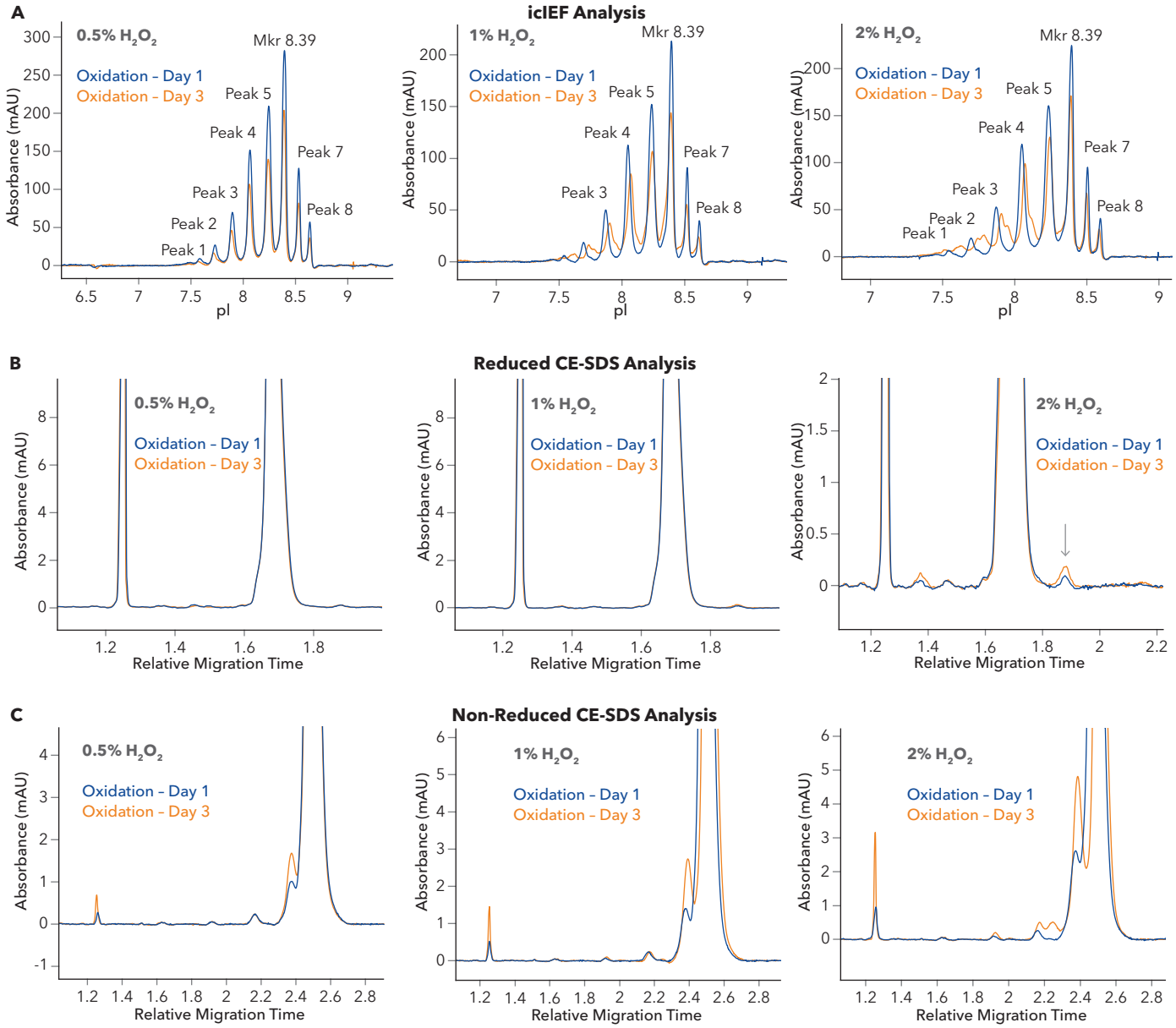

FIGURE 8. Effects of oxidation on Cetuximab using three different concentrations (05%, 1.0%, and 2.0%) of hydrogen peroxide. The (**A**) icIEF showed a decrease in the peak areas and percent peak areas of both acidic and basic variants by Day 3, with the sample clearly degraded at 2% H_2O_2. (**B**) Reduced CE-SDS analysis did not show any major changes for samples treated with 0.5% and 1% H_2O_2 even on the 3rd day, but at an increase in the peak area of non-reducible species was observed at 2% H_2O_2. (**C**) In contrast, non-reduced CE-SDS analysis showed an increase in the percent peak area of LMW species at all three concentrations of H_2O_2.

A

OXIDATION (DAY 1)	PEAK 1			PEAK 2			PEAK 3			PEAK 4		
CETUXIMAB	pI	AREA	% AREA	pI	AREA	% AREA	pI	AREA	% AREA	pI	AREA	% AREA
Control	7.6	85.3	0.7	7.7	322.2	2.7	7.9	960	8.1	8.1	2057.5	17.3
0.5% H_2O_2	7.5	237.7	1.3	7.7	632.3	3.4	7.8	1545.9	8.4	8.0	3176.3	17.3
1% H_2O_2	7.4	104.9	0.8	7.6	379	2.9	7.7	1049	8	7.9	2276.6	17.3
2% H_2O_2	7.4	143.2	1	7.5	463.4	3.2	7.7	1178.8	8.2	7.8	2571.7	17.9

B

OXIDATION (DAY 1)	PEAK 5			PEAK 6			PEAK 7			PEAK 8		
CETUXIMAB	pI	AREA	% AREA	pI	AREA	% AREA	pI	AREA	% AREA	pI	AREA	% AREA
Control	8.2	3053.5	25.7	8.4	3540.8	29.7	8.6	1329.7	11.2	8.7	498.8	4.2
0.5% H_2O_2	8.2	4608.3	25.1	8.3	5285	28.8	8.5	1980.3	10.8	8.6	774.2	4.2
1% H_2O_2	8.1	3389	25.8	8.2	3914.1	29.7	8.4	1423.7	10.8	8.5	574.7	4.4
2% H_2O_2	7.9	3611.4	25.2	8.1	4198.3	29.3	8.2	1519.8	10.6	8.4	601.5	4.2

TABLE 3. Results from the icIEF analysis of Cetuximab oxidized with varying concentrations of H_2O_2 after 1 day. The apparent pI, peak area and percent peak area are reported for (**A**) peaks 1–4 and (**B**) 5–8.

Glycation Study

Sugars are routinely used as nutrients during cell culture. Glycation occurs because of reducing sugars reacting with exposed lysine residues or N-terminal primary amine groups of the heavy or light chains, thus forming protein aggregates[12,13].

Cetuximab samples were treated with varying concentrations of D-glucose—250 mM, 500 mM, and 1M. The samples were kept at room temperature for 3 days and analyzed on the 1st and 3rd day. Comparing the results from both days, as shown in **FIGURE 9A**, icIEF analysis did not show any significant changes to the samples even at various concentrations of D-glucose. The samples also appeared stable at 250 mM and 500 mM D-glucose with reduced CE-SDS analysis, but at 1M, the heavy chain peak had completely degraded by Day 3 (**FIGURE 9B**), likely due to the formation of insoluble aggregates. Similarly, with non-reduced CE-SDS, Cetuximab samples appeared relatively stable at the two lower sugar concentrations on both days, but a degradation of the 2H1L peak was observed on day 3 with 1M D-glucose (**FIGURE 9C**).

Conclusion

This application note shows how automated icIEF and CE-SDS methods with Maurice were used to evaluate the stability of Cetuximab under different stress conditions. The distinct charge and size profiles obtained throughout the study show that both methods serve as stability-indicating assays. A study of this nature also becomes useful as a reference for both the stability evaluation of biosimilars and corresponding innovators. One of the biggest advantages of using Maurice for such a study is that both critical CE methods are in one instrument, thus saving significant costs, labor, and bench space. Furthermore, it eliminates tedious steps like capillary loading and manual instrument clean-up, providing unparalleled ease of use. In turn, single-day method development is made possible, and the high-quality reproducible data generated makes it easy to transfer methods to formulation development and QC.

To learn more about how to accelerate your biotherapeutic development with next-gen CE tools, meet Maurice.

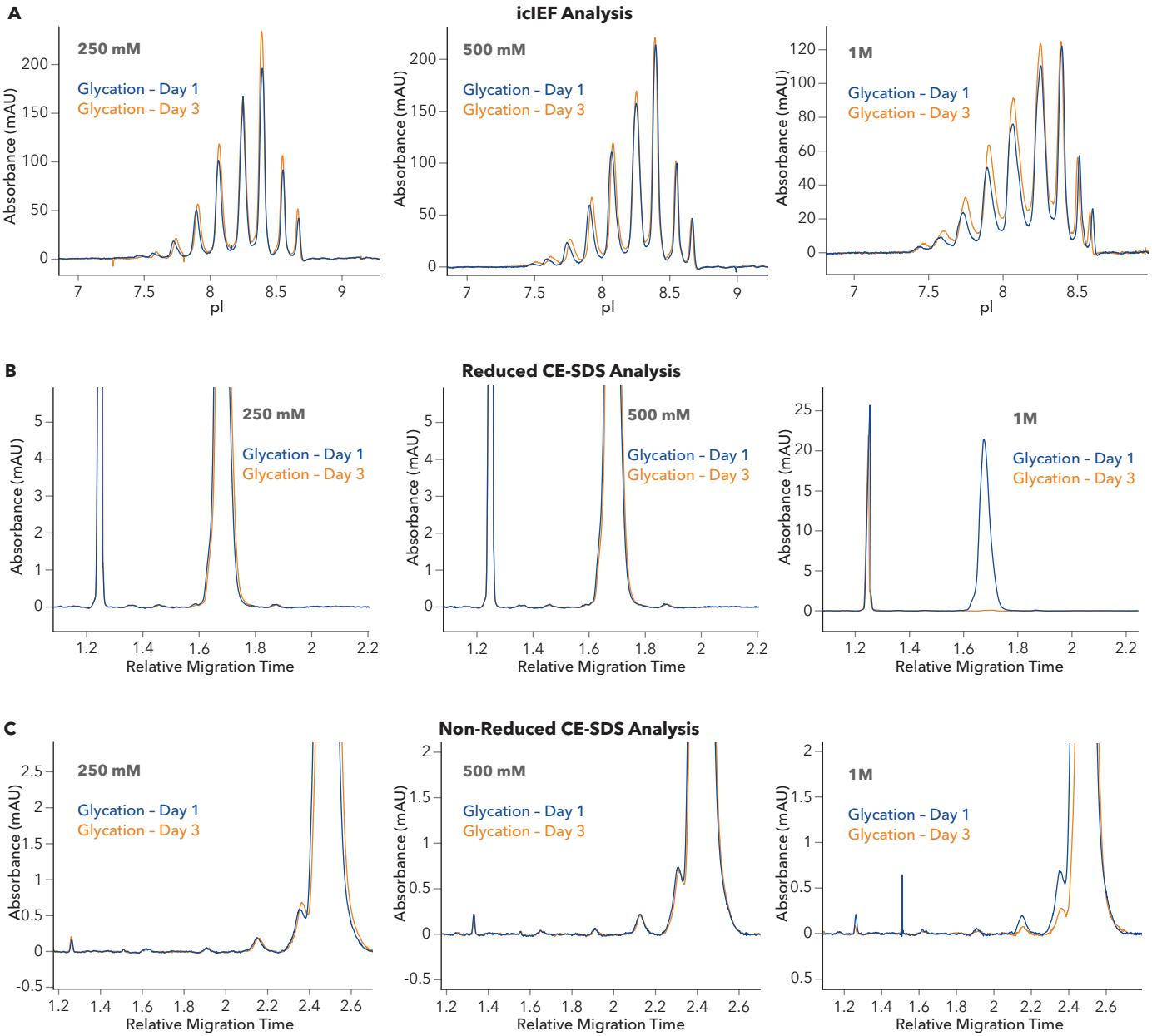

FIGURE 9. Effects of glycation on Cetuximab after treatment with three different concentrations of D-glucose. (A) No significant changes to the samples were observed with icIEF analysis, even at 1M D-glucose. (B) Reduced CE-SDS analysis showed that the samples were stable at 250 mM and 500 mM D-glucose, but degradation of the heavy chain peak was observed at 1M D-glucose on the 3rd day. (C) Non-reduced CE-SDS also showed stable Cetuximab samples at the two lower sugar concentrations on both days, but a degradation of the 2H1L peak was seen on day 3 with 1M D-glucose.

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