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Removing the Veil from Adhesive Characterization - Does Your Biomedical Device Adhesive Withstand Hydrolysis?

BACKGROUND:

Hydrolytic stability of implantable biomedical devices is often essential to their performance, safety, biocompatibility and thus ultimately to their success in the clinic. In some applications such as drug delivery and scaffold based tissue engineering, controlled hydrolytic processes may be critical to both function and performance. Hydrolytic testing of biomedical devices and their components is not only a key R&D activity necessary to material selection and product development but is also a key element of regulatory submissions.

Hydrolytic testing requires exposure of the biomedical device to aqueous physiological conditions, generally accelerated by elevated temperature. Not only is the effect of exposure on device functionality evaluated, but sensitive chemical analysis of the aqueous solvent (hydrolysate) is typically performed to screen for hydrolytic products. Optimally, selected analytical methods should chemically identify hydrolytic products, their source, and provide their quantitation for accurate risk analysis.

Liquid chromatography coupled to UV and mass spectrometry (MS) detectors has been increasingly used for the detection of biomedical device material leachables and extractables and hydrolytic products. This technique affords chromatographic separation, UV and MS detection in a single experiment, and routinely allows detection of analytes at sub part per million (ppm) levels in high sensitivity instruments. LC-MS analysis can be expected to provide rich chemical information on important analytes, e.g. polar aliphatic non-volatiles, otherwise not detectable by more traditional GC-MS and LC-UV techniques.

Adhesives are used in a wide range of applications in the biomedical industry, most often in assembly of multicomponent parts and in medical adhesives (e.g. bone and skin). The pivotal function of adhesives in maintaining medical device integrity under physiological conditions often puts them near the top of the list of failure modes in product development risk analyses. Therefore, molecular level understanding of adhesives, including their raw materials, their contaminants, their extent of cure and their hydrolytic resistance can be critical not only to the adhesive selection process but also to minimizing downstream risk. In the following case study we characterize and quantitate hydrolytic products of a polyether urethane acrylate adhesive using Ultra Performance Liquid Chromatogram –UV Detector-quadrupole Time of flight Mass Spectrometry (UPLC-UV-qTof MS).

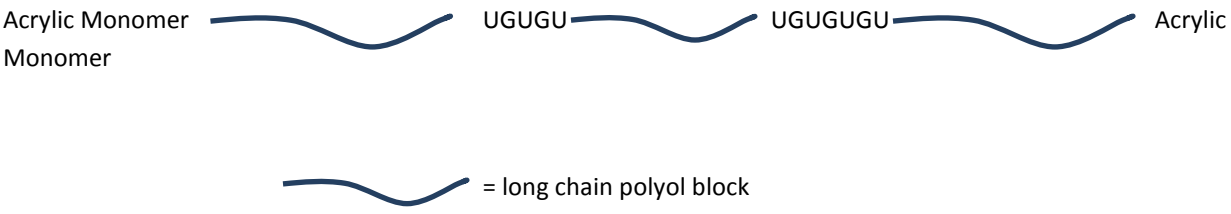
PROBLEM:

A novel implantable acrylic device utilizes a UV curable adhesive for joining two components of the device. The adhesive is a custom formulation comprised of a polyether urethane acrylate end-capped macromer, a crosslinker, and a photoinitiator. The polyether urethane acrylate macromer is a viscous liquid with exceptional adhesive and curing properties, flexibility (high elongation), optical transmission,

resistance to UV light, and resistance to water, polar solvents, acidic and basic pH. The block copolymer macromer structure shown in Scheme A joins urethane polymer blocks with polyol blocks and caps the linear chain at each end with active acrylic monomer. The curing process crosslinks the oligomers into an elastomeric network to form an adhesive bond.

The cured adhesive and bonding was found to be stable even after incubation of the assembled and cured device in phosphate buffered saline (PBS) at 85°C for approximately two months, an incubation equivalent to five years of real time aging. UPLC/MS screening of adhesive joint device hydrolysates detected adhesive-related analytes which required characterization, source verification, and quantification. It was thus essential to determine whether or not the detected adhesive analytes were chemical indicators of hydrolytic degradation of the adhesive.

Scheme A



INSTRUMENT AND SOFTWARE:

System:	Acquity UPLC I-Class with Xevo G2-S QToF mass detector and Acquity UPLC I-Class PDA detector (Waters) in tandem.
Column:	Acquity UPLC BEH C18 1.7µm (2.1mm x 50mm).
Software:	MassLynx 4.1 SCN 884

PROBLEM: Chemically characterize medical device hydrolysates

RESULTS:

IDENTIFY AND CHARACTERIZE

UPLC-UV-qTof MS analysis of the device hydrolysate showed the presence of a hydrophilic fraction (*i.e.*, fraction with an early retention time in reverse phase UPLC) with minimal UV, but strong MS response. The water soluble fraction was absent in hydrolysates of individual device components (no adhesive); see Figure 1. These data identified the device adhesive as the most likely source of the hydrophilic fraction.

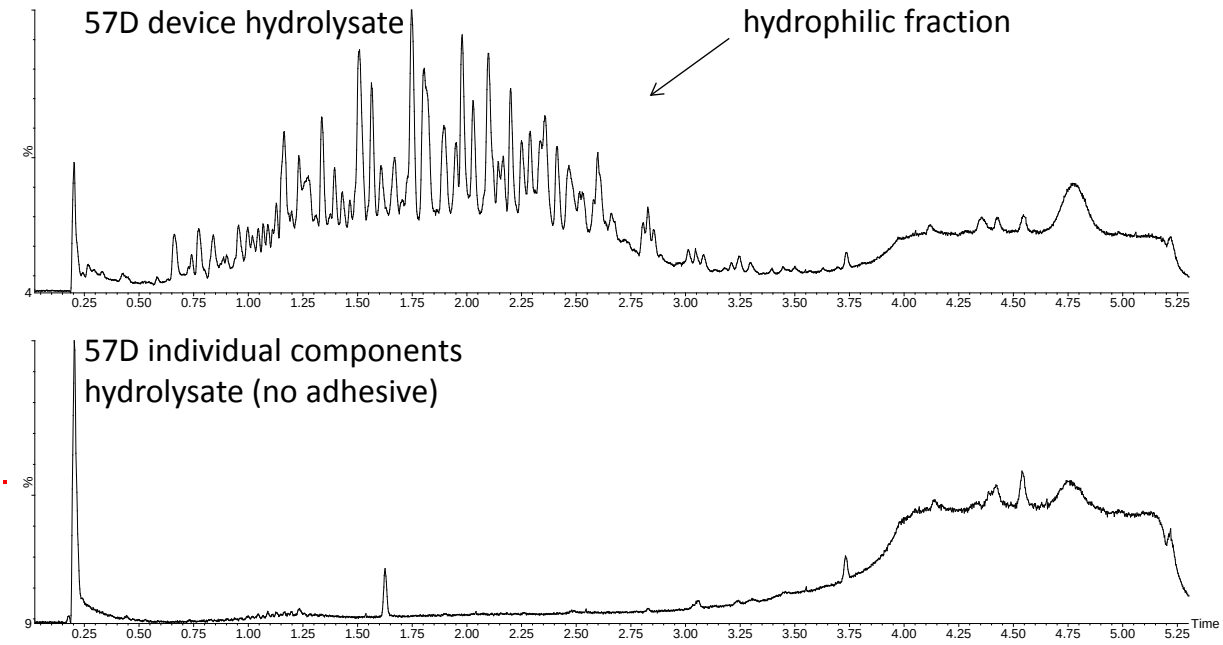


Figure 1. *UPLC-MS total ion chromatograms (TICs) of the 57 day hydrolysates of the individual components with no adhesive (bottom) vs finished (i.e. adhesively joined) medical device (top). Hydrophilic (water soluble) fraction was detected in the finished medical device hydrolysate with chromatographic retention time of ca. 0.6 to 3.5 minutes.*

COMPARE

We then analyzed a DI water solution standard of the macromer and compared its TIC to the hydrolysate TIC (Figure 2). The hydrophilic fraction was found to be closely related in chemical structure to the macromer. The macromer TIC exhibited a repeating quartet peak pattern, a conspicuous analytical fingerprint, which was also exhibited by the hydrophilic fraction. Mass spectra of the hydrophilic fraction and macromer distribution (Figure 3) both reveal a dominant peak separation of 72 mass to charge (m/z) which is a characteristic of the urethane's butoxy (CH_2-CH_2-CH_2-CH_2-O) structure. This provided compelling evidence that the macromer was a fundamental source of the water soluble fraction.

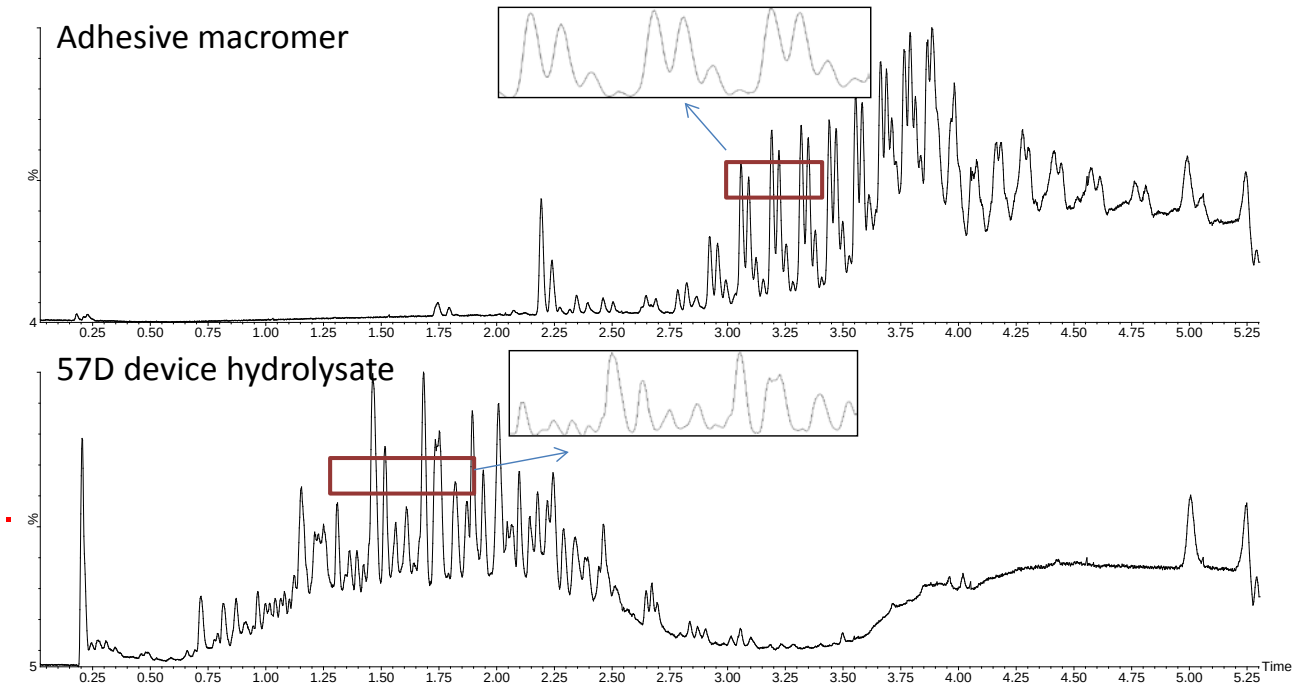


Figure 2. *Comparison of the 57D hydrolysate(bottom) and adhesive macromer (top) TIC traces. Note the macromer repeating quartet peak pattern, the insets are magnified portions of the respective chromatograms in bracketed retention time regions.*

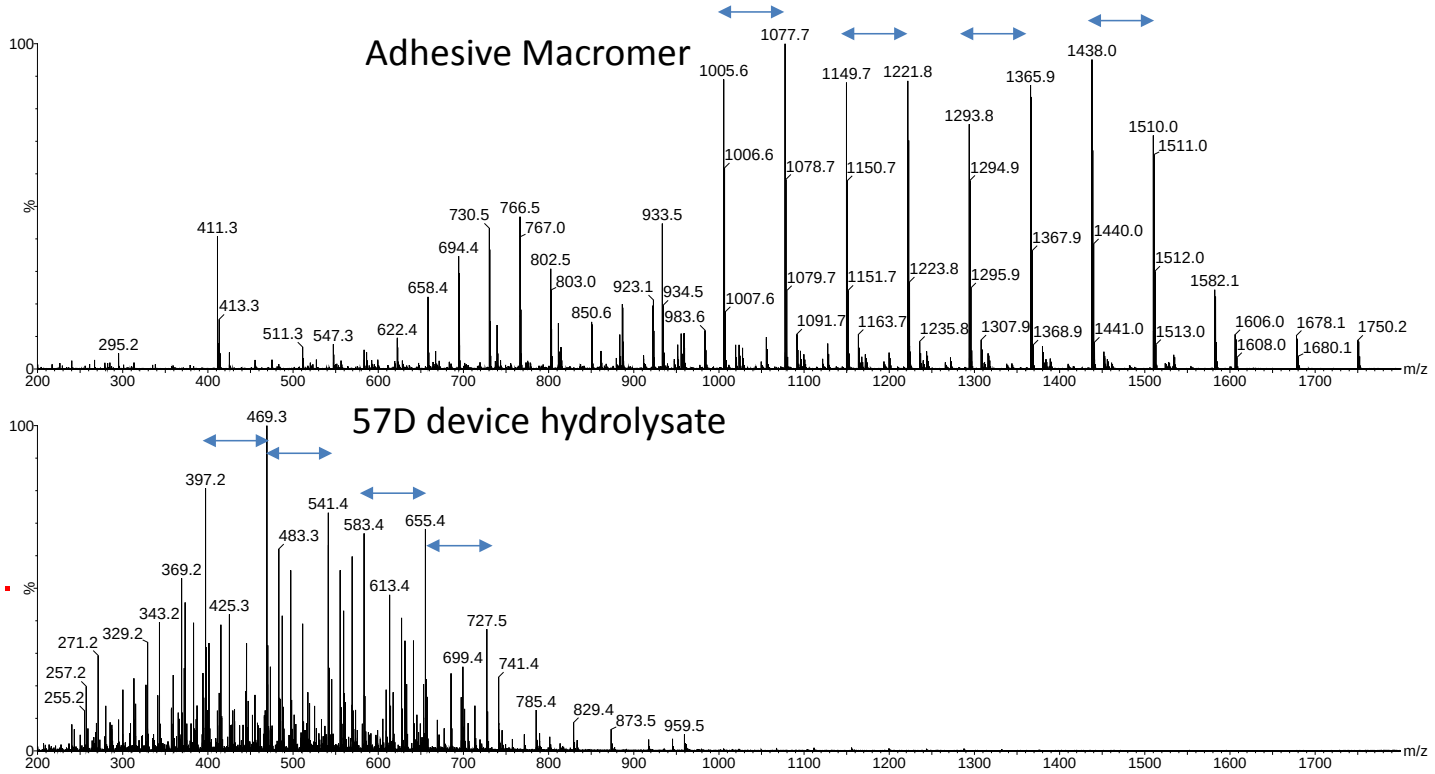


Figure 3. *Comparison of the 57D hydrolysate(bottom, RT region 1.0 to 2.5 min) and adhesive macromer (top, RT region 2.5 to 4.0 min) combined MS traces. Note the 72 m/z peak separation characteristic of the butoxy moiety.*

REFINE

The hydrophilic fraction detected in the medical device hydrolysate was clearly macromer related, but not directly (i.e.,

as a contaminant) since the early eluting hydrolytic fraction peaks were not detected in the macromer standard TIC (Figure 2). Since the hydrolytic study was conducted at an elevated temperature (85°C) for a period of nearly two months, we decided to investigate the kinetic process generating the hydrophilic fraction by subjecting a cured standard adhesive puck (8 mg) to 100°C incubation in deionized (DI) water. After 100 hours incubation, the UPLC MS peaks of the puck standard hydrolysate overlapped with those of the 57D medical device hydrolysate both chromatographically in retention time (Figure 4) and chemically as reflected in equivalent masses of the analytes in Figure 5.

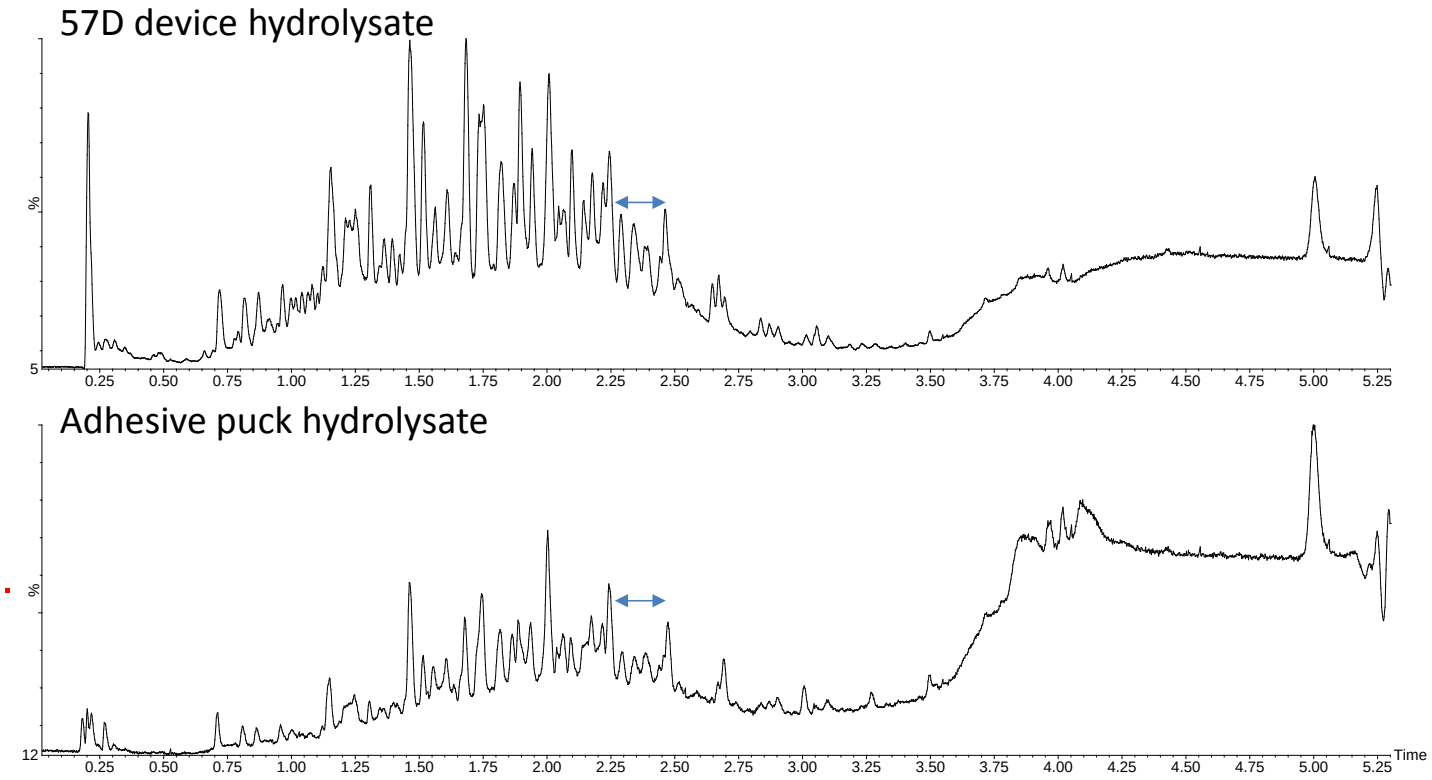


Figure 4. *UPLC-MS chromatograms of the adhesive puck standard hydrolysate (bottom) and the medical device hydrolysate (top). The two chromatogram traces appear nearly identical in the 0.6 to 2.5 min retention time region when overlaid. Combined spectra of the 2.25 to 2.42 regions noted with arrows were extracted for Figure 5 below*

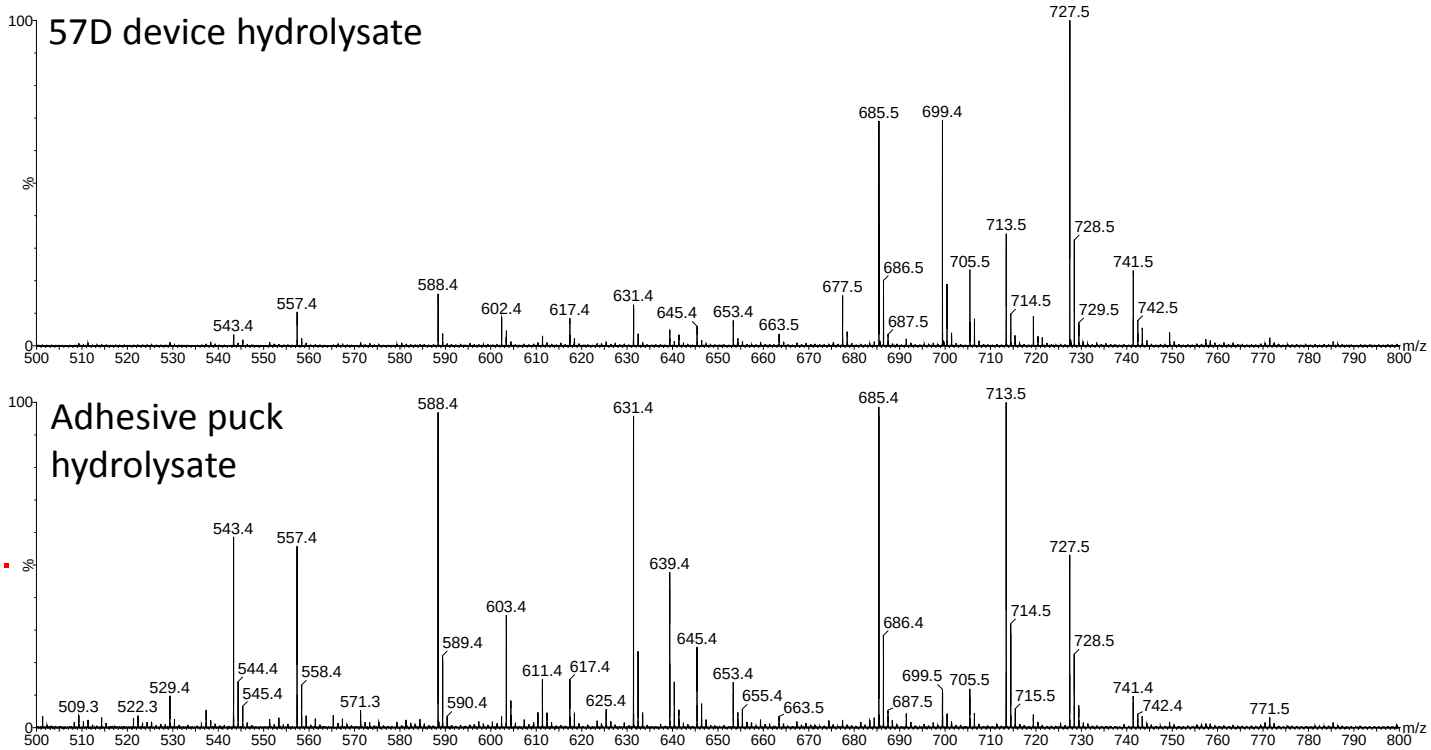


Figure 5. *Extracted MS spectra of the 2.25 to 2.42 min retention time region of the adhesive puck standard hydrolysate (bottom) and the medical device hydrolysate (top). The two MS spectra share a nearly identical MS signature.*

QUANTITATE

We then determined the concentration of the water soluble fraction in the 57D medical device hydrolysate. We prepared a 100 ppm solution of the macromer, determined the average molecular weight of both the macromer and the water soluble fraction (1300, and 550 g/mol, respectively, data not shown). Assuming equivalent MS ionization efficiencies for the macromer signals and water soluble fraction components, the water soluble fraction concentration was estimated at 44 ppm in the 57D medical device hydrolysate solution.

CONCLUSIONS

Early identification and quantitation of leachable hydrolytic products in biomedical device materials may prevent costly complications during clinical studies. Here, using UPLC-UV-qTof MS, we identified a water soluble fraction with minimal UV response in the 57D hydrolysate solution of the finished medical device. Due to the likely polar aliphatic nature of the fraction, and no UV response, we would not have been able to detect it without the MS detector using more common methods such as LC-UV and GC-MS typically used in biomedical device leachables and extractables analysis. We verified that the sole source of the water soluble fraction was the adhesive, and determined the concentration of the water soluble fraction in the base hydrolysate at 44 ppm.

The primary purpose of this study was to evaluate the hydrolytic stability of the adhesive joint. The level of adhesive detected in the hydrolysate was considered a low risk to adhesion and adhesive joint strength for several reasons. The back-calculation of the detected 44 ppm concentration showed that the water soluble fraction constituted only about 1% of the applied adhesive. We also found that the water soluble fraction stopped forming after 170hr of incubation of the acrylic puck standard at 100°C (data not shown), indicating that the water soluble fraction was limited in quantity and must have formed via solubilization or hydrolysis of either a macromer contaminant or incompletely crosslinked adhesive fraction.

Additional work could be done in the future to characterize the structure of molecules present in the water soluble fraction. Better understanding of their source, quantity, and structure may help to control the presence and release of these analytes, either by better control of the adhesive curing process, control of adhesive contaminants with raw material QC, or perhaps through rationally derived process changes.

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