Electronic Supplementary Material (ESI) for Analyst.
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Supporting Information

Raman Mapping of Fentanyl Transdermal Delivery Systems with Off-Label Modifications

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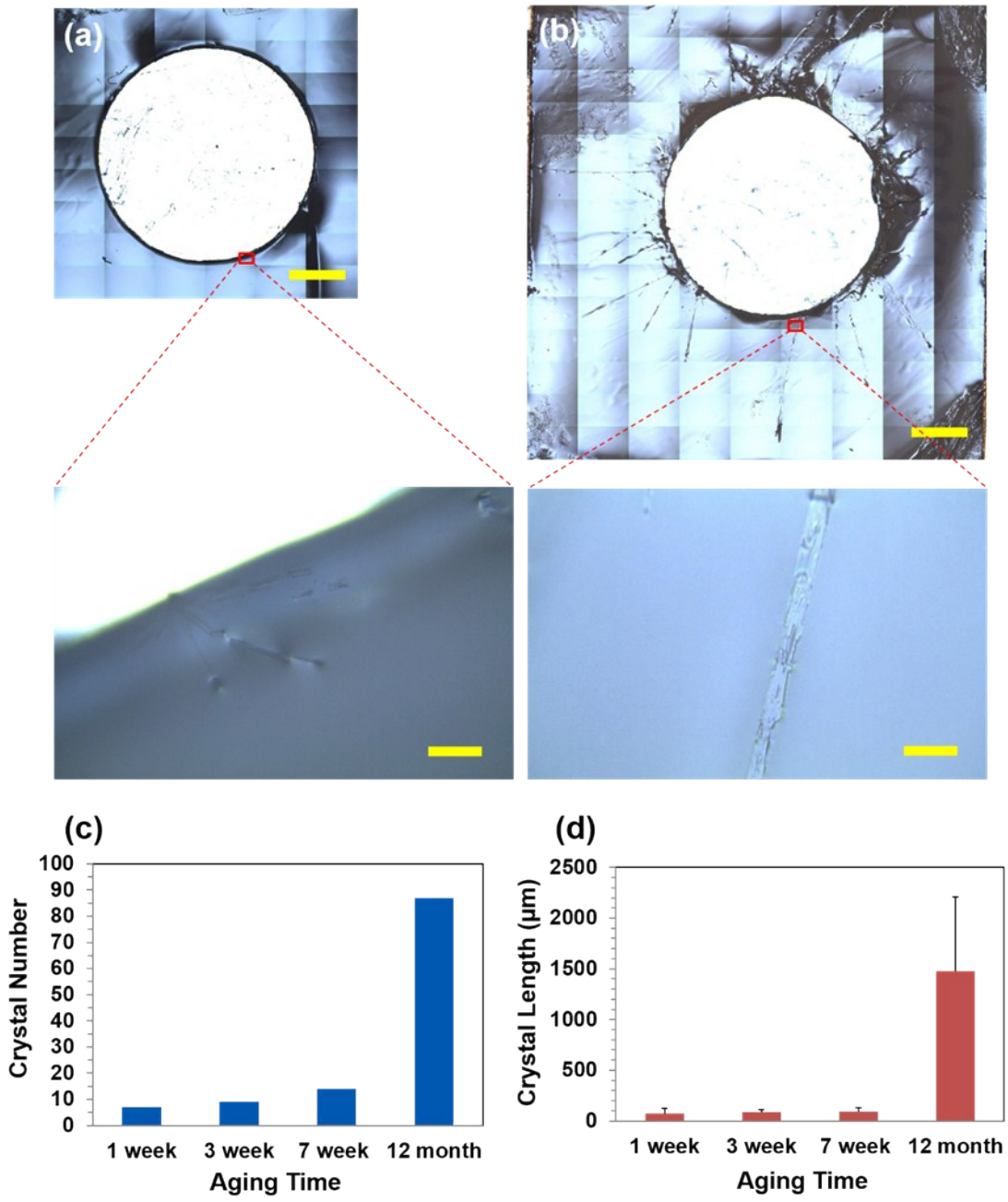
Time lapse study on crystal growth for TDS-4

A time lapse experiment on crystallization was performed on TDS-4. The top image of Figure S1 (a) shows an overall view around the die cutting area of TDS-4 after 1-week aging. The bottom image shows that elongated fentanyl crystals grew from the fresh die cutting edge: $<L>$ = 75.8 μm with length standard deviation δ_L = 47.8 μm; $<W>$ = 2.4 μm with width standard deviation δ_W = 0.6 μm. These observations show that fentanyl crystallization can be detected as early as one week after die cutting. Figure S1 (b) are optical images of TDS-4 after aging over 12 months. The top image shows an overview of the long-elongated fentanyl crystal emanating from the die cutting edge with $<L>$ = 1480.3 μm and length standard deviation δ_L = 728.0 μm. The broken drug-in-adhesive (DIA) surface near the die cutting edge is due to the crystallization of fentanyl changing the viscoelastic properties of the DIA matrix and leading to the blocking or lock-up (i.e., failure of the release liner to cleanly or easily peeling away from the DIA matrix[1]). The bottom figures show the enlarged images of a fentanyl crystal near the die cutting edge. The $<W>$ = 22.6 μm with width standard deviation δ_W = 3.0 μm. Figure S1 (c) and (d) show the effect of aging time on the crystal number and average crystal length grown from the die cutting



edge.

Figure S1 (a) Optical image of TDS-4 sample after aged for 1 week; (b) Optical image of TDS-4 sample after aged for more than 12 months. The scale bars for the top images are 2 mm; The scale bars for the bottom images are 50 μm. (c) Effect of aging time on crystal number; (d) Effect of aging time on crystal length.

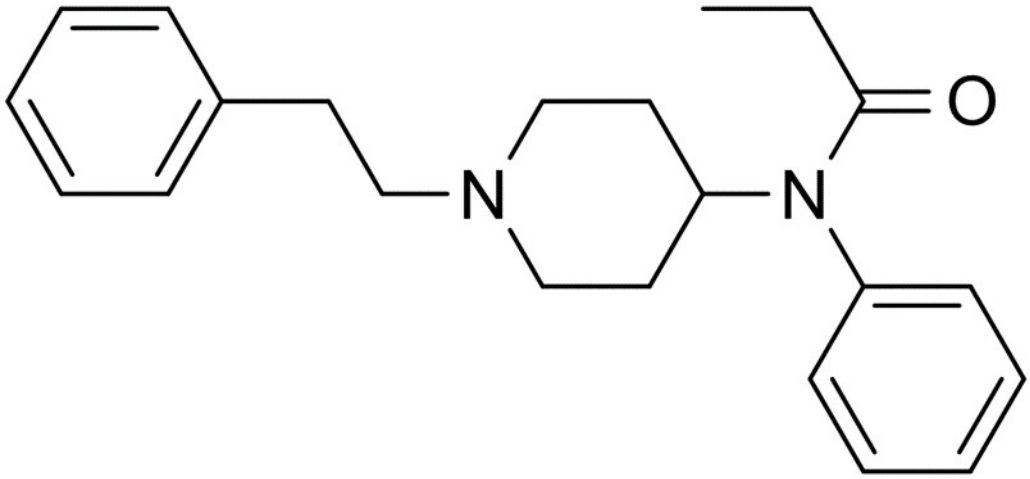


Figure S2. Chemical structure of fentanyl. The breathing mode vibration of the aromatic carbon ring at 1001 cm^{-1} has the largest fentanyl Raman cross section

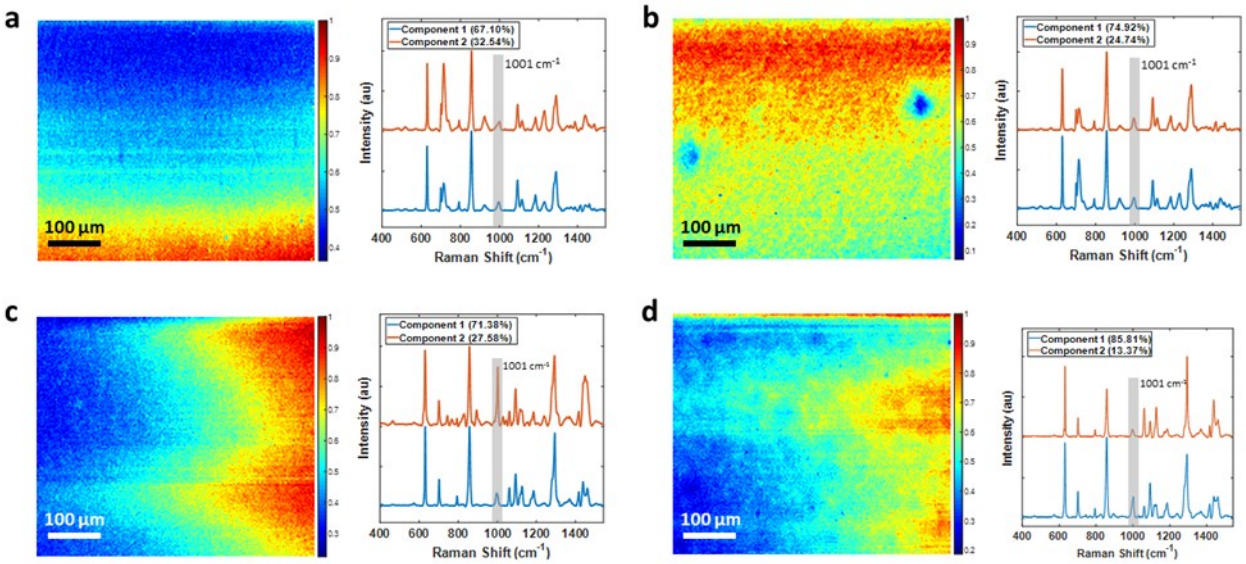


Figure S3. Confocal Raman map of the second components (left) and spectra of the two components (right) of unmodified TDS-1 (a), die-cut and aged TDS-1 (b), unmodified TDS-2 (c) and die-cut and aged TDS-2 (d). Scale bars are 100 µm.

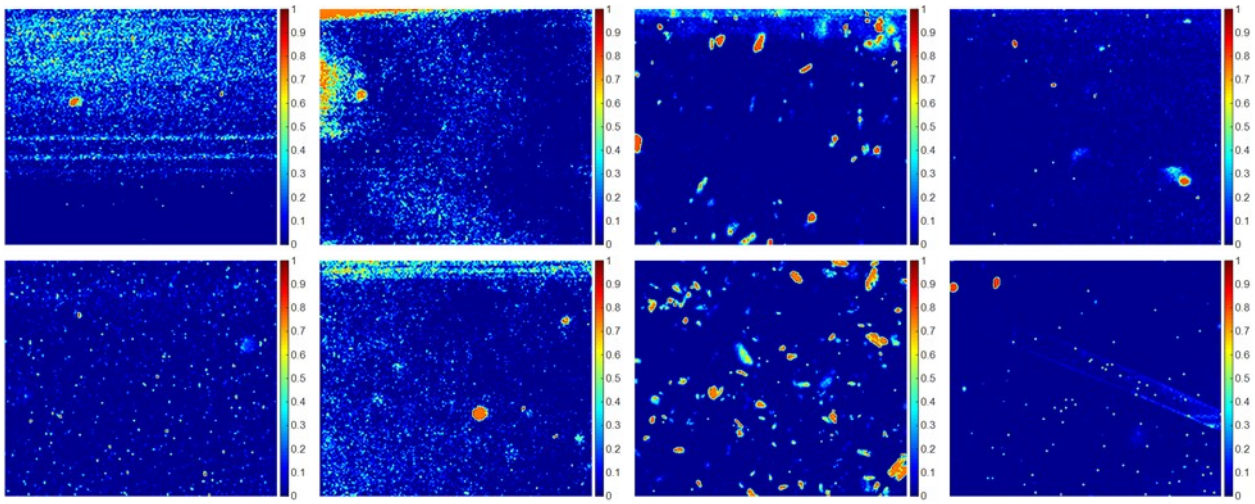


Figure S4. MCR-ALS Residuals of confocal Raman maps of unmodified (top) and die-cut and aged (bottom) TDS-1, TDS-2, TDS-3 and TDS-4 from left to right.

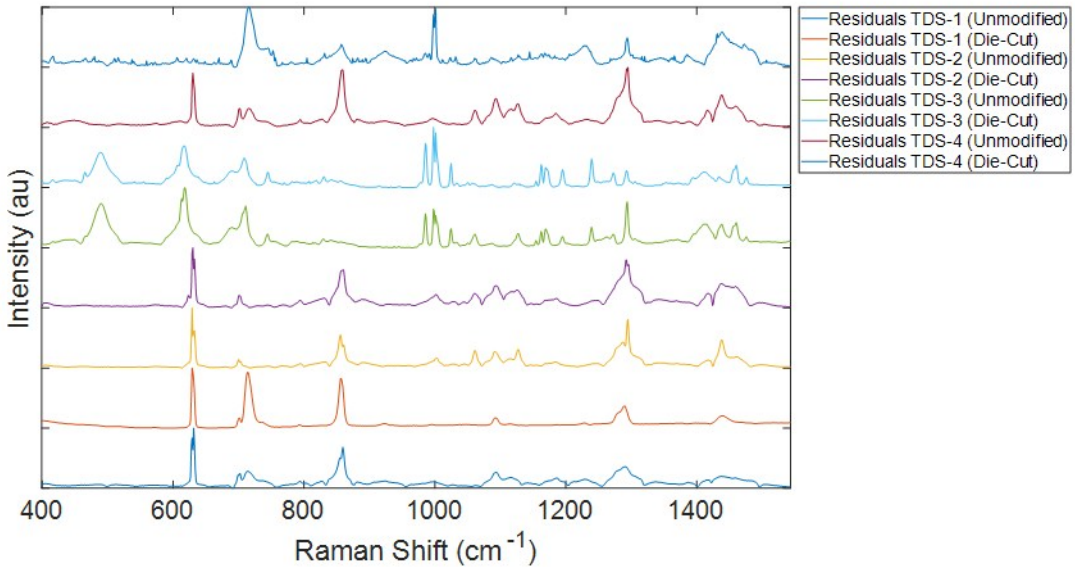


Figure S5. Spectra of the MCR-ALS residuals of all TDS samples.

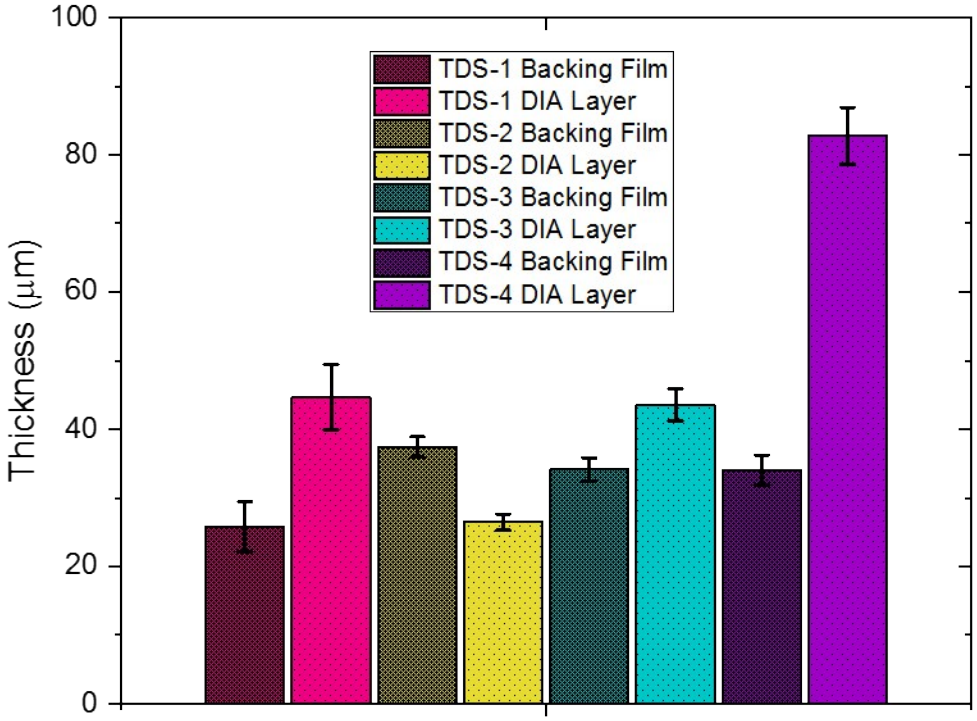


Figure S6. Thickness of the backing films and DIA layers of TDS samples measured using depth profiling via a Keyence high-accuracy digital microscope.

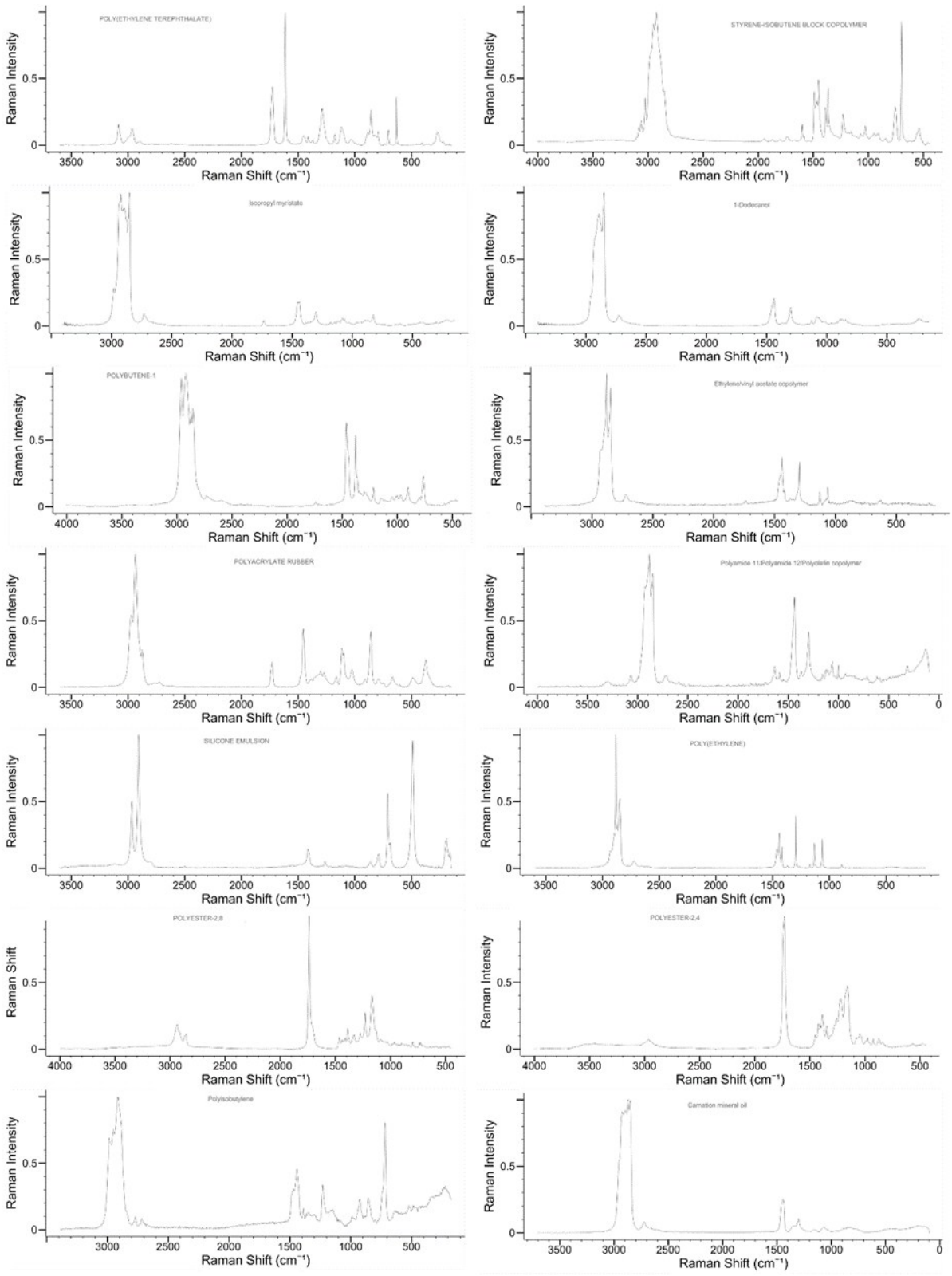


Figure S7. Raman spectra of inactive ingredients found in TDS samples.

References

1. *Transdermal and Topical Drug Delivery Principles and Practice*. John Wiley & Sons, Inc.: Hoboken, New Jersey, 2012.