

ELECTRONIC SUPPORTING INFORMATION

New amino acid propyl ester ibuprofenates from synthesis to use in drug delivery systems

Paula Ossowicz-Rupniewska^{a}, Kaja Szczepkowska^a, Paulina Bednarczyk^a, Małgorzata Nowak^a, Anna Nowak^b, Wiktoria Duchnik^b, Łukasz Kucharski^b, Łukasz Struk^c, Adam Klimowicz^b, and Zbigniew Czech^a*

^a *West Pomeranian University of Technology, Szczecin, Faculty of Chemical Technology and Engineering, Department of Chemical Organic Technology and Polymeric Materials, Piastów Ave. 42, 71-065 Szczecin, Poland*

^b *Pomeranian Medical University in Szczecin, Department of Cosmetic and Pharmaceutical Chemistry, Powstańców Wielkopolskich Ave. 72, 70-111 Szczecin, Poland*

^c *West Pomeranian University of Technology, Szczecin, Faculty of Chemical Technology and Engineering, Department of Organic and Physical Chemistry, Piastów Ave. 42, 71-065 Szczecin, Poland*

*Corresponding author: Tel: +48914494801. E-mail: possowicz@zut.edu.pl;

Number of pages: 28

Number of figures: 46

Number of tables: 2

Table of Contents

Compounds - [AAOPr][IBU]

The NMR spectra of [AAOPr][IBU]	S2
The ATR-FTIR spectra of [AAOPr][IBU]	S7
The TG curves of [AAOPr][IBU]	S9
The DSC curves of [AAOPr][IBU]	S11
X-ray diffraction (XRD) patterns of [AAOPr][IBU]	S13
Skin permeation results	S15

Transdermal patches

The ATR-FTIR spectra of patches	S18
The TG curves of patches	S21
The DSC curves of patches	S24
Skin permeation results	S27

COMPOUNDS - [AAOPr][IBU]

The NMR spectra of [AAOPr][IBU]

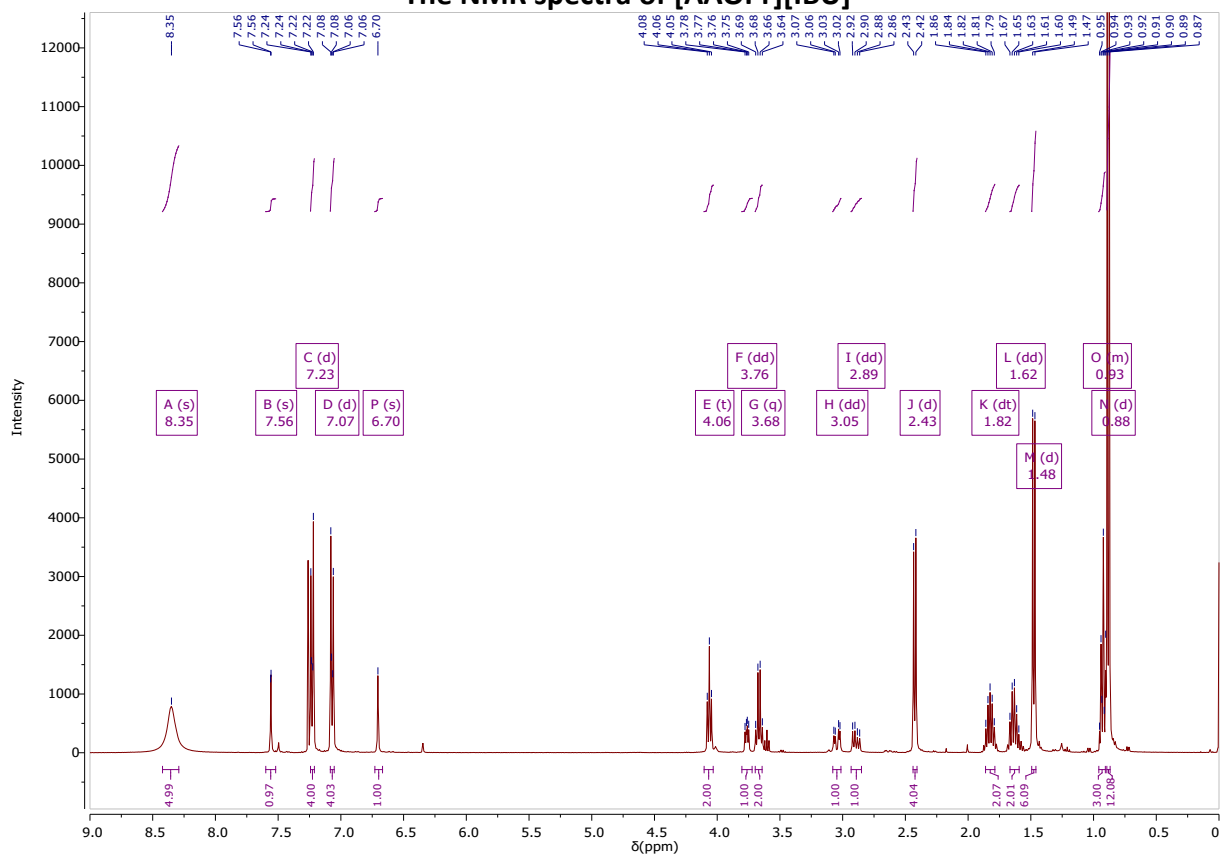


Figure S1. ¹H NMR spectrum of L-histidine propyl ester bis(ibuprofenate).

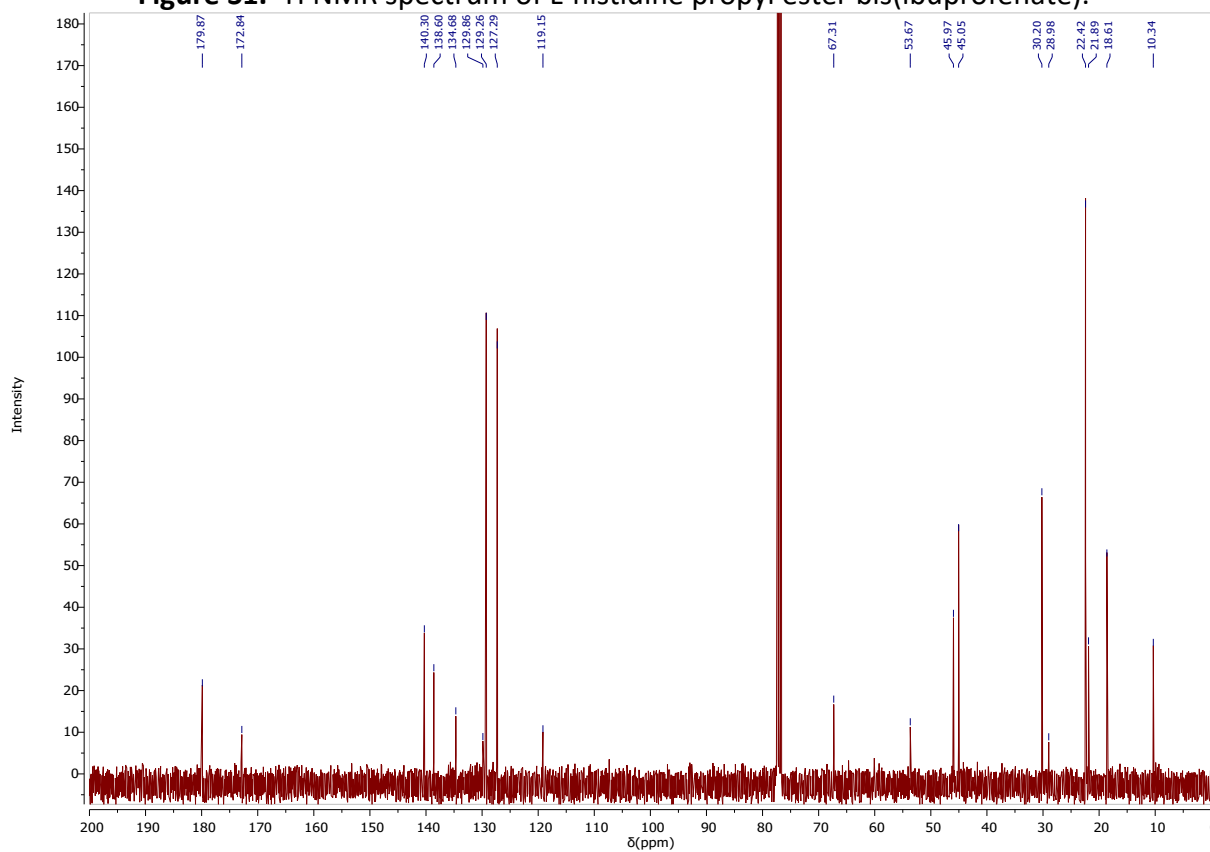


Figure S2. ¹³C NMR spectrum of L-histidine propyl ester bis(ibuprofenate).

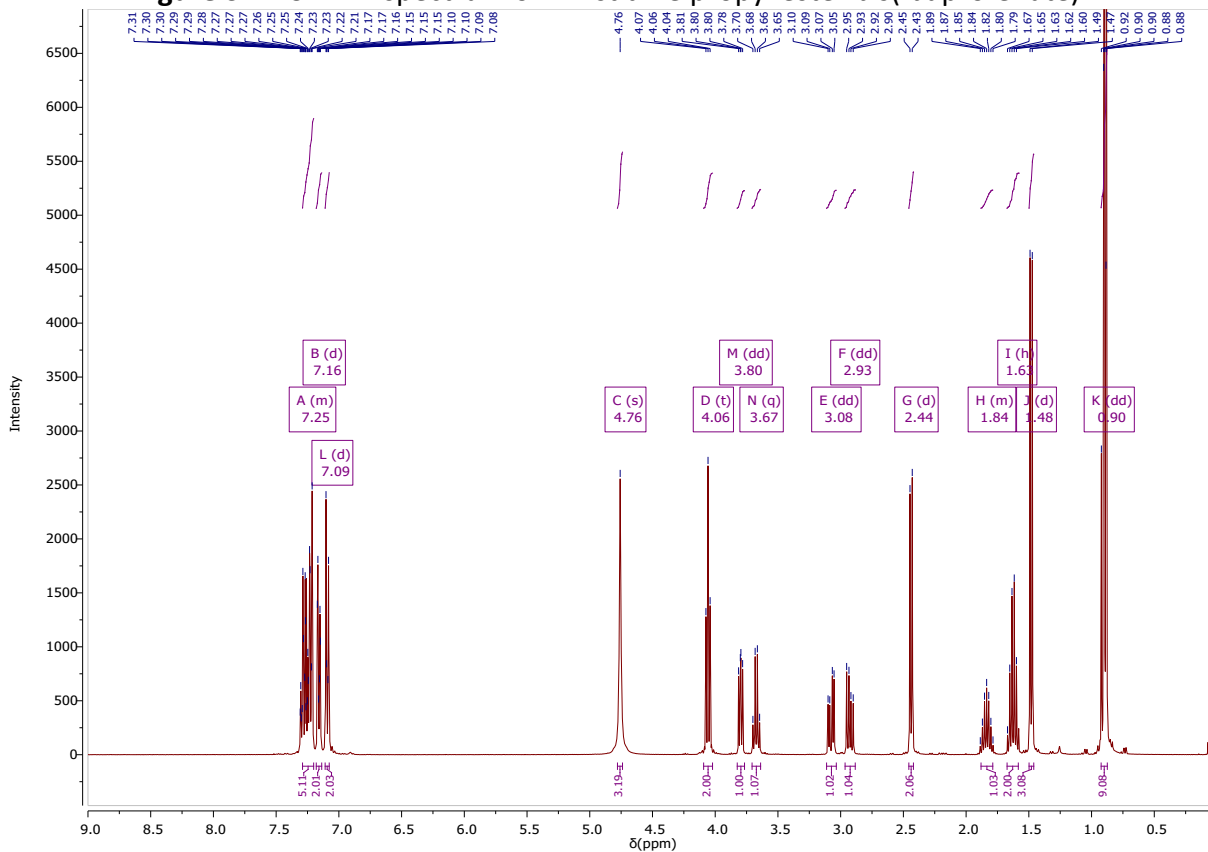


Figure S3. ¹H NMR spectrum of L-phenylalanine propyl ester ibuprofenate.

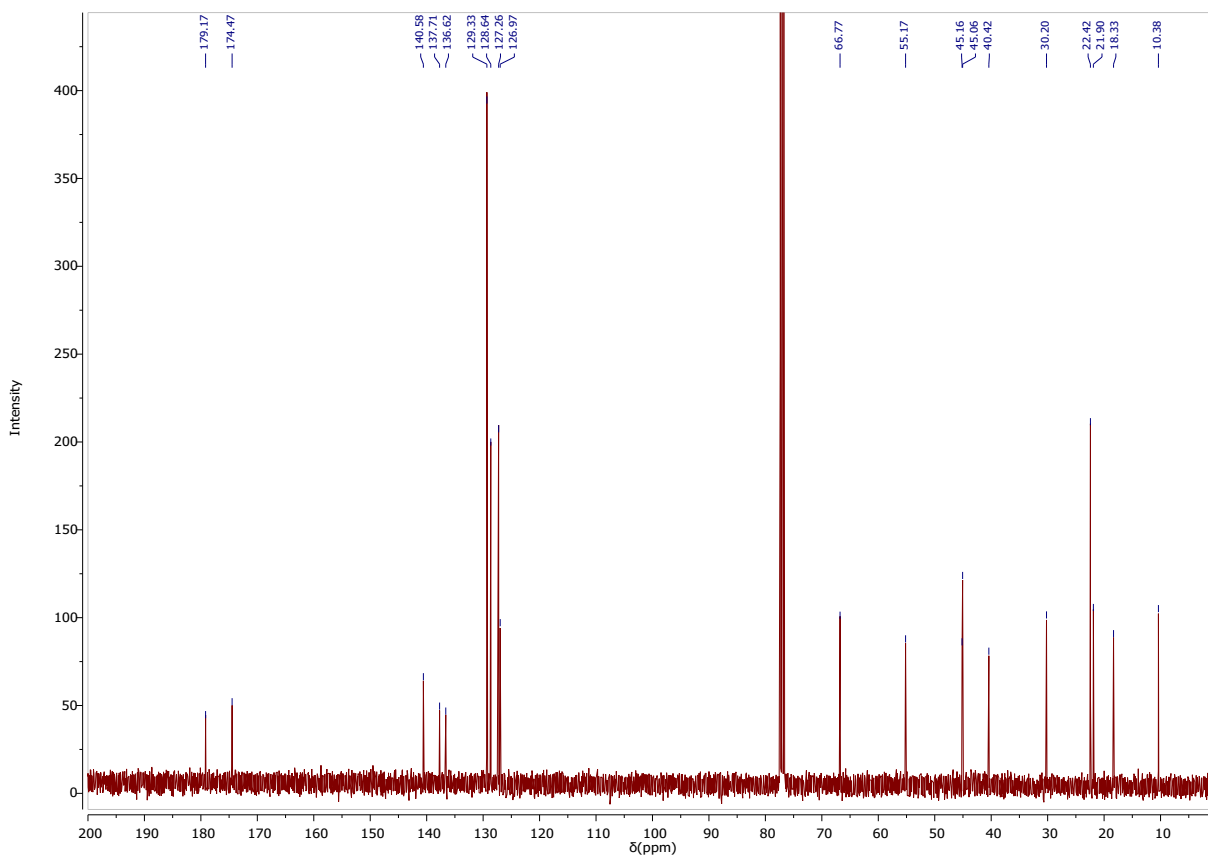


Figure S4. ¹³C NMR spectrum of L-phenylalanine propyl ester ibuprofenate.

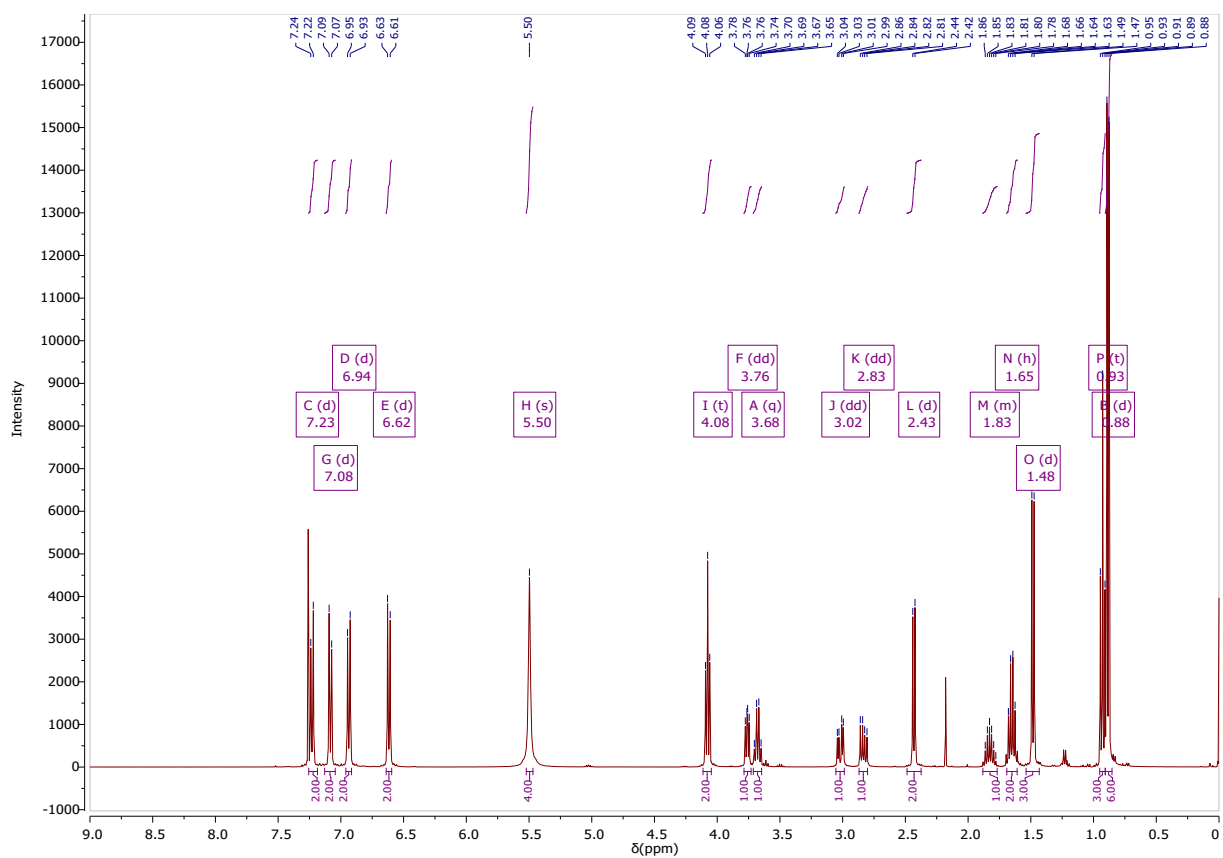


Figure S5. ¹H NMR spectrum of L-tyrosine propyl ester ibuprofenate.

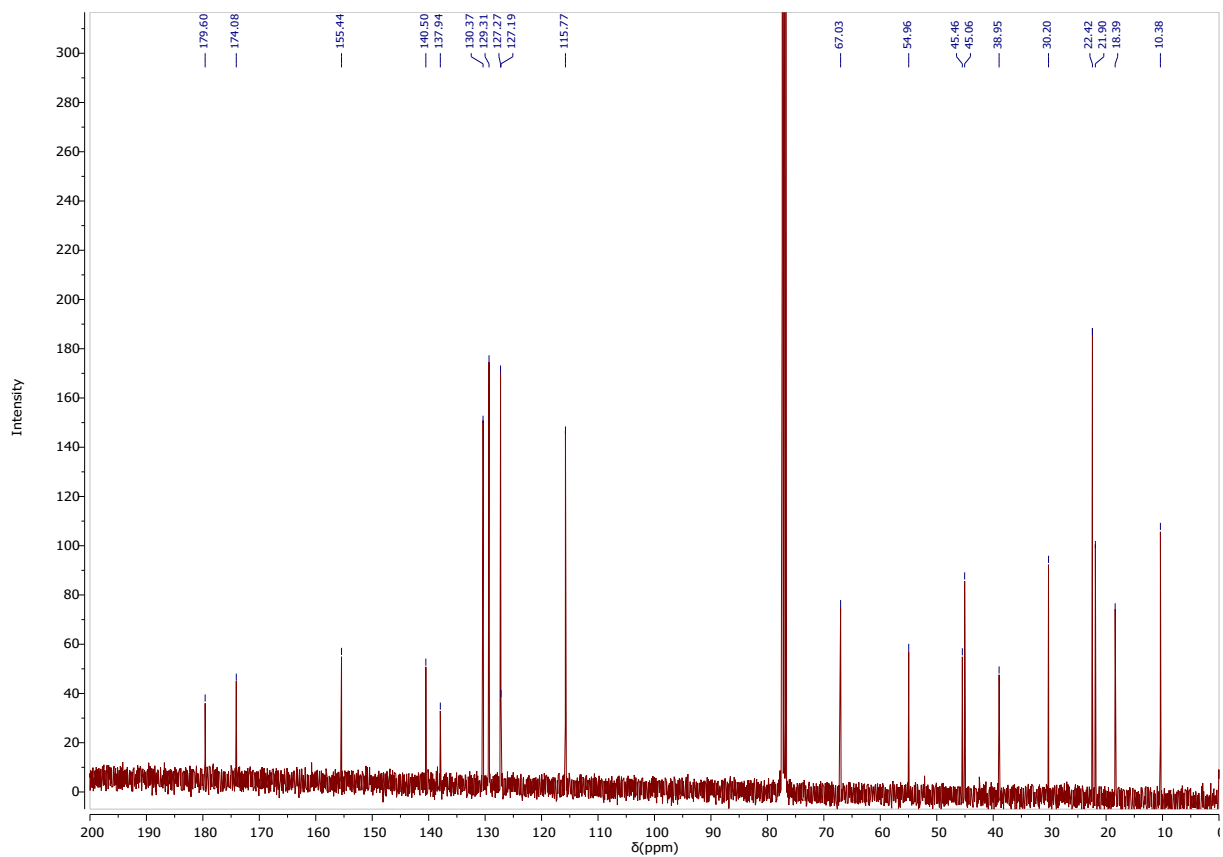


Figure S6. ¹³C NMR spectrum of L-tyrosine propyl ester ibuprofenate.

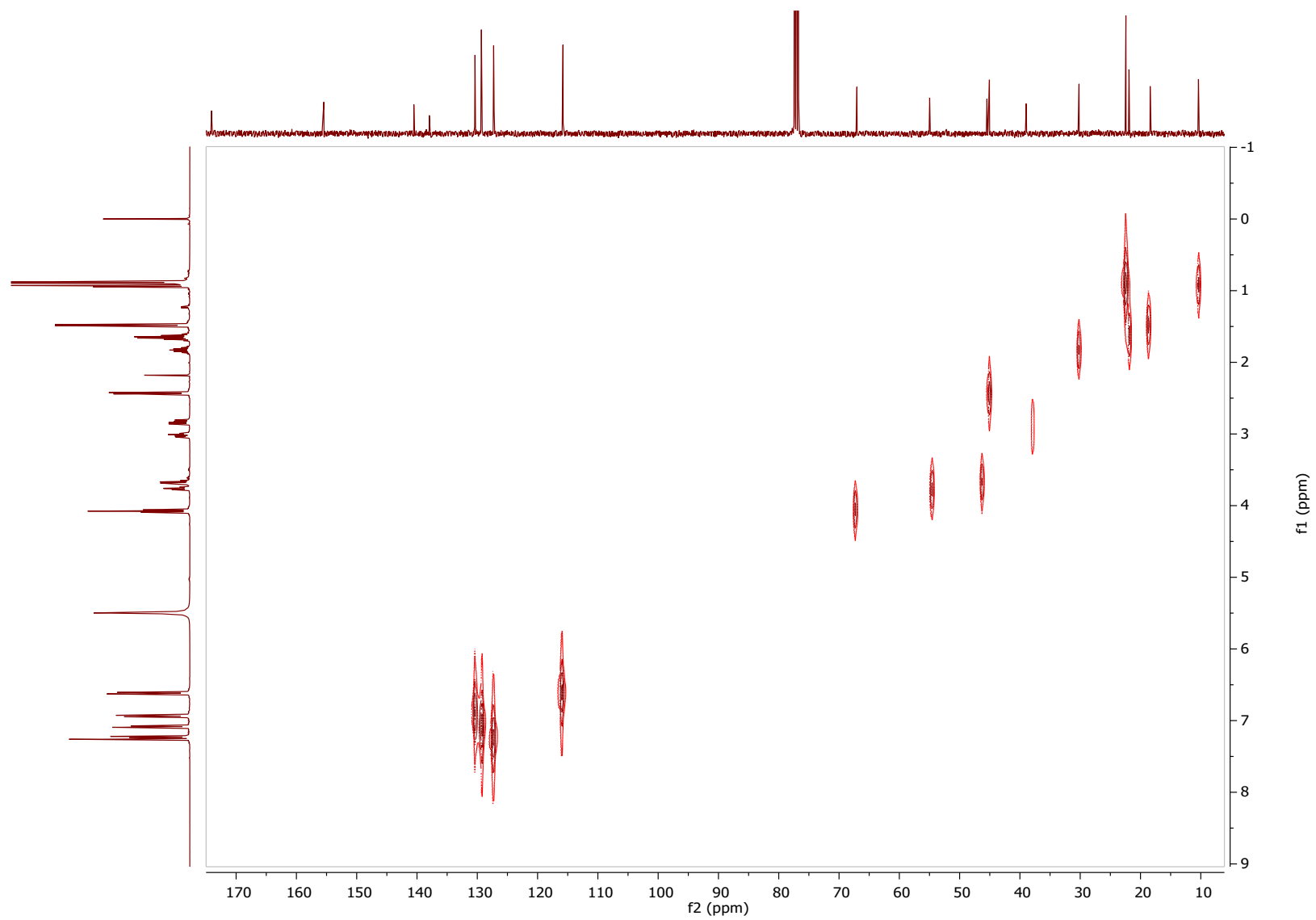


Figure S7. ^1H - ^{13}C COSY NMR spectrum of L-tyrosine propyl ester ibuprofenate.

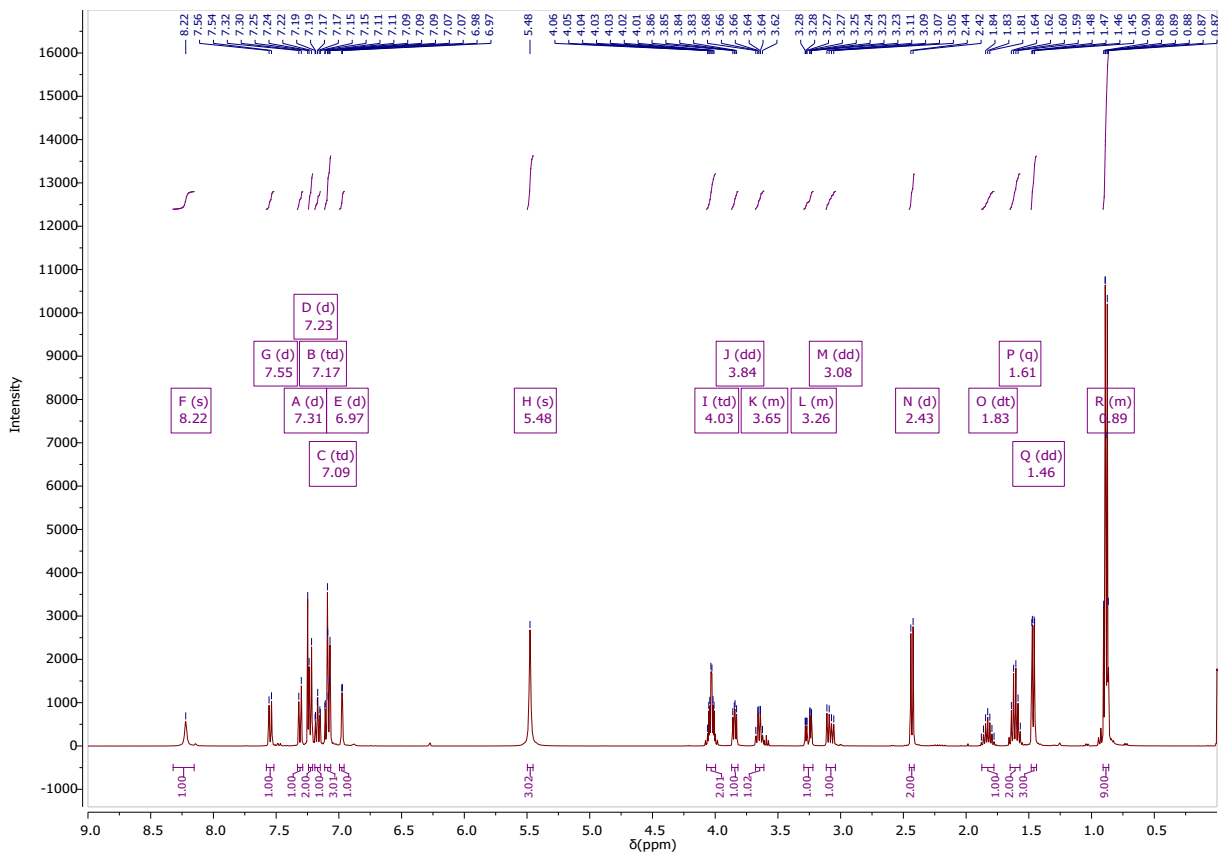


Figure S8. ¹H NMR spectrum of L-tryptophane propyl ester ibuprofenate.

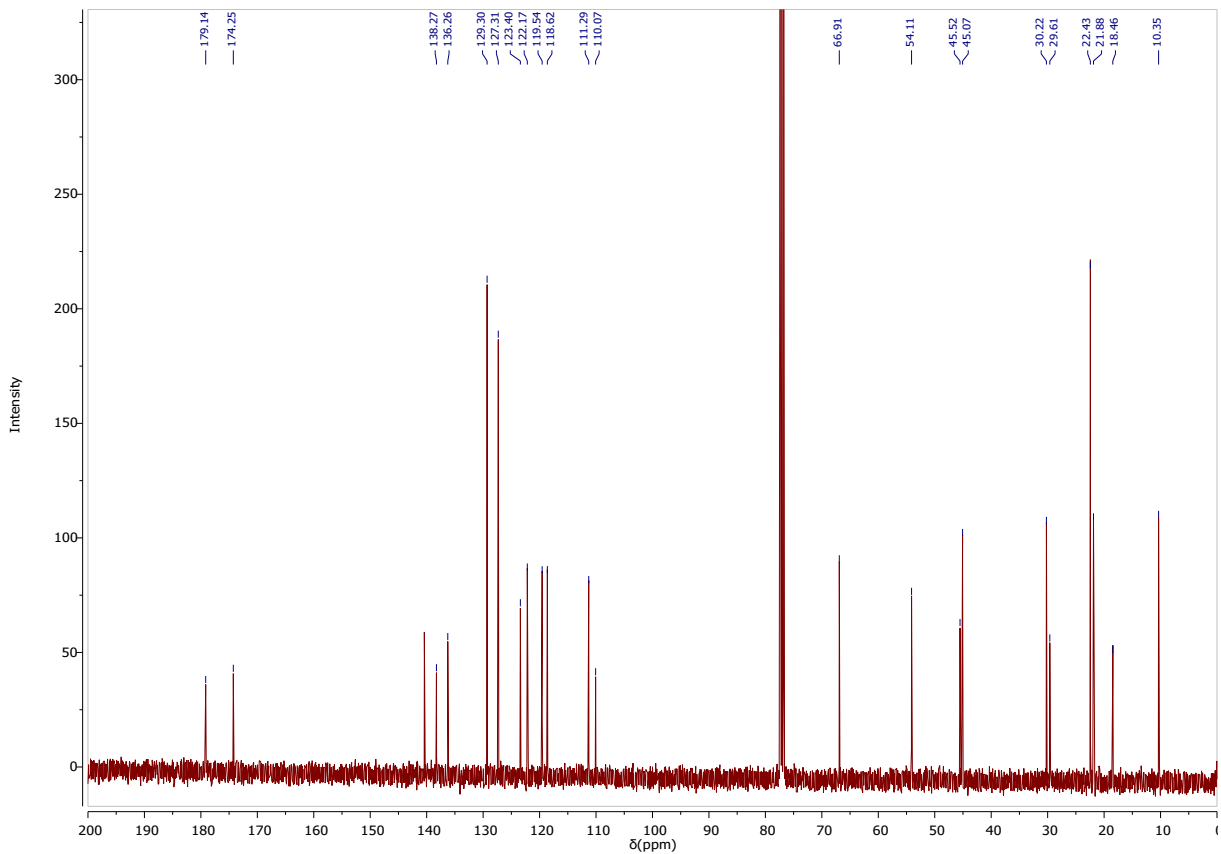


Figure S9. ¹³C NMR spectrum of L-tryptophane propyl ester ibuprofenate.

The ATR-FTIR spectra of [AAOiPr][IBU]

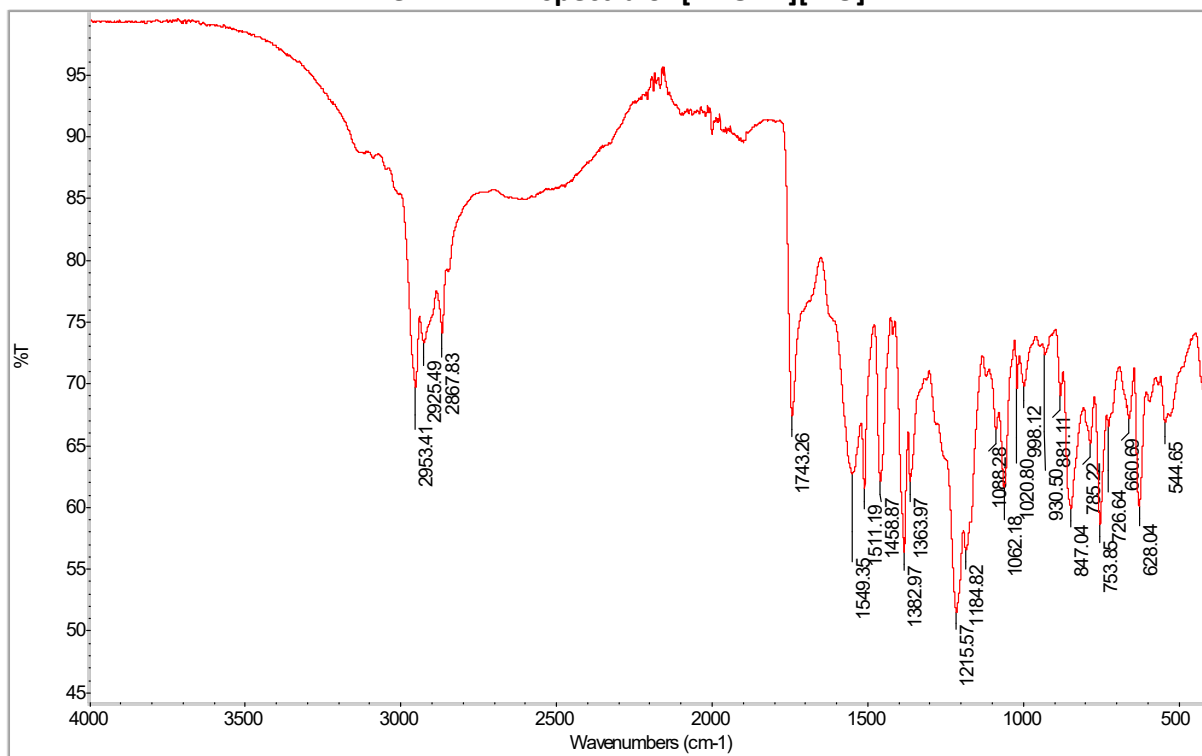


Figure S10. FTIR spectrum of L-histidine propyl ester bis(ibuprofenate).

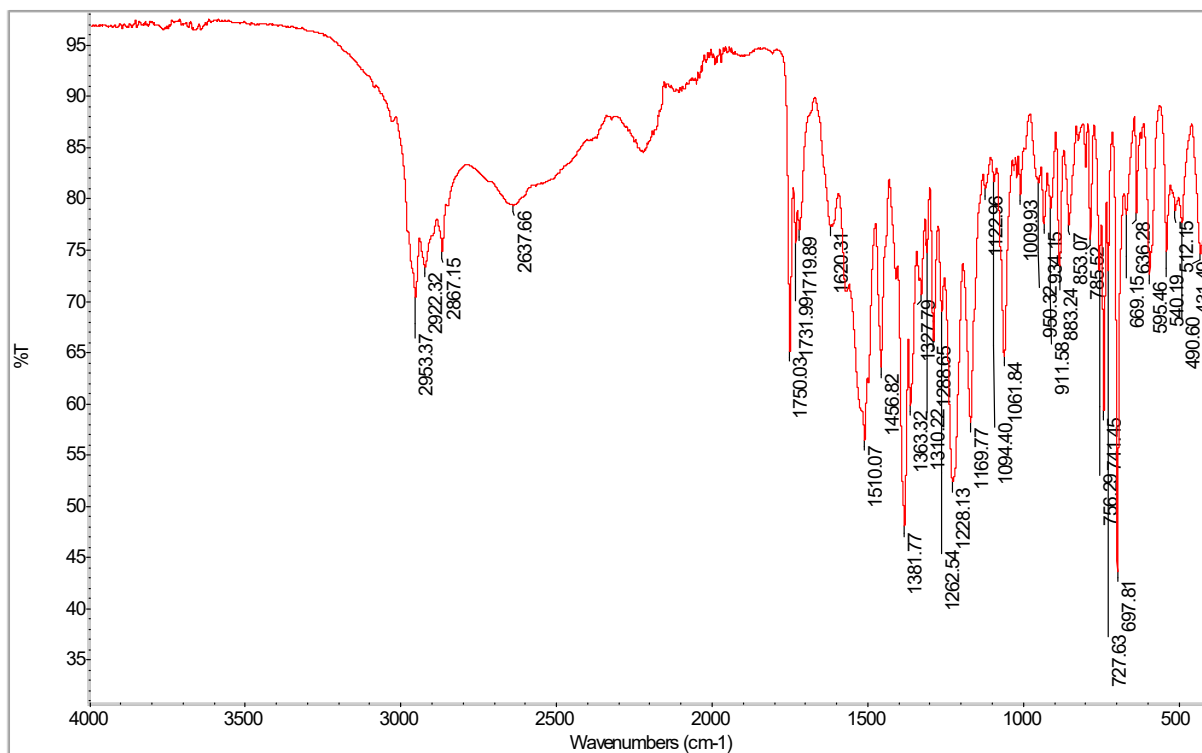


Figure S11. FTIR spectrum of L-phenylalanine propyl ester ibuprofenate.

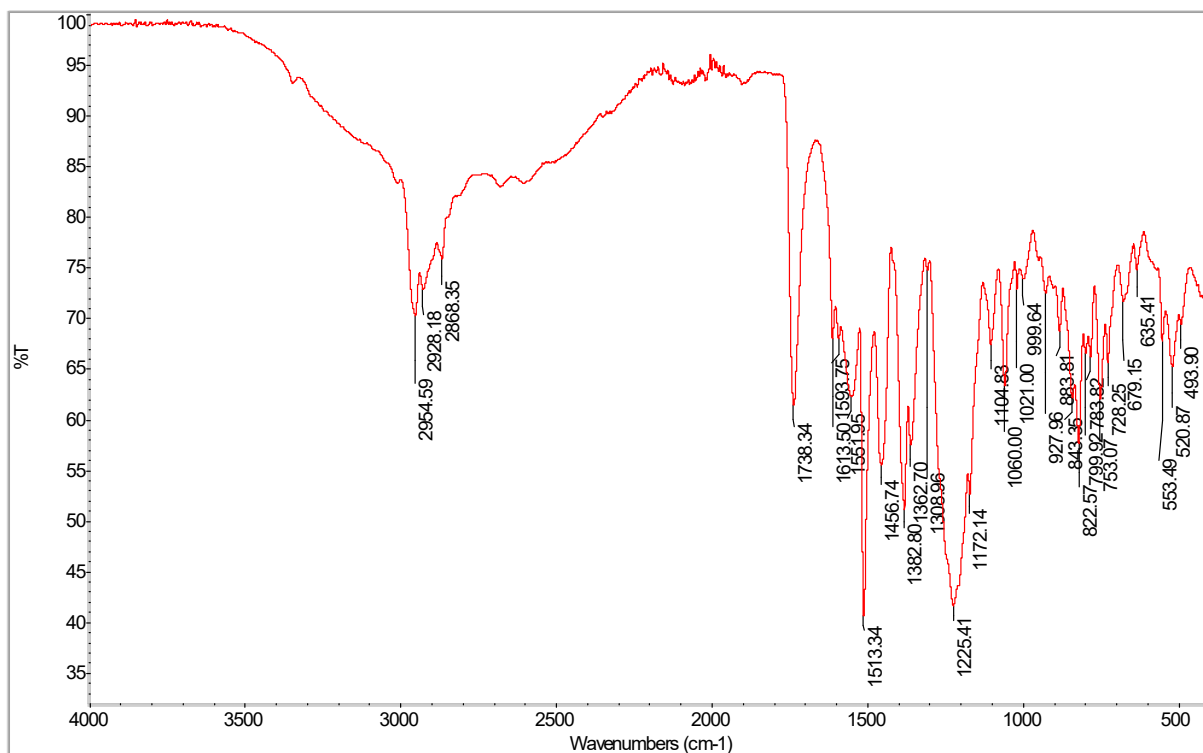


Figure S12. FTIR spectrum of L-tyrosine propyl ester ibuprofenate.

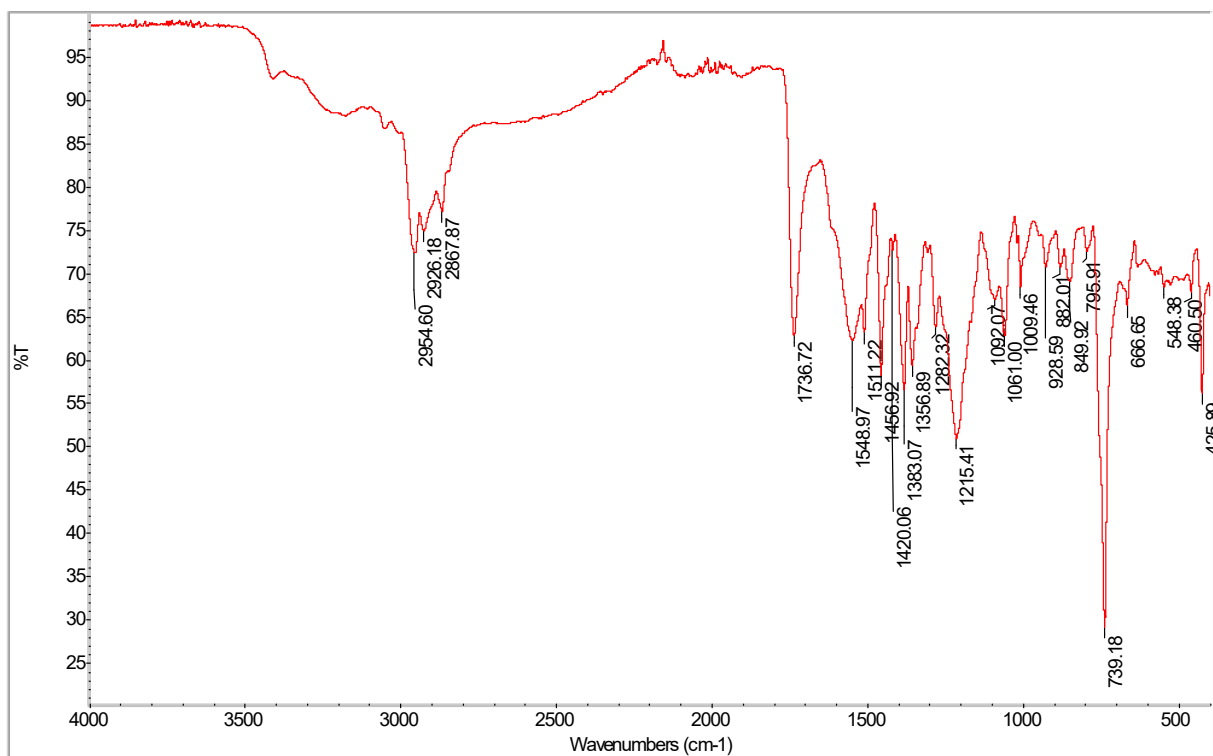


Figure S13. FTIR spectrum of L-tryptophane propyl ester ibuprofenate.

The TG curves of [AAOPr][IBU]

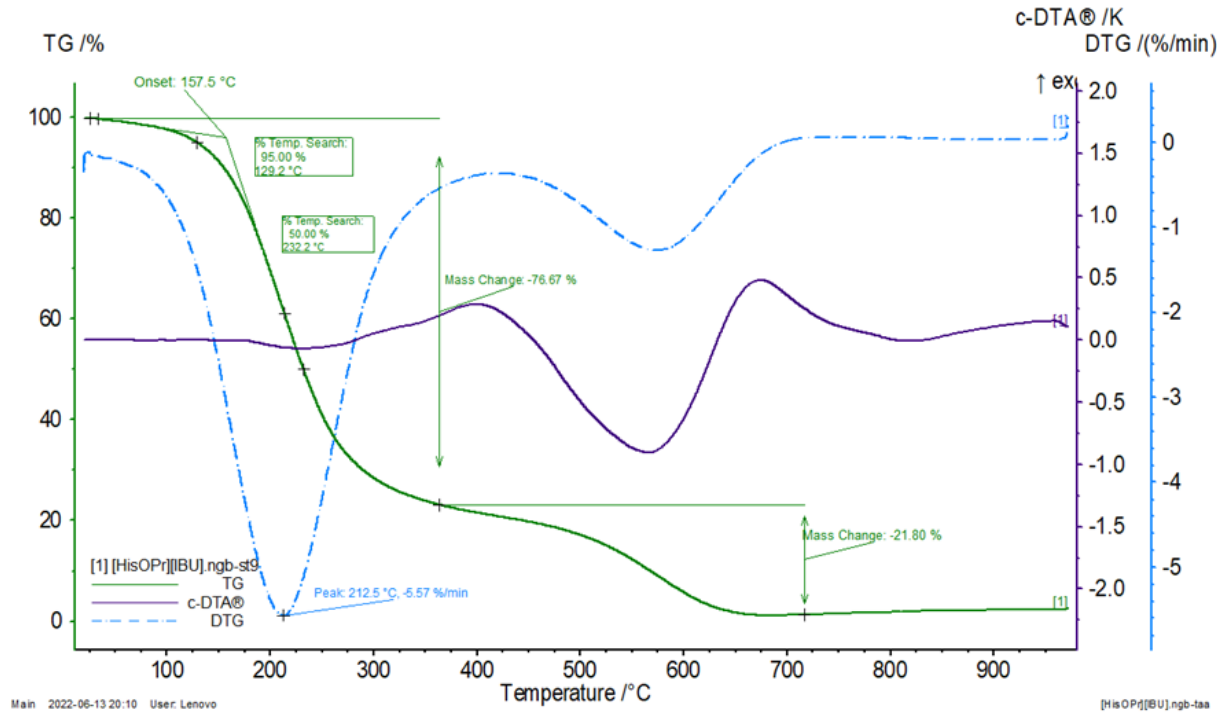


Figure S14. The TG, DTG, and c-DTA curves of L-histidine propyl ester bis(ibuprofenate).

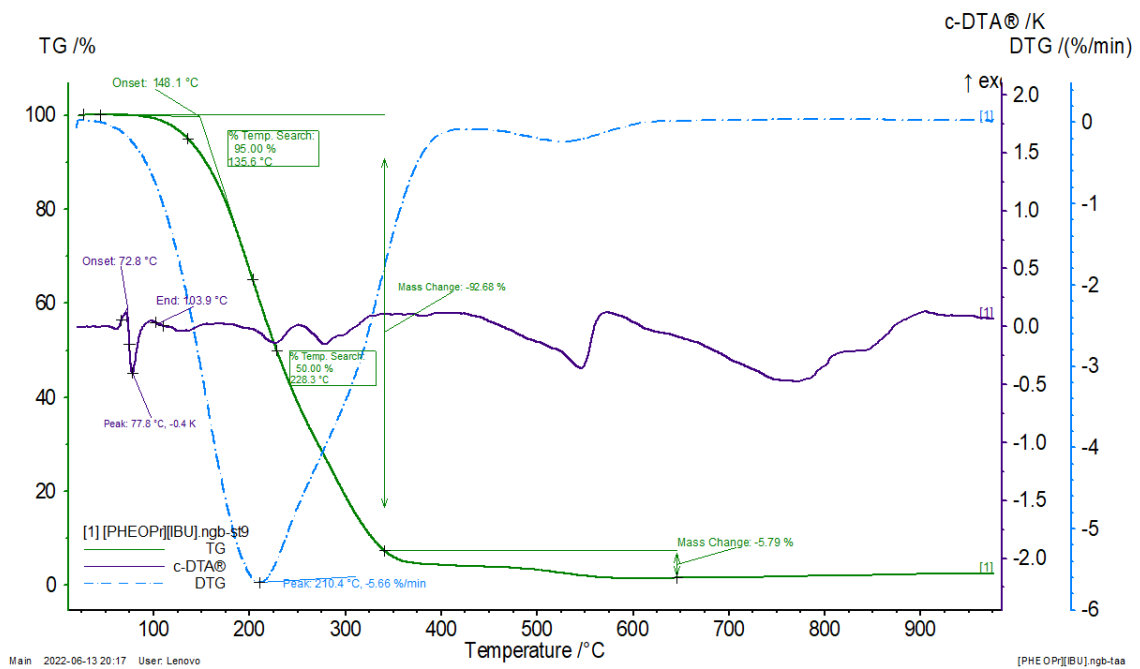


Figure S15. The TG, DTG, and c-DTA curves of L-phenylalanine propyl ester ibuprofenate.

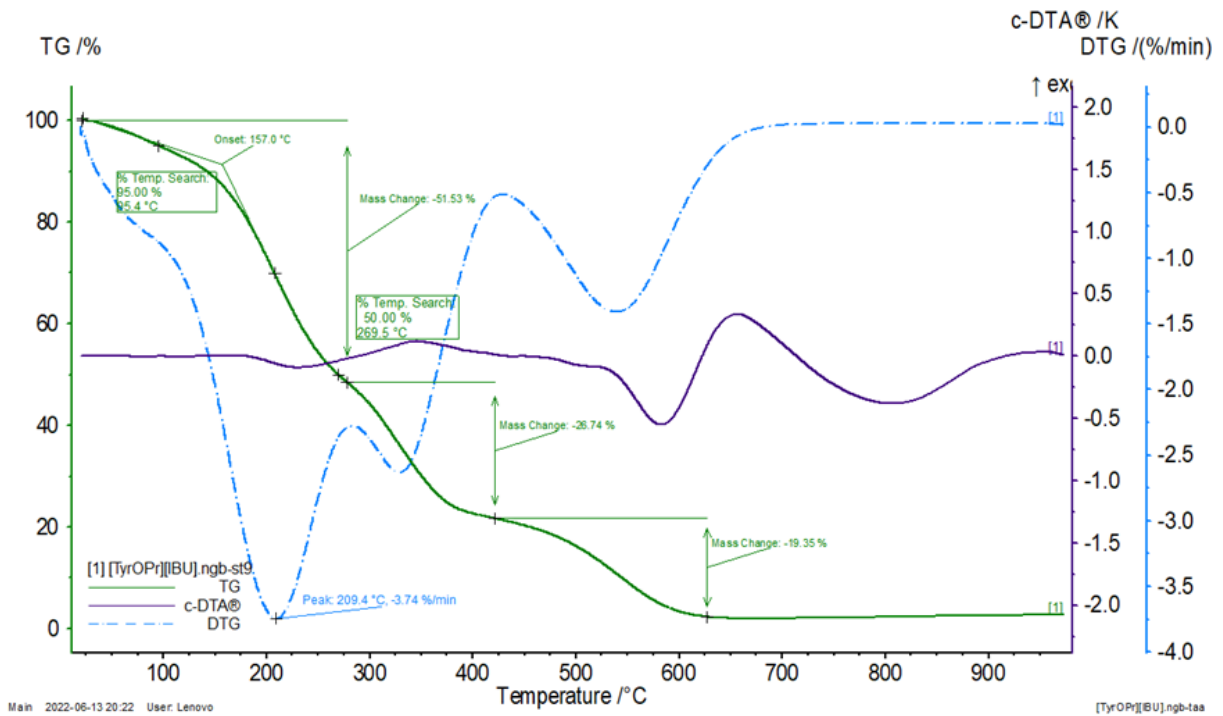


Figure S16. The TG, DTG, and c-DTA curves of L-tyrosine propyl ester ibuprofenate.

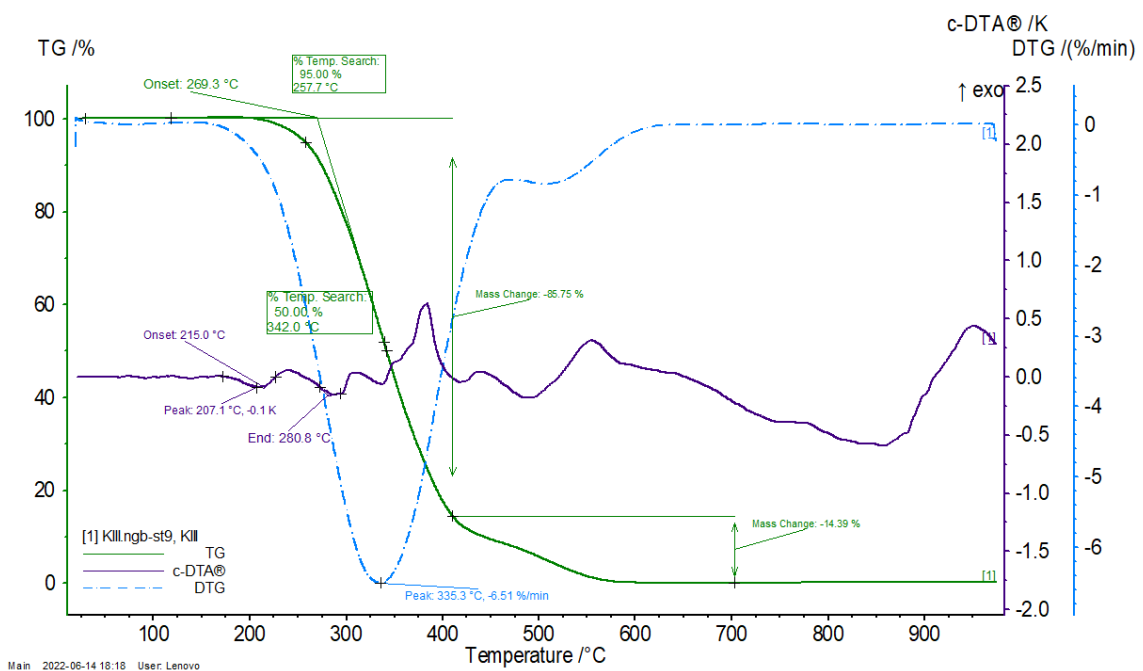


Figure S17. The TG, DTG, and c-DTA curves of L-tryptophan propyl ester ibuprofenate.

The DSC curves of [AAOPr][IBU]

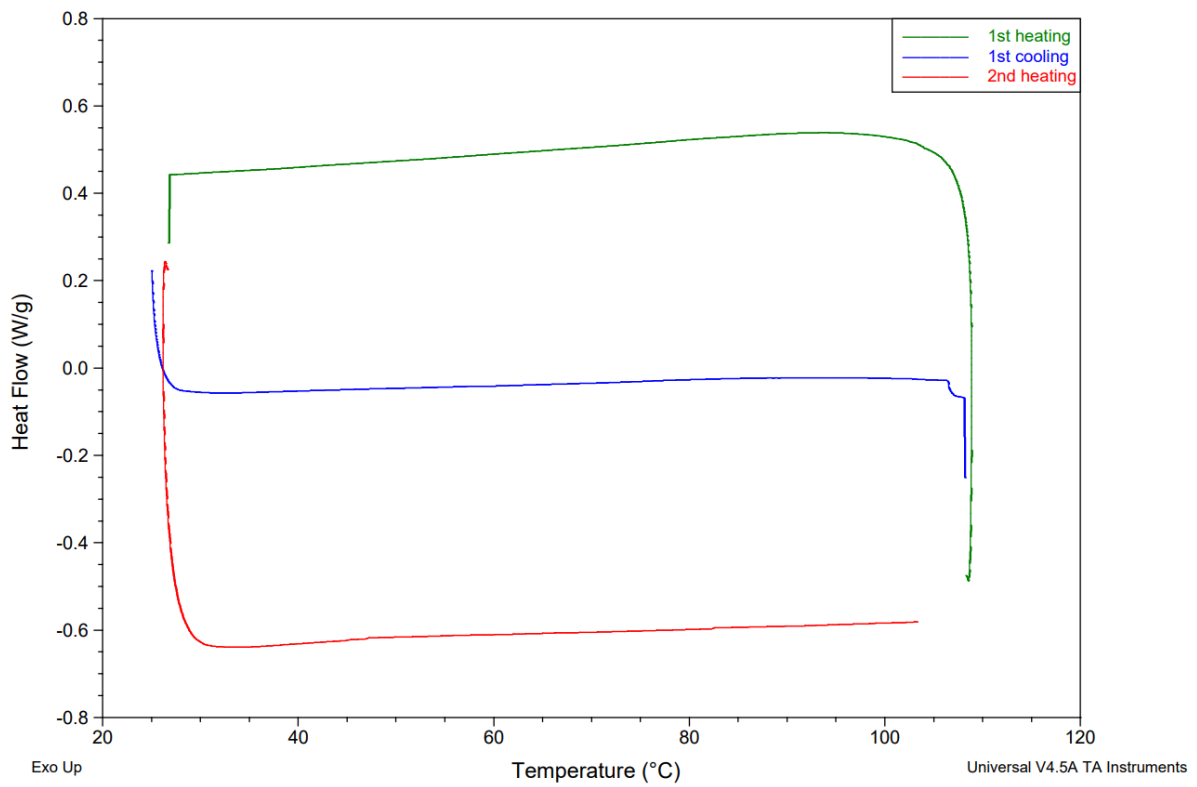


Figure S18. The DSC curves of L-histidine propyl ester bis(ibuprofenate).

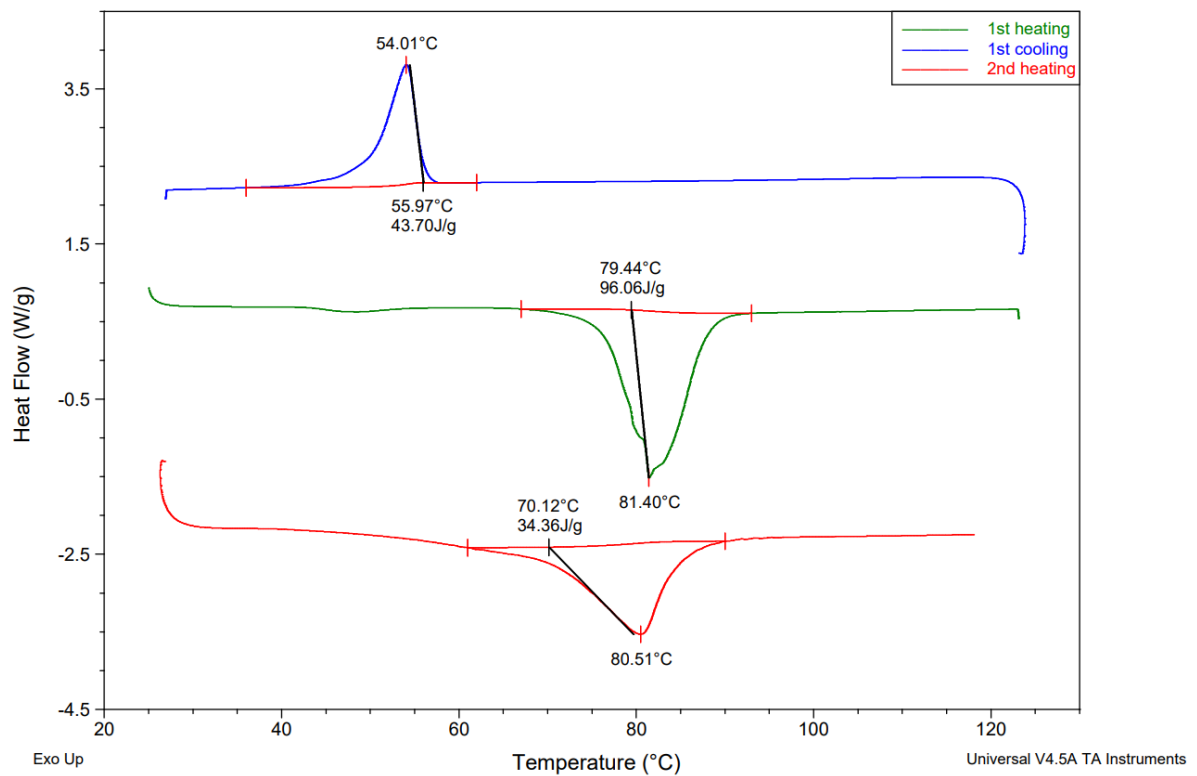


Figure S19. The DSC curves of L-phenylalanine propyl ester ibuprofenate.

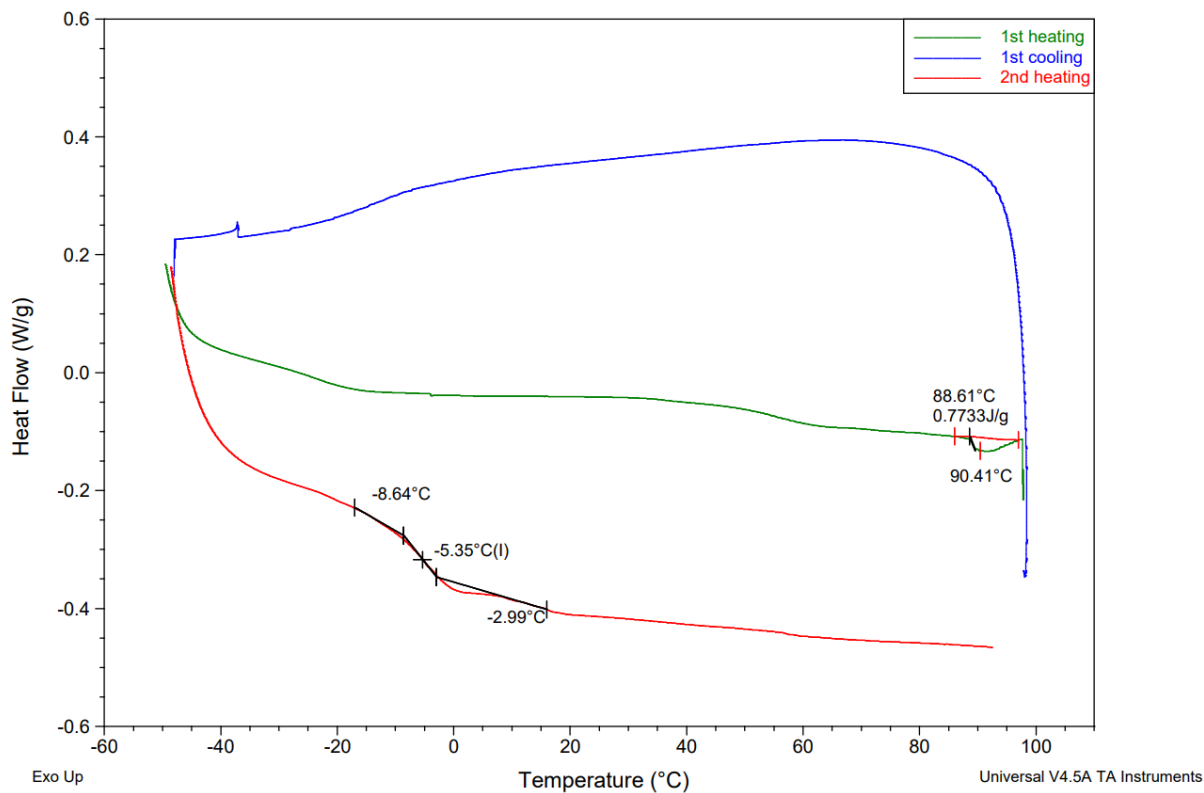


Figure S20. The DSC curves of L-tyrosine propyl ester ibuprofenate.

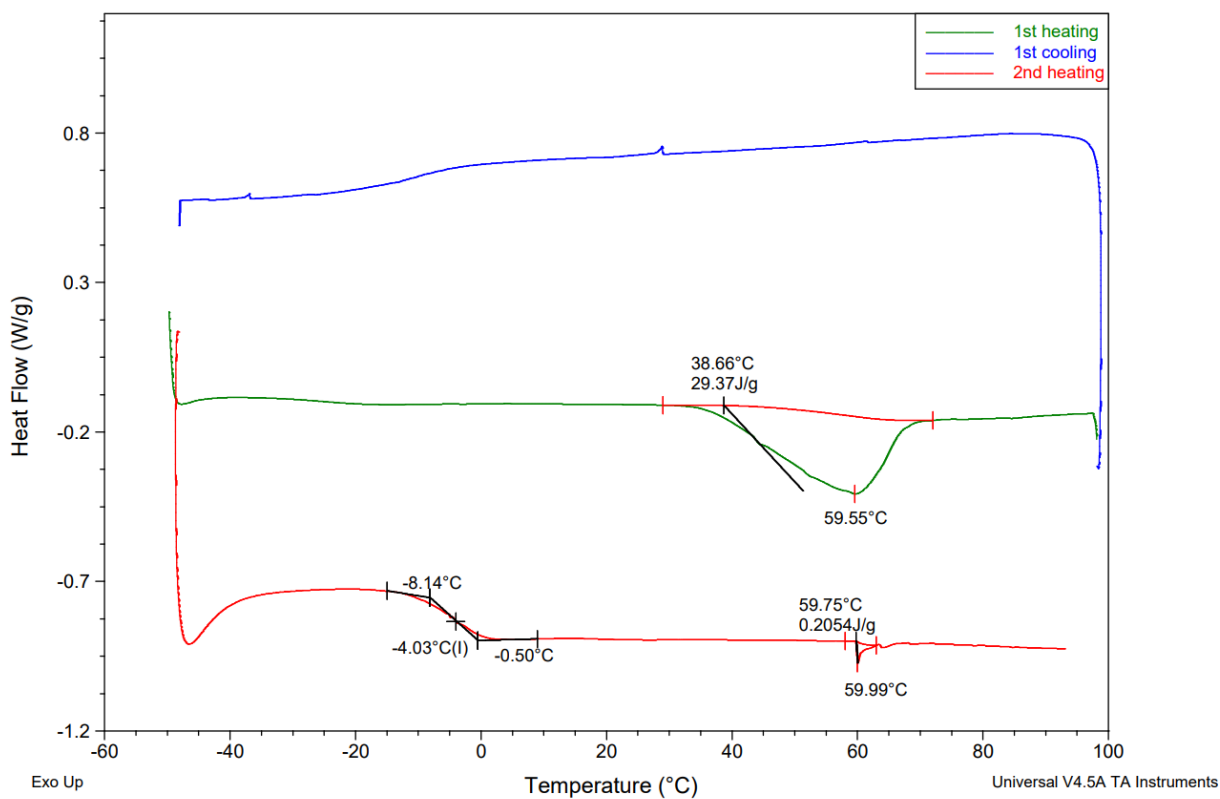


Figure S21. The DSC curves of L-tryptophane propyl ester ibuprofenate.

X-ray diffraction (XRD) patterns of [AAOPr][IBU]

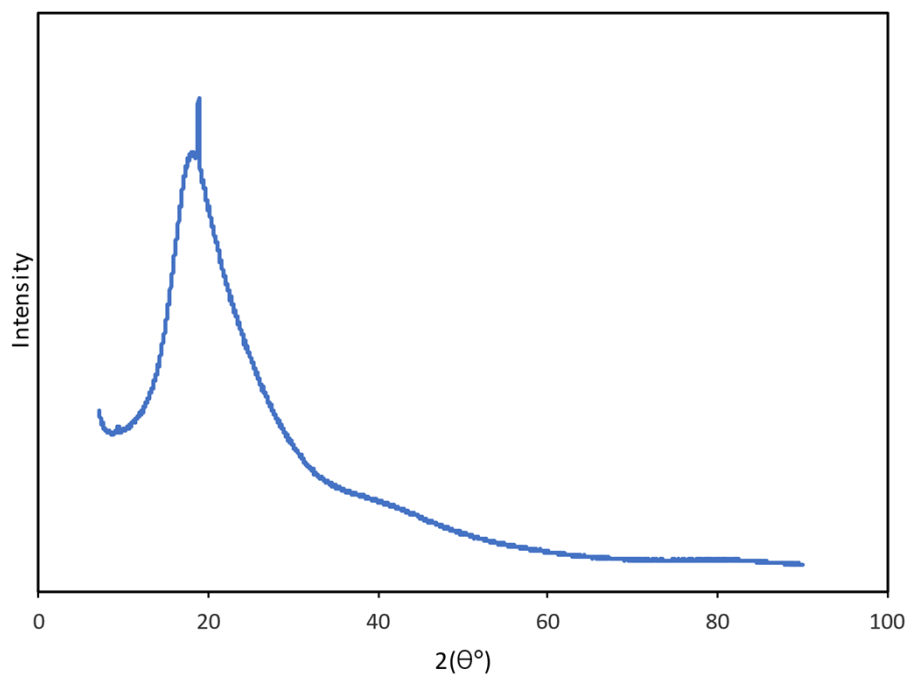


Figure S22. XRD pattern of L-histidine propyl ester bis(ibuprofenate).

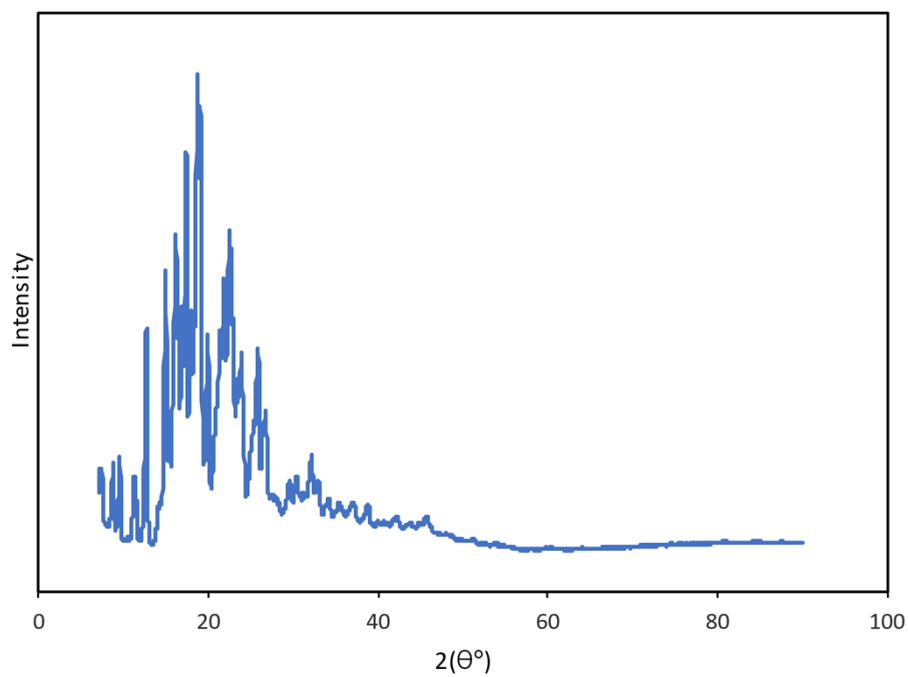


Figure S23. XRD pattern of L-phenylalanine propyl ester ibuprofenate.

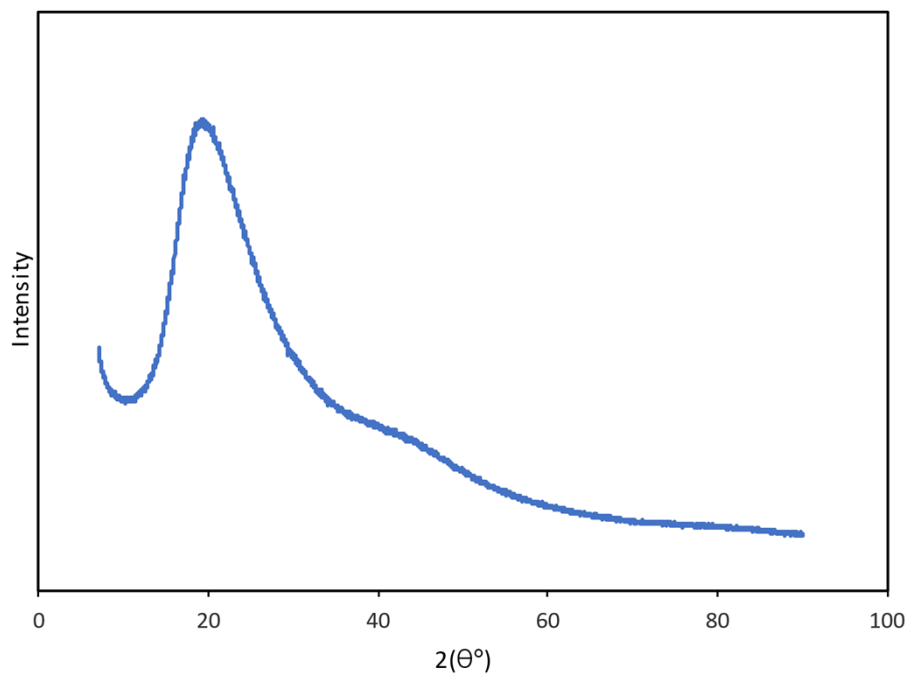


Figure S24. XRD pattern of L-tyrosine propyl ester ibuprofenate.

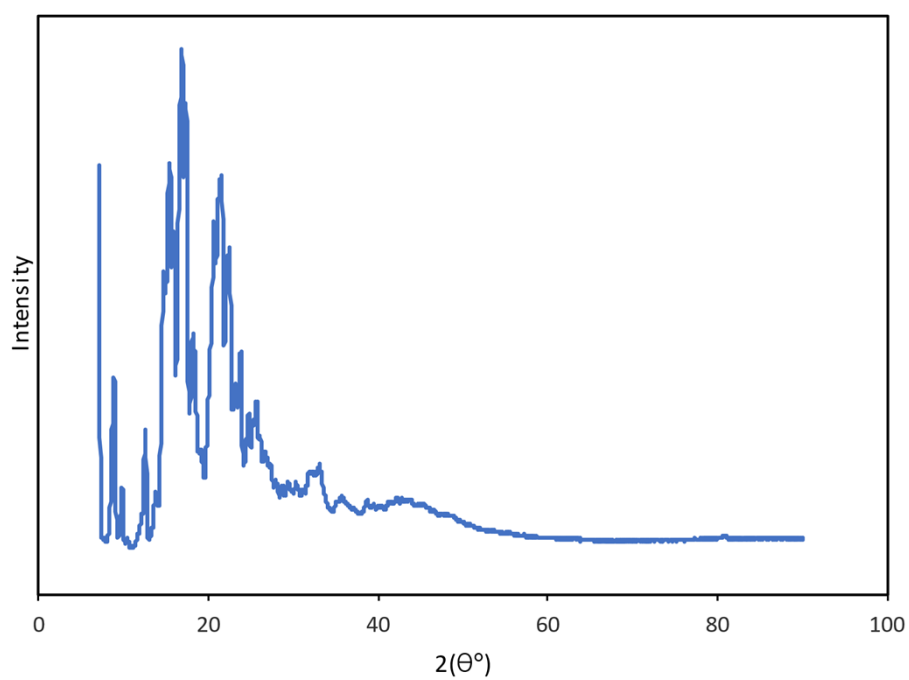


Figure S25. XRD pattern of L-tryptophan propyl ester ibuprofenate.

Skin permeation results

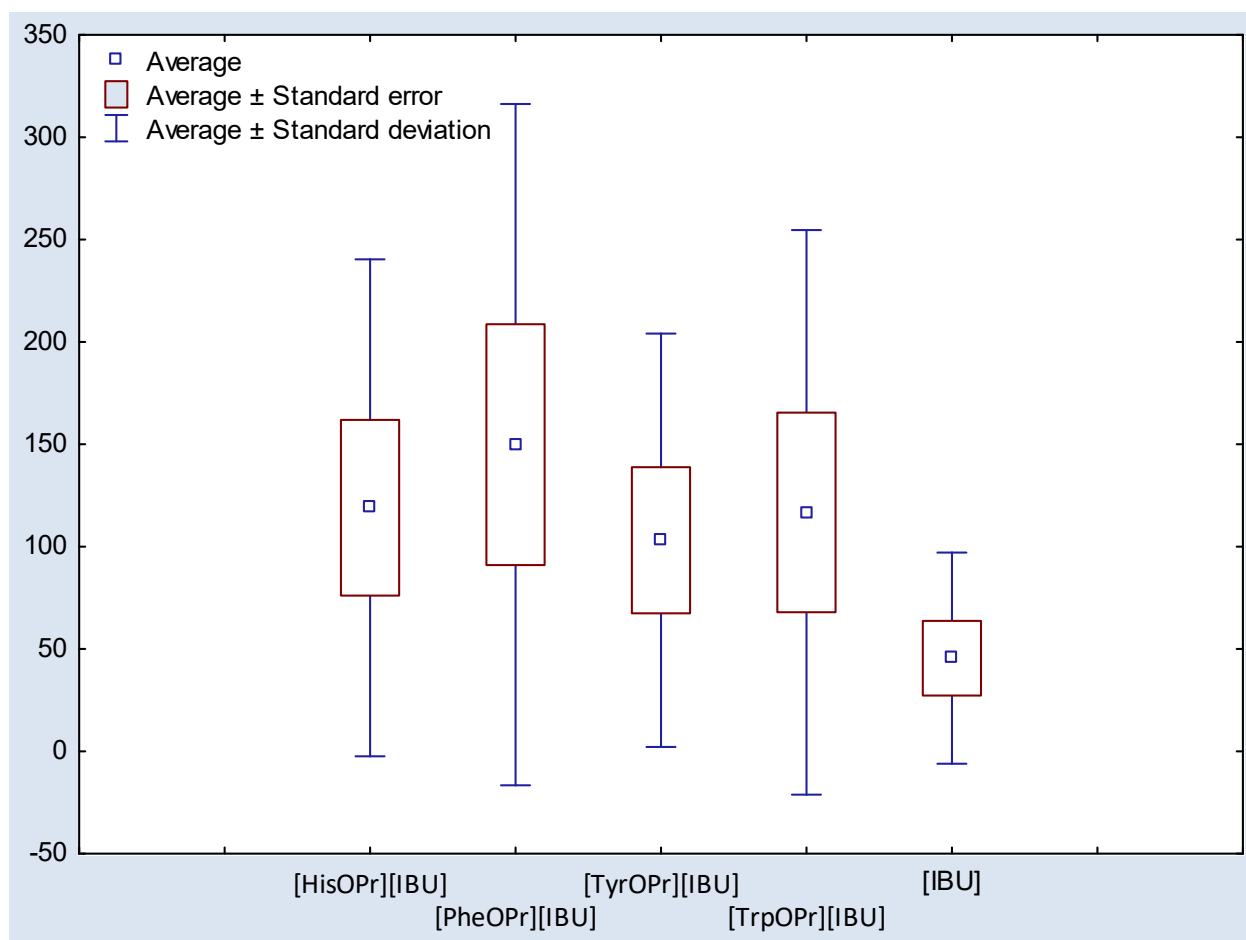


Figure S26. The box plot of cumulative mass for ibuprofen and amino acid propyl ester ibuprofenates during the 24-hour permeation.

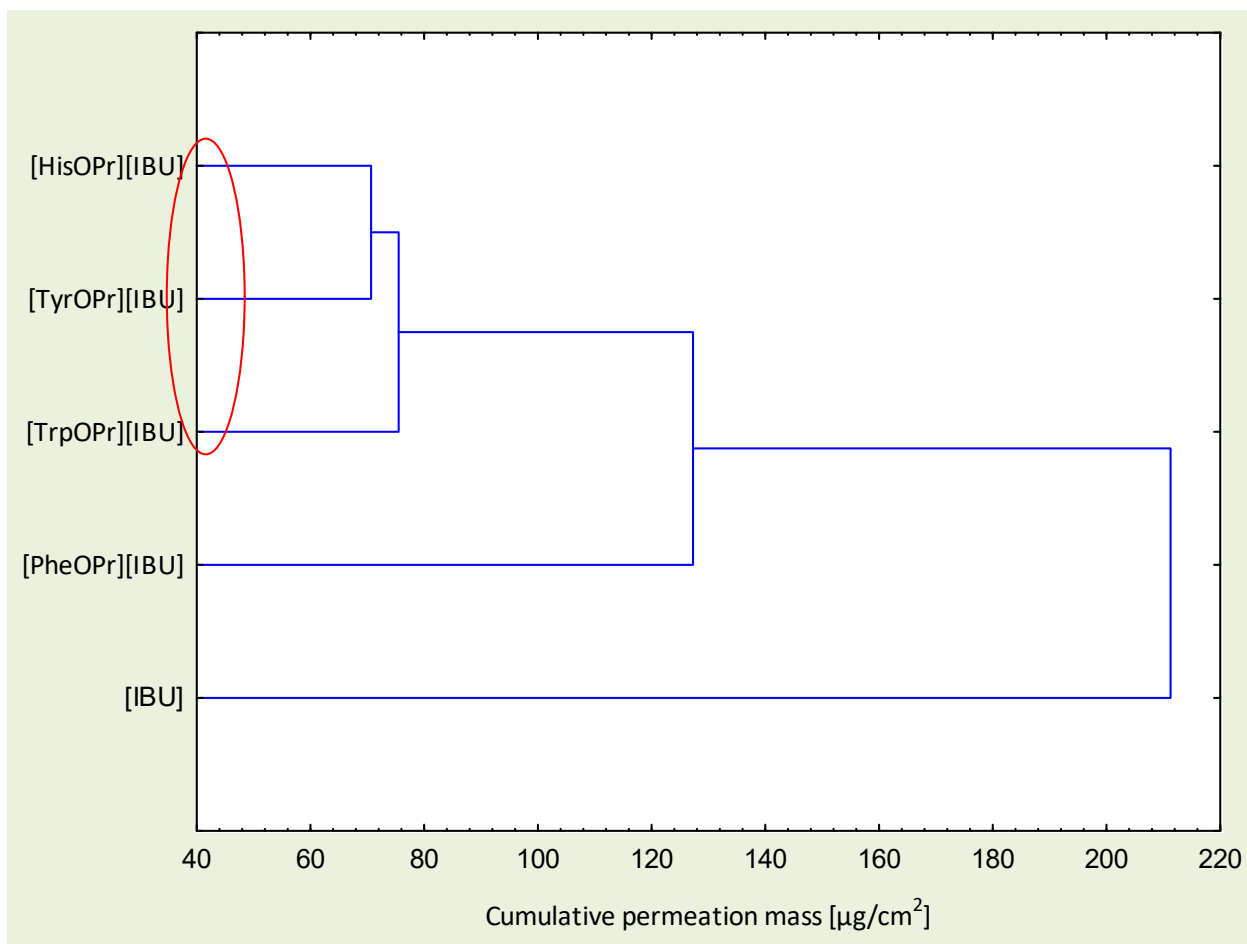


Figure S27. Cluster analysis graph for the mean accumulated mass for ibuprofen and amino acid propyl ester ibuprofenates during the 24-hour permeation. Compounds with similar and highest permeation values are marked in the red circle.

Table S1. Significant differences in the cumulative mass between all analyzed compounds, taking into account all time points during the entire 24 h permeation, were estimated by the Wilcoxon test.

	[HisOPr][IBU]	[PheOPr][IBU]	[TyrOPr][IBU]	[TrpOPr][IBU]	[IBU]
[HisOPr][IBU]		Z = 1.8201 <i>p</i> = 0.0870	Z = 1.8201 <i>p</i> = 0.0870	Z = 0.7001 <i>p</i> = 0.4838	Z = 2.3804 <i>p</i> = 0.0172*
[PheOPr][IBU]			Z = 1.6800 <i>p</i> = 0.0928	Z = 2.5205 <i>p</i> = 0.0117*	Z = 2.5205 <i>p</i> = 0.0117*
[TyrOPr][IBU]				Z = 0,4200 <i>p</i> = 0.18744	Z = 2.5205 <i>p</i> = 0.0117*
[TrpOPr][IBU]					Z = 2.3804 <i>p</i> = 0.0172*

TRANSDERMAL PATCHES

The ATR-FTIR spectra of patches

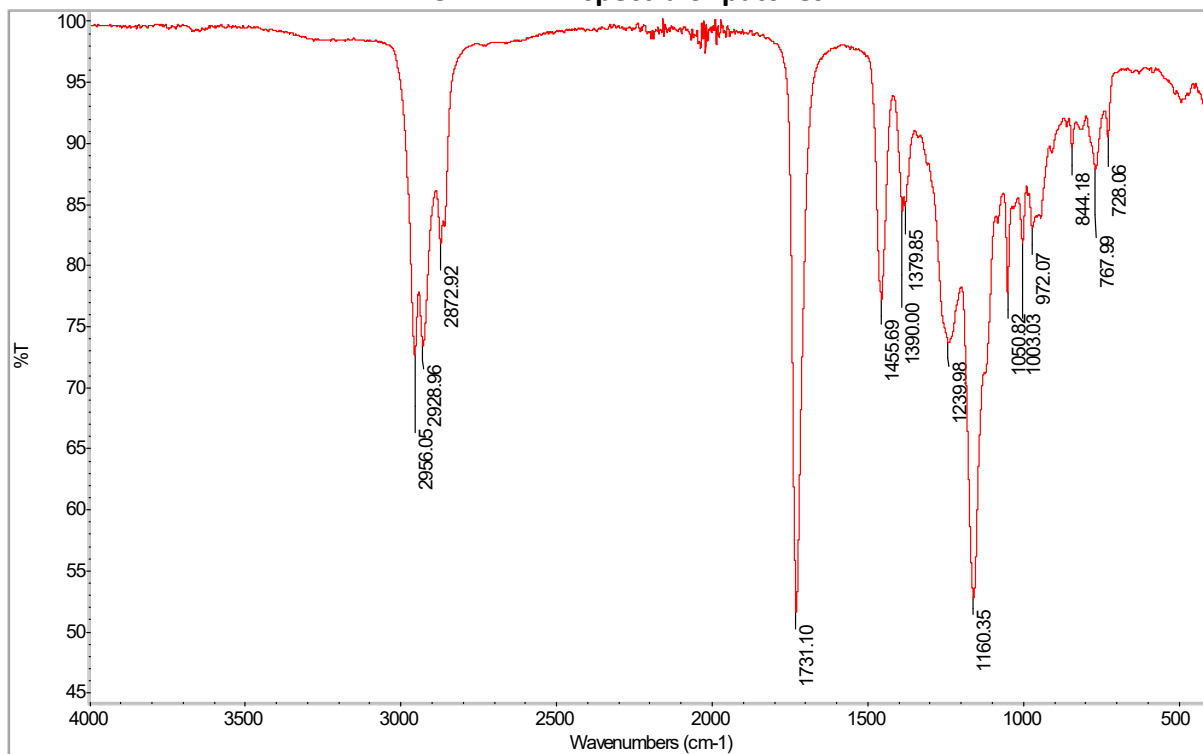


Figure S28. FTIR spectrum of the adhesive layer of the patch without API.

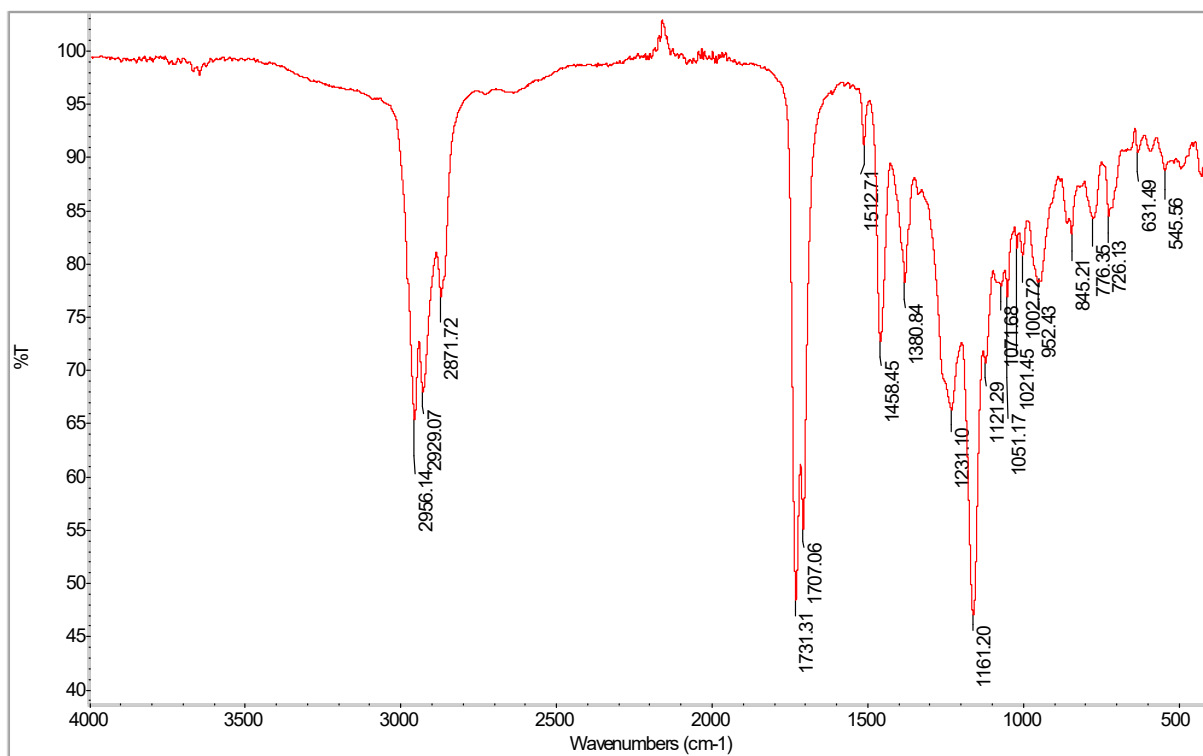


Figure S29. FTIR spectrum of the adhesive layer of the patch with ibuprofen.

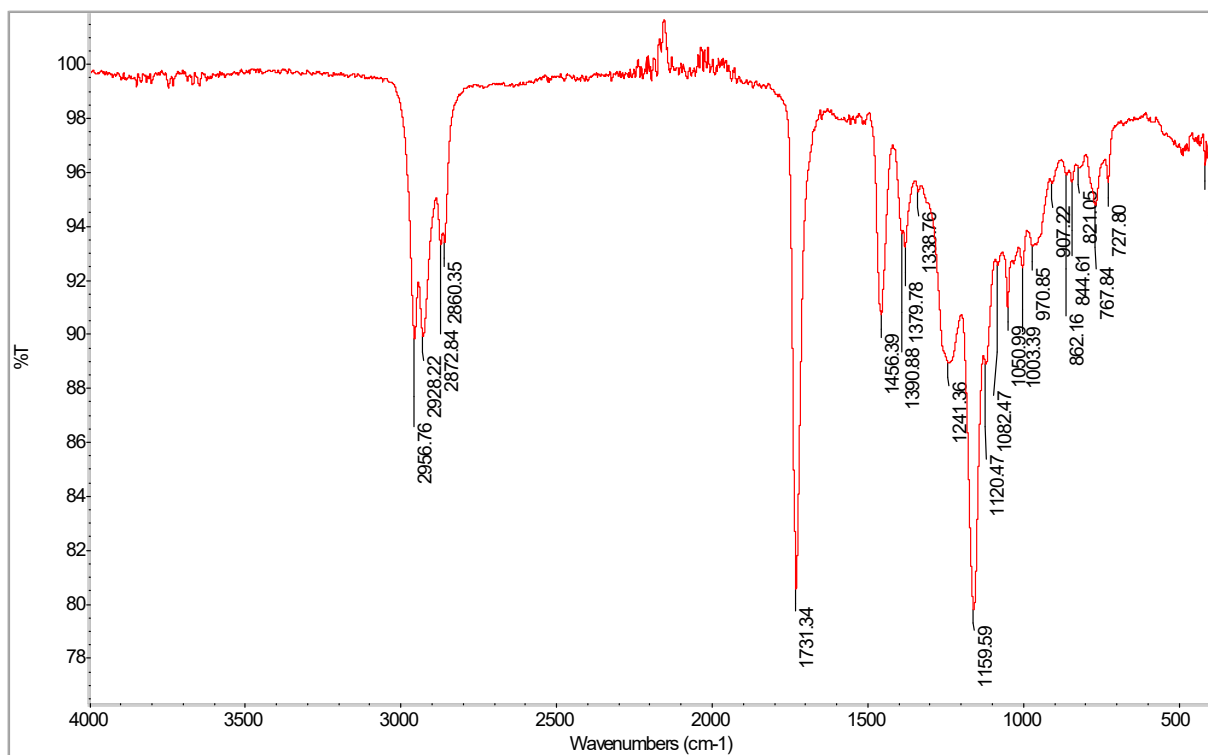


Figure S30. FTIR spectrum of the patch with sodium ibuprofenate.

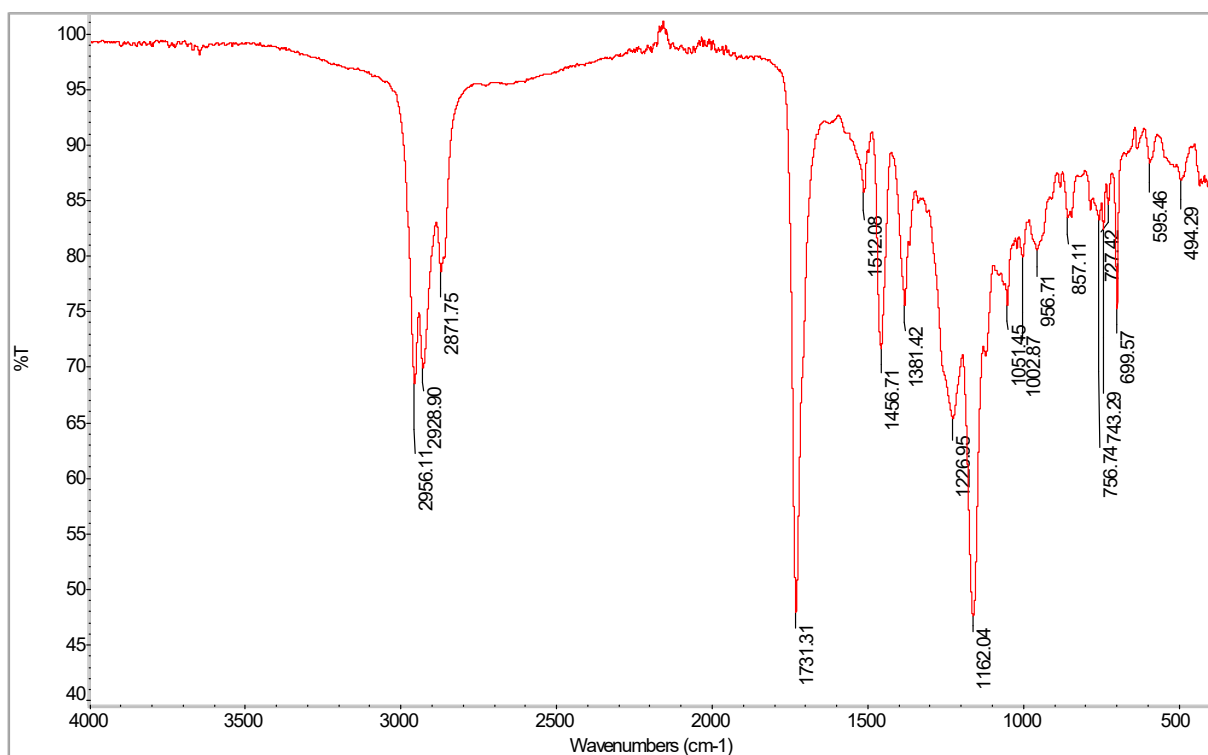


Figure S31. FTIR spectrum of the patch L-phenylalanine propyl ester ibuprofenate.

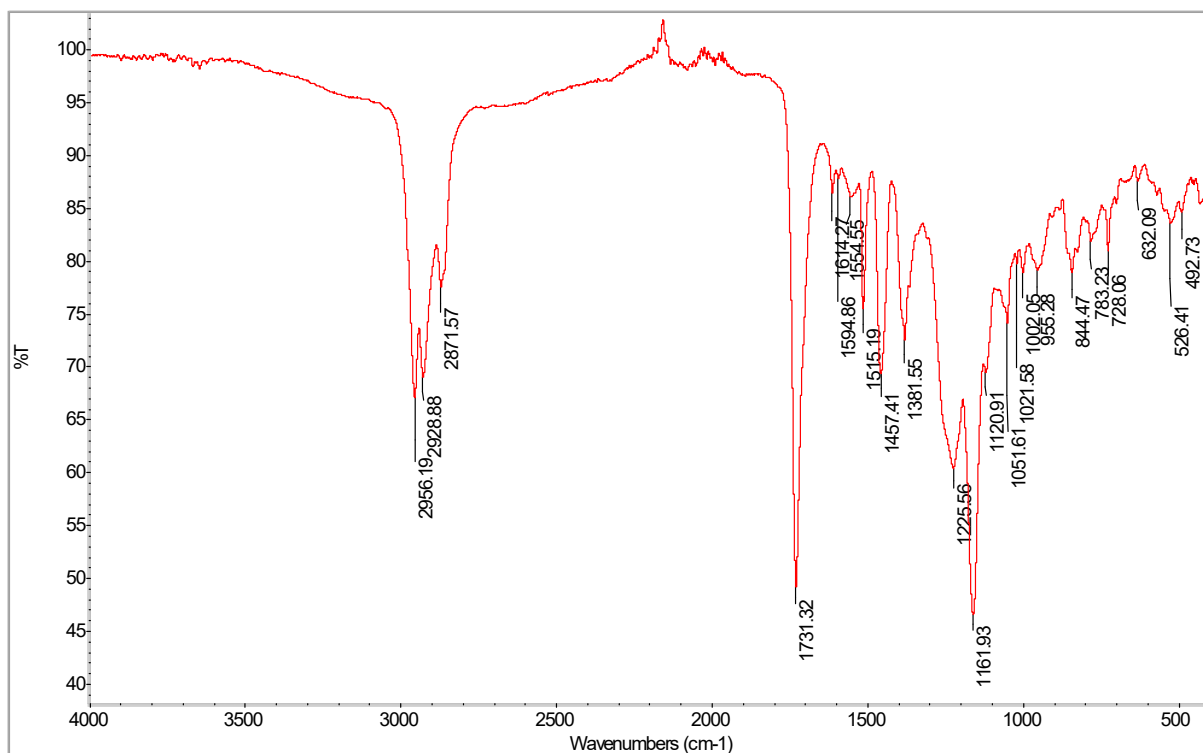


Figure S32. FTIR spectrum of the patch L-tyrosine propyl ester ibuprofenate.

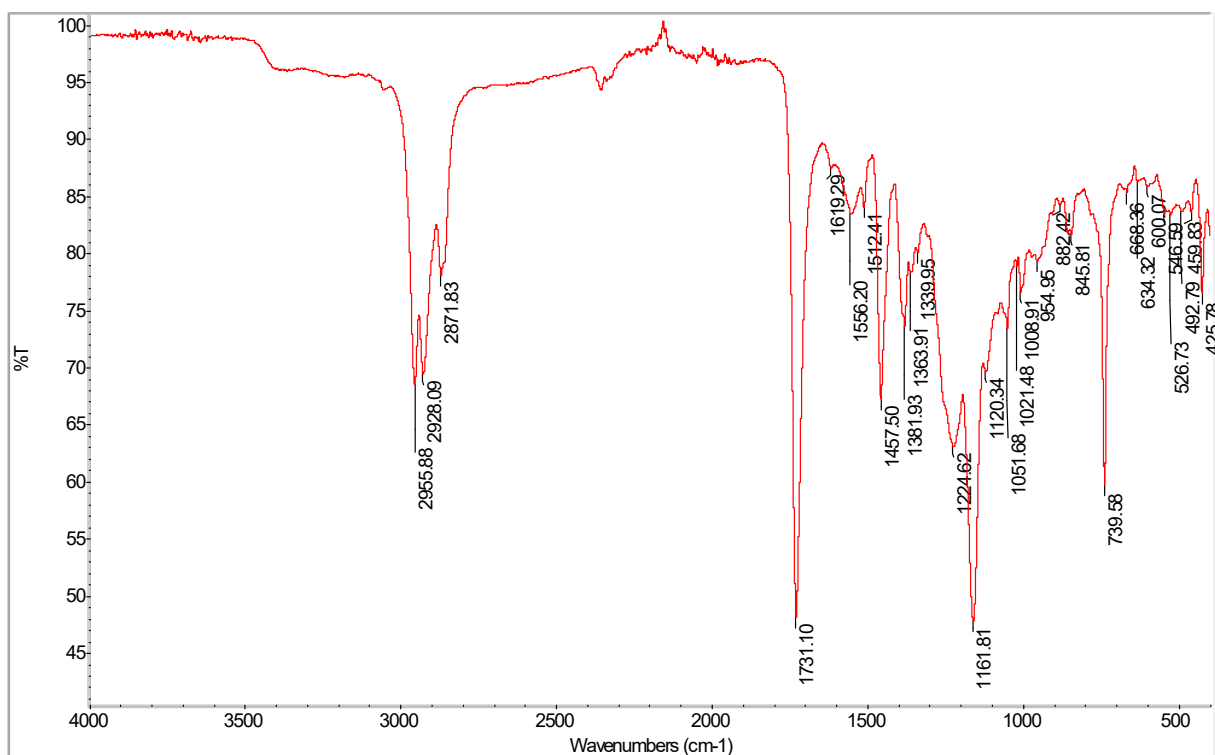


Figure S33. FTIR spectrum of the patch L-tryptophane propyl ester ibuprofenate.

The TG curves of patches

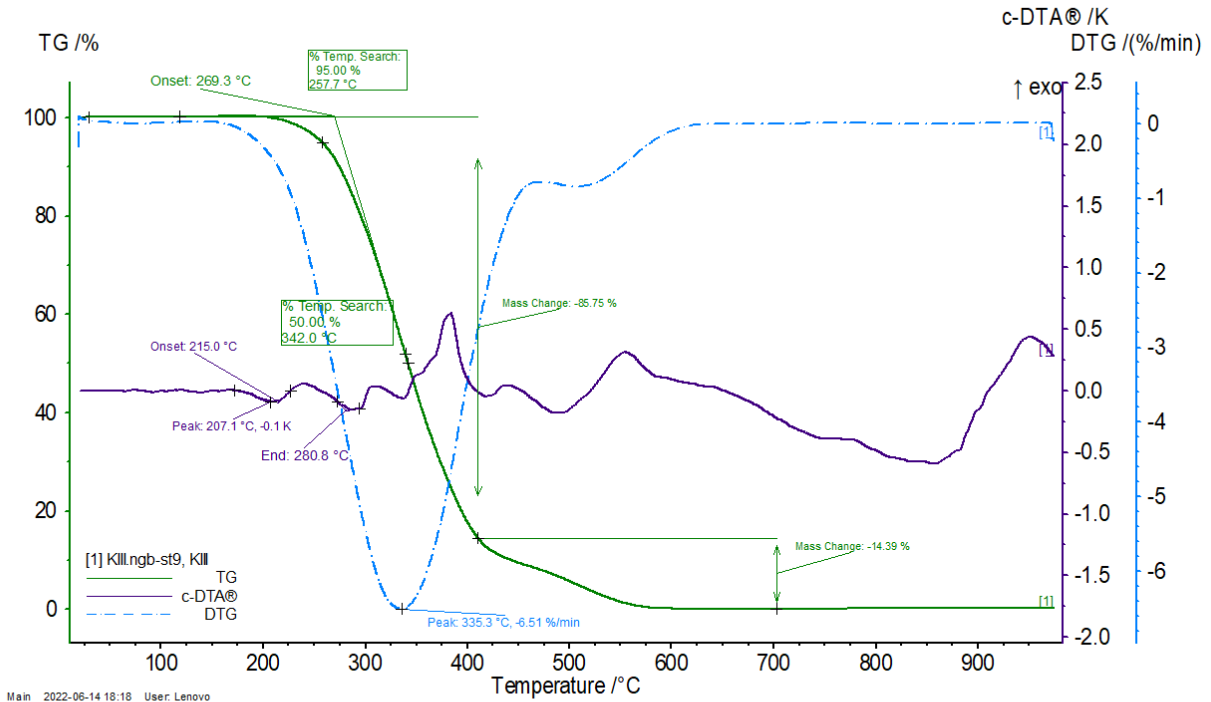


Figure S34. The TG, DTG, and c-DTA curves of the adhesive layer of the patch without API.

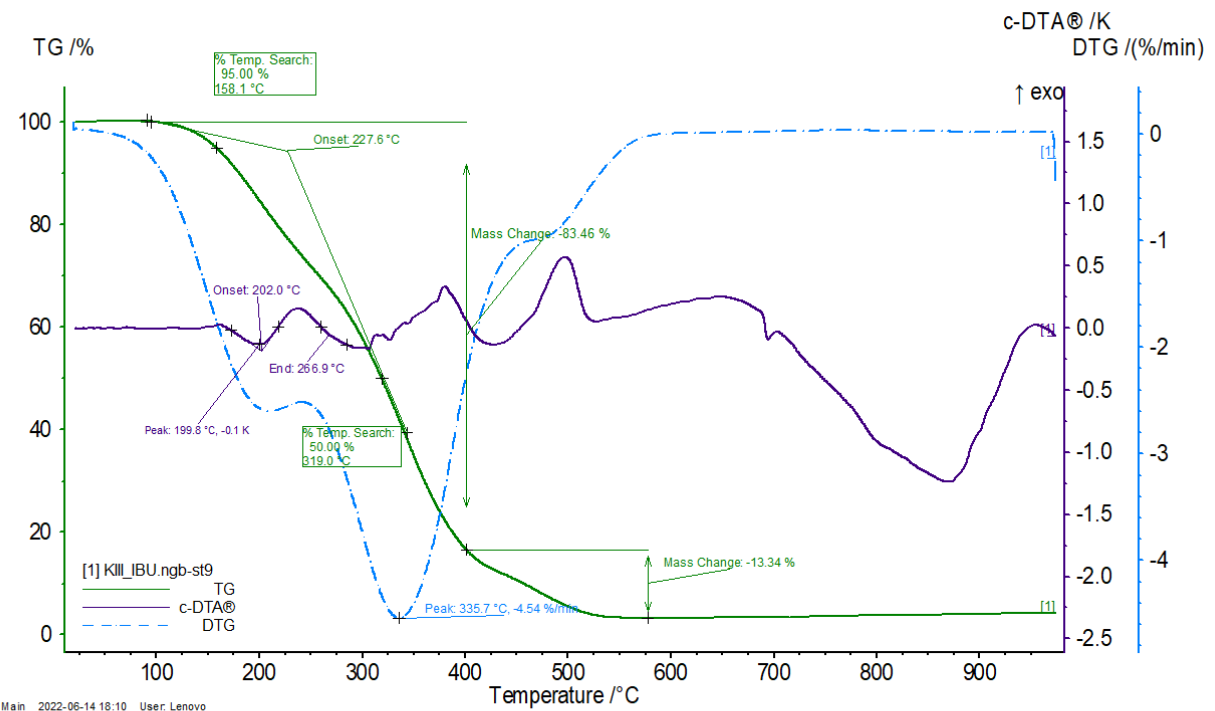


Figure S35. The TG, DTG, and c-DTA curves of the adhesive layer of the patch with ibuprofen.

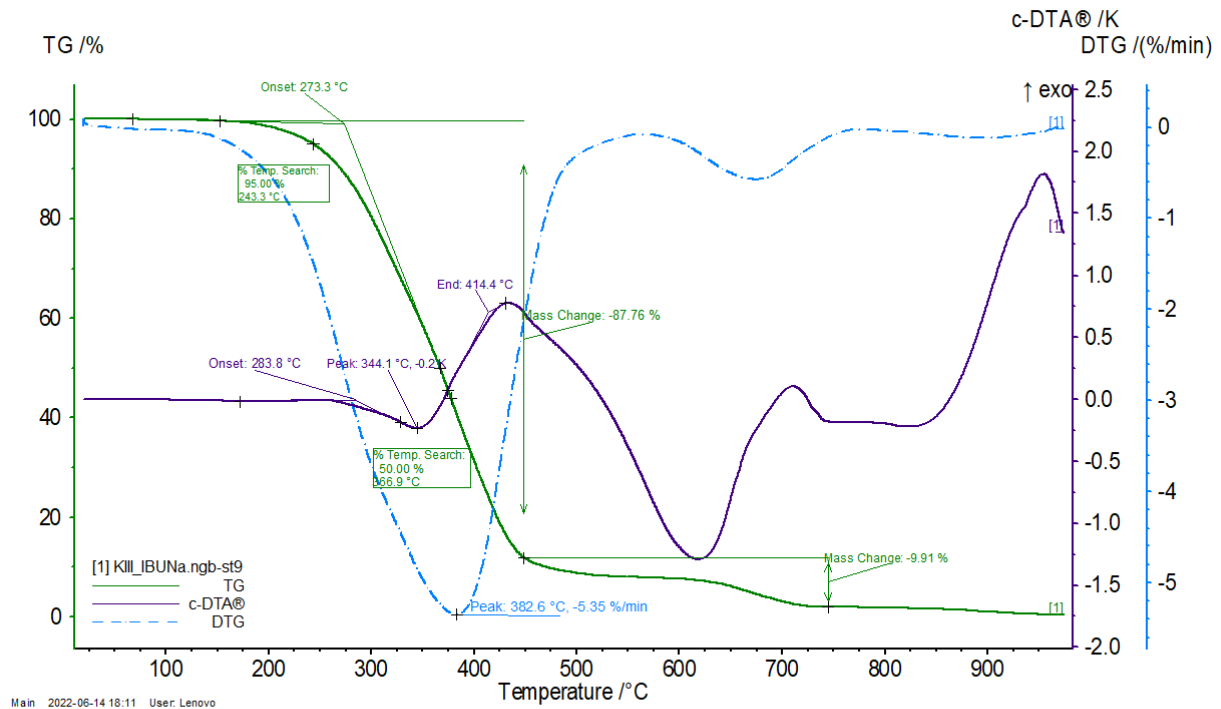


Figure S36. The TG, DTG, and c-DTA curves of the patch with sodium ibuprofenate.

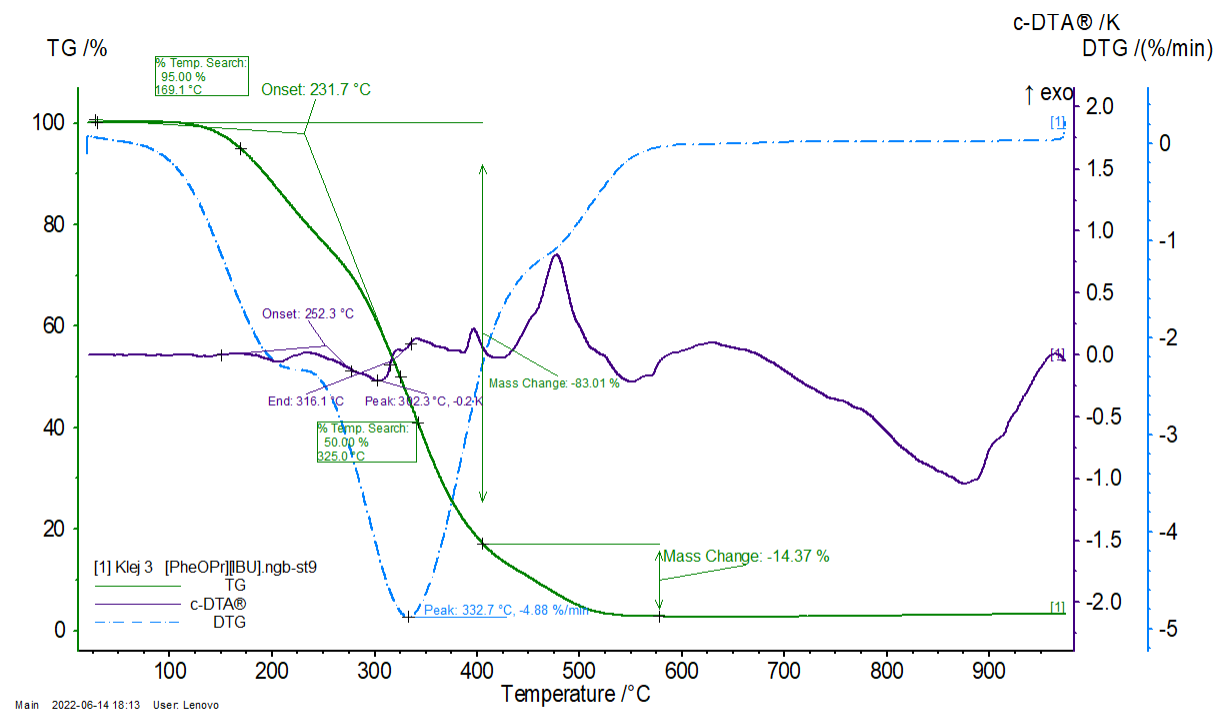


Figure S37. The TG, DTG, and c-DTA curves of the patch L-phenylalanine propyl ester ibuprofenate.

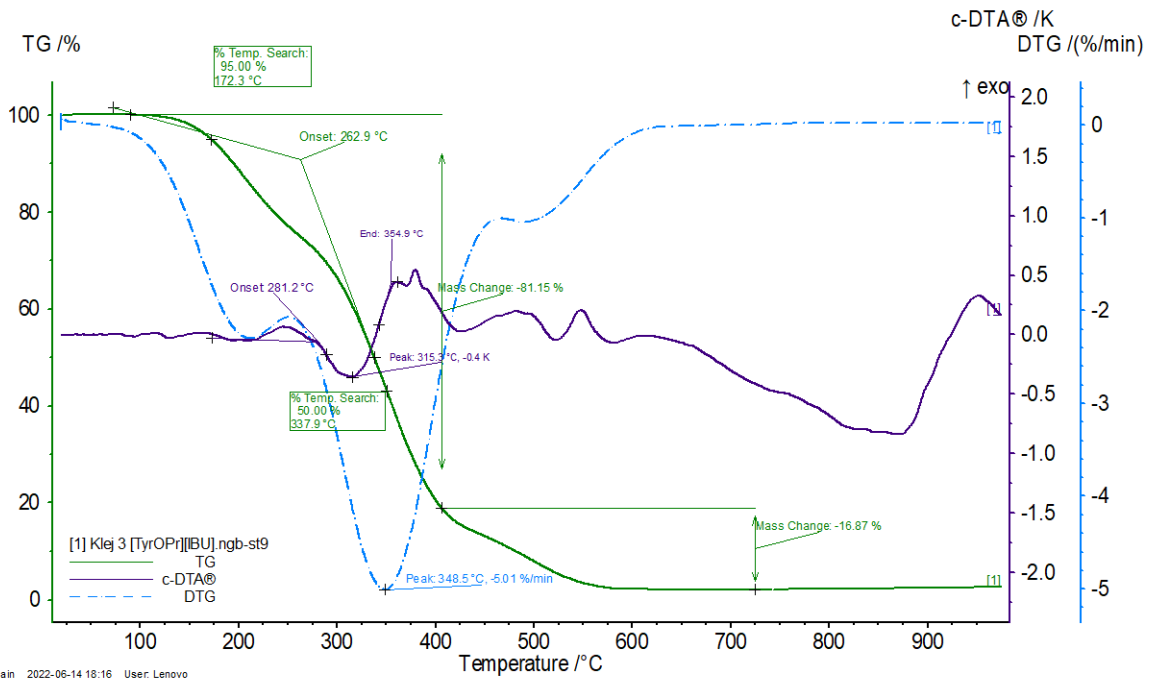


Figure S38. The TG, DTG, and c-DTA curves of the patch L-tyrosine propyl ester ibuprofenate.

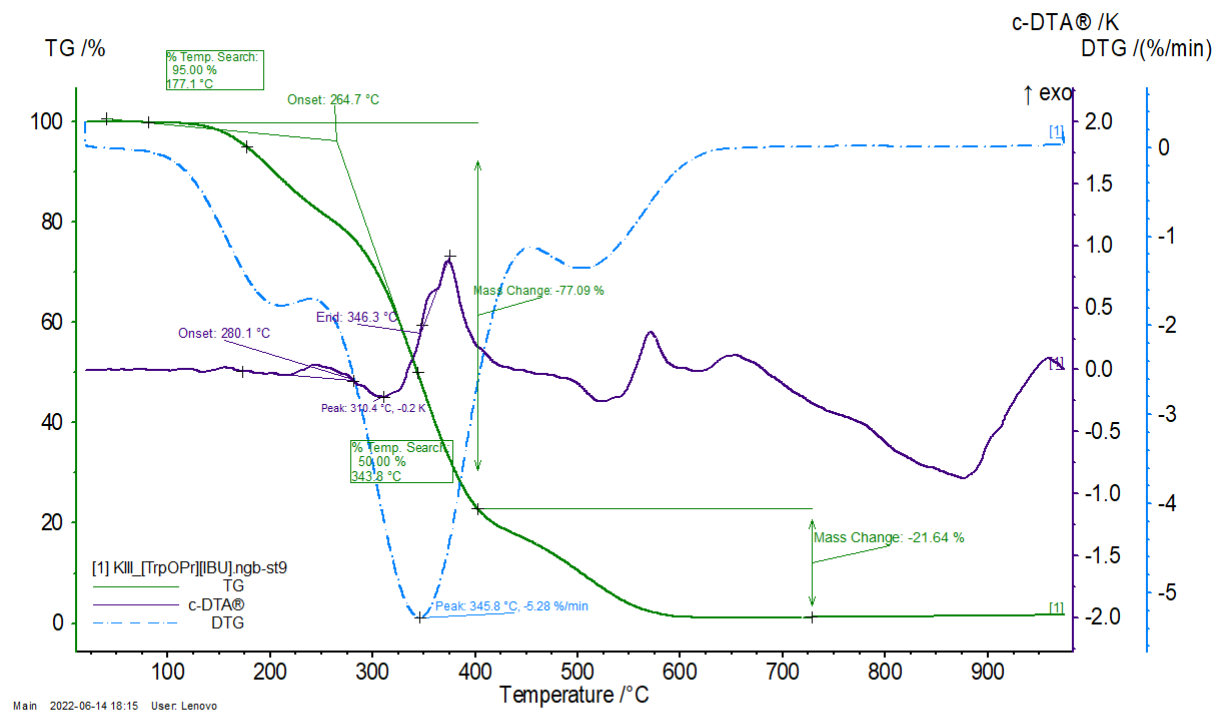


Figure S39. The TG, DTG, and c-DTA curves of the patch L-tryptophan propyl ester ibuprofenate.

The DSC curves of patches

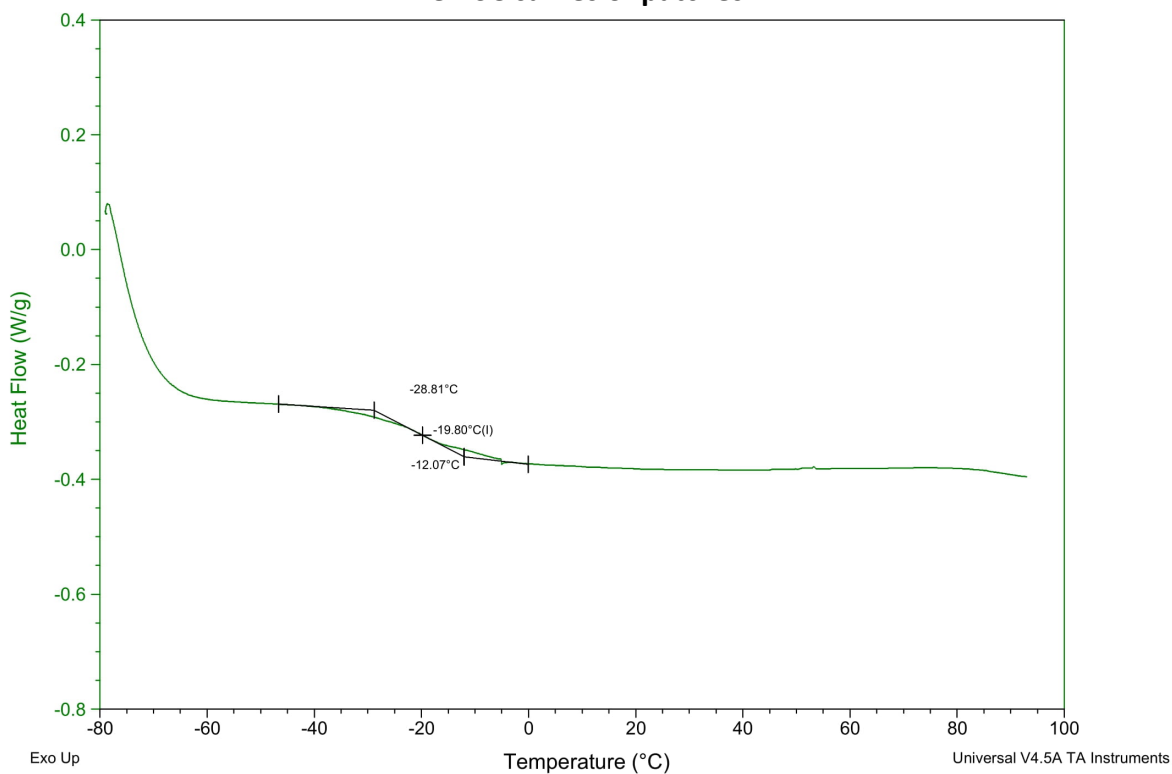


Figure S40. The DSC curves of the adhesive layer of the patch without API.

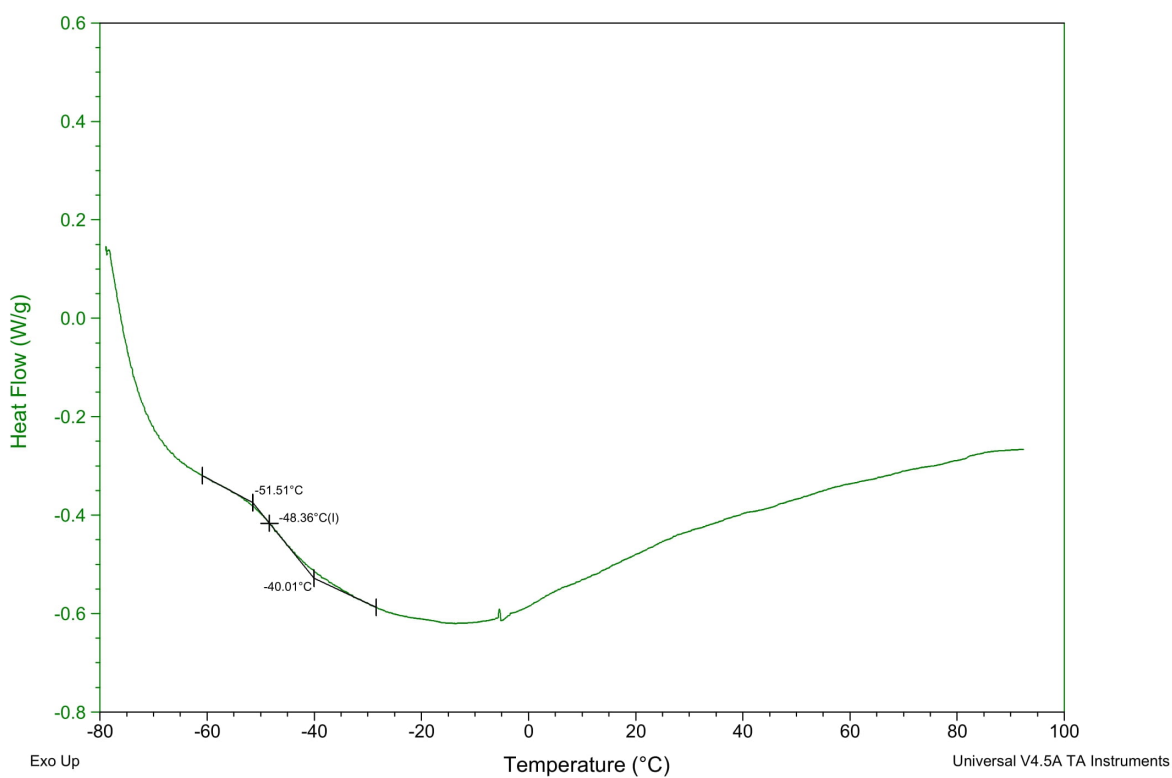


Figure S41. The DSC curves of the adhesive layer of the patch with ibuprofen.

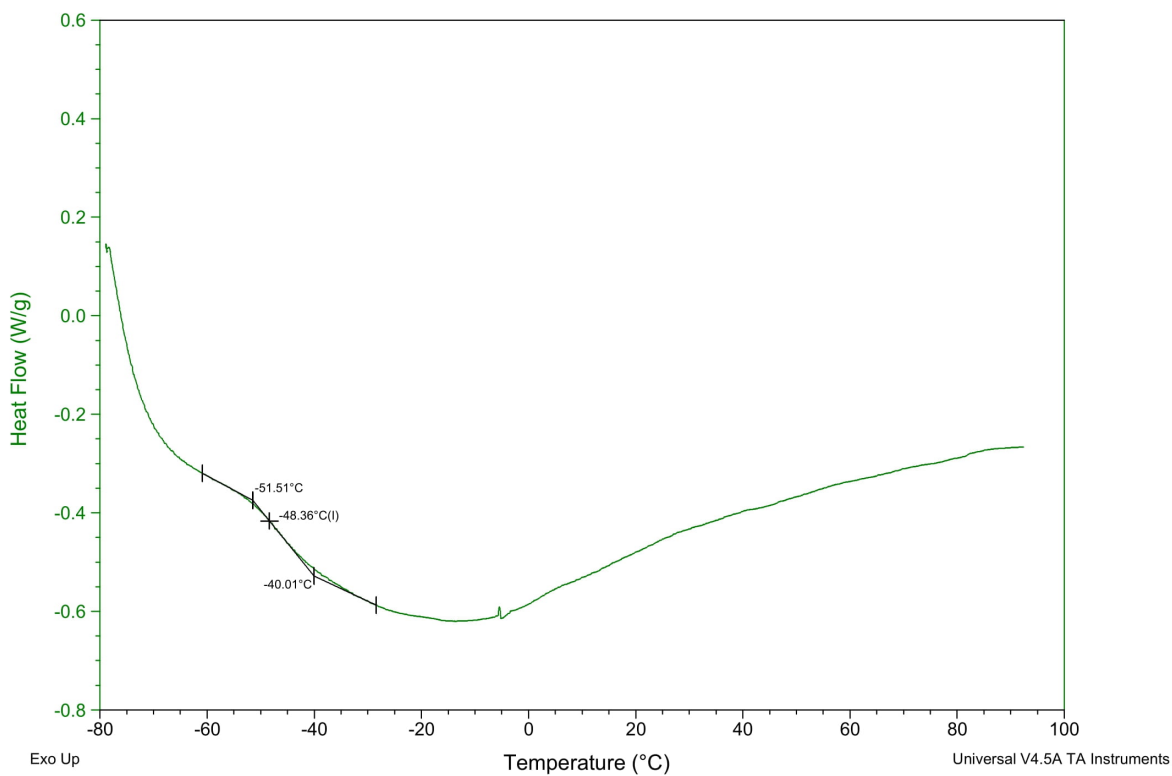


Figure S42. The DSC curves of the adhesive layer of the patch with sodium ibuprofenate.

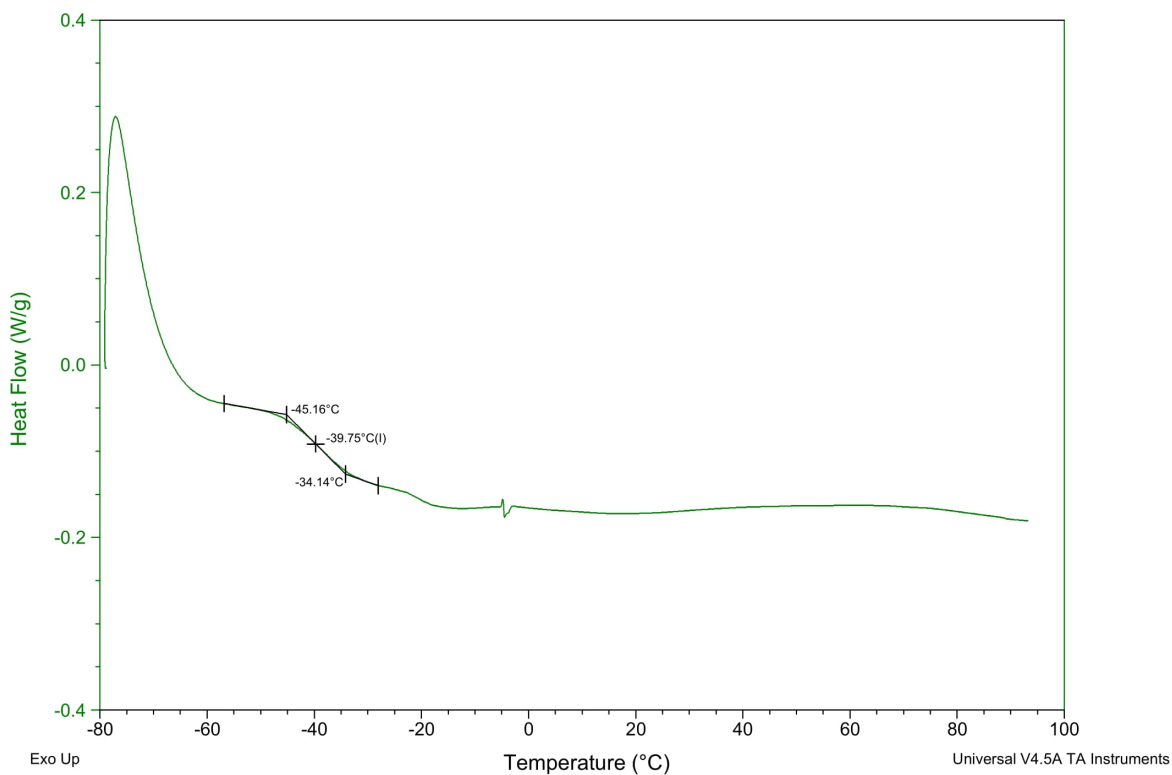


Figure S43. The DSC curves of the adhesive layer of the patch L-phenylalanine propyl ester ibuprofenate.

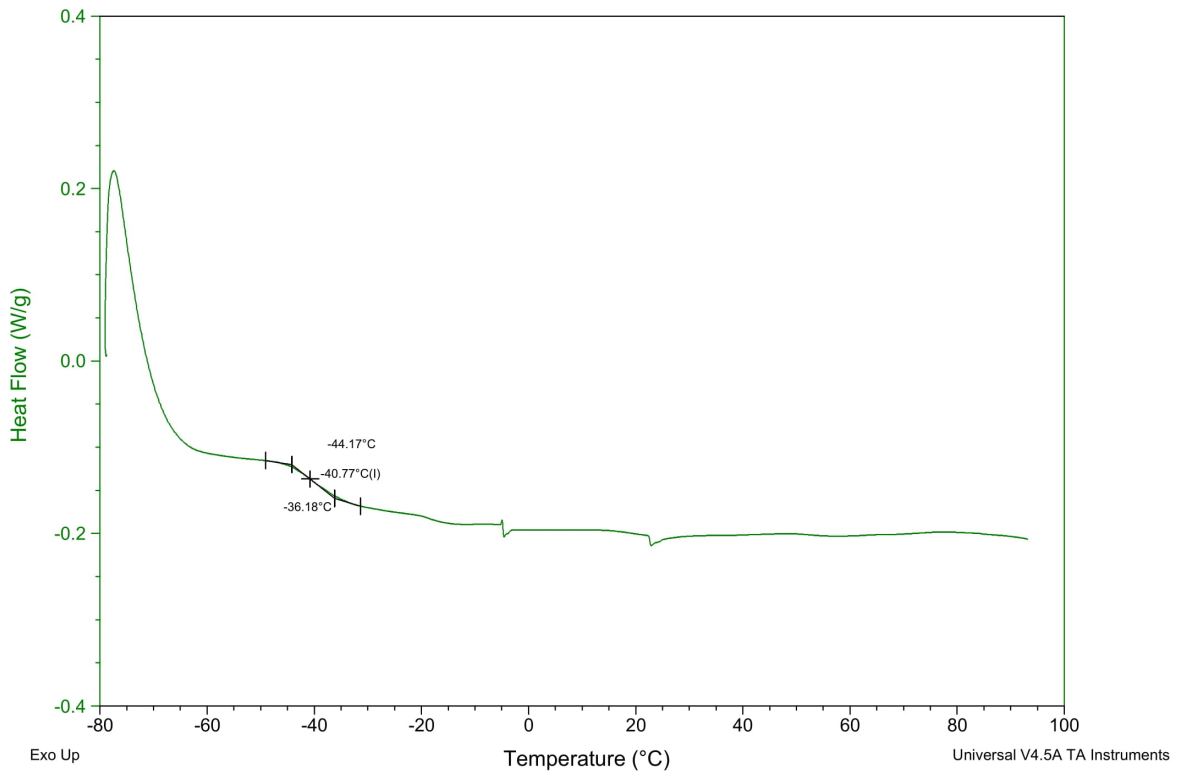


Figure S44. The DSC curves of the adhesive layer of the patch L-tyrosine propyl ester ibuprofenate.

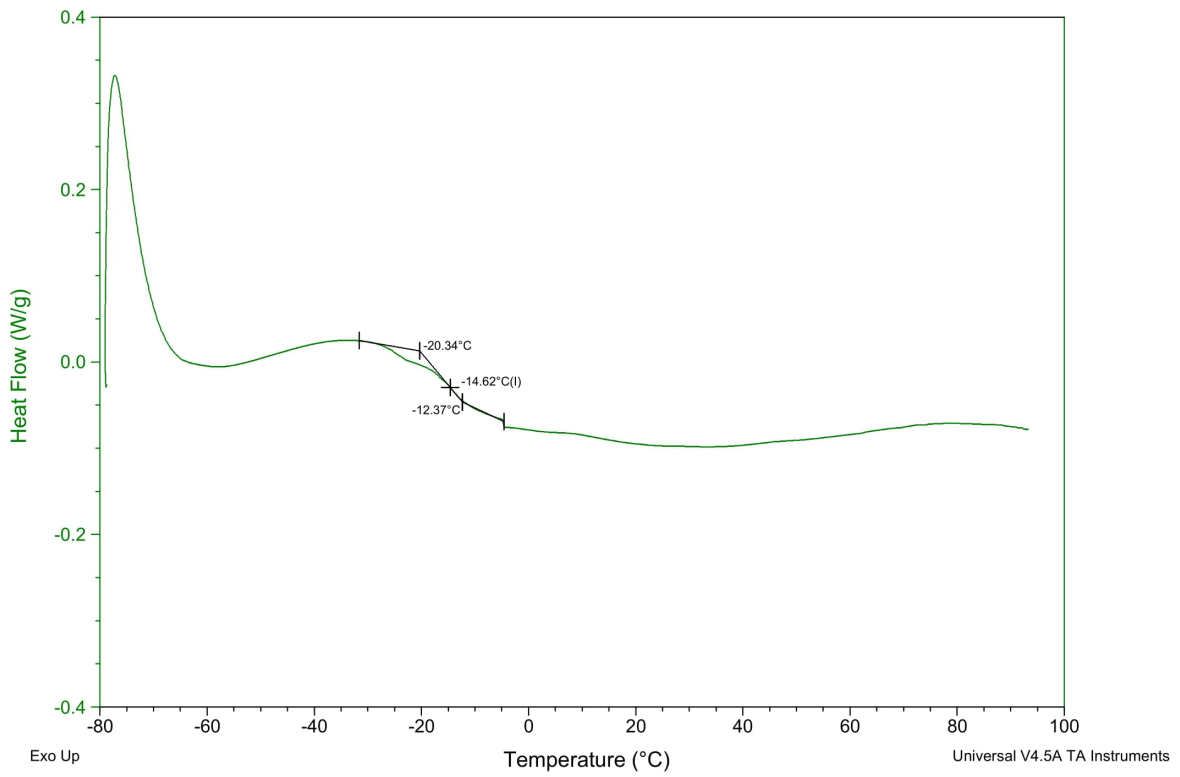


Figure S45. The DSC curves of the adhesive layer of the patch L-tryptophan propyl ester ibuprofenate.

Characteristics of obtained transdermal patches

Skin permeation results

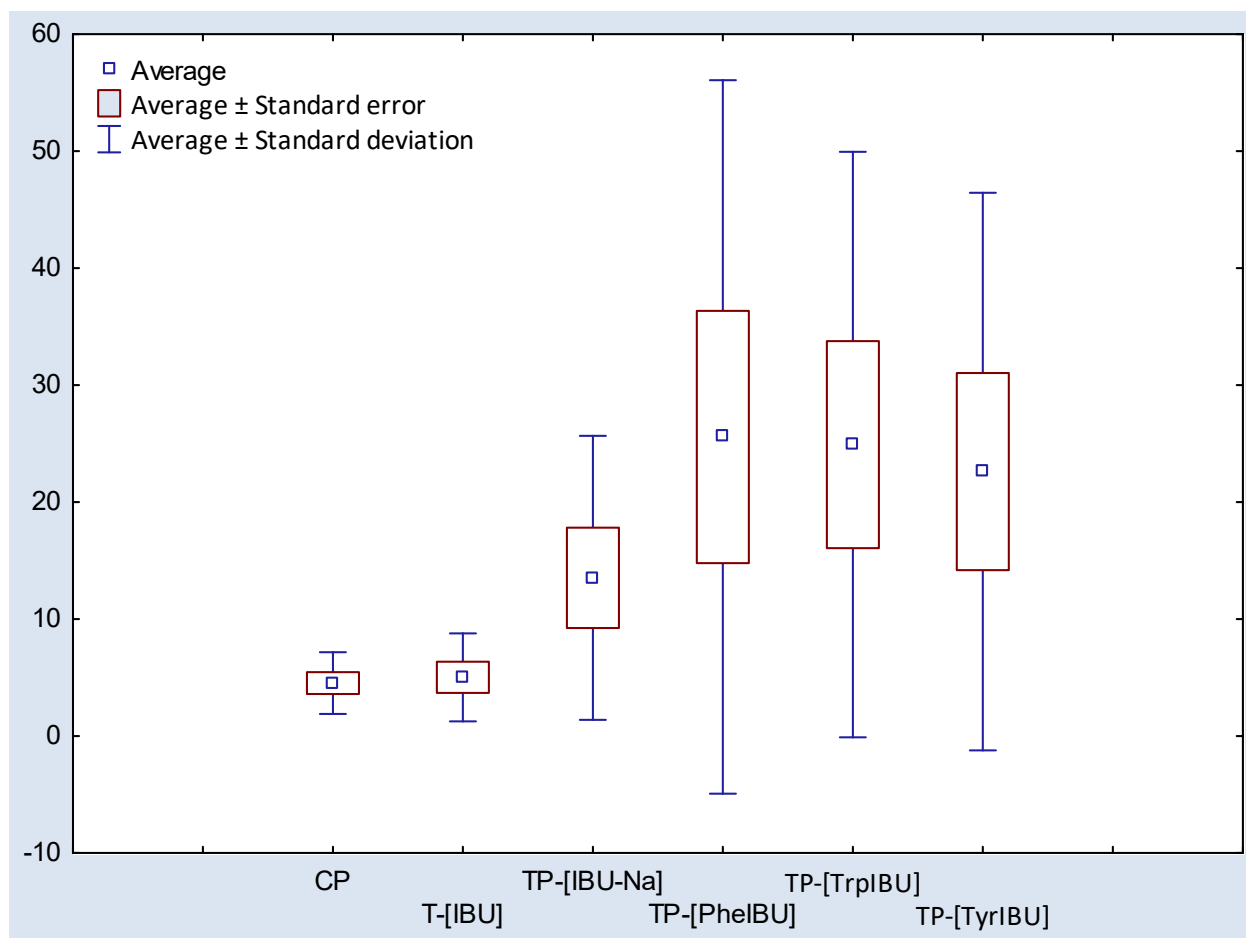


Figure S46. The box plot of cumulative mass for ibuprofen and amino acid propyl ester ibuprofenates permeation profiles for obtained transdermal patches during the 24-hour permeation; CP – commercial product.

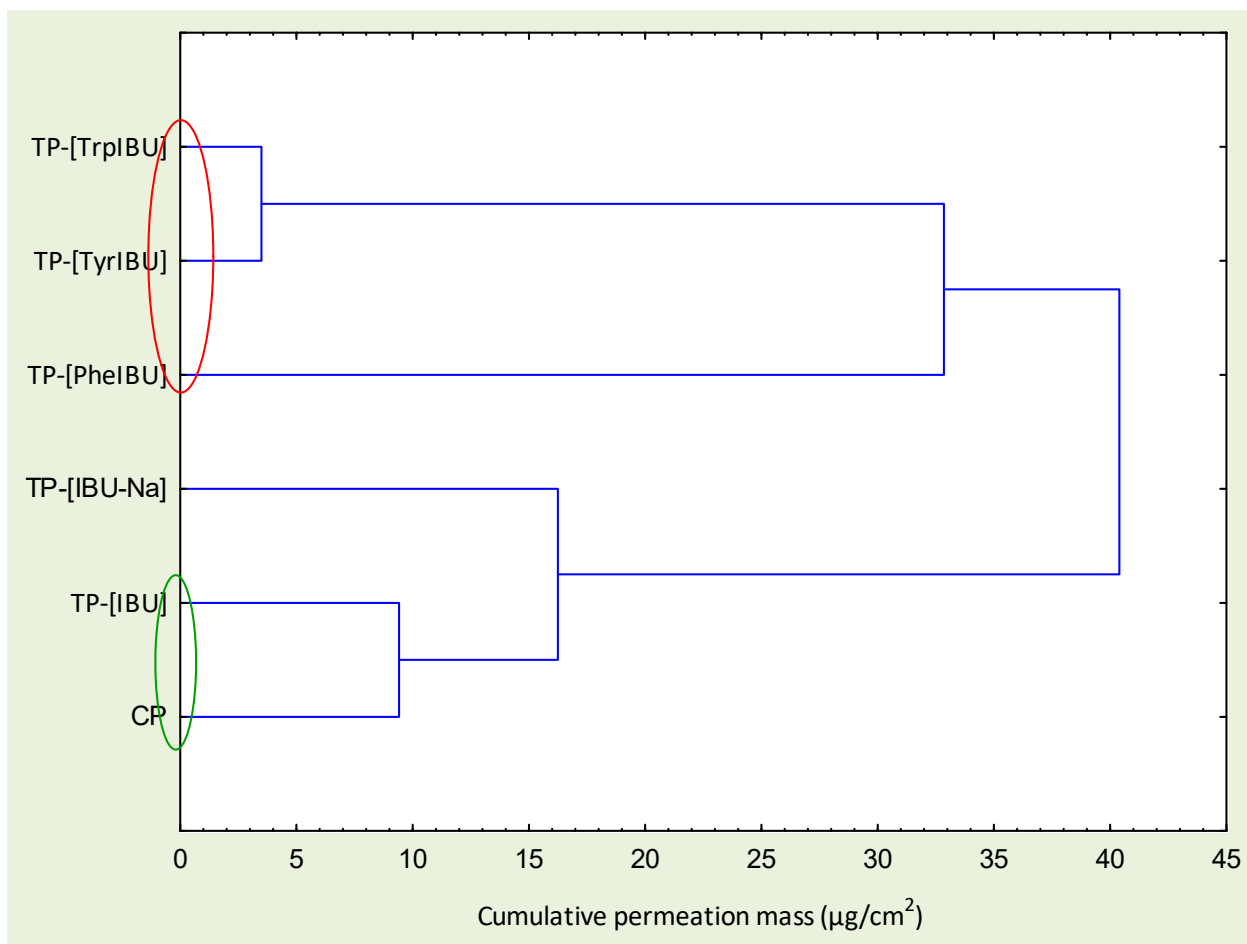


Figure S47. Cluster analysis graph for the mean accumulated mass for ibuprofen and amino acid propyl ester ibuprofenates permeation profiles for obtained transdermal patches during the 24-hour permeation test, CP – commercial product. Compounds with similar permeation values are marked in different color circles; CP – commercial product.

Table S2. Significant differences in the cumulative mass between all analyzed compounds, for ibuprofen and amino acid propyl ester ibuprofenates permeation profiles from obtained transdermal patches during the 24-hour permeation, were estimated by the Wilcoxon test; CP – commercial product.

	TP- [PheOPr][IBU]	TP- [TyrOPr][IBU]	TP- [TrpOPr][IBU]	TP-[IBU][Na]	TP-[IBU]	CP
TP- [PheOPr][IBU]		Z = 2.5205 <i>p</i> = 0.0117*	Z = 2.5205 <i>p</i> = 0.0117*	Z = 1.6803 <i>p</i> = 0.0928	Z = 2.3804 <i>p</i> = 0.0172*	Z = 1.9603 <i>p</i> = 0.0499*
TP- [TyrOPr][IBU]			Z = 0.7001 <i>p</i> = 0.4838	Z = 2,5205 <i>p</i> = 0.0117*	Z = 2,5205 <i>p</i> = 0.0117*	Z = 2.1004 <i>p</i> = 0.0356*
TP- [TrpOPr][IBU]				Z = 2,5205 <i>p</i> = 0.0117*	Z = 2,5205 <i>p</i> = 0.0117*	Z = 2.1004 <i>p</i> = 0.0356*
TP-[IBU][Na]					Z = 0,1400 <i>p</i> = 0.8886	Z = 0.8401 <i>p</i> = 0.4008
TP-[IBU]						Z = 2.3804 <i>p</i> = 0.0172*
CP						