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**Synthesis, characterization and evaluation of the
physicochemical properties of new multicomponent
pharmaceutical systems of valsartan and norfloxacin**

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PATRÍCIA OSÓRIO FERREIRA

Tese apresentada à Faculdade de Ciências, pelo Programa de Pós-graduação em Ciências e Tecnologia de Materiais (POSMAT), como parte dos requisitos para obtenção de título de doutora em Ciência dos Materiais com ênfase em Química de Materiais, da Universidade Estadual Paulista.

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Thesis submitted to the School of Sciences through the Science and Technology of Materials program (POSMAT) as part of the requirements for the degree of Doctor of Materials Sciences with emphases in Materials Chemistry at the São Paulo State University.

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Prof. Dr. FLAVIO JUNIOR CAIRES

*I dedicate this thesis to everyone who has
assisted me on this journey, especially my
family:
my husband Miguel, my parents Francina
and Vitorio, and my brother José Rubens.
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FOR ALL YOUR SUPPORT <3*

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*"You get in life what you have the courage
to ask for."*

Oprah Winfrey

*" It always seems impossible until it's
done"*

Nelson Mandela

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Resumo

Um dos grandes desafios no desenvolvimento de novos fármacos é um problema frequente nos já comercializados é a baixa solubilidade aquosa, que pode afetar diretamente a biodisponibilidade de um princípio ativo. A busca por novas abordagens de como melhorá-la recebem destaque da comunidade acadêmica e do setor farmacêutico. Nesse contexto, a prospecção e estudo de formas multicomponentes farmacêuticas visa a melhoria de propriedades físico-químicas de fármacos, com grande foco no aumento da solubilidade aquosa. Dessa forma, este estudo visou a obtenção de novas formas farmacêuticas multicomponentes do anti-hipertensivo com baixa solubilidade aquosa valsartana e sua caracterização térmica, espectroscópica e estrutural, além do estudo de viabilidade de escalonamento de cocristais de norfloxacin. Os coamorfos e misturas eutéticas foram preparados utilizando o método mecanoquímico, bem como síntese em solução para obtenção dos novos sais de valsartana. A partir dos dados de análise térmica foram ainda construídos diagramas de fase binários, o que possibilitou a compreensão do equilíbrio sólido-líquido para as misturas eutéticas, e gráficos que demonstram o comportamento vítreo-borrachoso dos coamorfos. A partir do estudo de cristalização em solução foram construídos diagramas ternários para determinar melhores condições de síntese em solução de cocristais do antibiótico norfloxacin. Ainda foram utilizadas técnicas difratométricas e espectroscópicas na caracterização dos sistemas obtidos e ensaios de dissolução, permeação e solubilidade para avaliar suas propriedades. Foram obtidos nesse trabalho, utilizando a valsartana, coamorfos com menor solubilidade, formulações líquidas com maior permeação para o sistema valsartana-mentol, e sais de alta solubilidade com os coformadores roxadustat, ácido fólico e ácido 4-aminobenzóico.

Palavras-chave: Sistemas farmacêuticos multicomponentes; Análise térmica; Diagramas de fase; Mecanoquímica.

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Abstract

One of the biggest challenges in developing new drugs and a frequent problem in those already marketed is low aqueous solubility, which can directly affect the bioavailability of an active ingredient. The search for new approaches to improve this issue is highlighted by the academic community and the pharmaceutical field. In this context, the prospecting and study of multicomponent pharmaceutical forms aims to improve the physicochemical properties of drugs, with a strong focus on increasing aqueous solubility. Thus, this study aimed to obtain new multicomponent pharmaceutical forms of the antihypertensive with low aqueous solubility valsartan and their thermal, spectroscopic, and structural characterization, in addition to the feasibility study of scaling up norfloxacin cocrystals. The coamorphous and eutectic mixtures were prepared using the mechanochemical method, and solution synthesis was used to obtain the new valsartan salts. From the thermal analysis data, binary phase diagrams were constructed, allowing the understanding of the solid-liquid equilibrium for the eutectic mixtures and graphs demonstrating the glassy-rubbery behavior of the coamorphous. From the study of crystallization in solution, ternary diagrams were constructed to determine the best conditions for the synthesis in solution of cocrystals of the antibiotic norfloxacin. Diffractometric and spectroscopic techniques were also used to characterize the systems obtained, and dissolution, permeation, and solubility tests were used to evaluate their properties. In this work, coamorphous with lower solubility, liquid formulations with higher permeation for the valsartan-menthol system, and high-solubility salts with the cofomers roxadustat, folic acid, and 4-aminobenzoic acid were obtained using valsartan.

Keywords: Multicomponent pharmaceutical systems; Thermal analysis; Phase diagrams; Mechanochemistry.

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LIST OF ABBREVIATIONS AND SYMBOLS

ABS	Absorbance
AFOL	Folic Acid
ANVISA	Agência Nacional de Vigilância Sanitária
API	Active Pharmaceutical Ingredient
ARB	Angiotensin II Receptor Blocker
BB	B-Blocker
BCS	Biopharmaceutics Classification System
CAR	Carvedilol
CAT	Catechol
CCDC	Cambridge Crystallographic Data Centre
CSD	Cambridge Structural Database
DES	Deep Eutectic Solvents
DM	Dialysis Membrane
DSC	Differential Scanning Calorimetry
EtOH	Ethanol
FDA	Food And Drug Administration
FTIR	Fourier-Transform Infrared Spectroscopy
GRAS	Generally Regarded as Safe
INCA	Isonicotinic Acid
LAG	Liquid Assisted Grinding
LTTM	Low Transition Temperature Mixture
MENT	Menthol
NaOH	Sodium Hydroxide
NAR	Naringenin
NCA	Nicotinic Acid
NG	Neat Grinding
NOR	Norfloxacin
PABA	4-Aminobenzoic Acid
PCA	Picolinic Acid
PM	Physical Mixture
PXRD	Powder X-Ray Diffractometry
ROX	Roxadustat
SAC	Saccharin
T_g	Glass Transition
TG - DTA	Simultaneous Thermogravimetry and Differential Thermal Analysis

TG/DTG - DTA	Simultaneous Thermogravimetry, Derivate Thermogravimetry and Differential Thermal Analysis
THEDES	Therapeutic Deep Eutectic Systems
THY	Thymol
UV-VIS	Ultraviolet – Visible Spectroscopy
VAL	Valsartan
VALa	Amorphous Form of Valsartan
VALc	Crystalline Form of Valsartan
WHO	World Health Organization
λ	Wavelength
ν	Stretching
ν_{Asym}	Asymmetric Stretching
ν_{Sym}	Symmetric Stretching

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ACADEMIC PRODUCTIONS

Below are all the articles published during the doctoral period, whether related to this work or not (partnerships).

Productions throughout the doctorate:

1. COSTA, GIOVANNA; ISQUIBOLA, GUILHERME; **FERREIRA, PATRÍCIA**; PORTO, MARIA VITÓRIA; MAGDALENA, AROLDO GERALDO; CAIRES, FLÁVIO. Norfloxacin nanocrystals through surfactant assisted grinding. Materials Research (Online). 2024
2. DE ALMEIDA, AMANDA COSMO; **FERREIRA, PATRÍCIA OSÓRIO**; PORTO, MARIA VITÓRIA; CANOTILHO, JOÃO; DE CASTRO, RICARDO ANTÔNIO ESTEVES; CAIRES, FLÁVIO JUNIOR; DA SILVA EUSÉBIO, MARIA ERMELINDA. Novel nimesulide multicomponent solid forms: screening, synthesis, thermoanalytical study and characterization. Journal of Thermal Analysis and Calorimetry (Online). v.1, p. Online, 2024.
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2. DE ALMEIDA, AMANDA COSMO; TORQUETTI, CAROLINA; **FERREIRA, PATRÍCIA OSÓRIO**; FERNANDES, RICHARD PEROSA; DOS SANTOS, EVERTON CARVALHO; KOGAWA, ANA CAROLINA; CAIRES, FLÁVIO JUNIOR. Cocrystals of ciprofloxacin with nicotinic and isonicotinic acids: mechanochemical synthesis, characterization, thermal and solubility study. THERMOCHIMICA ACTA, p.178346, 2019.
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6. MACHADO, RAFAEL DE GODOI; **FERREIRA, PATRÍCIA OSÓRIO**; GAGLIERI, CAROLINE; CAIRES, FLÁVIO JUNIOR. Synthesis, Characterization and Thermoanalytical Studies of Neodymium Norfloxacinates. BRAZILIAN JOURNAL OF THERMAL ANALYSIS, v.6, p. Artigo 19, 2017.

Chapter 1 – Introduction and Theoretical Background

1.1. INTRODUCTION

The low aqueous solubility of active pharmaceutical ingredients (APIs) is one of the main reasons that make the process of launching new drugs expensive and time-consuming. It is estimated that around 40% of approved drugs and 90% of those in the pipeline development have this issue (FERREIRA et al., 2009; PINDELSKA; SOKAL; KOLODZIEJSKI, 2017). For that reason, there is a need to continue studying drugs already on the market, to make them better for the final consumer.

Solid forms are strategies to improve the solubility as well as other physicochemical properties of drugs (physical and chemical stability, dissolution rate and oral bioavailability), as well as helping to decrease toxicity and increase therapeutic efficacy (CHAUDHARI et al., 2018; KAVANAGH et al., 2019). The main multicomponent solid forms that can be found are salts, cocrystals, eutectic mixtures, coamorphous and hydrates/solvates (BOLLA; SARMA; NANGIA, 2022).

This work focuses on study different solid forms of two drugs. Valsartan (VAL) is an antihypertensive drug that acts as an angiotensin II receptor blocker (ARB). Belonging to the sartan family, it is one of the first to be commercialized, developed by Novartis, holding the largest market share of drugs of this type (SARKAR et al., 2011). VAL is classified as Biopharmaceutical Classification System (BCS) class II (it has a low aqueous solubility and high intestinal permeability) (HAMED; ALNADI, 2018; HUANG et al., 2017), improving its solubility is of great importance for bioavailability and even for reducing the adverse effects of this drug.

Norfloxacin (NOR) is a broad-spectrum antibiotic and 2nd generation fluoroquinolone, widely used mainly in the treatment of infections of the urinary tract, been classified by the BCS as class IV (low aqueous solubility and low intestinal permeability) (BEARDEN; DANZIGER, 2001; BREDI et al., 2009; DE SOUZA, 2005; HOLMES; BROGDEN; RICHARDS, 1985; VILA, 2005), which makes it compelling for this type of study.

For a better reading flow, this thesis is divided into five chapters. The first is a brief bibliographical review. Chapters 2, 3, and 4 refer to solid forms of valsartan and chapter 5 cocrystals of norfloxacin. In this work, coamorphous, therapeutic deep eutectic systems (THEDES) and low transition temperature

mixtures (LTTMs) of valsartan, were synthesized through mechanochemical methods. They were all studied through the construction of binary phase diagrams (solid-liquid diagrams and Gordon-Taylor's amorphous diagrams), in addition salts of valsartan were synthesized through solution crystallization. All systems were characterized using Differential Scanning Calorimetry – DSC), Infrared Spectroscopy (FTIR) and Powder X-Ray Diffractometry (PXRD). Some systems present the thermogravimetry with simultaneous differential thermal analysis – TG-DTA, the evolved gas analysis (EGA) and some systems were selected to have their physical stability, solubility and dissolution evaluated. The coamorphous of valsartan with naringenin and carvedilol have a limited solubility, the liquid formulations hereby called LTTMs of valsartan with menthol, thymol and catechol presented a drug release profile higher with menthol, and the salts of valsartan with roxadustat, folic acid and 4-aminobenzoic acid have a higher aqueous solubility in comparison with valsartan. Furthermore, it is presented the study of the scale up viability in solution of norfloxacin cocrystals using ternary phase diagram as a tool to understand the best conditions of synthesis.

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6.1. FINAL CONSIDERATIONS

With all presented data it is possible to conclude that new entities with the potential to improve valsartan were obtained and successfully characterized. Coamorphous with low solubility, high solubility salts and a new liquid formulation were presented. Also, a study for scale up viability for norfloxacin cocrystals already published.

In summary:

- Chapter 2 presents the synthesis and characterization of two new coamorphous of valsartan with naringenin and carvedilol. The first one presented low stability to humid conditions, which presents NAR crystallization. And the second one (with carvedilol), even though has high stability, due to the strong interaction between the drugs, has a lower dissolution rate than the isolated components. Which goes against what is assumed for amorphous and coamorphous systems.
- Chapter 3 presents the synthesis and thermal characterization of the VAL-MENT, VAL-THY and VAL-CAT systems. The VAL-MENT and VAL-THY systems have a very similar behavior, in the first heating they present as a classic eutectic mixture, having a good fit to the theoretical liquidus line estimated by the Schröder-van Laar equation. In the second heat, the systems interact, as shown in the FTIR, and do not crystallize, forming LTTMs. The VAL-CAT system presents a considerable decrease in the melting point of the molar fractions $X_{VAL} = 0.3$ to 0.5 , which is a characteristic behavior of THEDES systems. The second heat also presents a LTTM. The drug release profile of the samples demonstrates that the least viscous sample (VAL-MENT) has the highest percentage of drug release, and the most viscous sample (VAL-CAT) has the lowest.
- Chapter 4 presents the studies of three new salts-solvates of valsartan, with roxadustat, folic acid (both hydrates) and 4-aminobenzoic acid (ethanol solvate), the synthesis method of the Entresto® drug was adapted and successfully applied for these systems. All new salts presented a significantly higher solubility in comparison to VAL alone.

- Chapter 5 presents the experimental path, to obtain a ternary phase diagram, from van't Hoff solubilities obtained using the Crystal16 equipment. With the diagrams, it was possible determine the experimental conditions to synthesized in solution four already published cocrystals of norfloxacin.

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APPENDIX A

Chapter 2 – Coamorphous

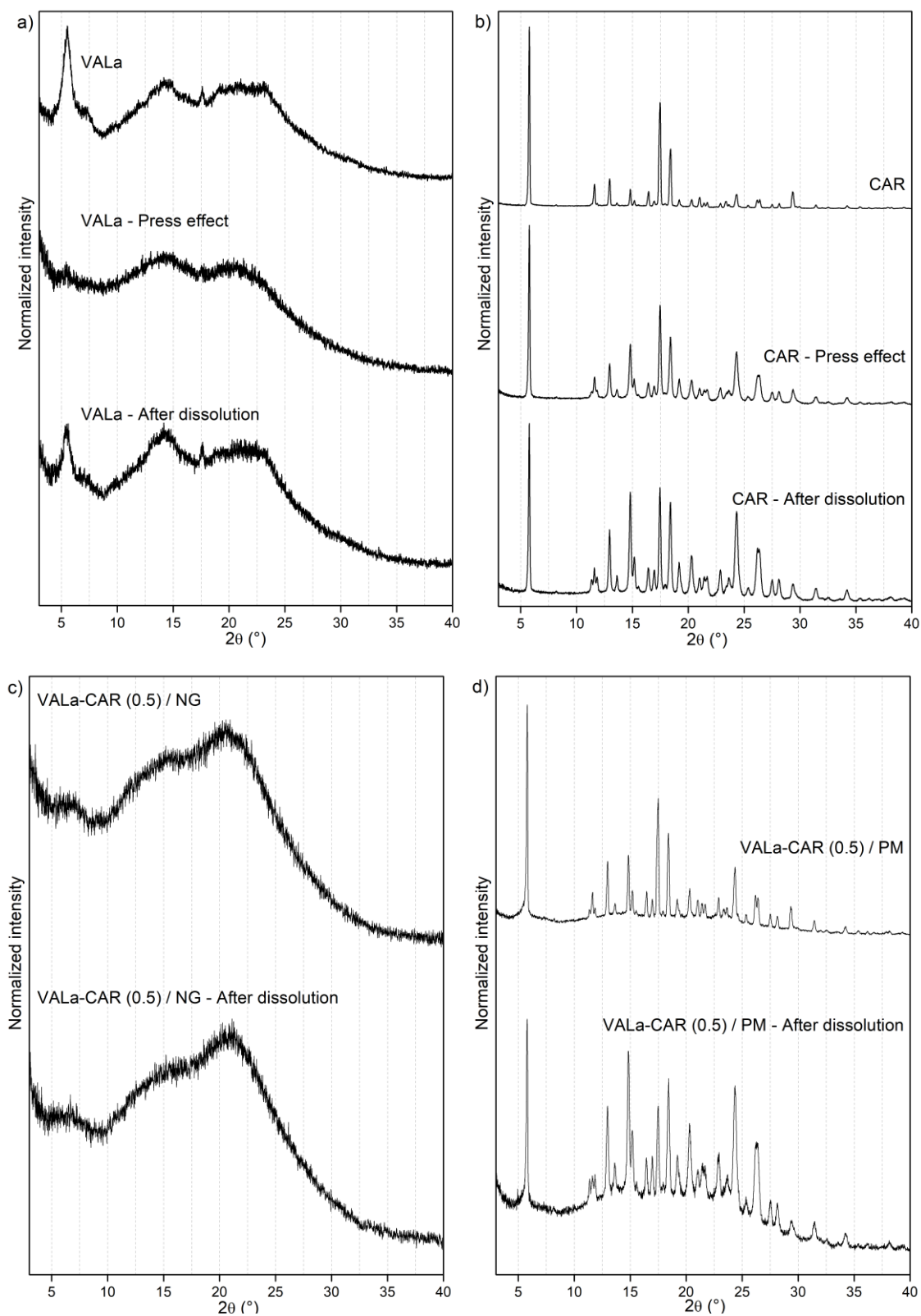


Figure A.1 – PXRD a) VALa, b) CAR, c) VALa-CAR (0.5) / NG and d) VALa-CAR (0.5) / PM after dissolution.

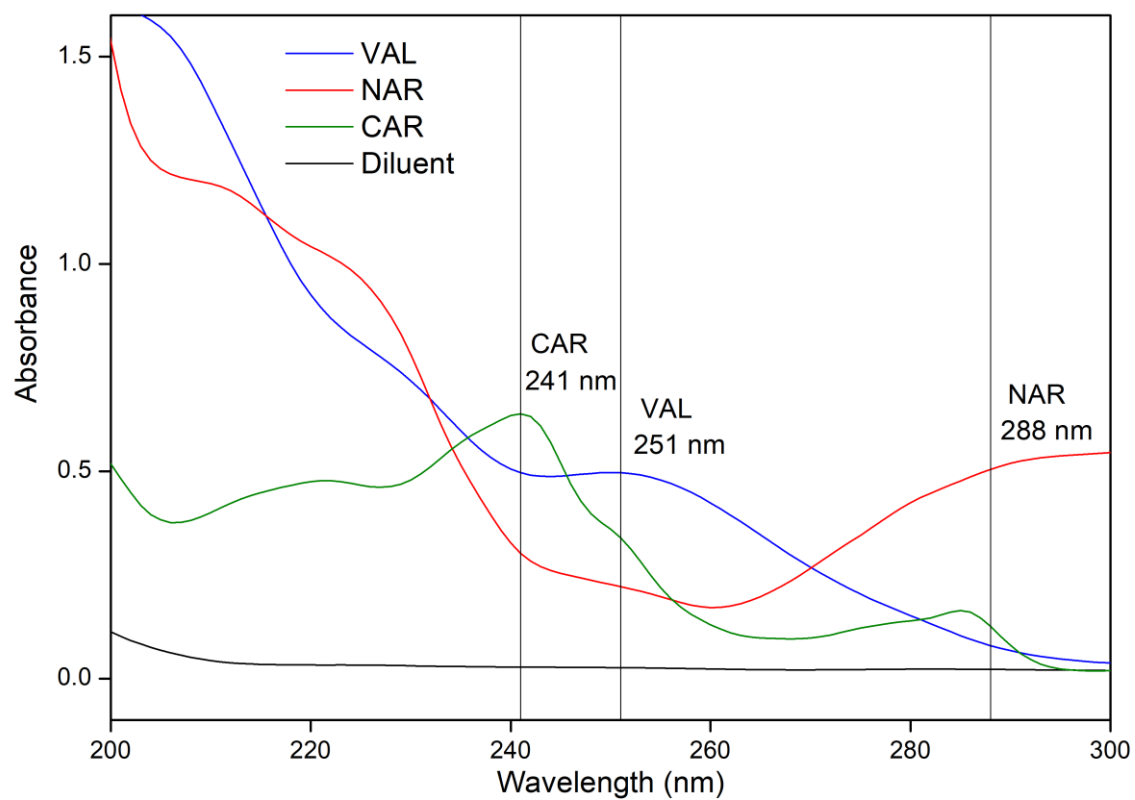
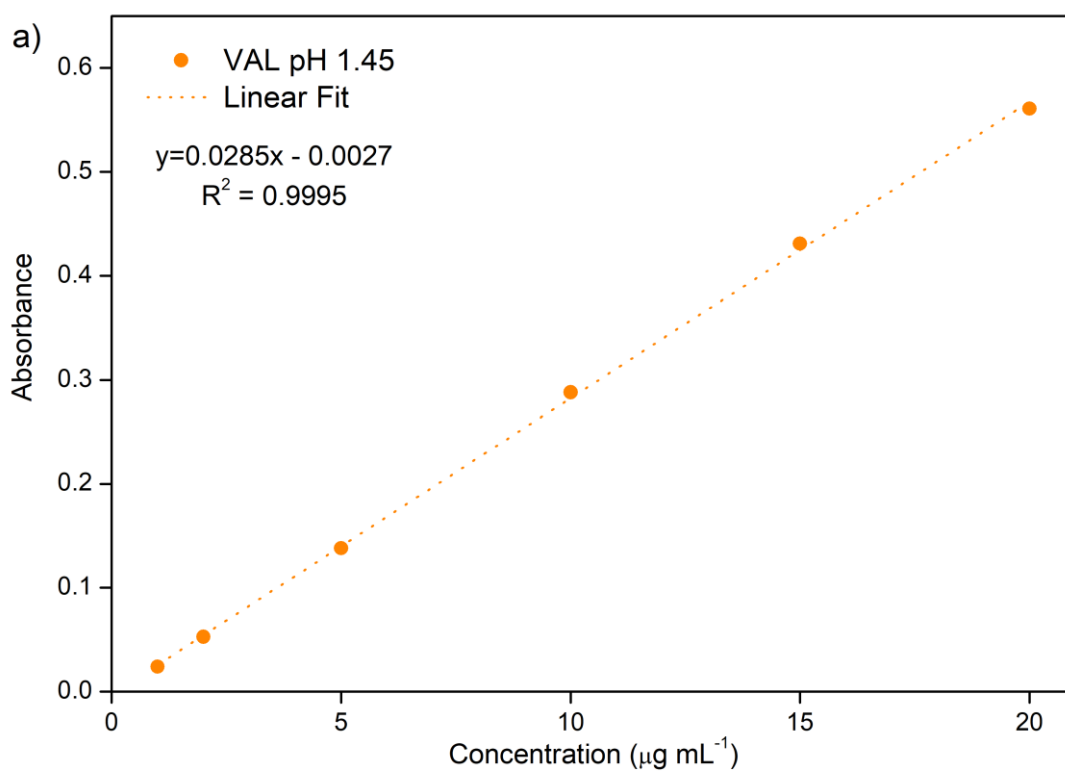
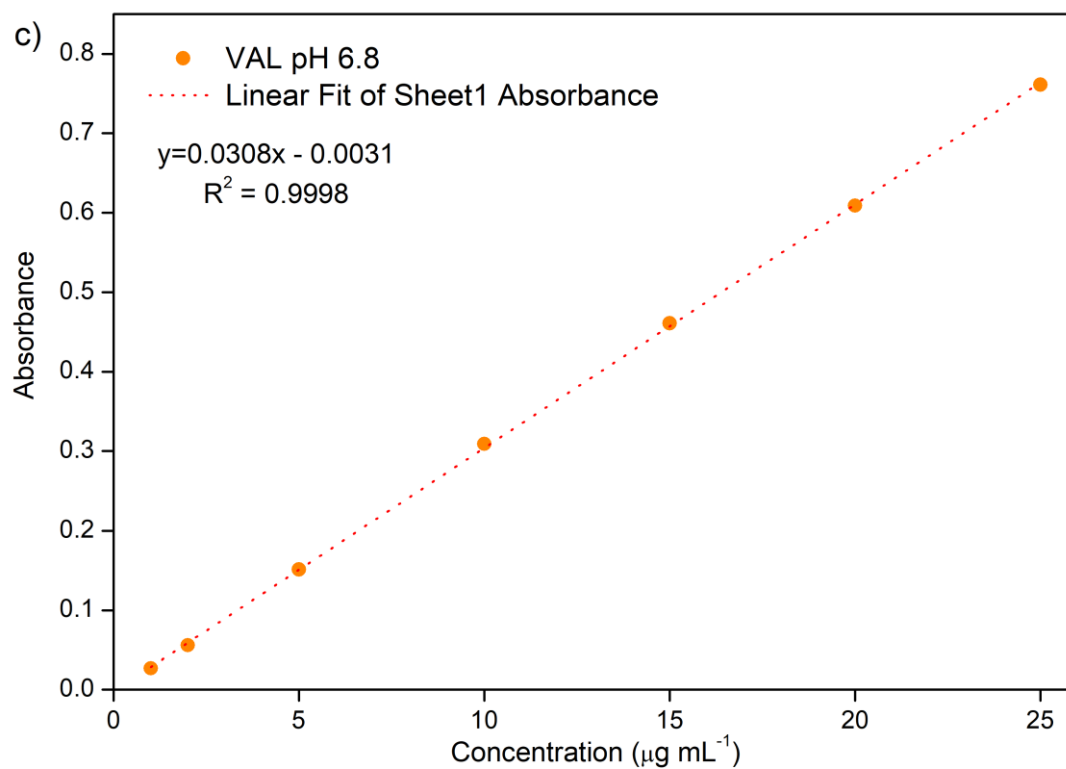
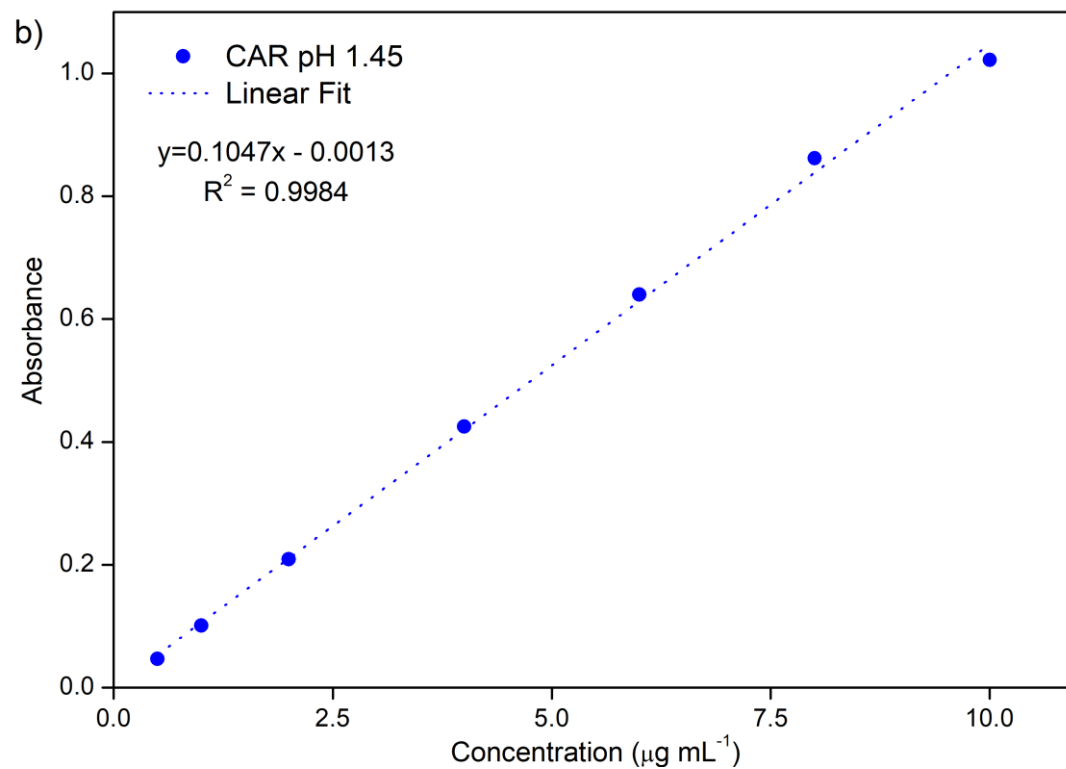


Figure A.2 – UV spectra of VAL, NAR, CAR and 6.8 buffer solution.





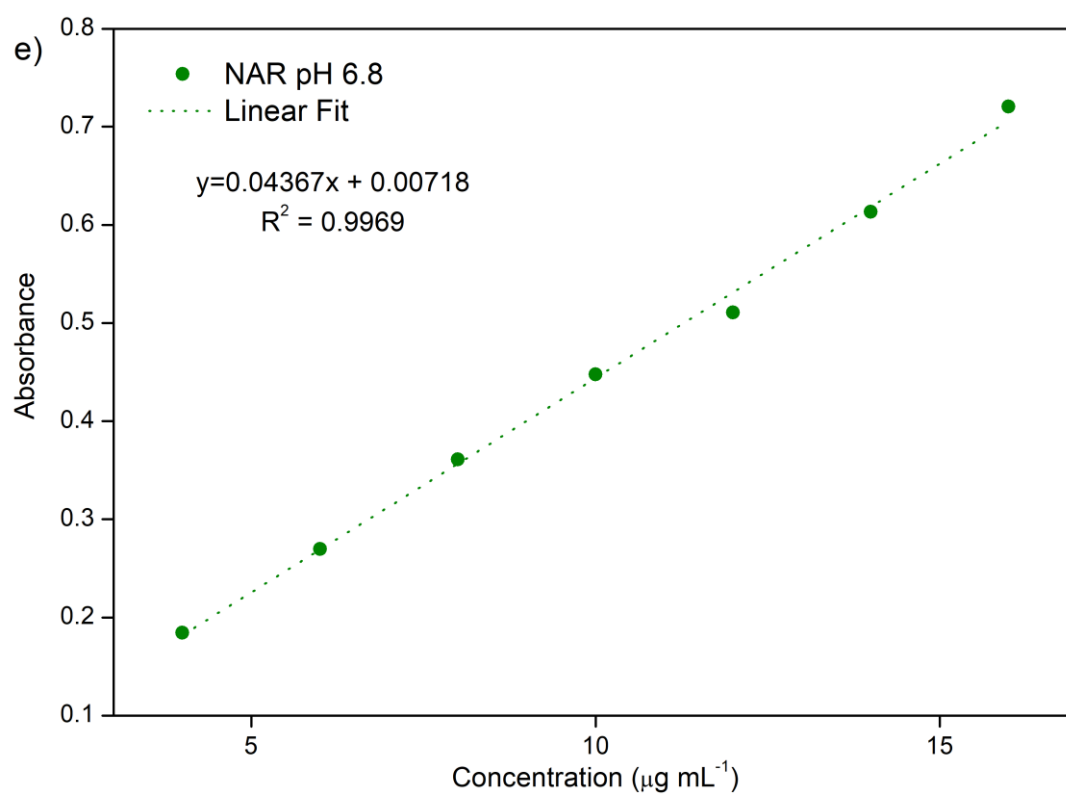
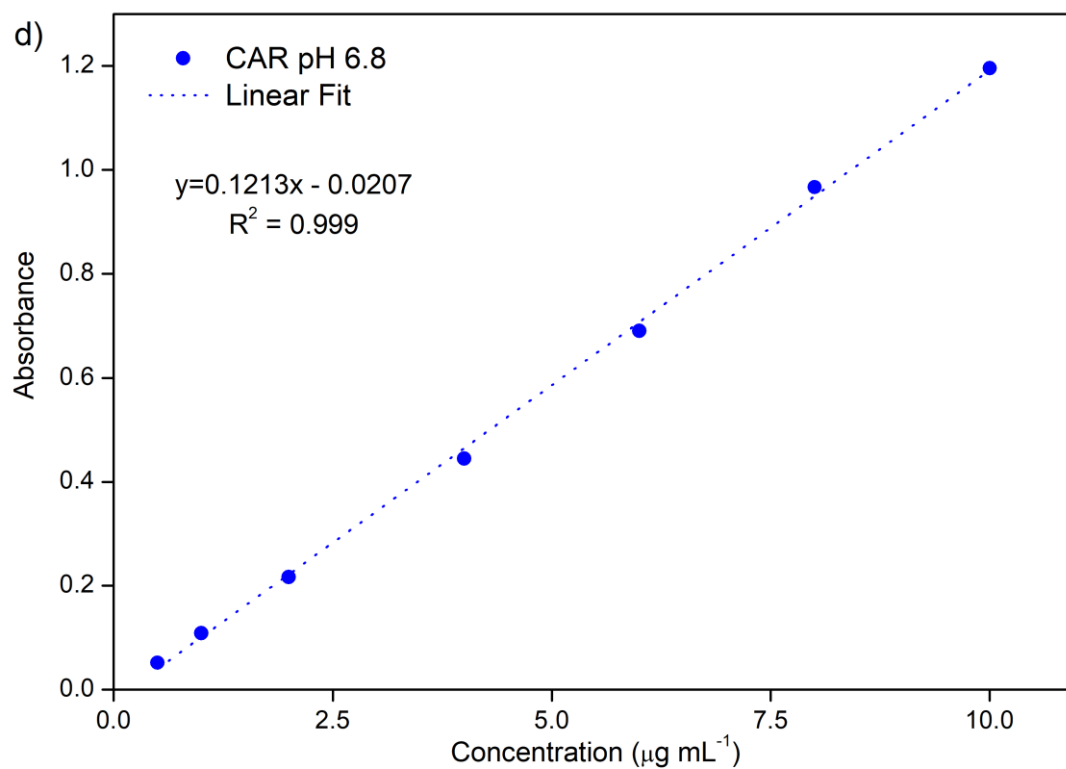
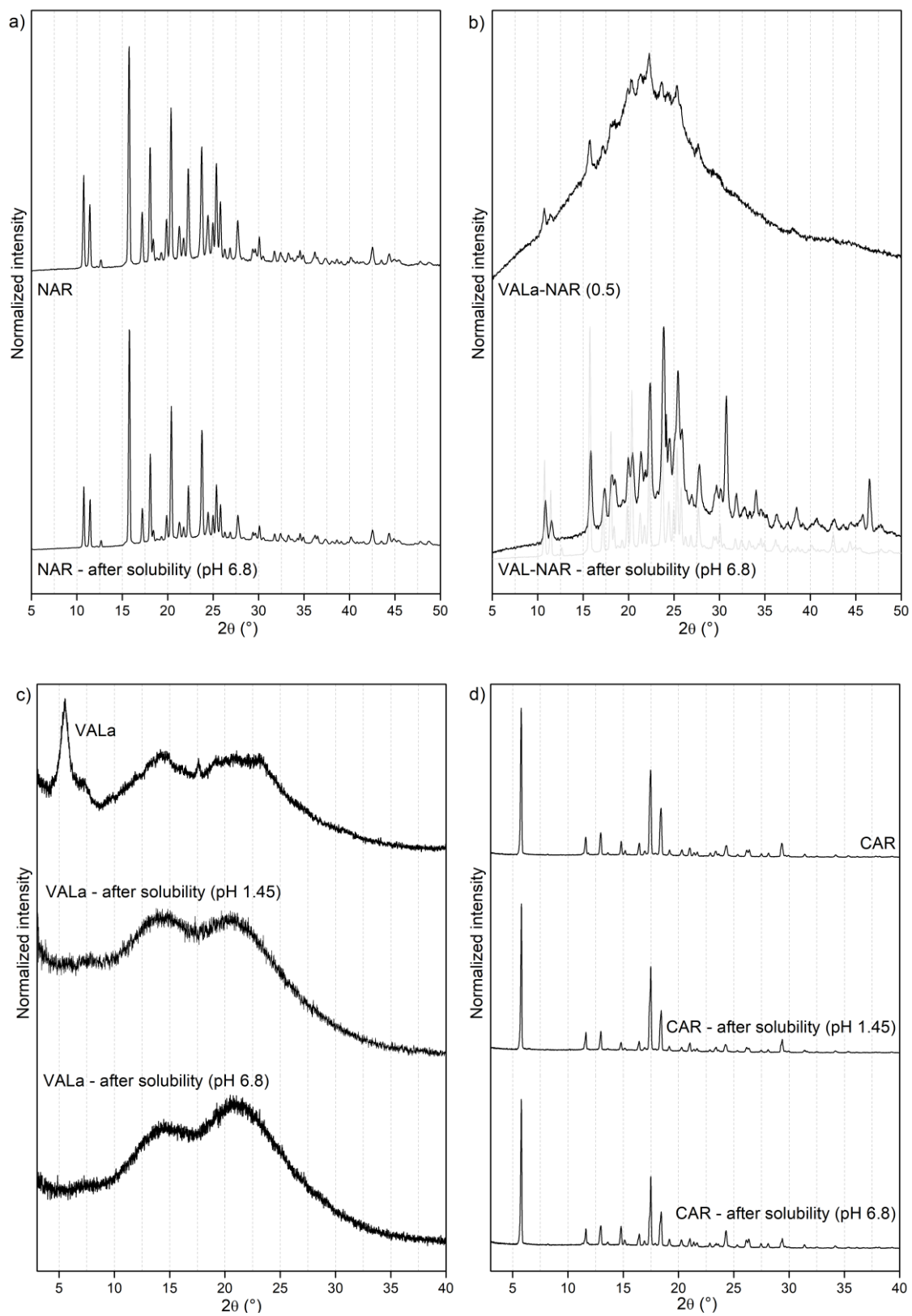


Figure A.3 – Analytical curves, linear equation (y) and correlation coefficient (R^2) of a) and c) VAL at $\lambda = 251$ nm, b) and d) CAR at $\lambda = 241$ nm in pH 1.45 and 6.8 buffers solutions respectively and e) NAR at $\lambda = 268$ nm in 6.8 buffer solution.



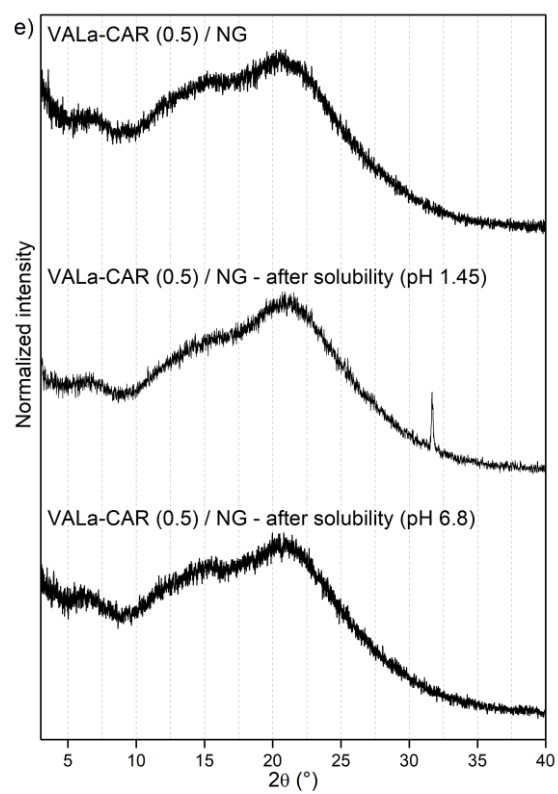


Figure A.4 – PXRd of a) VALa, b) CAR, c) VALa-CAR (0.5) / NG, d) NAR and e) VALa-NAR (0.5) before and after solubility study.

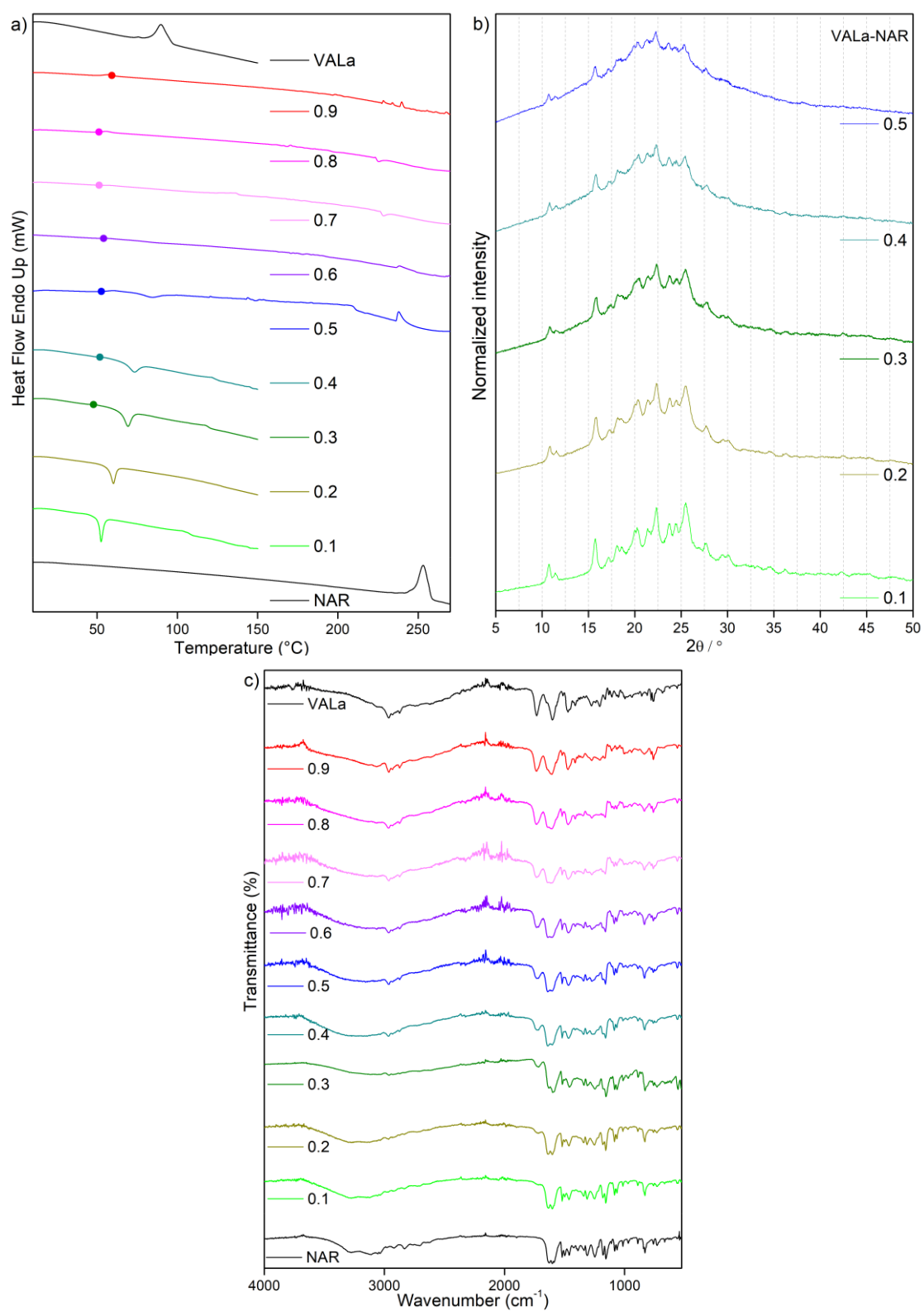


Figure A.5 – a) DSC curves of different molar fractions of VAL and b) FTIR of the different molar proportions of the VAL-NAR systems.

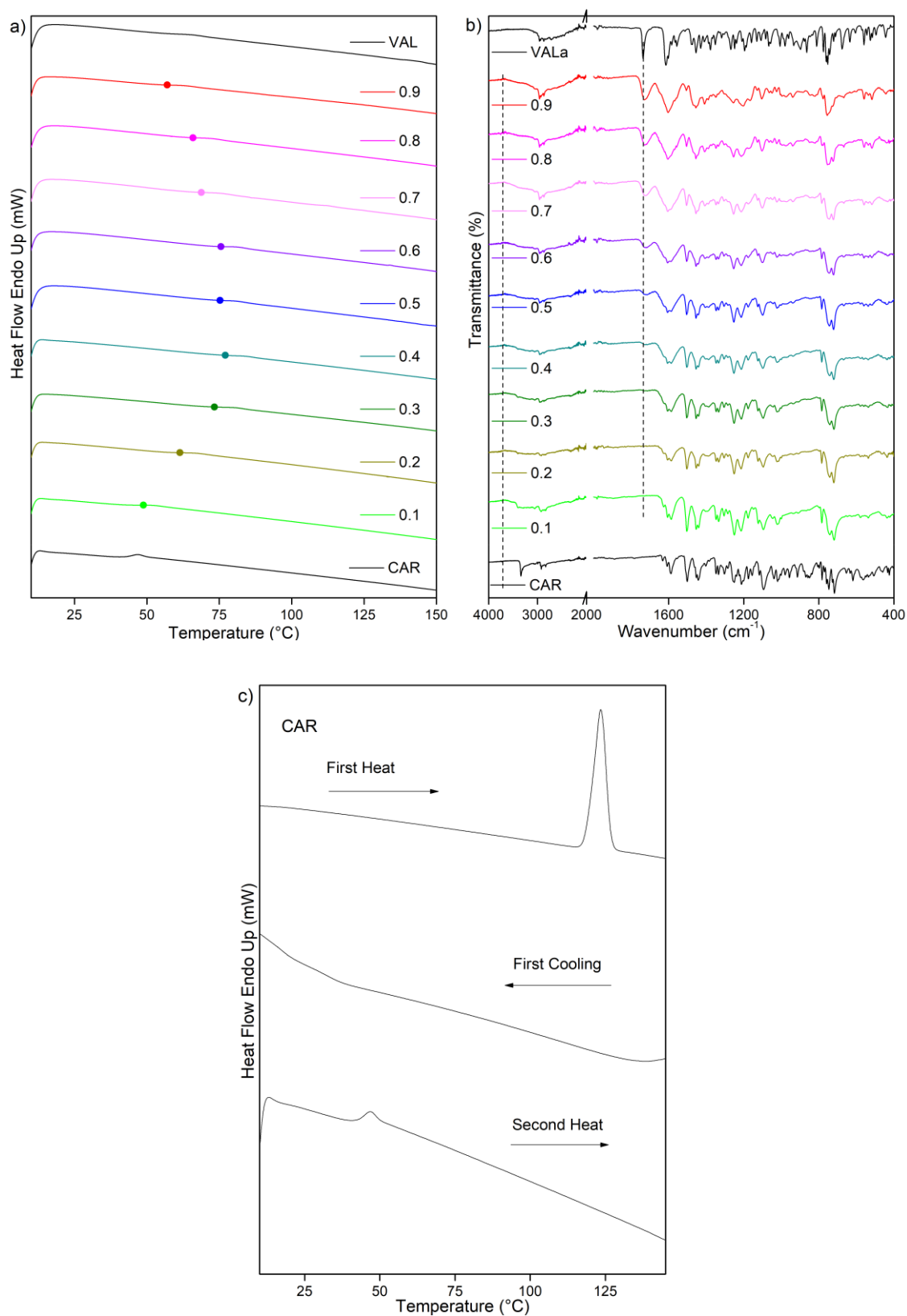


Figure A.6 – a) DSC curves of the different molar fractions of VAL-CAR system b) FTIR of the samples of different molar proportions of the VAL-CAR systems, and DSC of the heating/cooling cycle of the CAR sample.

APPENDIX B

Chapter 3 – THEDES / LTTM

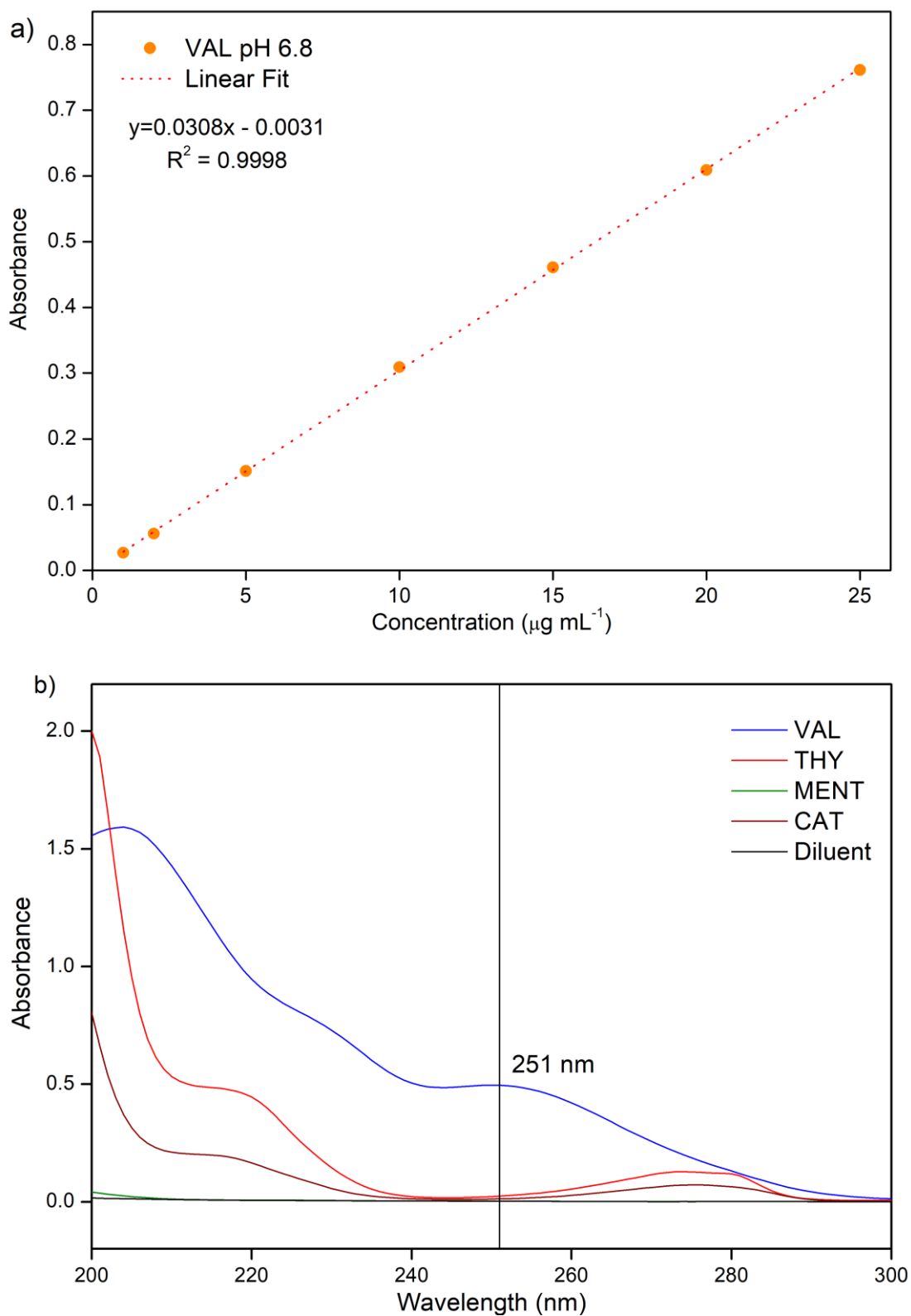


Figure B.1 – a) VAL Analytical curve at $\lambda = 251$ nm, linear equation (y) and correlation coefficient (R^2) in pH 6.8 buffer solution. b) UV spectra of VAL, the coformers (MENT, THY and CAT), and the buffer solution used as diluent (pH 6.8 phosphate buffer).

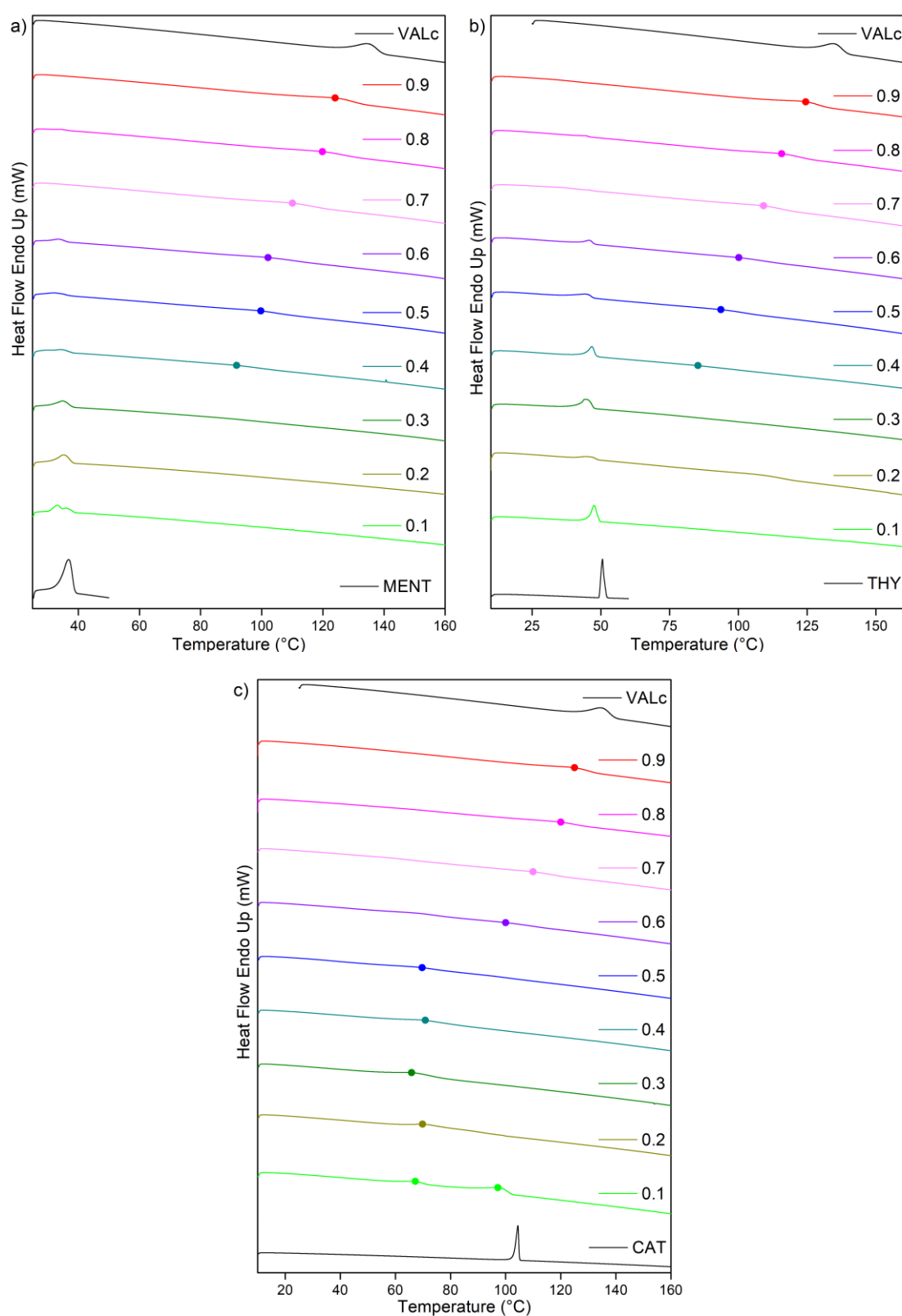


Figure B.2 – DSC curves of the first heating cycle of a) VALc-MENT systems, b) VALc-THY systems and c) VALc-CAT systems.

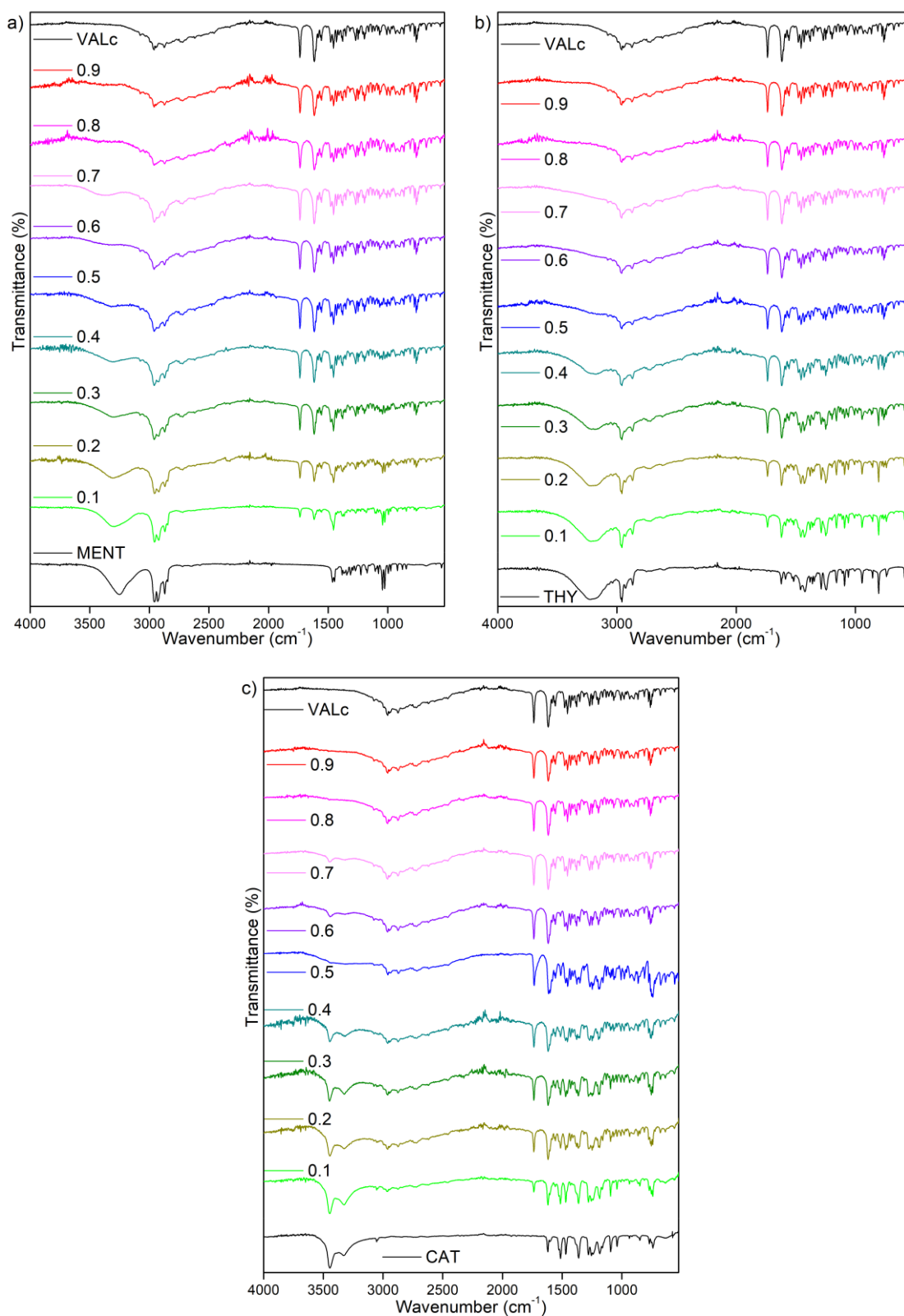


Figure B.3 – FTIR of the different molar proportions of the a) VAL-MENT systems, b) VAL-THY systems and c) VAL-CAT systems.

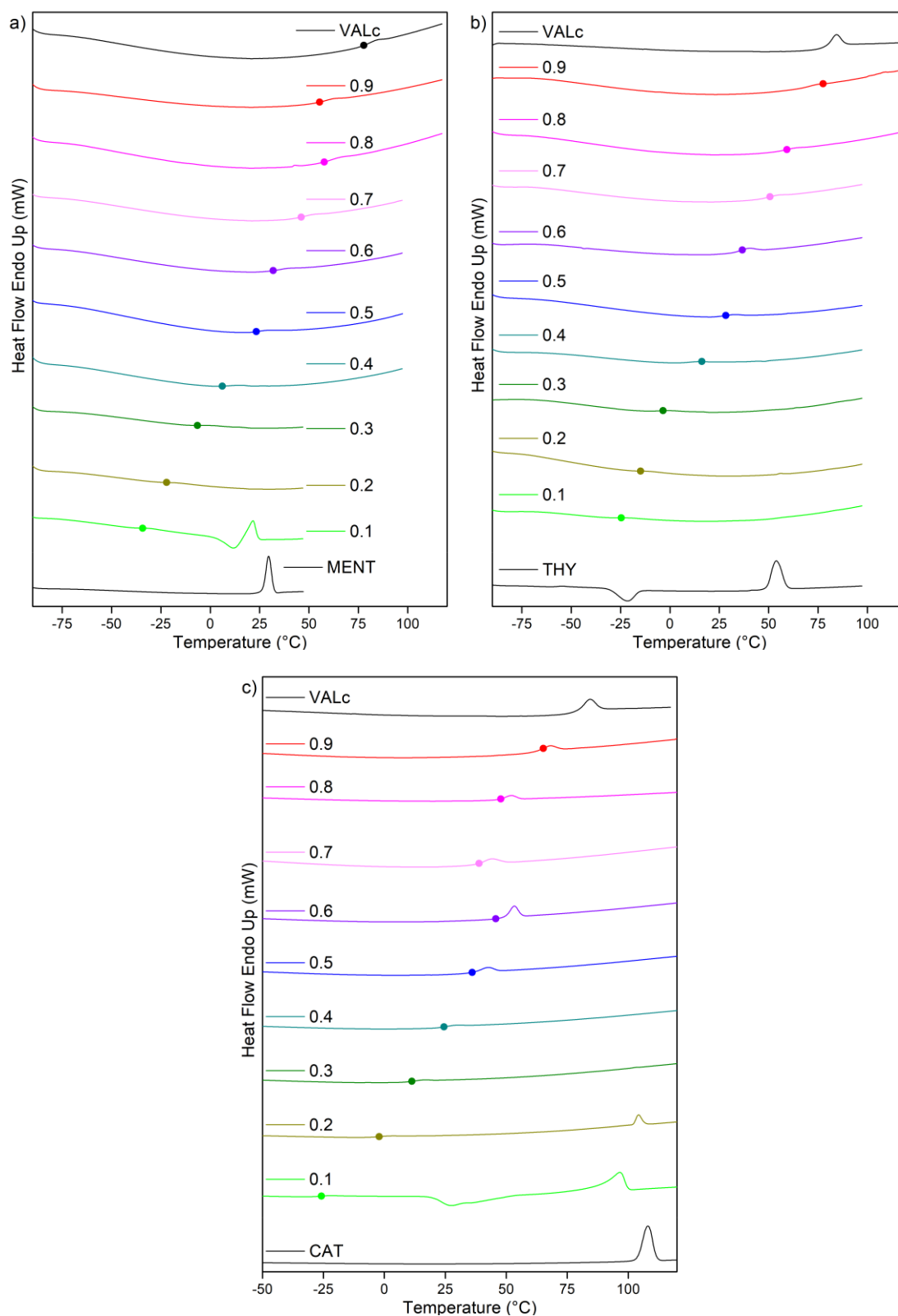


Figure B.4 – DSC curves of the second heat (-100 °C to 120 °C) of a) VALc-MENT systems, b) VALc-THY systems and c) VALc-CAT systems.

APPENDIX C
Chapter 4 – Salts

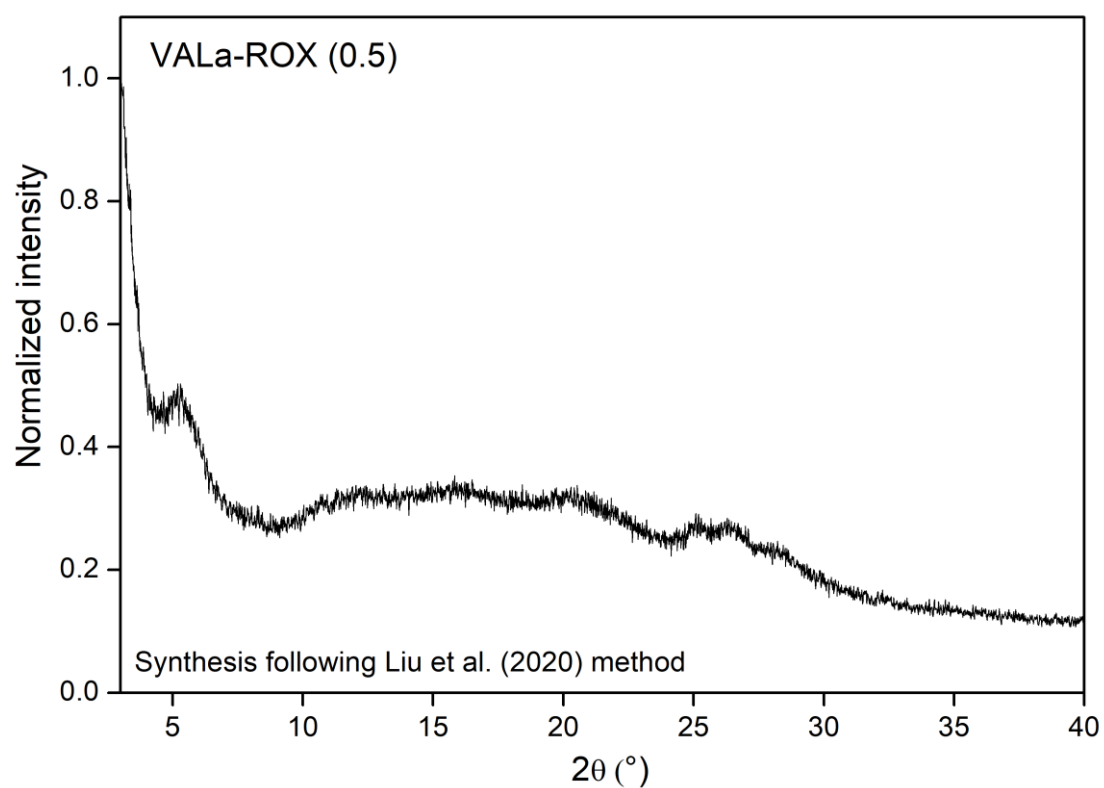


Figure C.1 – PXRD of the VALa-ROX (0.5) system (Synthesized following the method reported by Liu et al. (2020), using acetone as the solvent, stirring for 3 h, and drying the sample for 12h in a vacuum incubator).

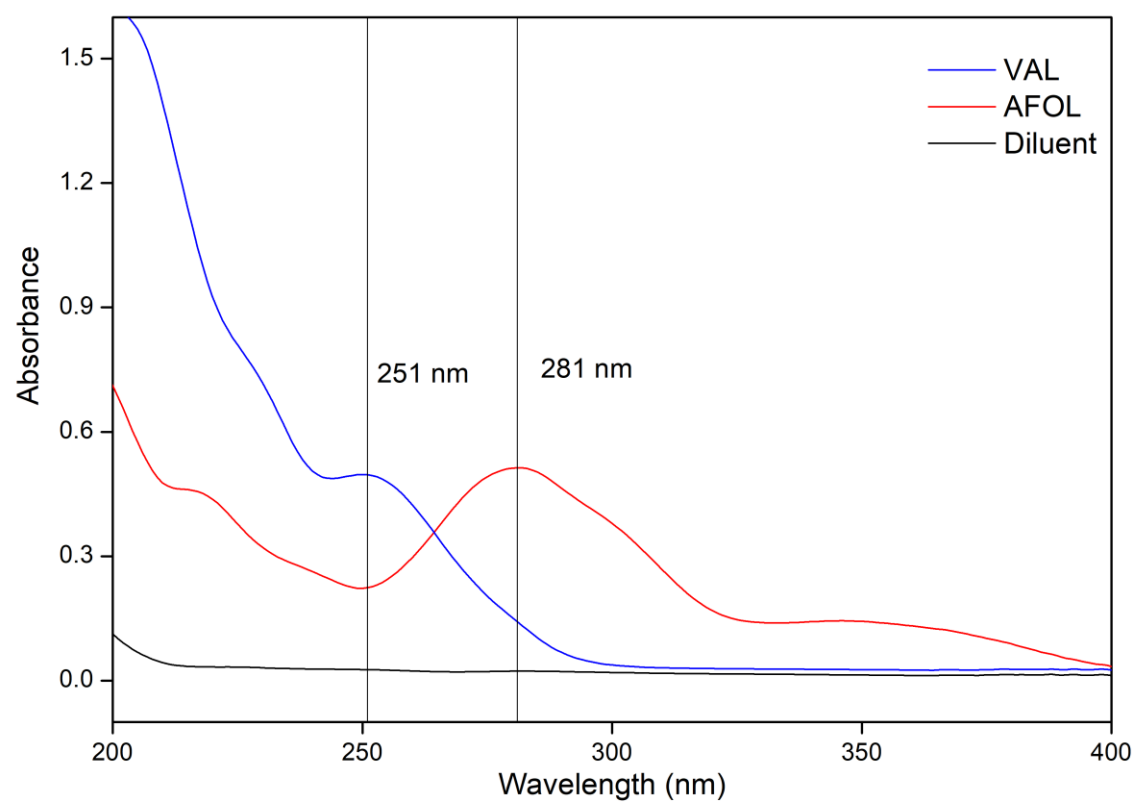


Figure C.2 – UV spectra of VAL, AFOL and the diluent used (buffer solution pH 6.8).

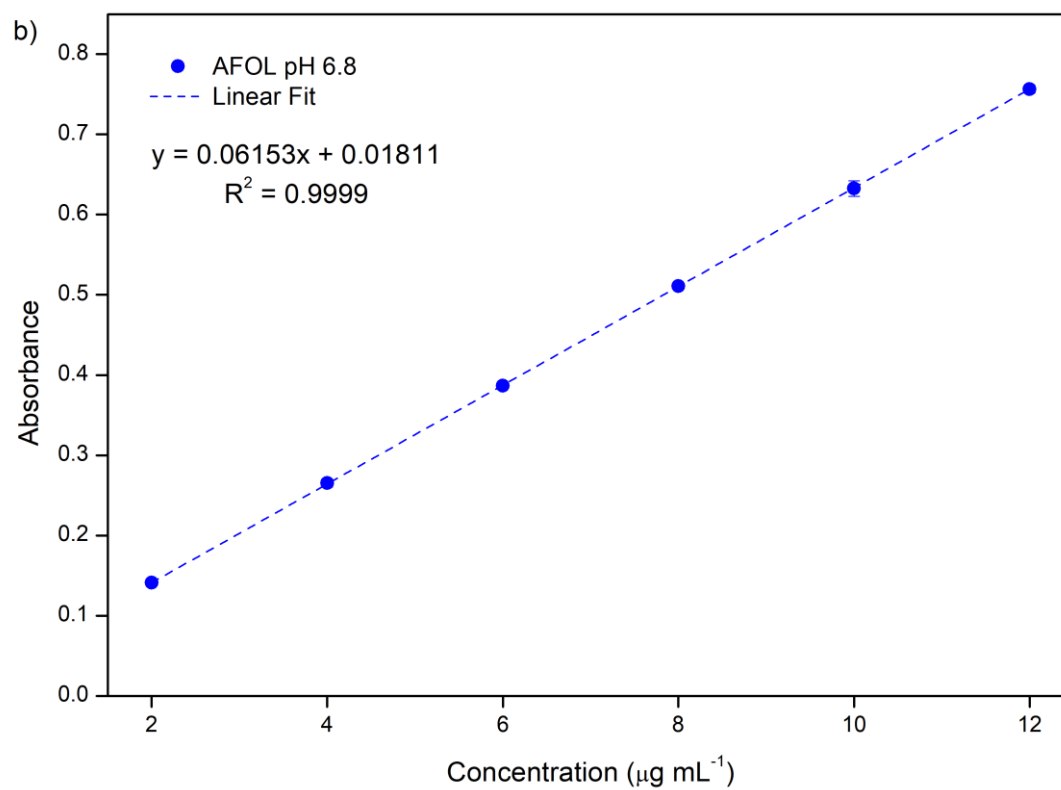
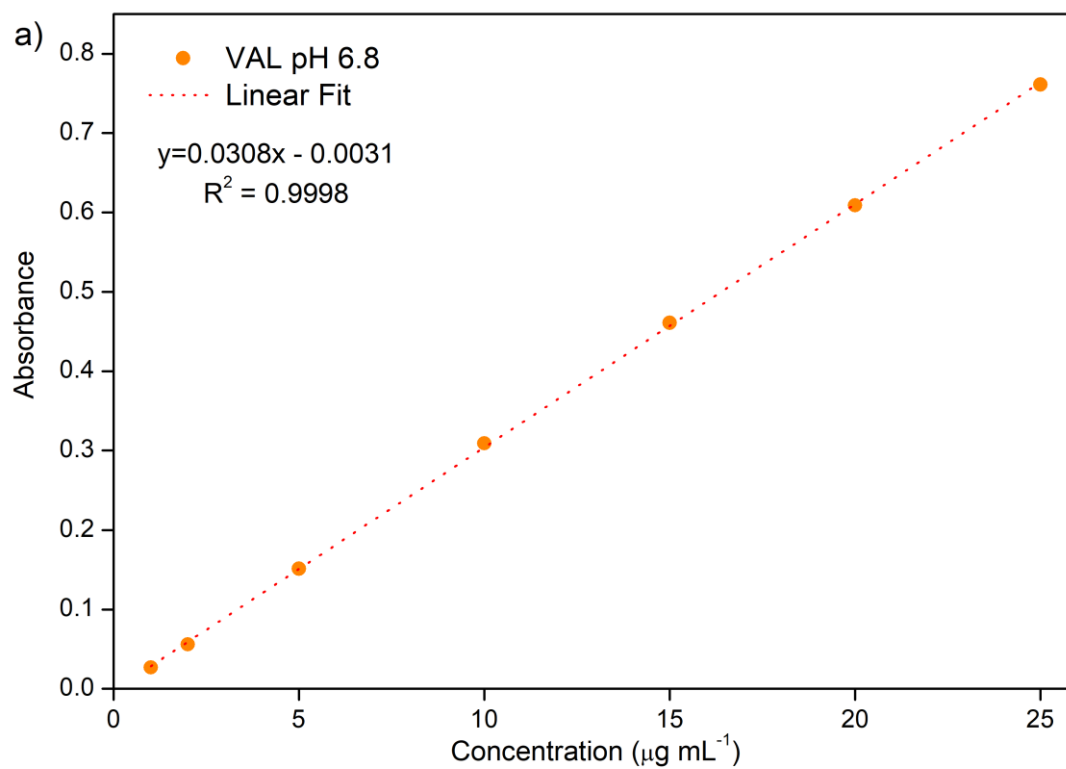


Figure C.3 – Analytical curves, linear equation (y) and correlation coefficient (R^2) of a) VAL at $\lambda = 251$ nm and b) AFOL at $\lambda = 281$ nm in pH 6.8 buffer solution.

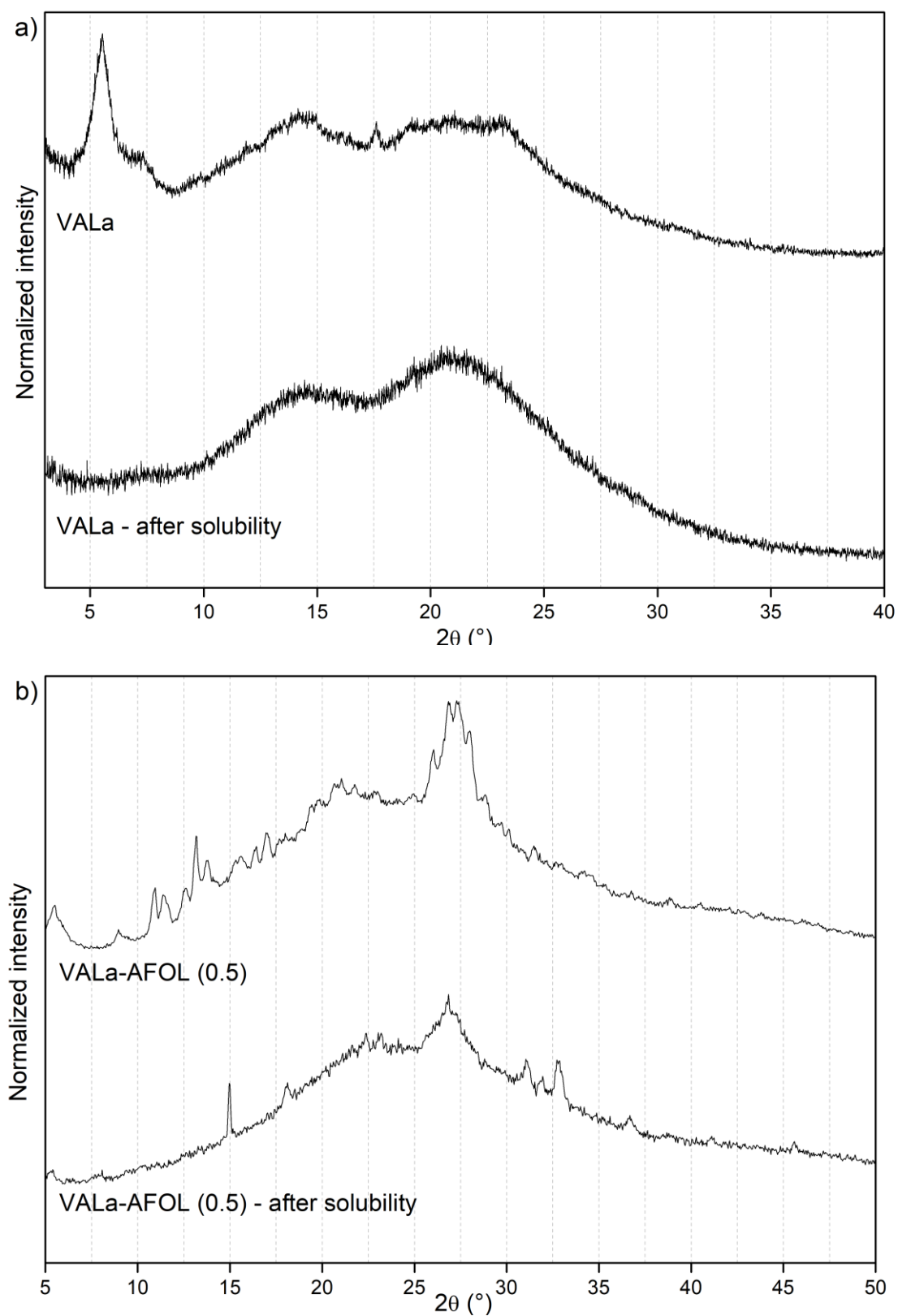


Figure C.4 – PXRD after solubility study of a) VALa, and b) VAL-AFOL sample.

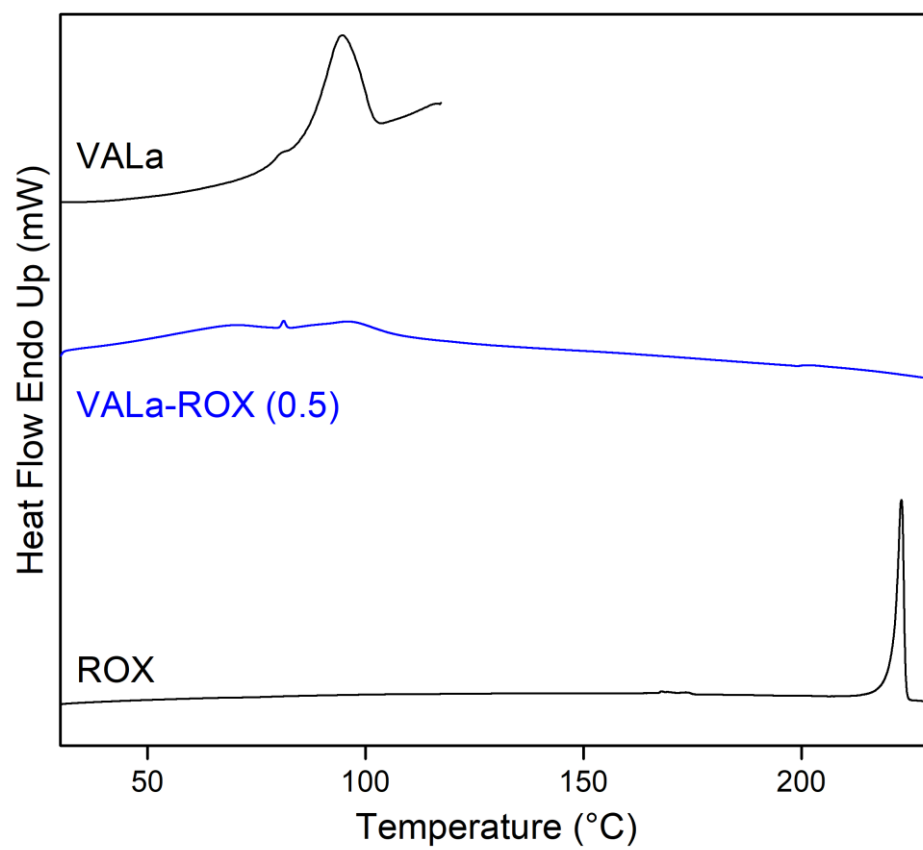
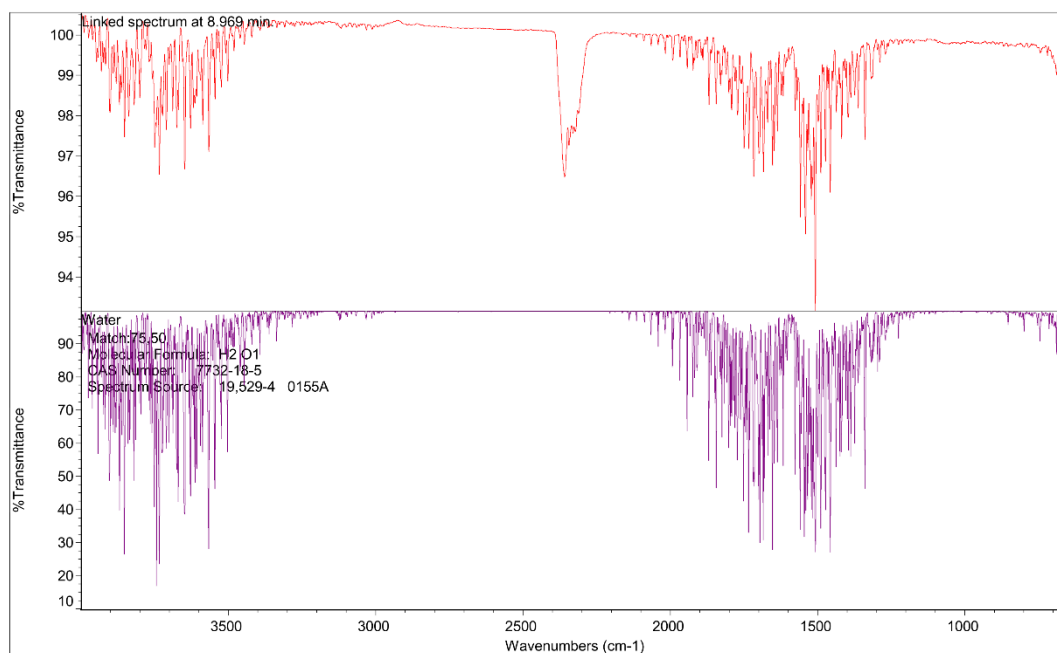


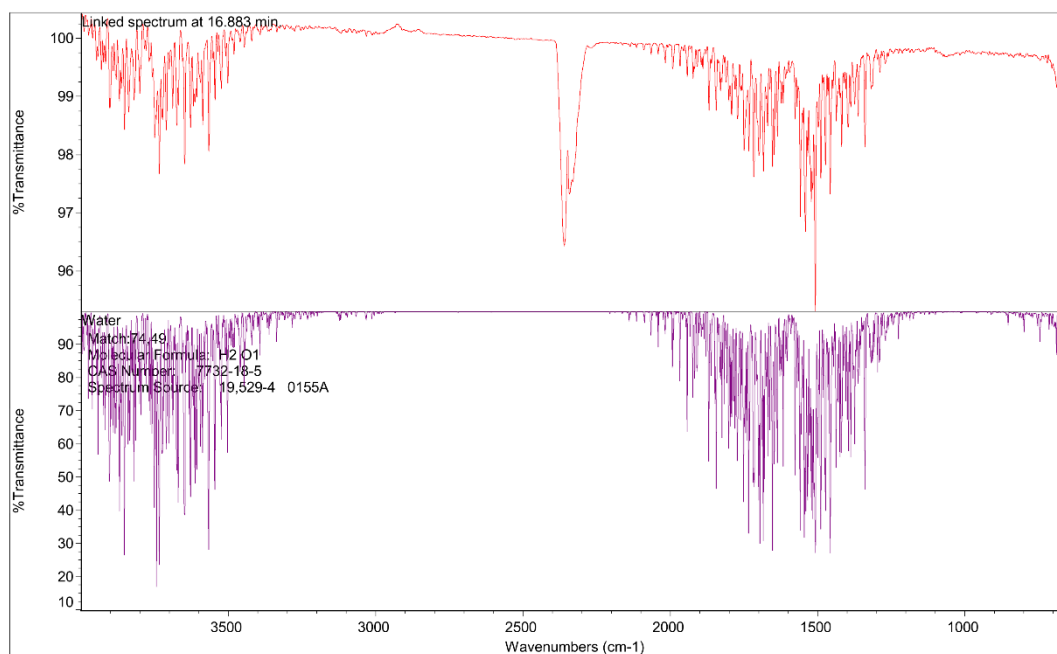
Figure C.5 – DSC curve of VALa, VALa-ROX and ROX.

a) VALa-ROX

Search results for: Linked spectrum at 8.969 min.
Date: Tue Jul 16 01:56:41 2024 (GMT-03:00)
Search algorithm: Correlation
Regions searched: 3495,26-455,13

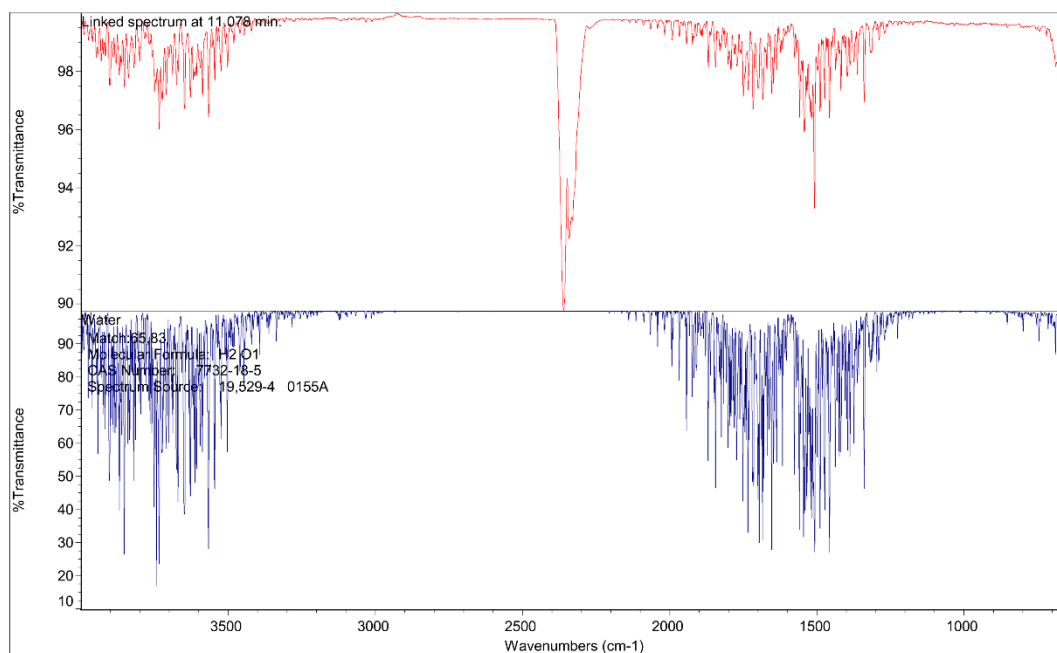


Search results for: Linked spectrum at 16.883 min.
Date: Tue Jul 16 02:00:35 2024 (GMT-03:00)
Search algorithm: Correlation
Regions searched: 3495,26-455,13

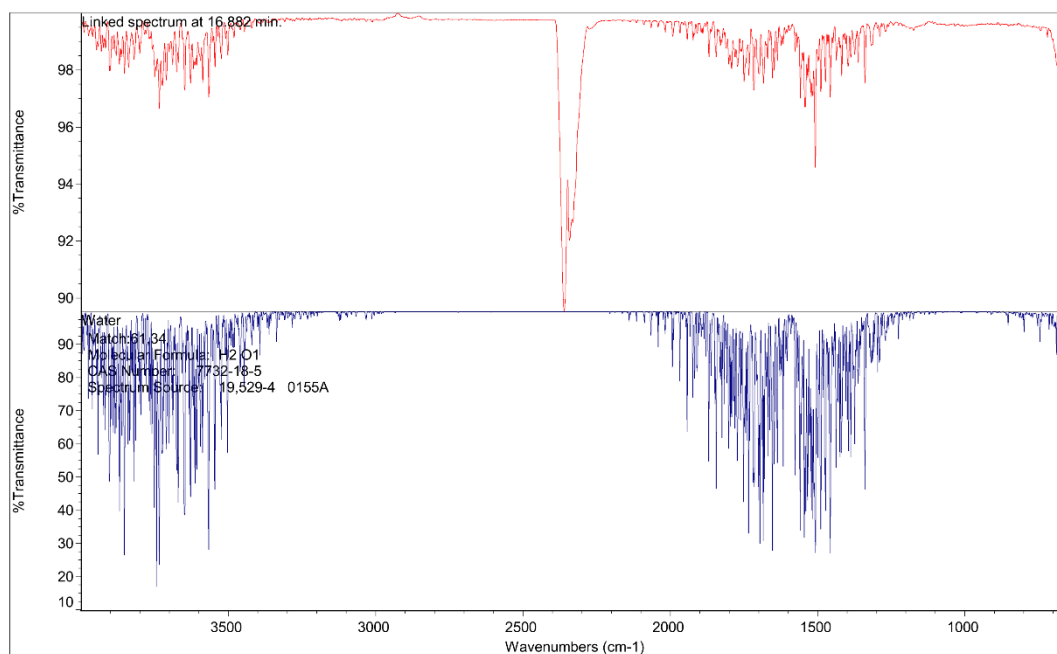


b) VALa-AFOL

Search results for: Linked spectrum at 11.078 min.
Date: Tue Jul 16 01:11:43 2024 (GMT-03:00)
Search algorithm: Correlation
Regions searched: 3495,26-455,13

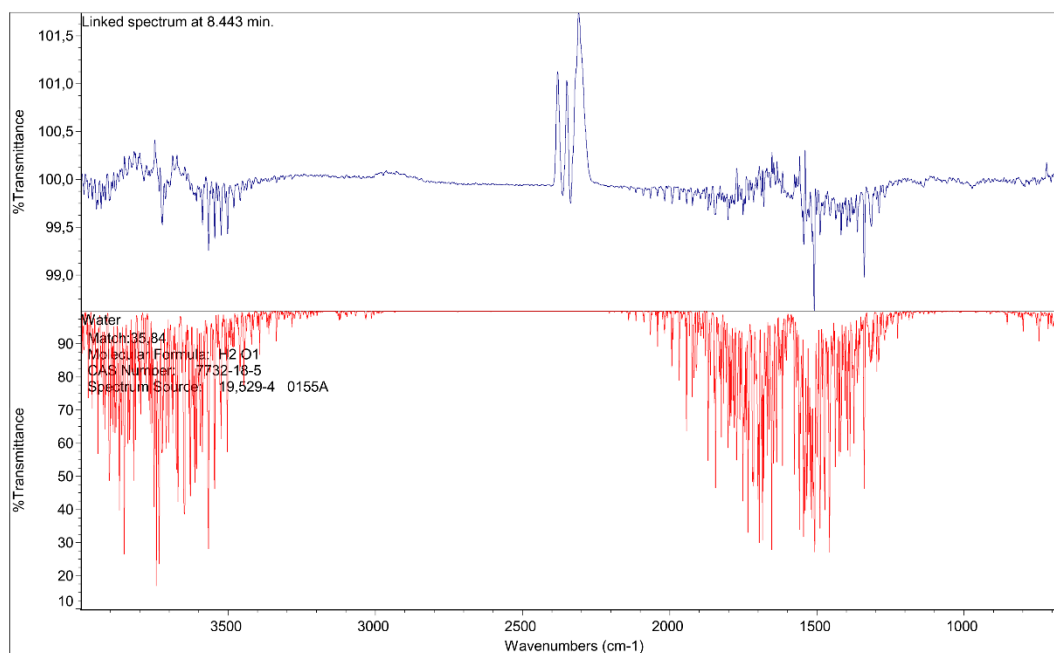


Search results for: Linked spectrum at 16.882 min.
Date: Tue Jul 16 01:18:45 2024 (GMT-03:00)
Search algorithm: Correlation
Regions searched: 3495,26-455,13



c) VALa-PABA

Search results for: Linked spectrum at 8.443 min.
 Date: Mon Jul 15 21:40:25 2024 (GMT-03:00)
 Search algorithm: Correlation
 Regions searched: 3495,26-455,13



Search results for: Linked spectrum at 20.051 min.
 Date: Mon Jul 15 21:44:34 2024 (GMT-03:00)
 Search algorithm: Correlation
 Regions searched: 3495,26-455,13

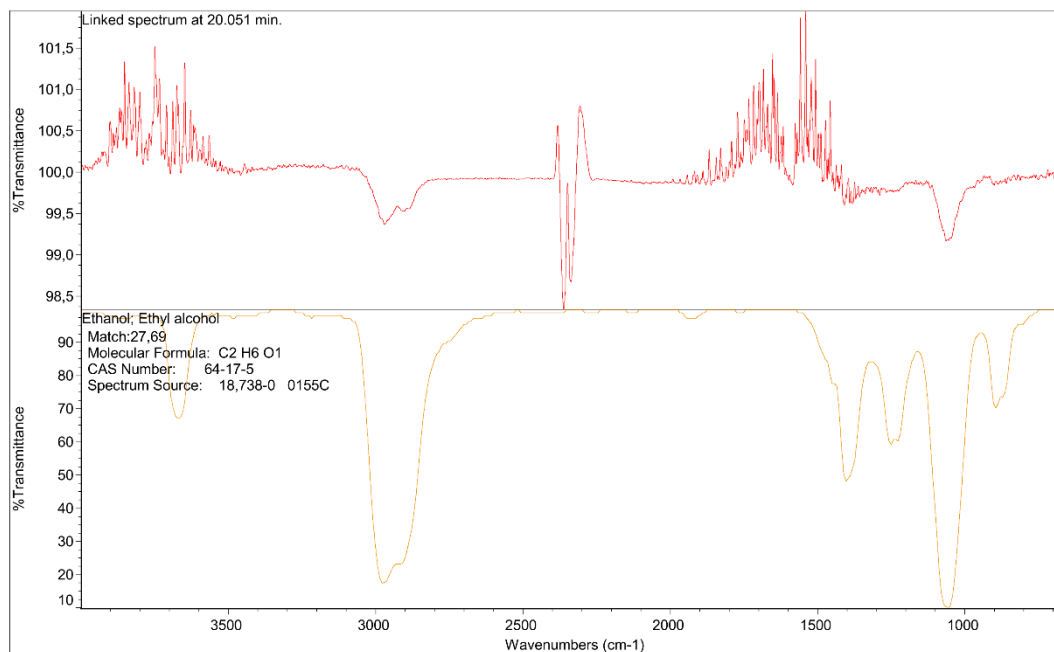


Figure C.6 – Data obtained through spectrum search in the software of the spectrophotometer OMNIC 8.0. a) VALa-ROX, b) VALa-AFOL and c) VALa-PABA

APPENDIX D
Chapter 5 – Cocrystals

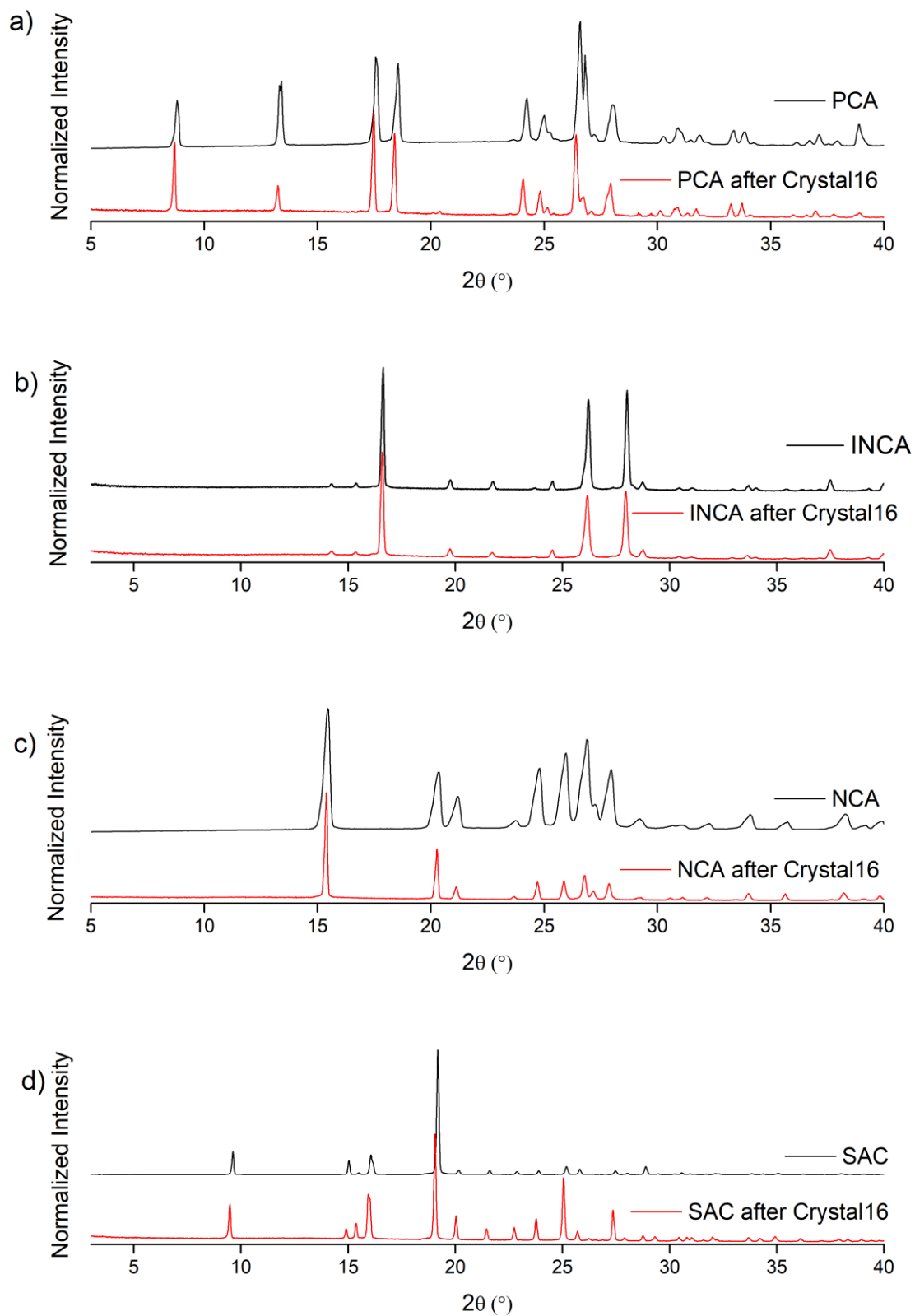


Figure D.1 – Comparison of starting powder X-ray diffractograms of a) PCA, b) INCA, c) NCA and d) SAC coformers with those obtained after Crystal16 experiments.

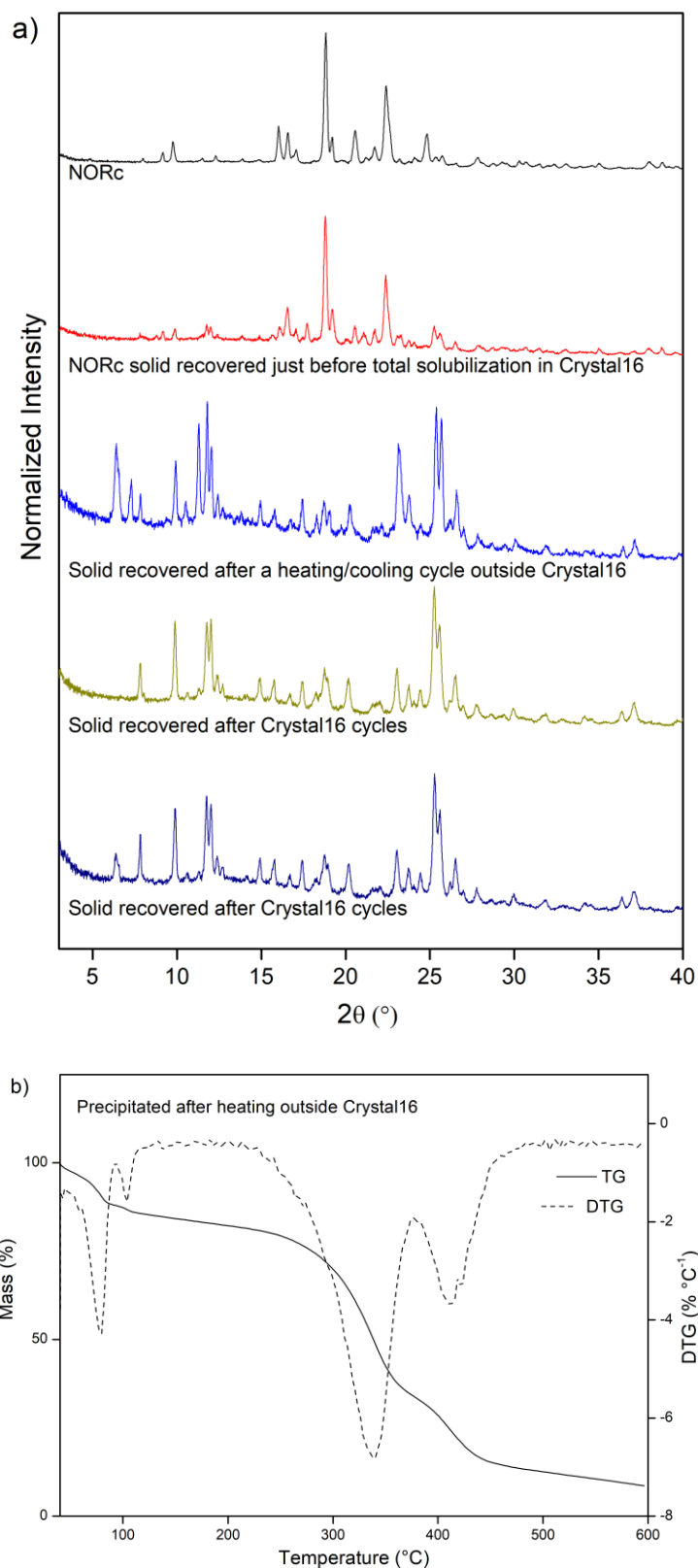


Figure D.2 – a) PXRD diffractograms of NORc, NORc solid recovered just before total solubilization in Crystal16, solid recovered after a heating/cooling cycle outside Crystal16, and two samples of solids recovered after Crystal16 cycles, and b) TG/DTG curves of the solid recovered after a heating/cooling cycle outside Crystal16, pointing to a 1NOR:1.5EtOH solvate; $\Delta m_{\text{calc.}} = 17.8\%$; $\Delta m_{\text{TG}} = 17.7\%$.

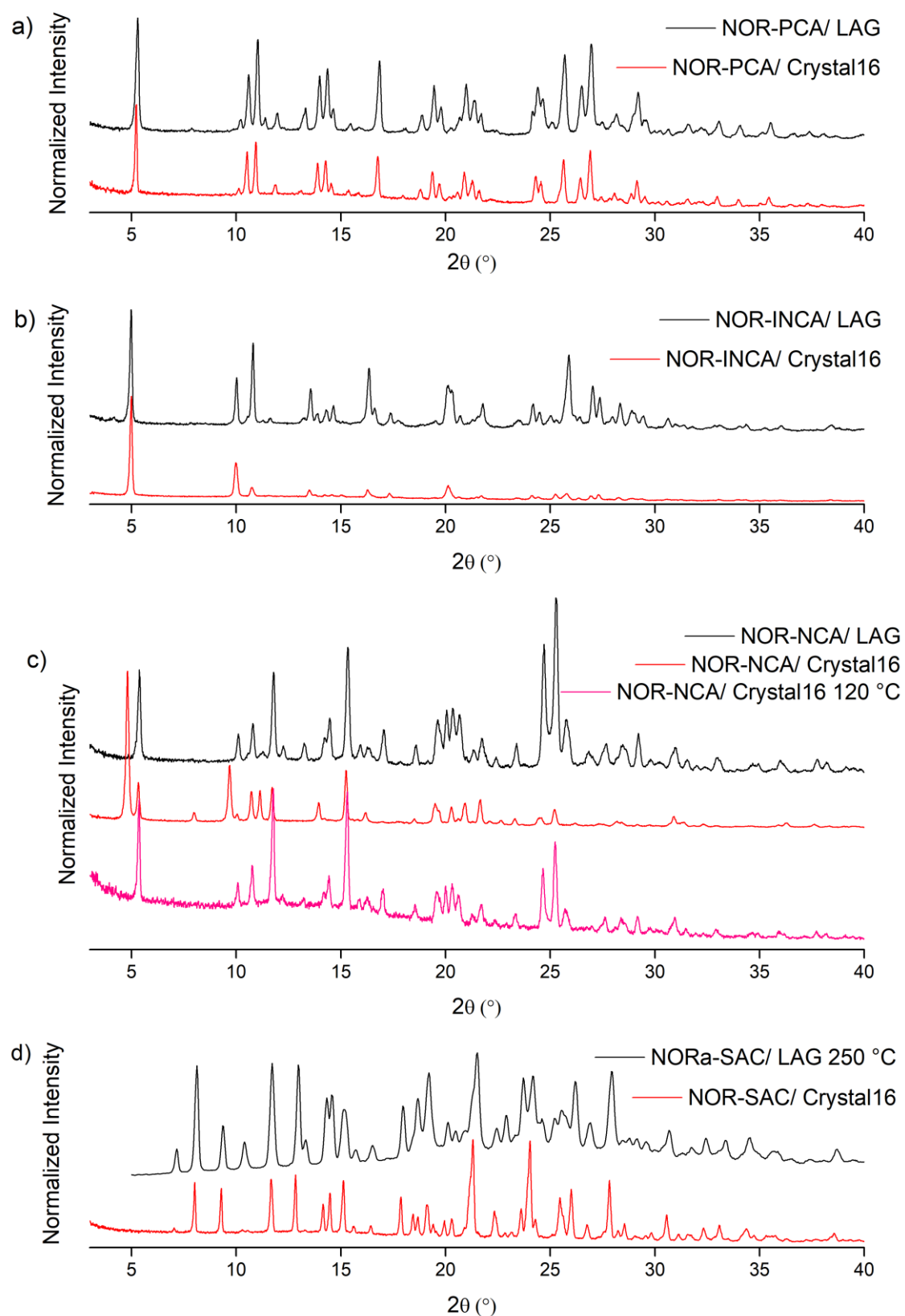


Figure D.3 – Comparison between diffractograms of cocrystals synthesized by mechanochemistry versus solvent crystallization of the a) NOR-PCA, b) NOR-INCA, c) NOR-NCA and d) NOR-SAC cocrystals.

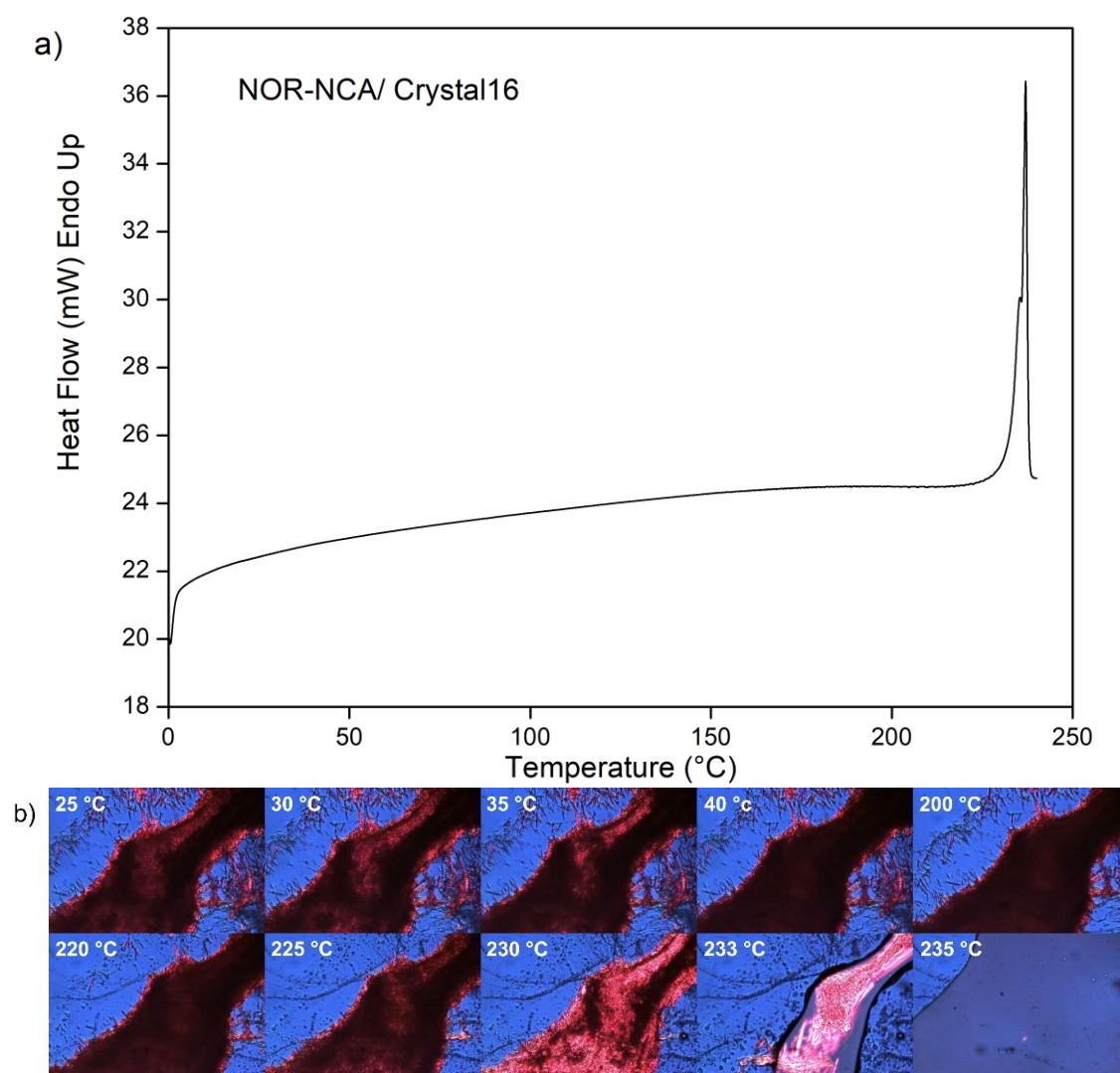


Figure D.4 – a) DSC and b) Thermomicroscopy images obtained on heating the NOR-NCA cocystal obtained in Crystal16 experiments, $\beta = 10\text{ }^{\circ}\text{C min}^{-1}$, x200 magnification.