STABILITY AND DESOLVATION KINETICS OF DROPERIDOL HYDRATES AND AN ETHANOL SOLVATE, STUDIED BY POWDER X-RAY DIFFRACTOMETRY AND DIFFERENTIAL THERMAL ANALYSIS/THERMOGRAVIMETRY

AGRIS BĒRZIŅŠ, ANDRIS ACTIŅŠ, EDGARS SKARBULIS

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LATVIA

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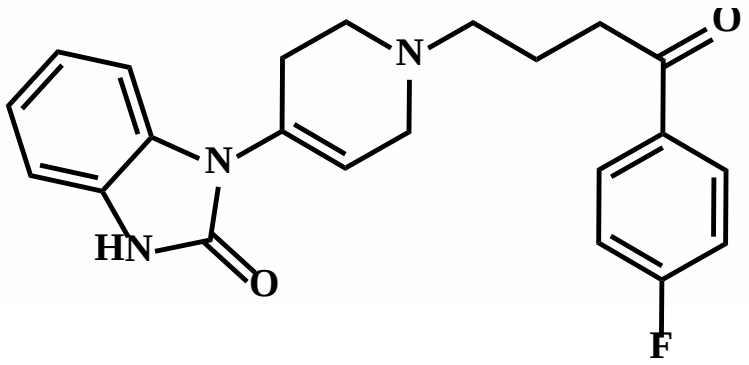
Background

Department of Chemistry, University of Latvia

Introduction

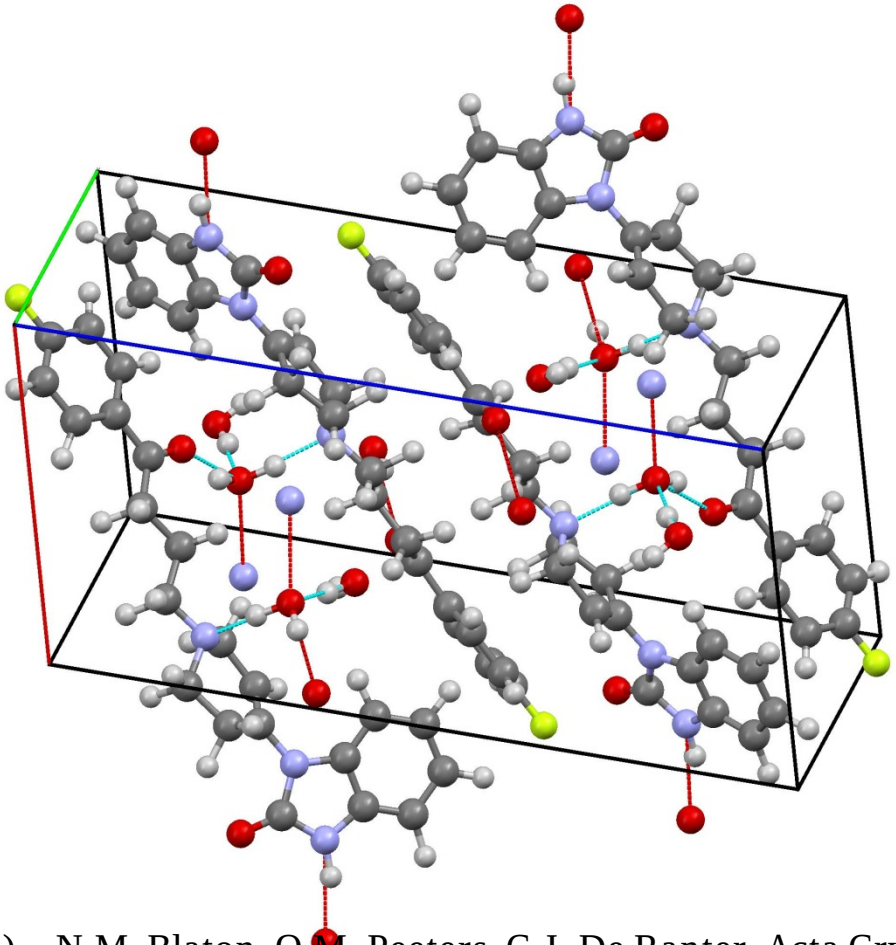
- Droperidol is known to exist in:
  - Two polymorphic forms [a,b]
  - Dihydrate [c]
  - Hemihydrate [a,b]
  - Ethanol solvate [d]



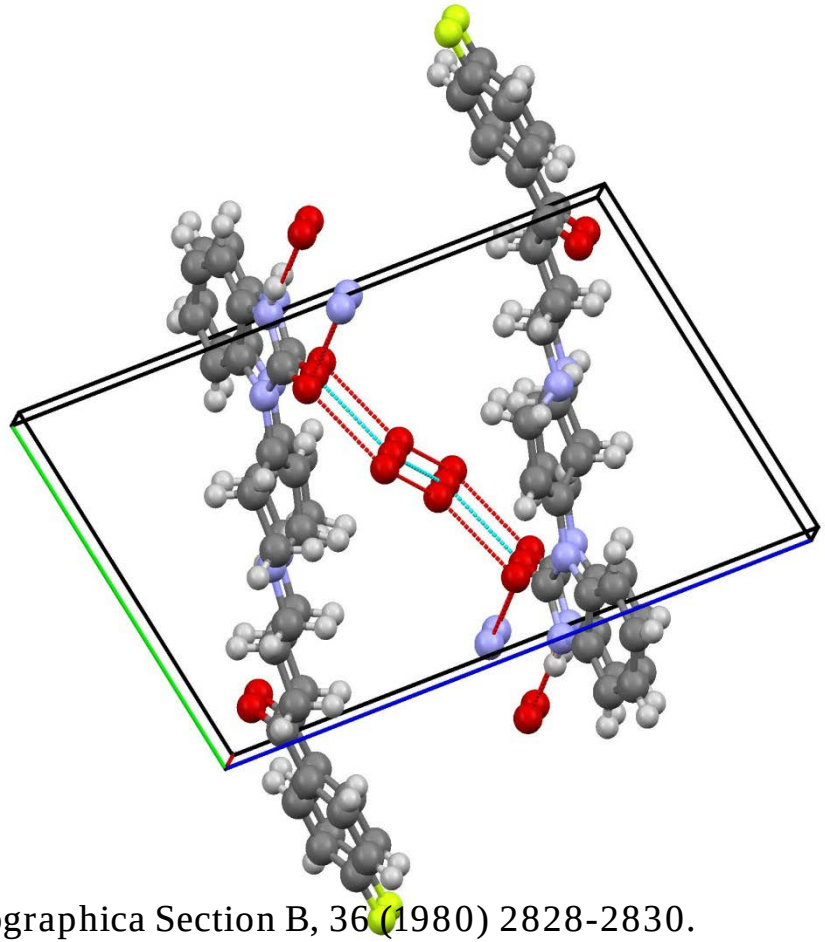
a) M. Azibi, M. Draguet-Brughmans, R. Bouche, Pharmaceutica Acta Helvetiae, 57 (1982) 182-188.
b) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, Journal of Chemical Crystallography, 38 (2008) 169-174.
c) N.M. Blaton, O.M. Peeters, C.J. De Ranter, Acta Crystallographica Section B, 36 (1980) 2828-2830.
d) C.L. Klein, J. Welch, L.C. Southall, Acta Crystallographica Section C, 45 (1989) 650-653.

Droperidol hydrates

Dihydrate[a]



Hemihydrate[b,c]

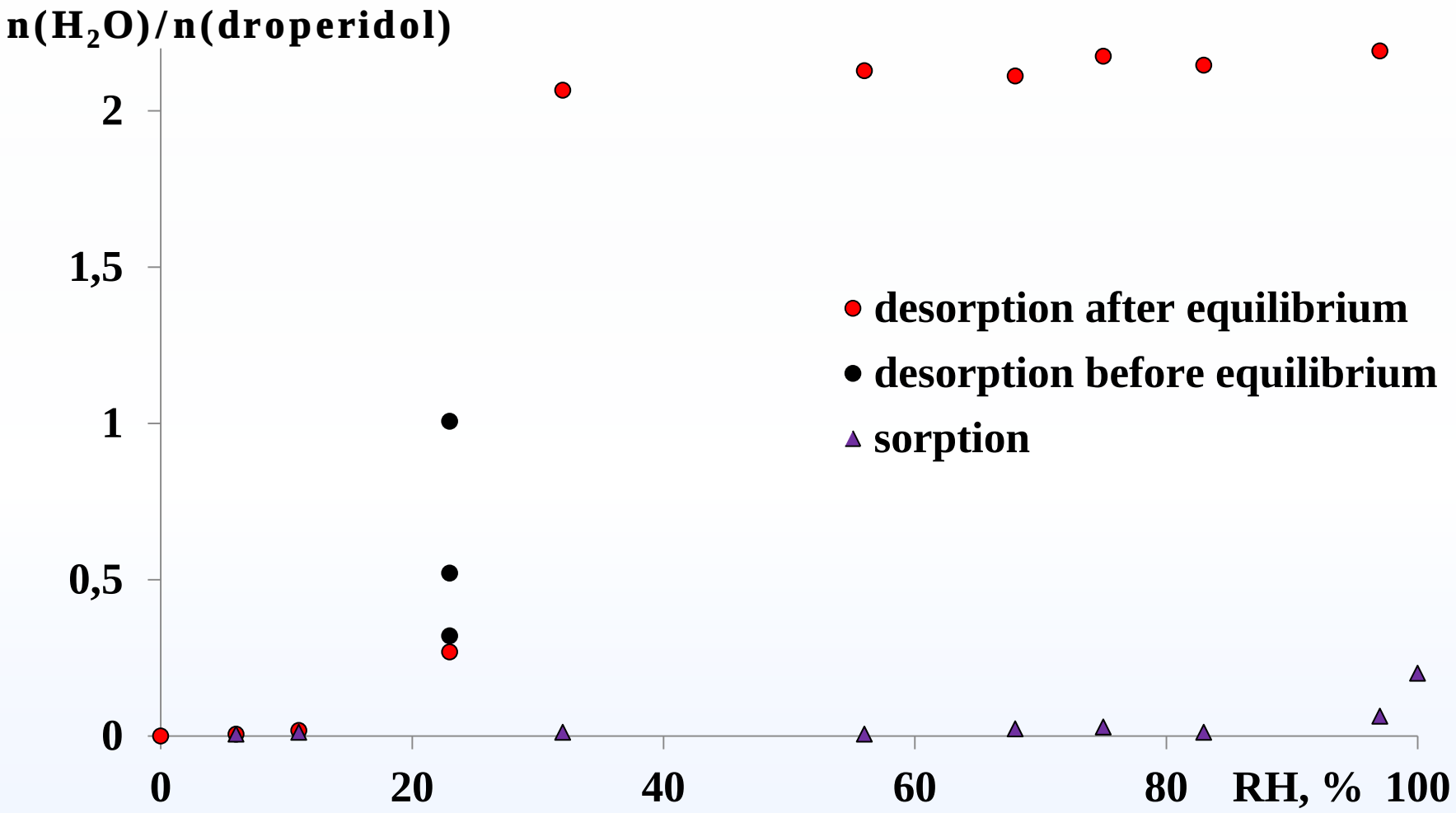


a) N.M. Blaton, O.M. Peeters, C.J. De Ranter, Acta Crystallographica Section B, 36 (1980) 2828-2830.
b) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, Journal of Chemical Crystallography, 38 (2008) 169-174.
c) L. Orola. Synthesis, structure and properties of crystalline forms of some active pharmaceutical ingredients. PhD Thesis, Riga Technical University, (2010) 170 p.

Outline

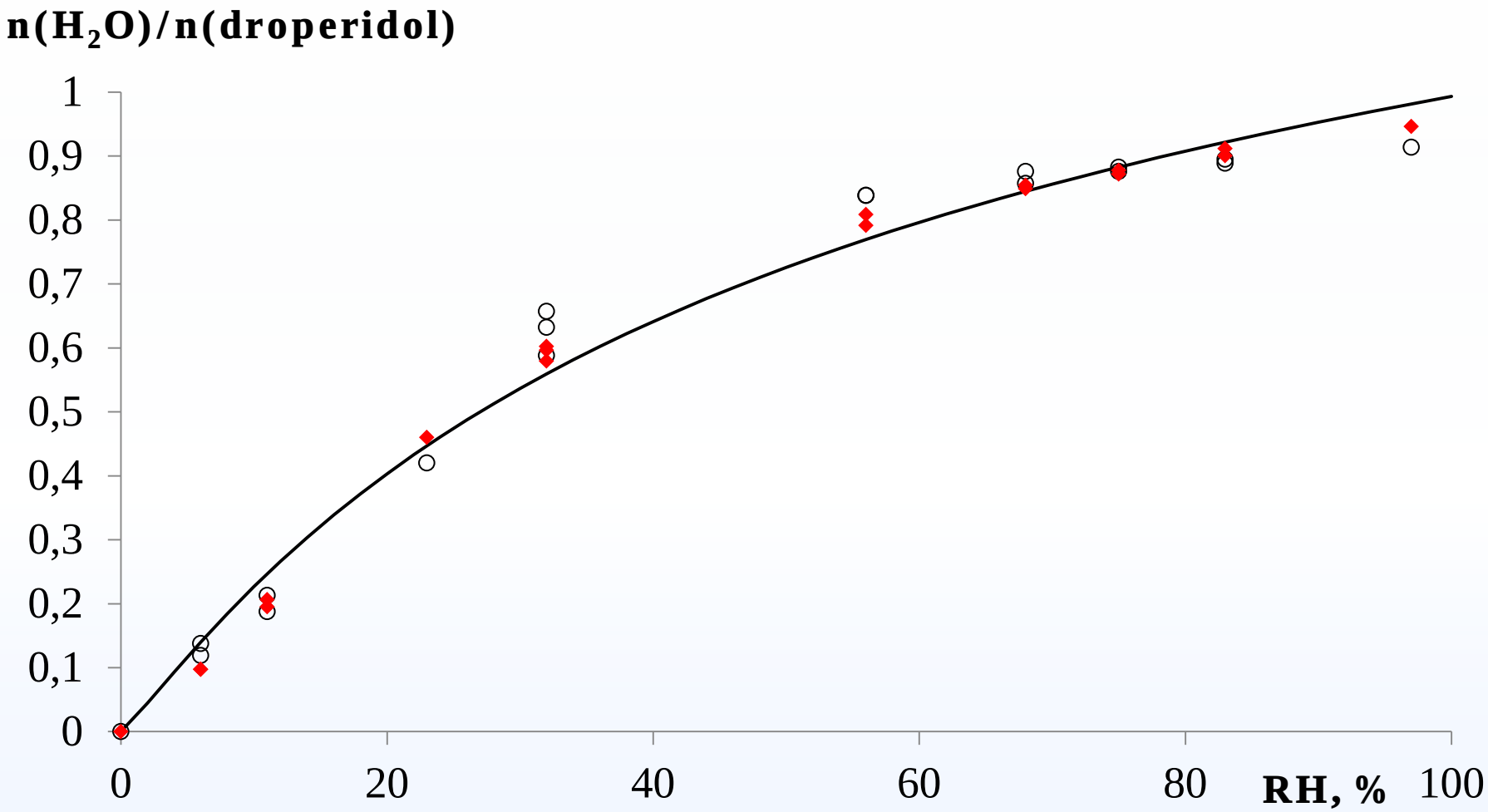
- Droperidol hydrates
  - Sorption-desorption isotherms
  - Dehydration products
  - Dehydration kinetics
  - Lattice parametres of droperidol hemihydrate
- Droperidol ethanol solvate
  - Similarity with hemihydrate
  - Lattice parametres of droperidol ethanol solvate
  - Desolvatation kinetics
- Conclusions

Desorption-sorption isotherms - dihydrate



Desorption-sorption isotherm of droperidol dihydrate in 25 °C temperature

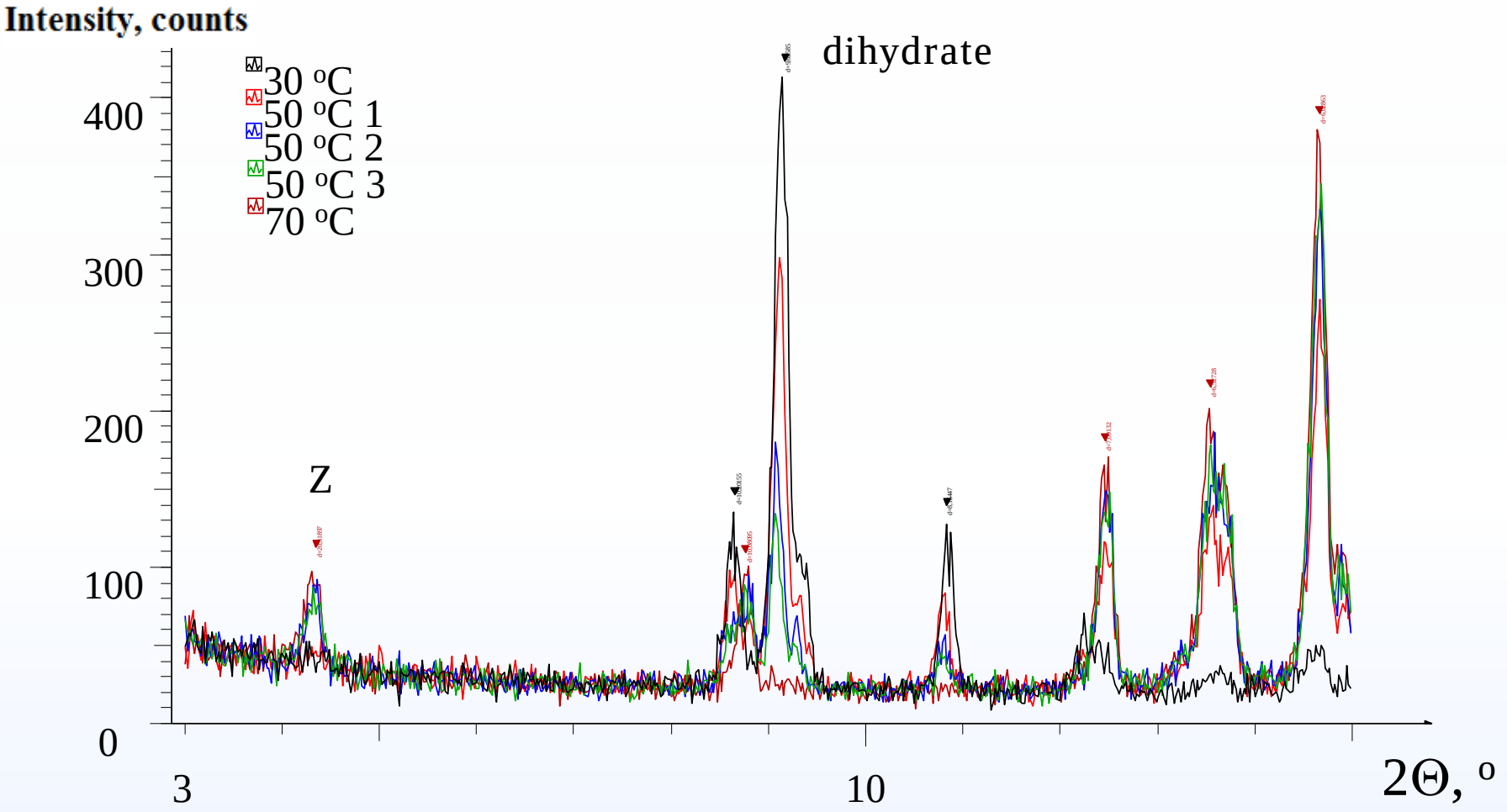
Desorption-sorption isotherms - hemihydrate



Desorption-sorption isotherm of droperidol hemihydrate in 25 °C temperature

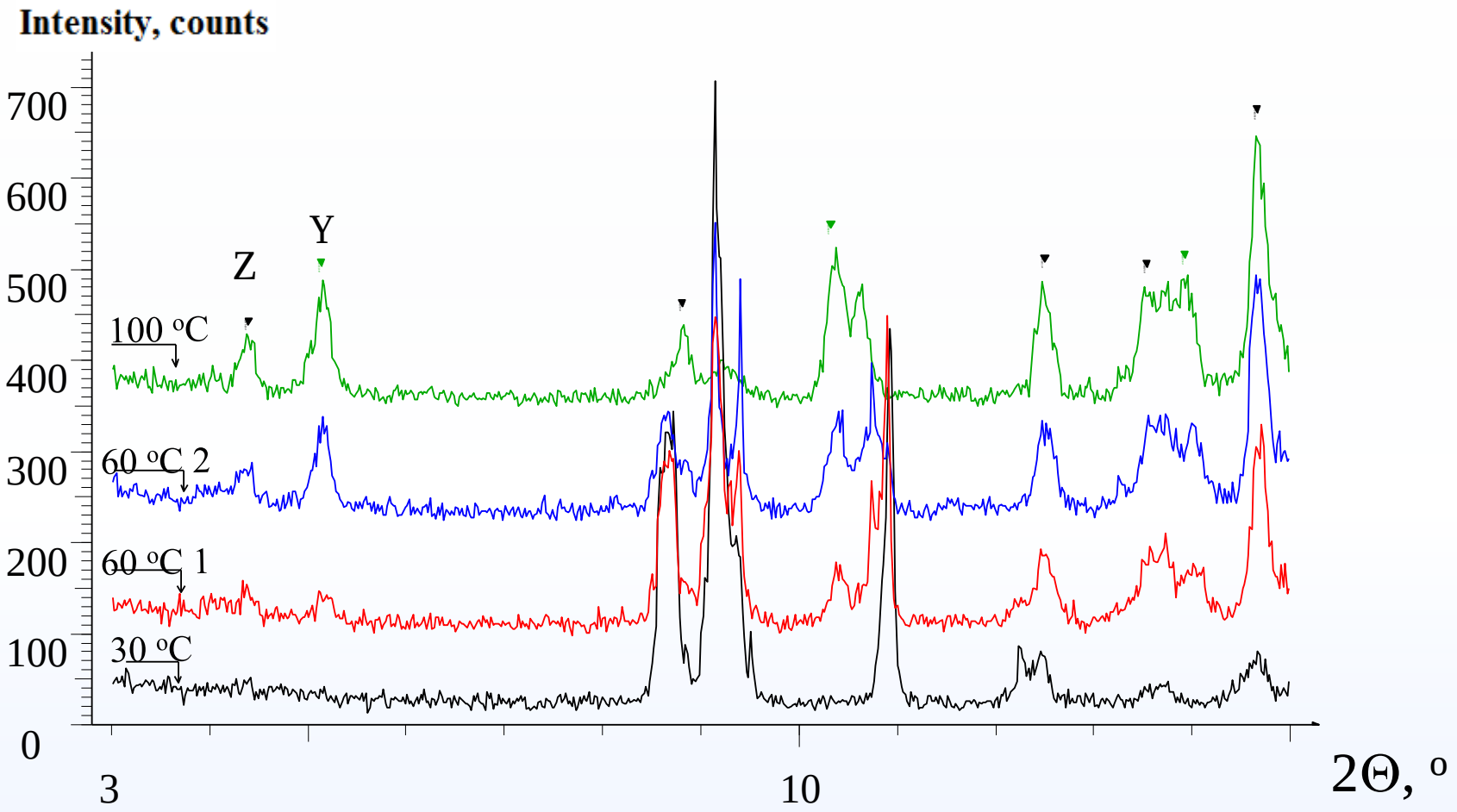
a) J.R. Authelin. International Journal of Pharmaceutics 303 (2005) 37–53

Dehydration products - dihydrate



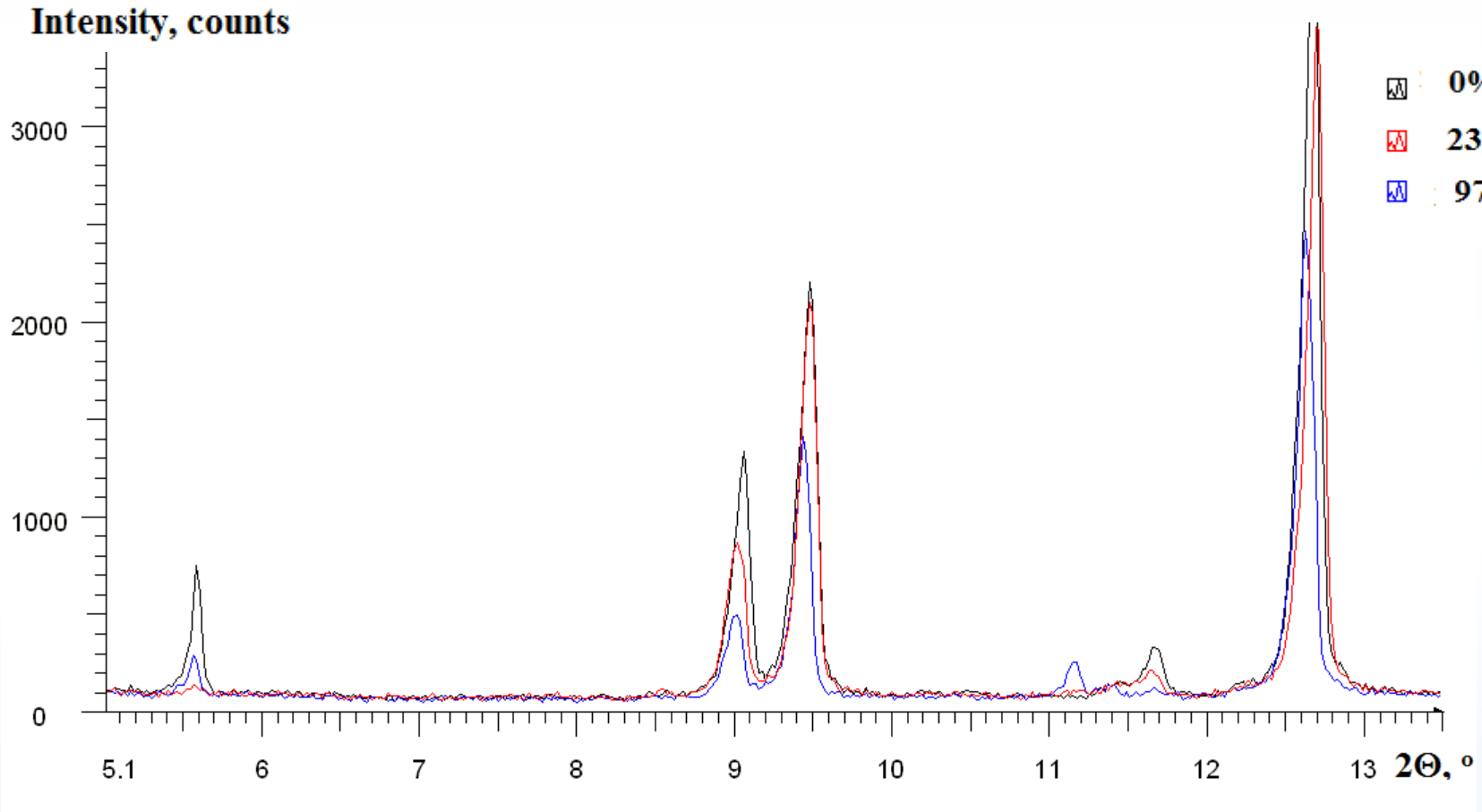
Dehydratation of droperidol dihydrate sample A by heating

Dehydration products - dihydrate



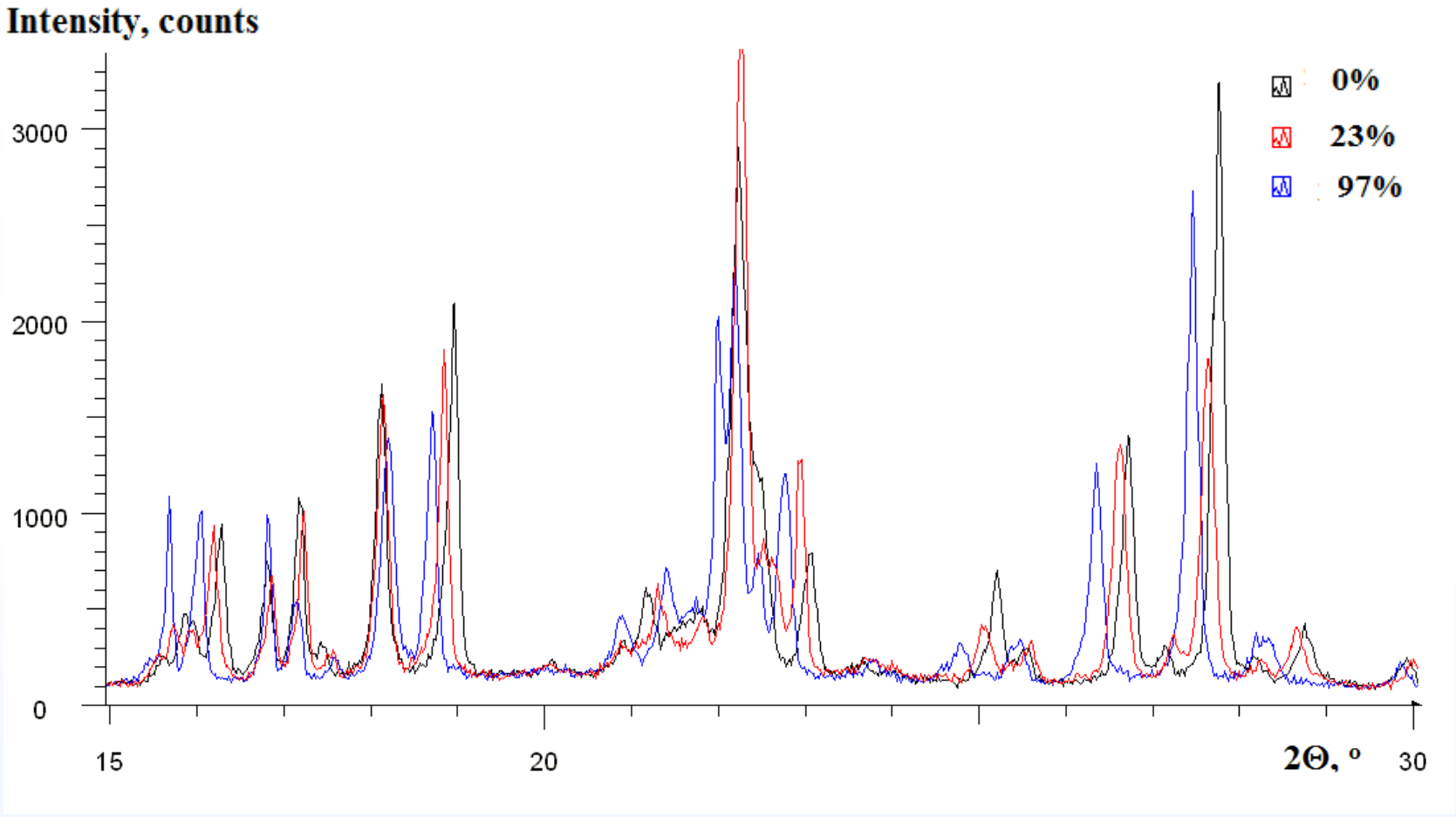
Dehydratation of untreated droperidol dihydrate sample C by heating

Dehydration products - hemihydrate



Dehydratation of droperidol hemihydrate by lowering relative humidity (1)

Dehydration products - hemihydrate

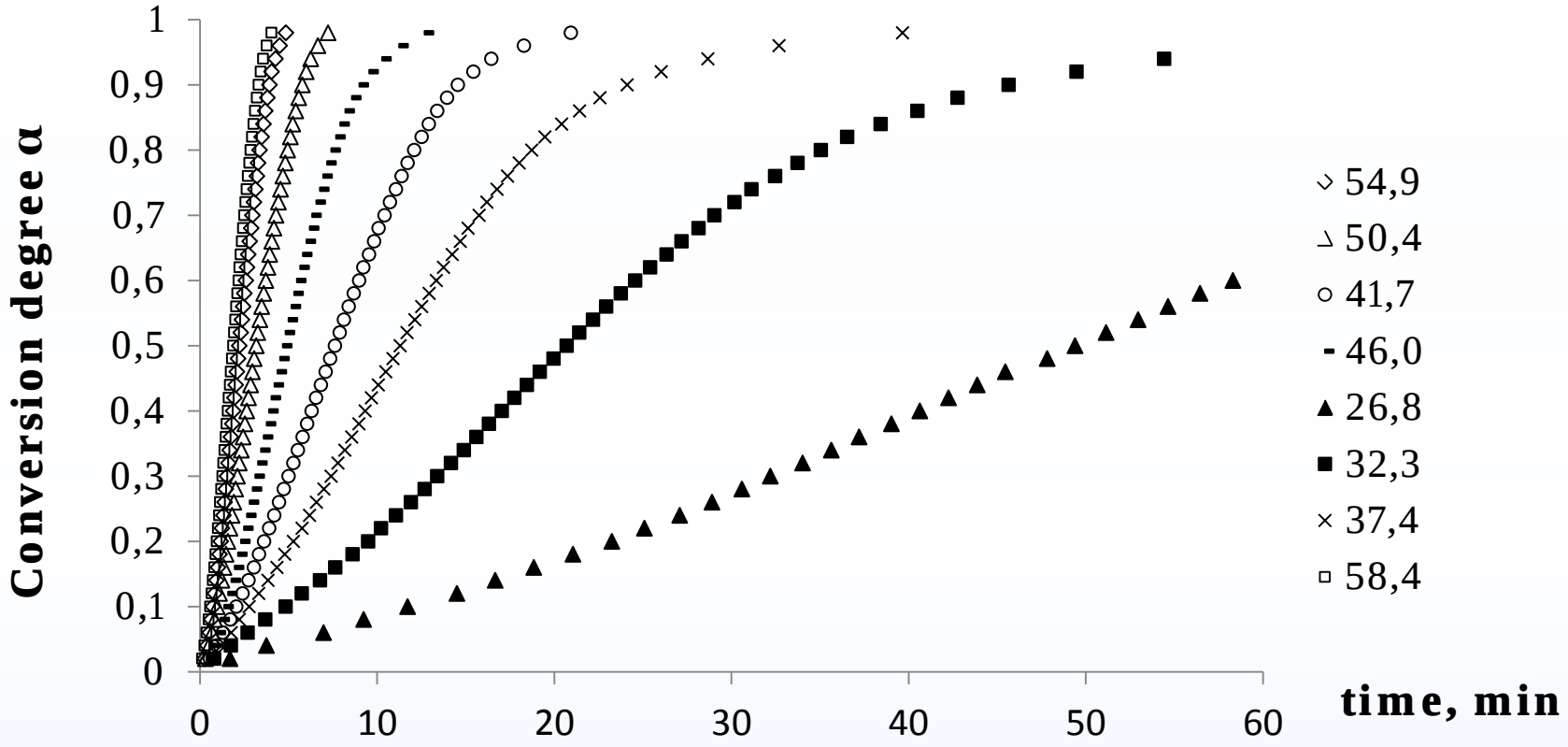


Dehydratation of droperidol hemihydrate by lowering relative humidity (2)

Droperidol hydrates - conclusions

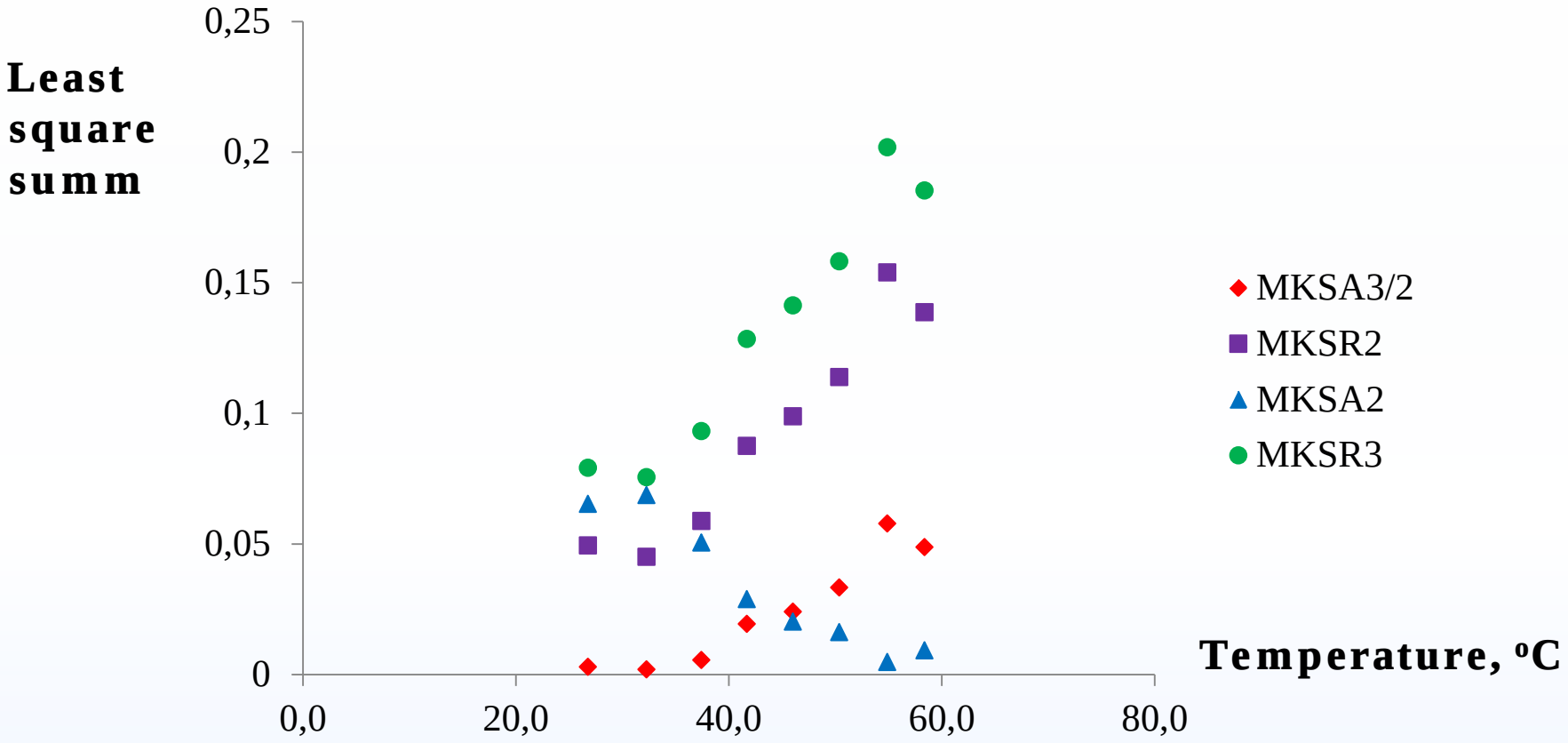
- Droperido dihydrate
  - typical stoichiometric hydrate
  - complicated dehydration process
- Droperidol hemihydrate
  - typical nonstoichiometric hydrate
  - Dehydration gives isomorphic dehydrate

Dehydration kinetics – dihydrate (1)



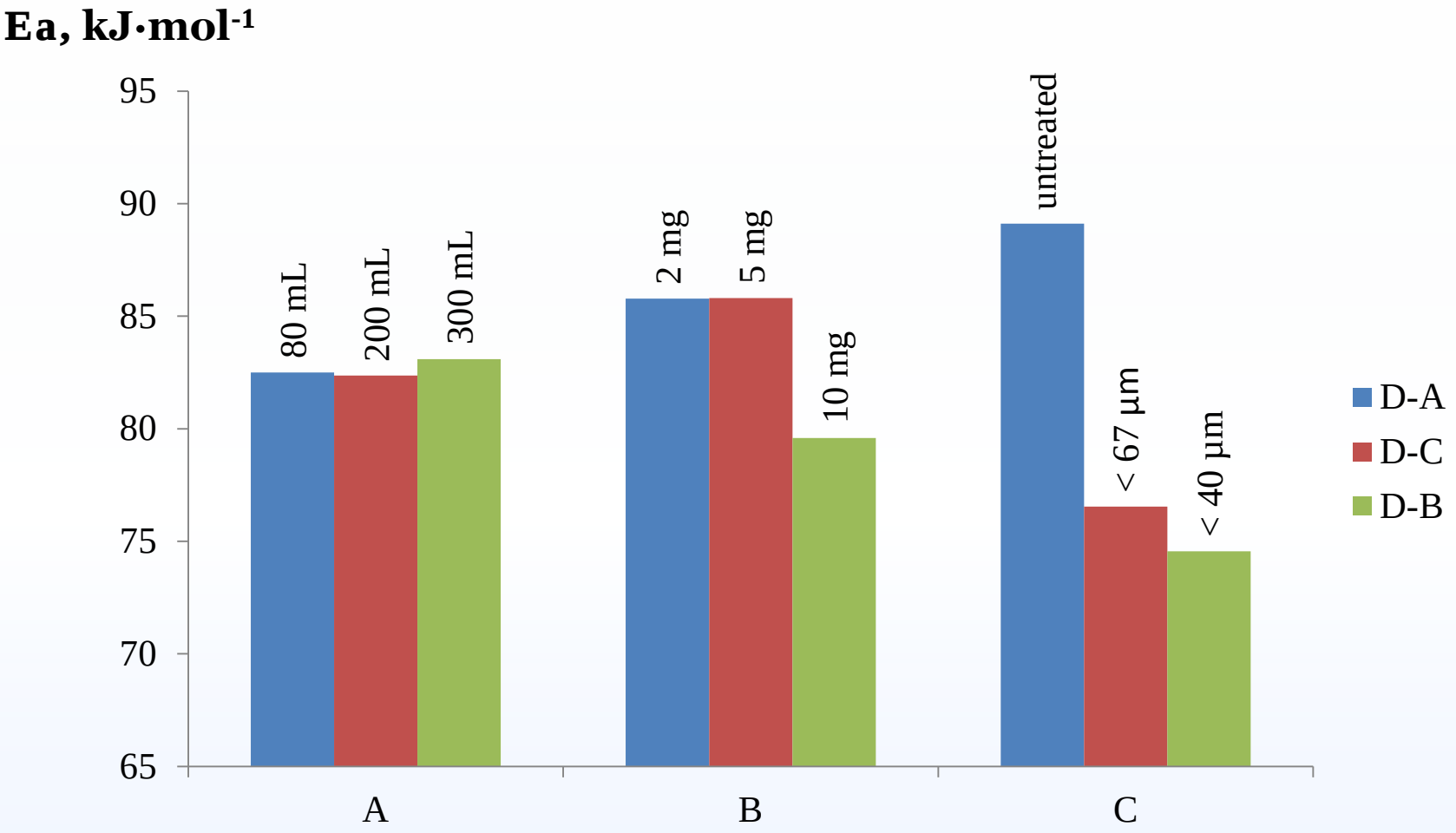
Dehydratation kinetic curves of droperidol dihydrate sample A in nitrogen flow with sample mass 5 mg

Dehydration kinetics – dihydrate (3)



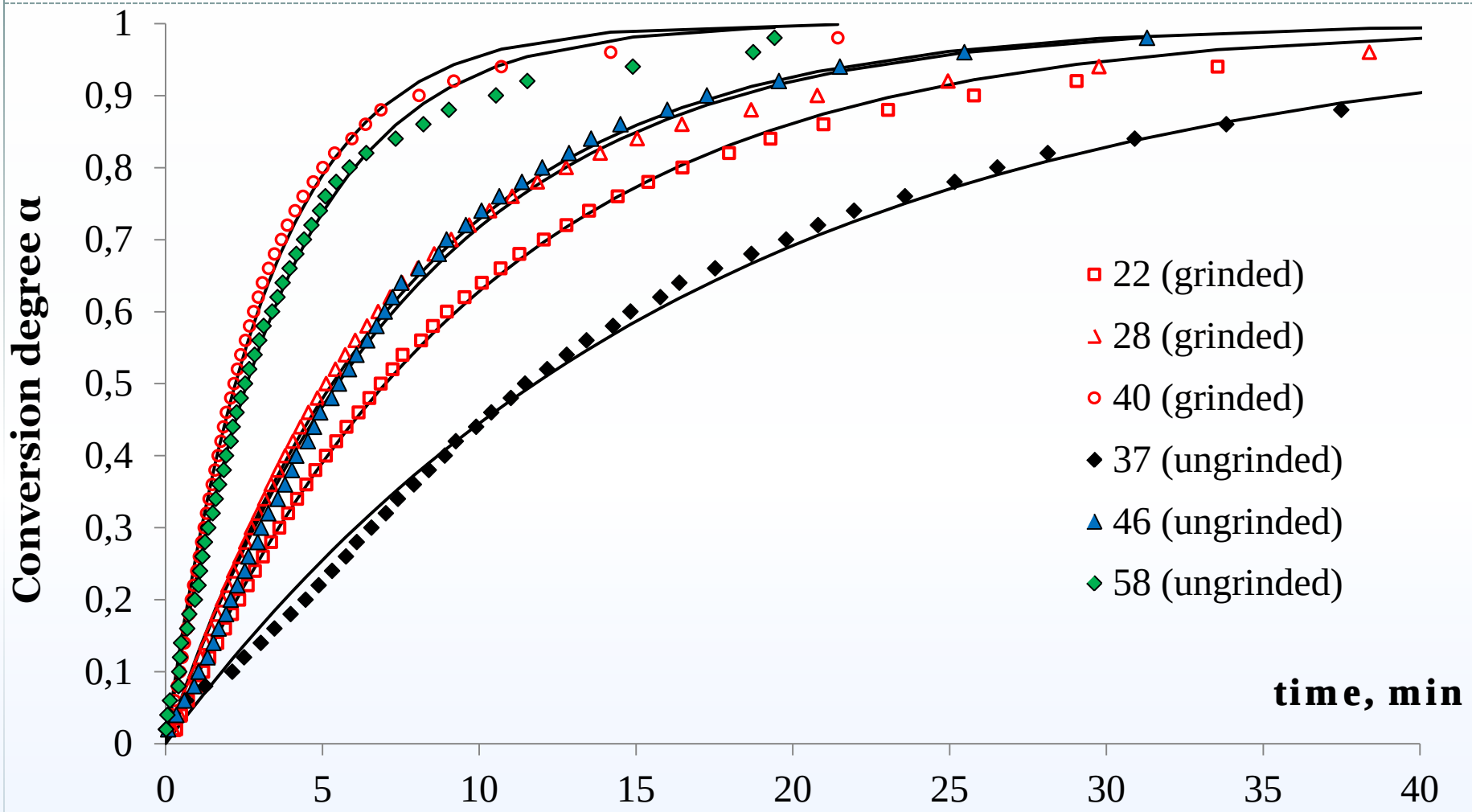
After optimization obtained least square sums for most appropriate kinetic models for droperidol dihydrate sample A with sample mass 5 mg

Dehydration kinetics – dihydrate (4)



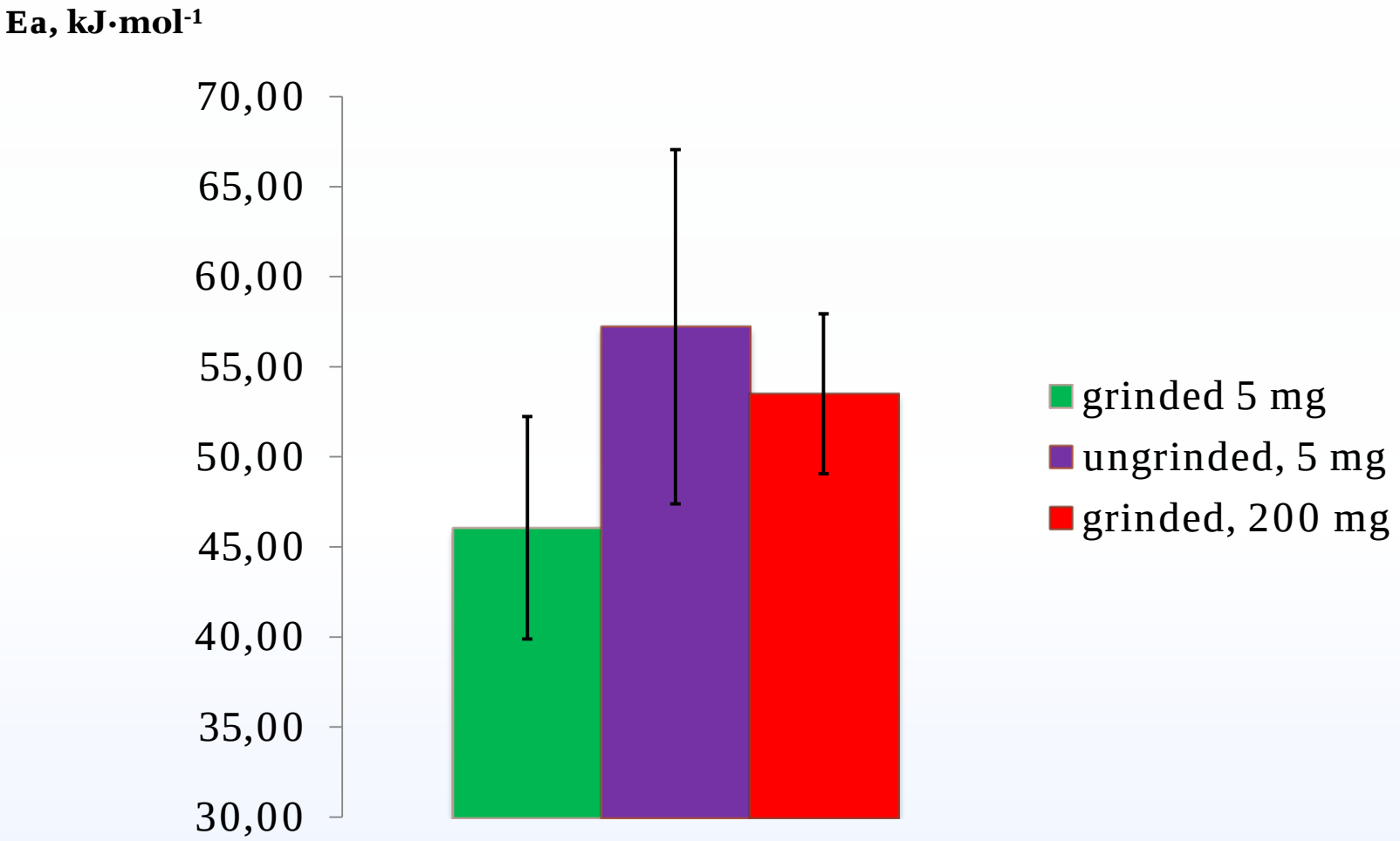
With optimization method calculated activation energy values for droperidol dihydrate samples

Dehydration kinetics – hemihydrate (1)



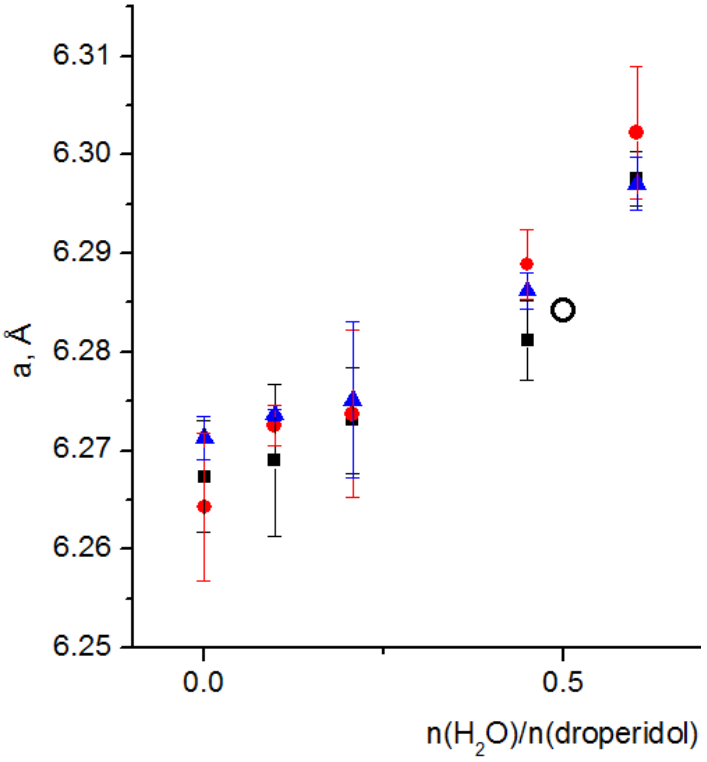
Dehydratation kinetic curves of grinded and ungrinded droperidol nonstoichiometric hydrate

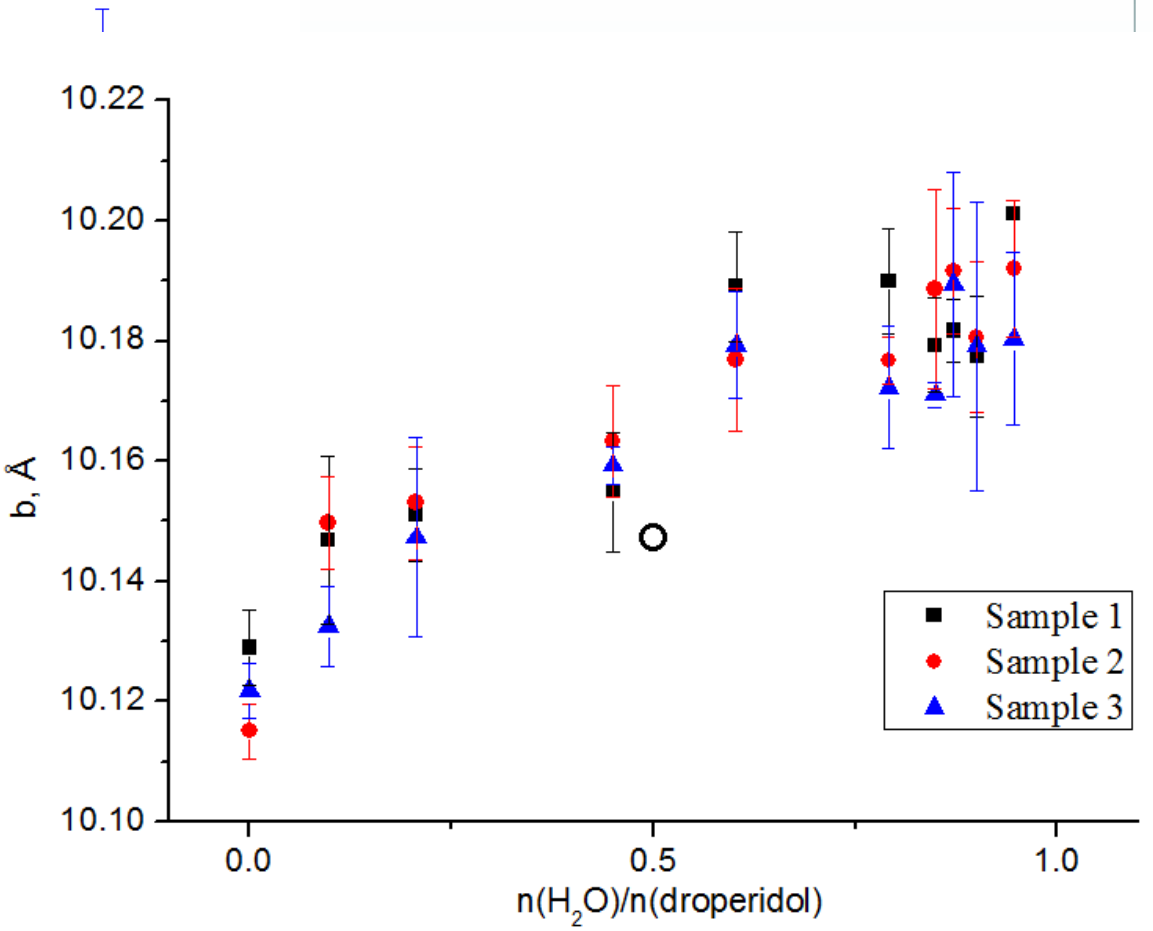
Dehydration kinetics – hemihydrate (1)



With optimization method calculated activation energy values for droperidol nonstoichiometric hydrate samples

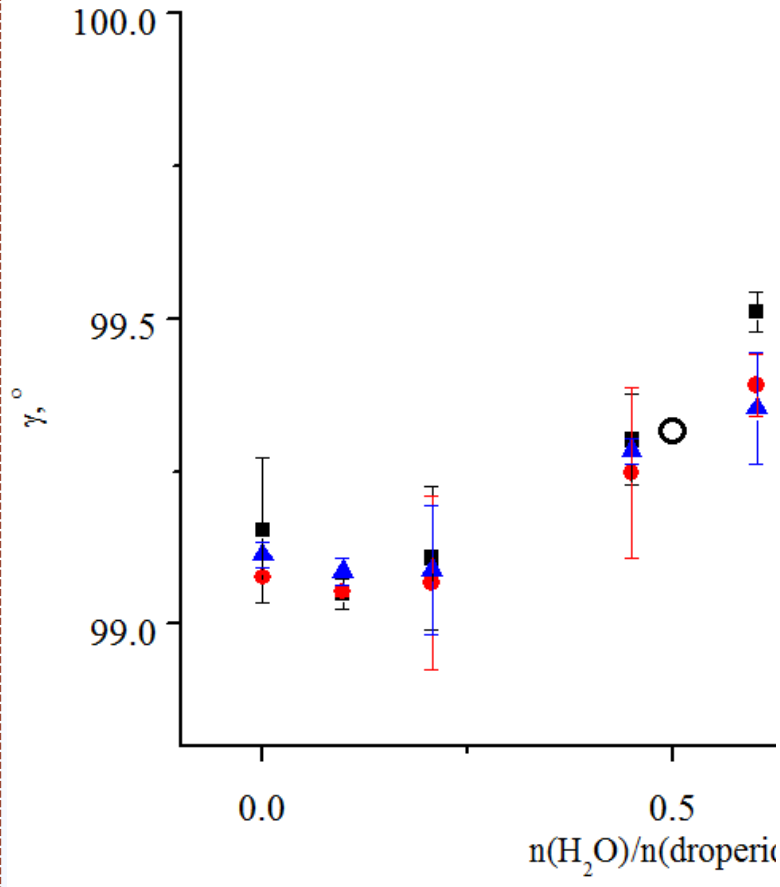
Hemihydrate water content influence on lattice parameters

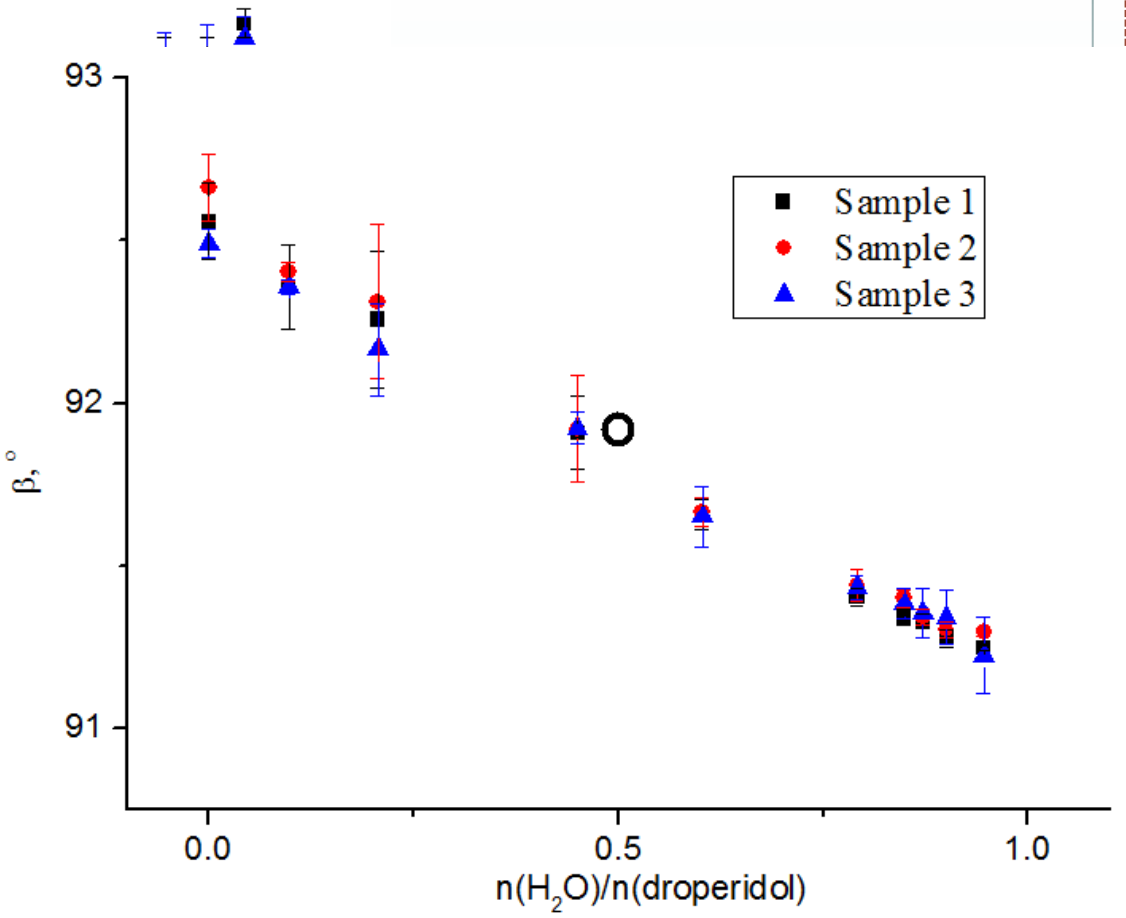




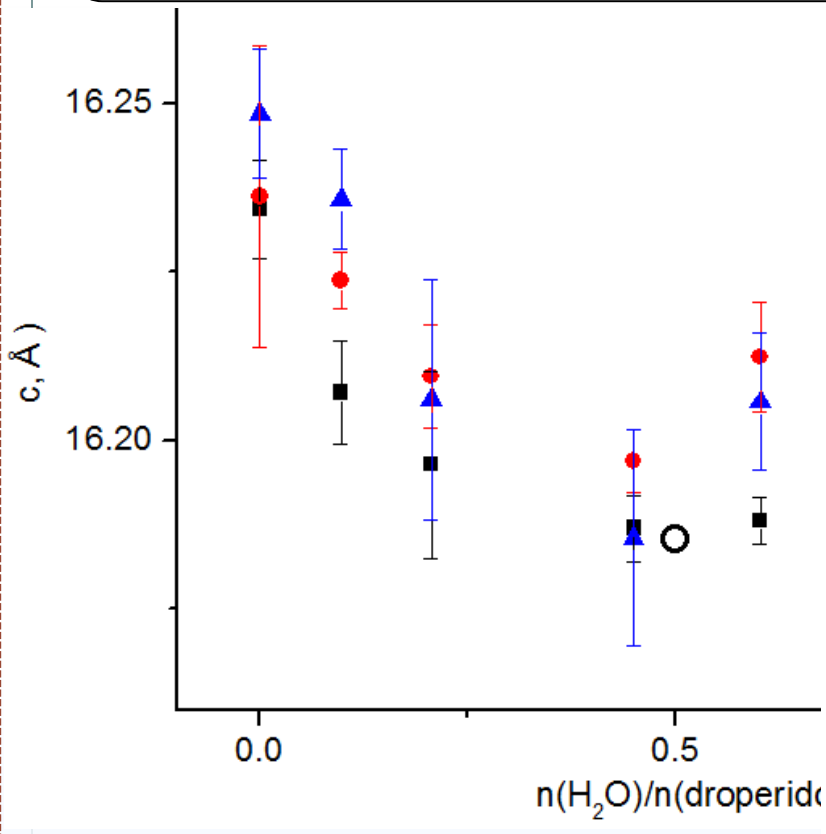
a) A. Actins, R. Arajs, S. Belakovs, L. Orola, M. Veidis, Journal of Chemical Crystallography,
b) 38 (2008) 169-174.

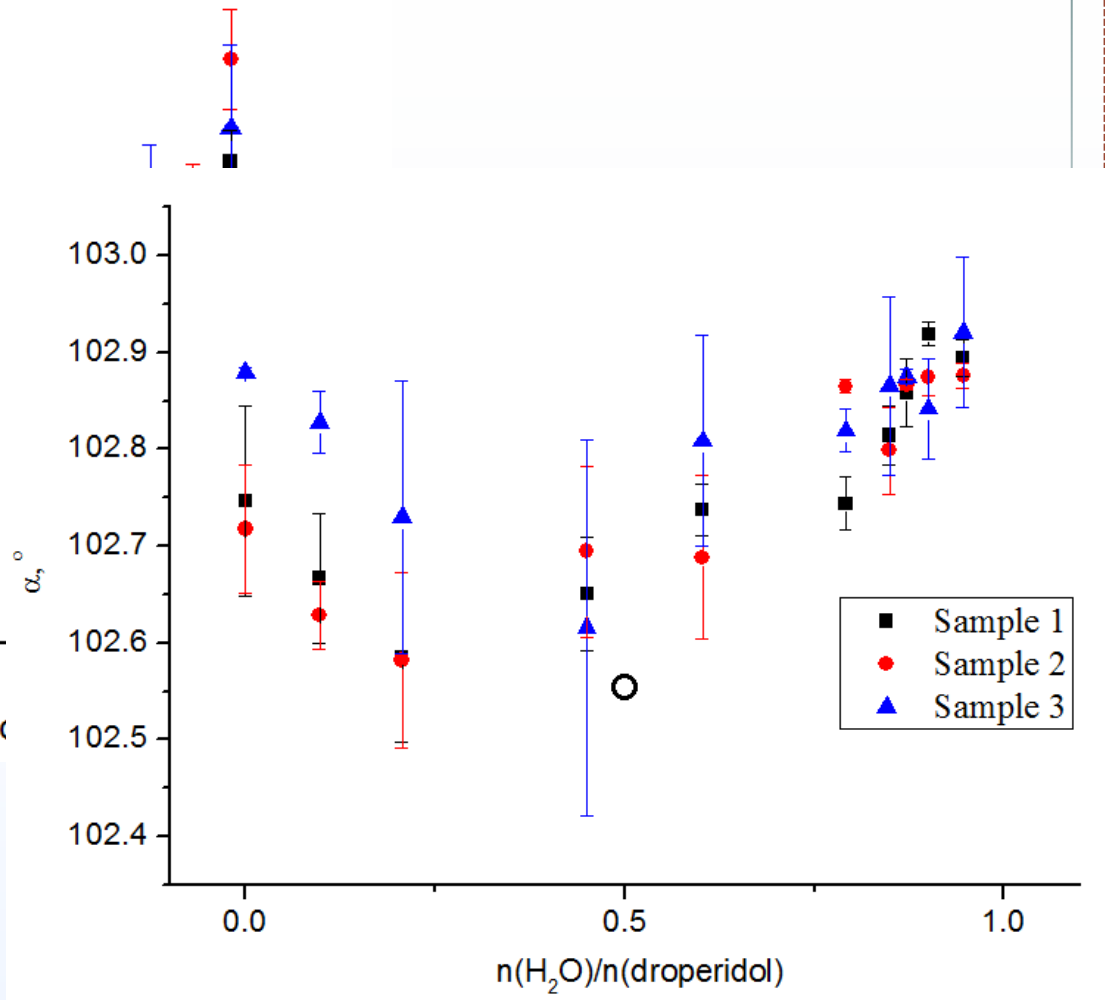
Hemihydrate water content influence on lattice parameters (2)



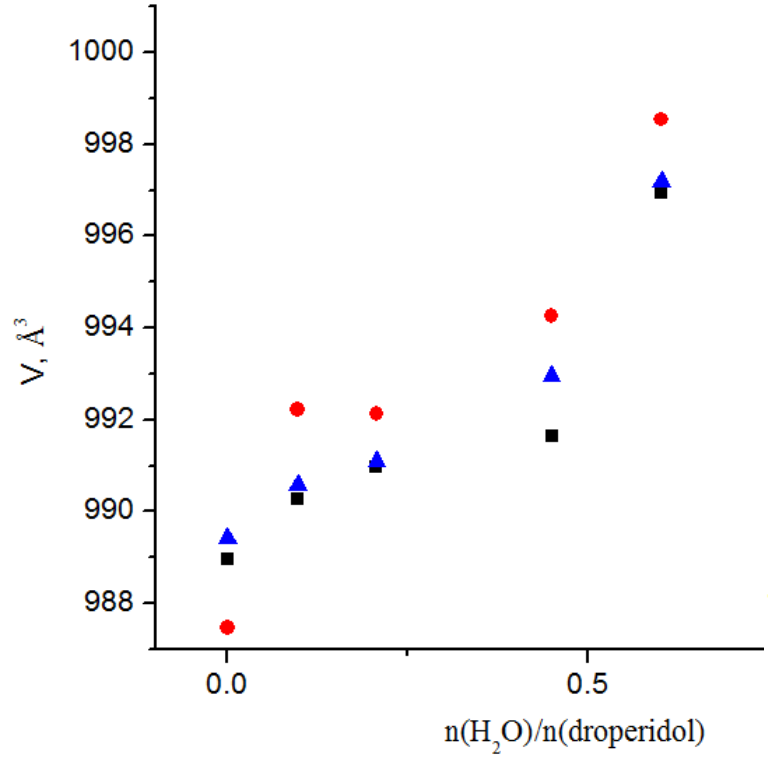


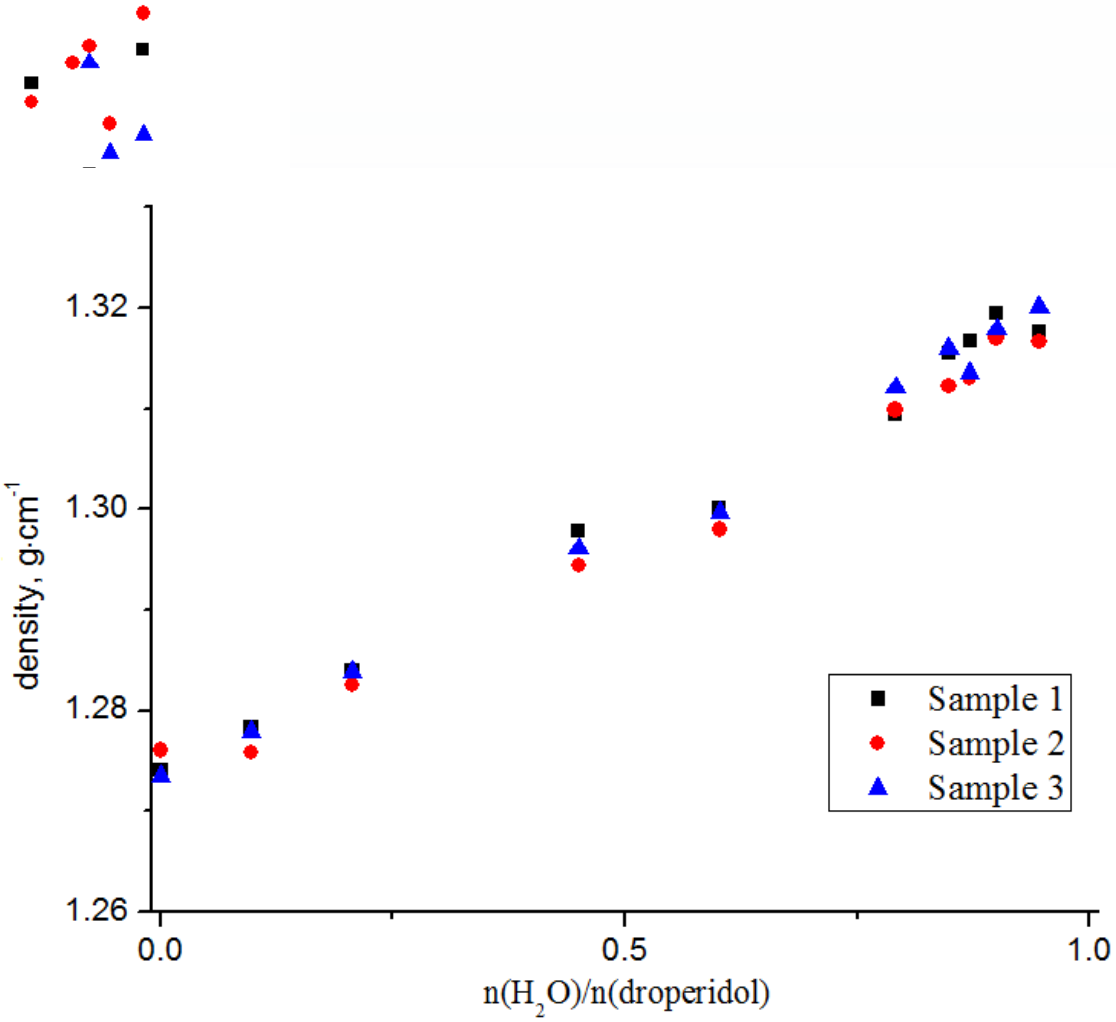
Hemihydrate water content influence on lattice parameters (3)



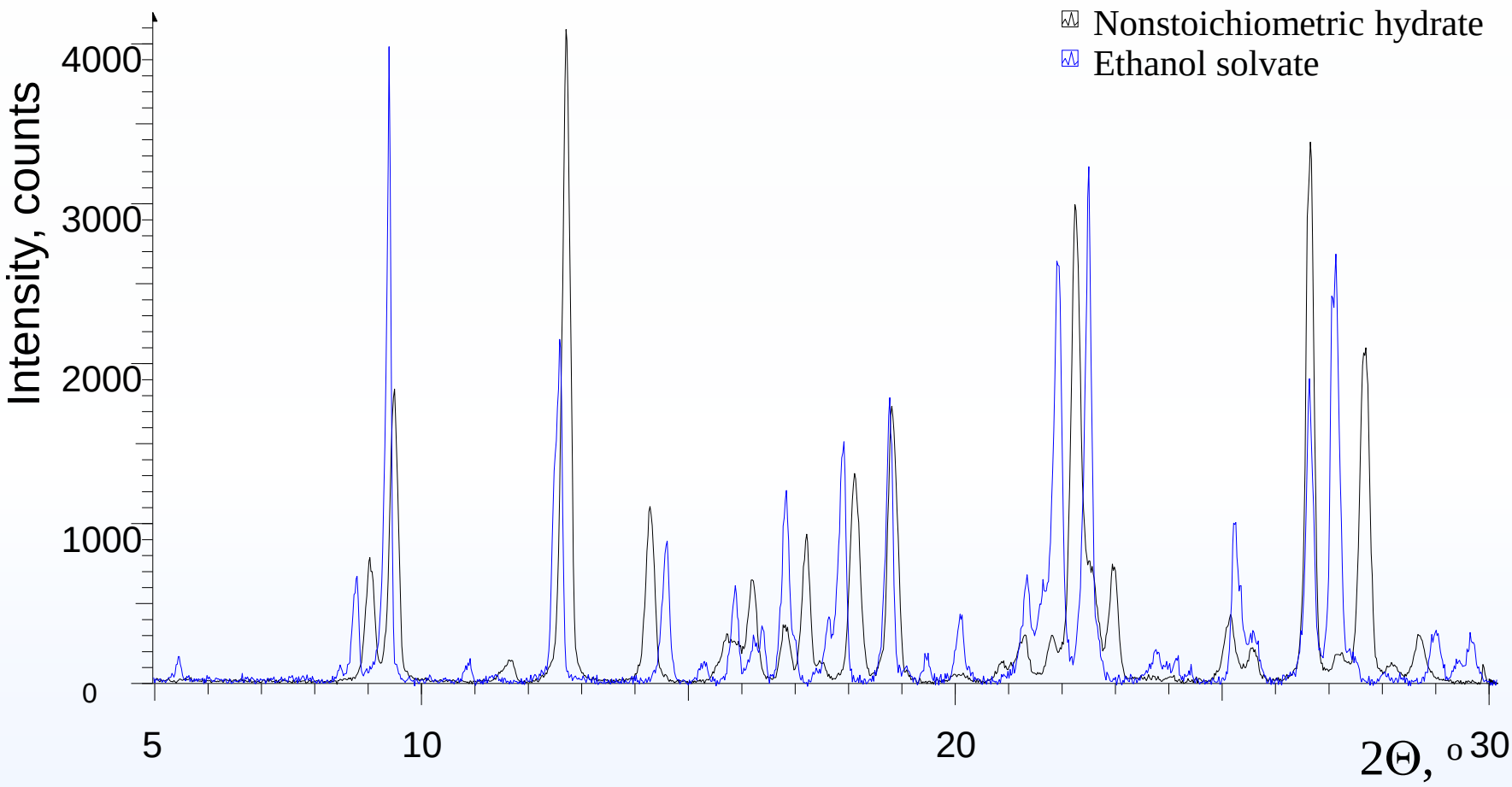


Hemihydrate water content influence on lattice parameters (4)



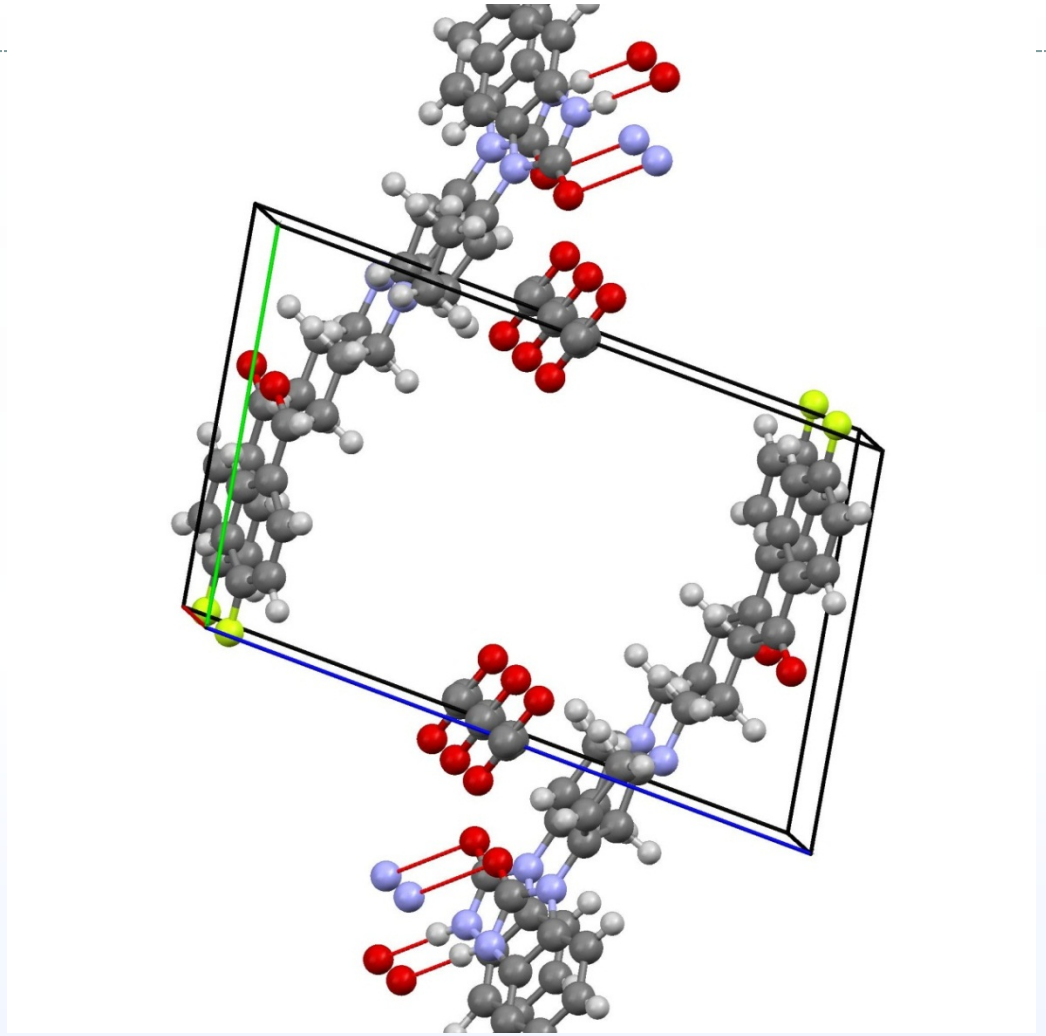


Droperidol ethanol solvate



PXRD patterns of droperidol nonstoichiometric hydrate and ethanol solvate

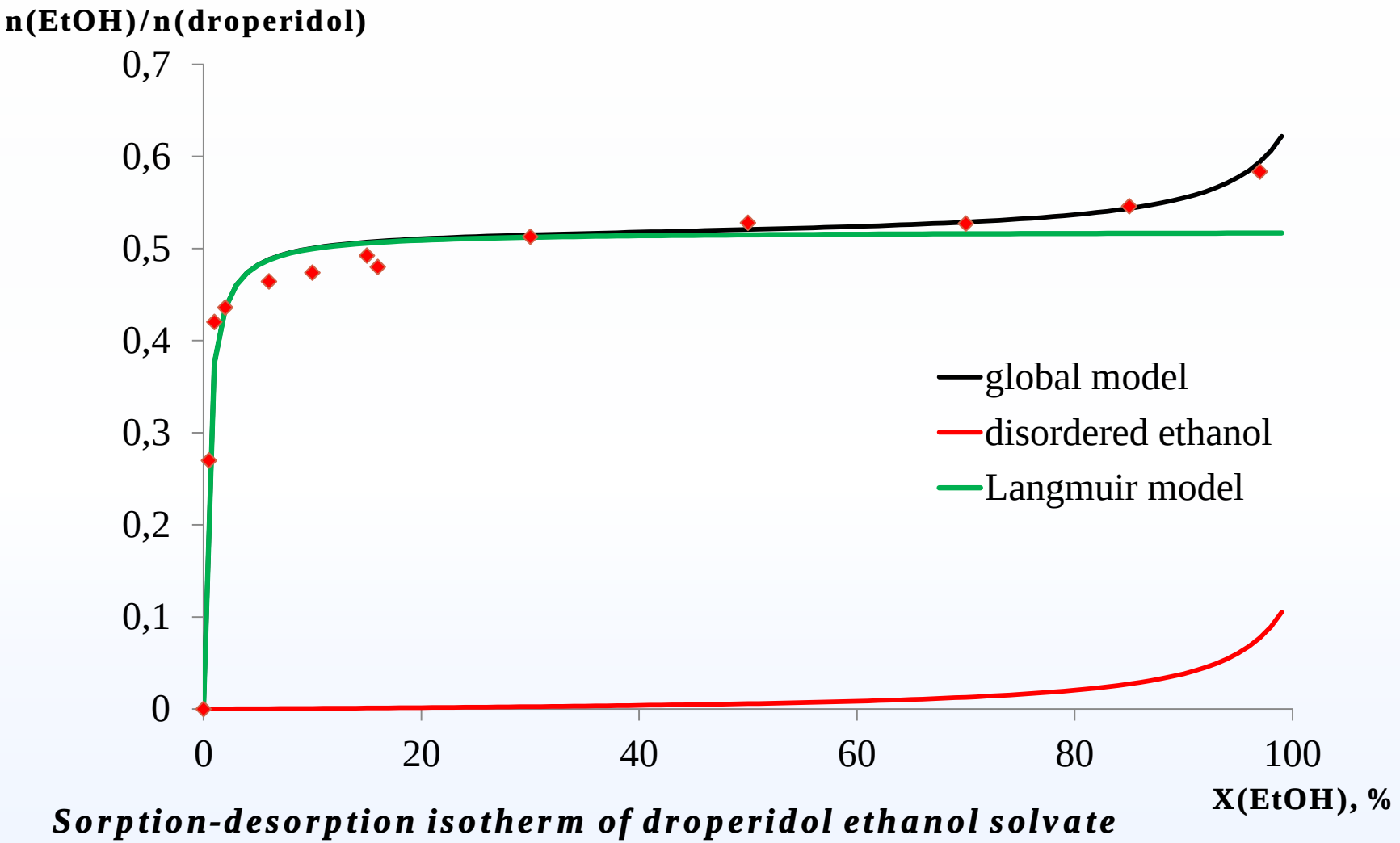
Droperidol ethanol solvate structure



Structure of droperidol ethanol solvate [a]

a) C.L. Klein, J. Welch, L.C. Southall, Acta Crystallographica Section C, 45 (1989) 650-653.

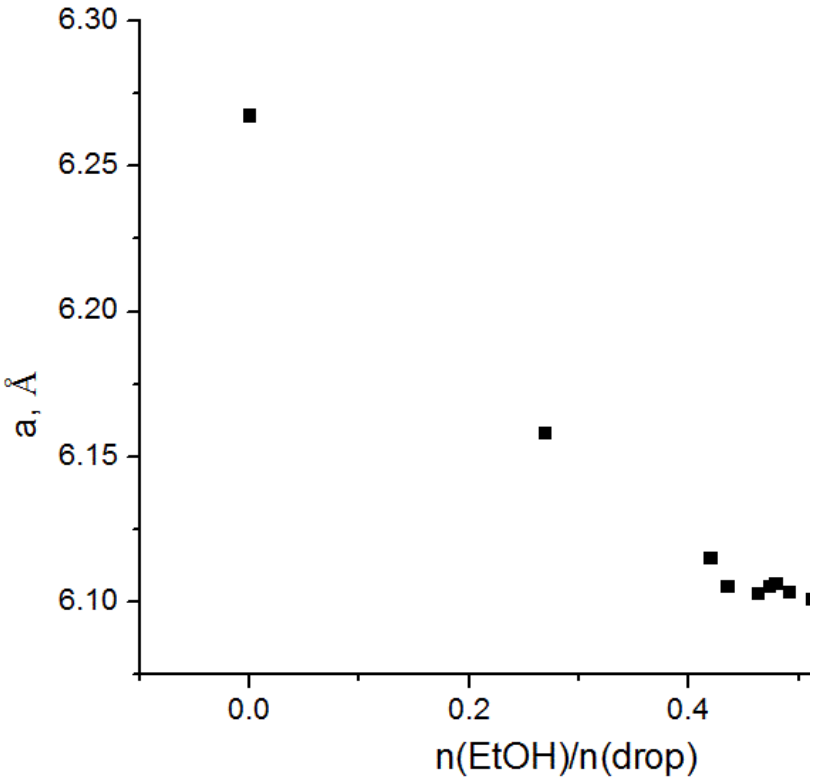
Sorption-desorption isotherm

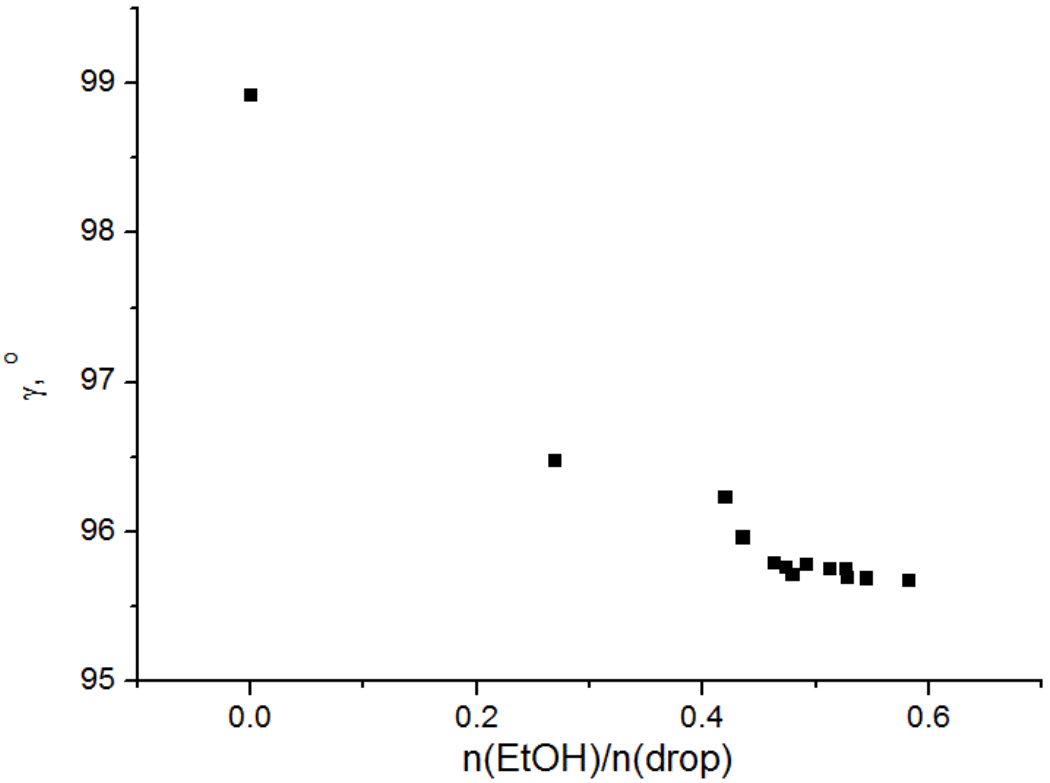


Sorption-desorption isotherm of droperidol ethanol solvate

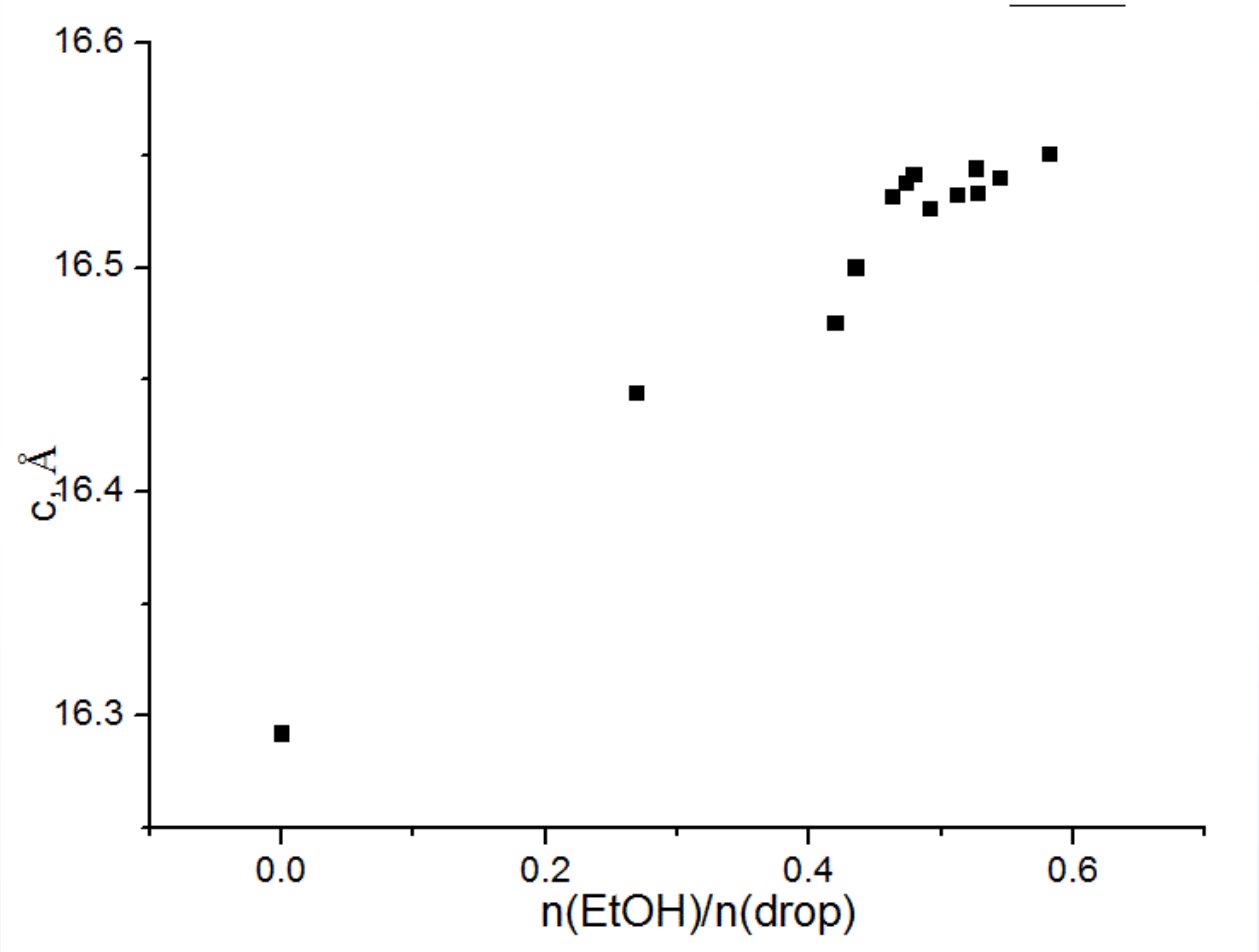
a) J.R. Authelin. International Journal of Pharmaceutics 303 (2005) 37–53

Lattice parameter changes

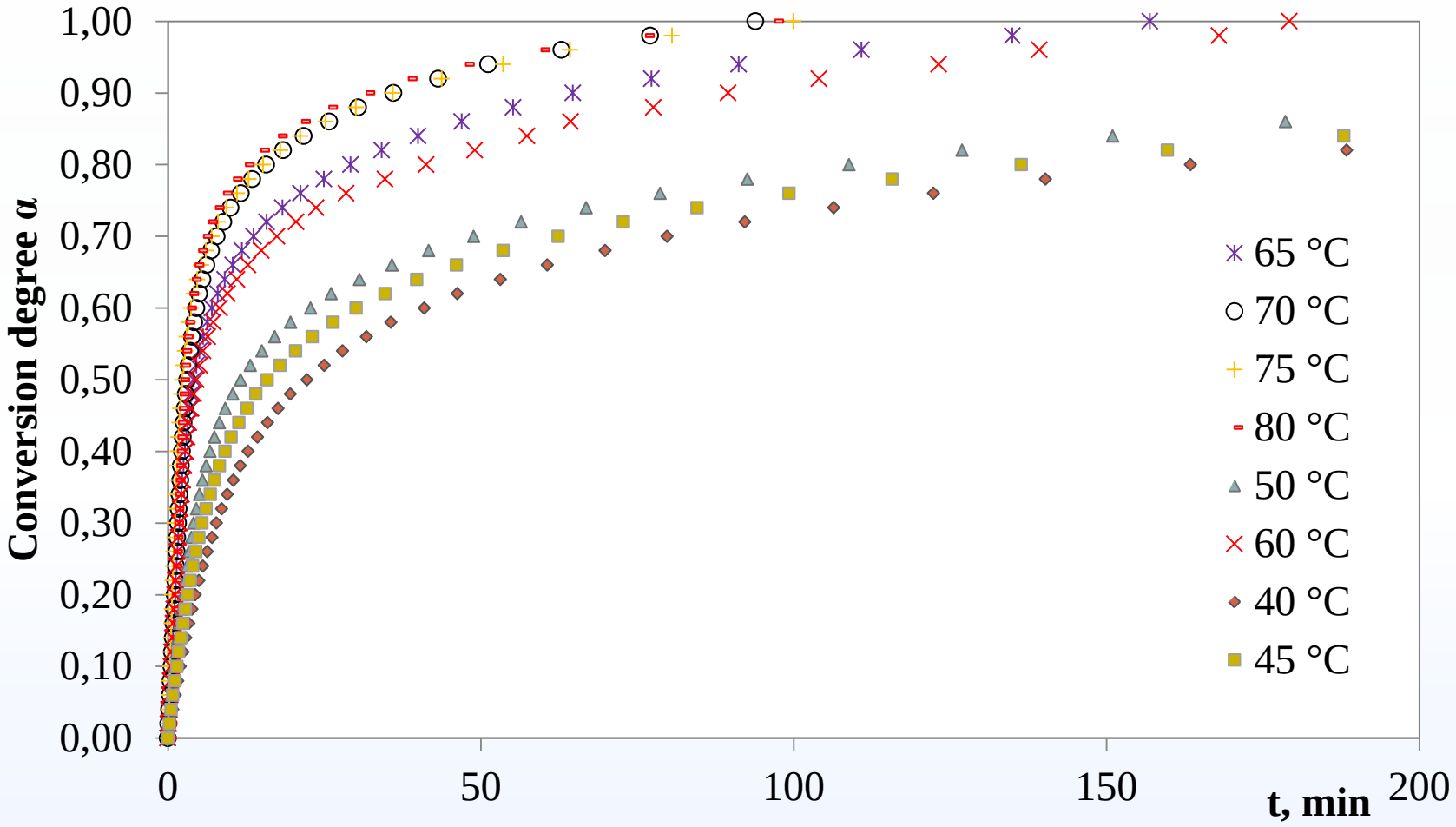




Lattice parameter changes (2)



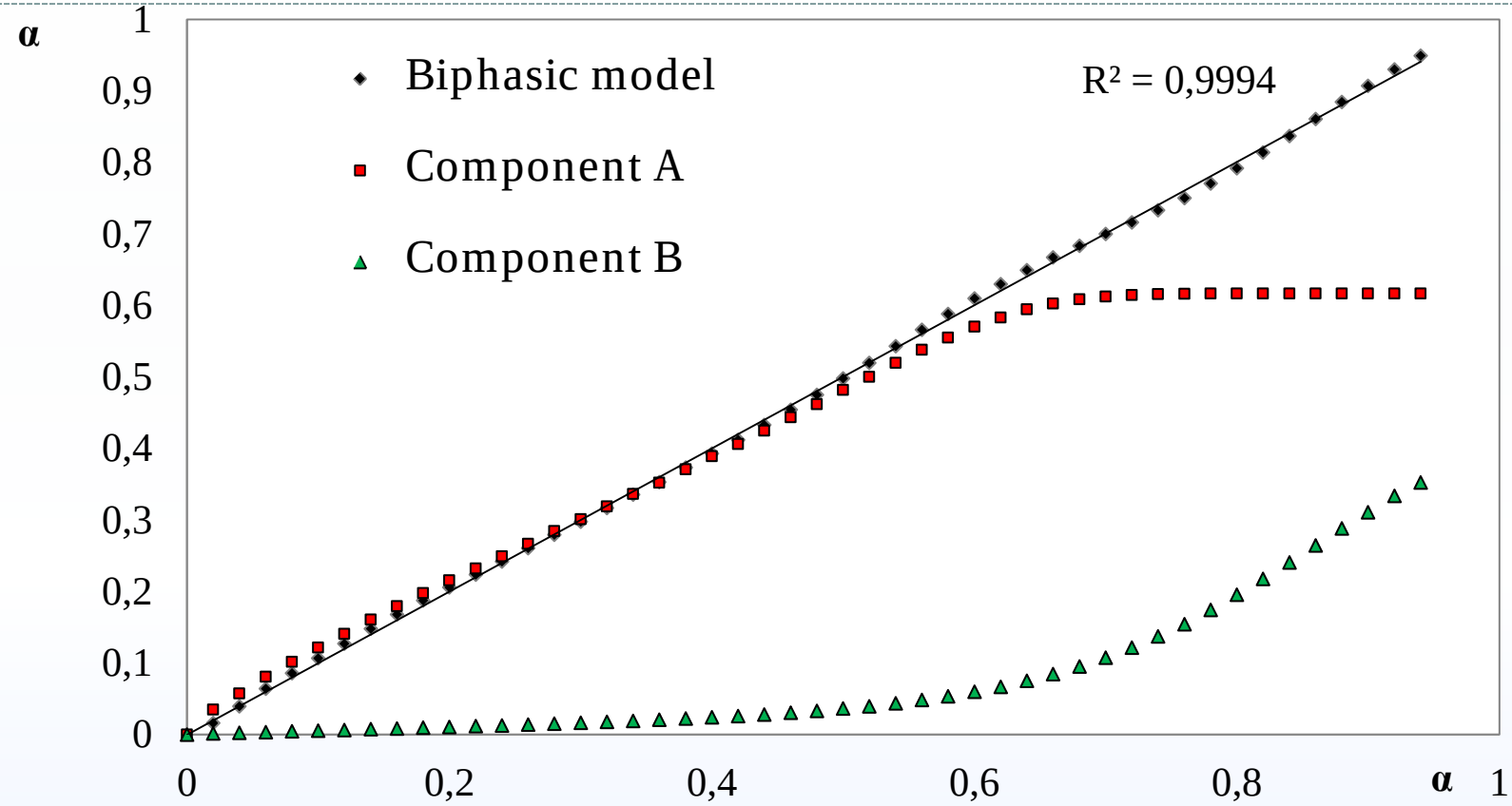
Desolvatation kinetics



Desolvatation kinetic curves of droperidol ethanol solvate

Desolvatation kinetics (2)

$$\alpha = 1 - (Ae^{-k_a t} + Be^{-k_b t})$$



Component A and B weight in kinetic curves of droperidol ethanol solvate

a) U.J. Griesser , A. Burger. International Journal of Pharmaceutics 120 (1995) 83-93

Biphasic model, component A	E_a **=(55±4) kJ·mol^{-1}**
Biphasic model, component B	E_a =(67±5) kJ·mol^{-1}

Conclusions

- Droperidol dihydrate is stoichiometric and its hemihydrate actually is nonstoichiometric hydrate.
- Dehydration-hydration of nonstoichiometric hydrate is reversible while that of dihydrate is irreversible.
- Dehydration of dihydrate can be described with Avrami-Erofeev while dehydartataion of nonstoichiometric hydrate can be described with first order kinetic model.

Conclusions (2)

- Nonstoichiometric hydrate's and ethanol solvate's lattice parametres systematically changes depending on solvent content in the structure.
- Most effective hydrogen bond structure in nonstoichiometric hydrate is for hemihydare stoichiometry.
- Almost maximum ethanol content in ethanol solvate are reached when ethanol content in atmosphere is about 5%.
- Ethanol solvate desolvatation can be described with biphasic model.

Thank you for your attention!

Acknowledgments:

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- **Liāna Orola**
- **European Social Fund for a scholarship to A. Bērziņš and Latvian Academy of Sciences Grant.**
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