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

AGRIS BĒRZIŅŠ, ANDRIS ACTIŅŠ, EDGARS SKARBULIS

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LATVIA
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 \(^{d}\)

\[\text{Structure of Droperidol}\]

\[\begin{align*}
\text{HN} & \quad \text{N} \\
\text{F} & \quad \text{HN} \\
\text{O} & \quad \text{O}
\end{align*}\]

Droperidol hydrates

**Dihydrate**


**Hemihydrate**

Outline

- **Droperidol hydrates**
  - Sorption-desorption isotherms
  - Dehydration products
  - Dehydration kinetics
  - Lattice parameters of droperidol hemihydrate

- **Droperidol ethanol solvate**
  - Similarity with hemihydrate
  - Lattice parameters of droperidol ethanol solvate
  - Desolvation kinetics

- **Conclusions**
Desorption-sorption isotherms - dihydrate

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

$n(H_2O)/n(\text{droperidol})$

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

Dehydration products - dihydrate

Dehydratation of droperidol dihydrate sample A by heating
Dehydration products - dihydrate

Dehydration 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)

Dehydration kinetic curves of droperidol dihydrate sample A in nitrogen flow with sample mass 5 mg
After optimization obtained least square sums for most appropriate kinetic models for droperidol dihydrate sample A with sample mass 5 mg.
With optimization method calculated activation energy values for droperidol dihydrate samples
Dehydration kinetics – hemihydrate (1)

Dehydration 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

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

Sorption-desorption isotherm of droperidol ethanol solvate

Lattice parameter changes

Graph showing the relationship between \( n(\text{EtOH})/n(\text{drop}) \) and lattice parameters \( a \) and \( c \).
Lattice parameter changes (2)
Desolvatation kinetics

Desolvatation kinetic curves of droperidol ethanol solvate
Desolvatation kinetics (2)

\[ \alpha = 1 - (Ae^{-kat} + Be^{-kbt}) \]

\[ R^2 = 0.9994 \]

- Biphasic model
  - Component A
  - Component B

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


Biphasic model, component A \( E_a = (55 \pm 4) \text{ kJ} \cdot \text{mol}^{-1} \)

Biphasic model, component B \( E_a = (67 \pm 5) \text{ kJ} \cdot \text{mol}^{-1} \)
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 dehydartaion of nonstoichiometric hydrate can be described with first order kinetic model.
Conclusions (2)

- Nonstoichiometric hydrate’s and ethanol solvate’s lattice parameters systematically changes depending on solvent content in the structure.

- Most effective hydrogen bond structure in nonstoichiometric hydrate is for hemihydrate 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!

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