STRUCTURAL ASPECTS OF FORMATION OF SOLID SOLUTIONS IN DIFFERENT BENPERIDOL – DROPERIDOL PHASES

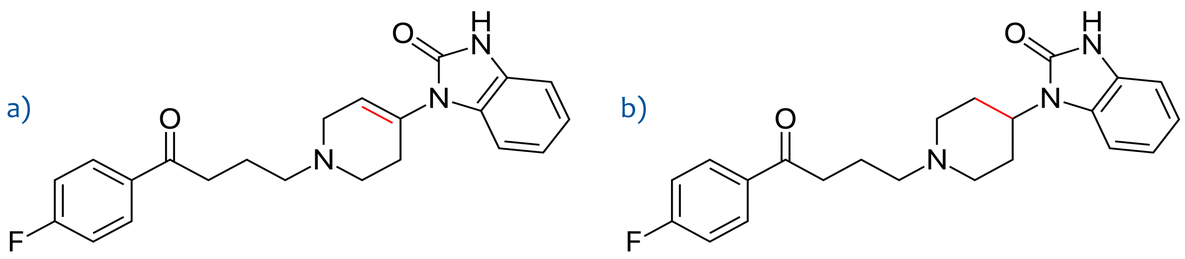
P1: Chemistry and Chemical physics

Kristaps Saršūns*, Agris Bērziņš, Elīna Sala

Faculty of Chemistry, University of Latvia, Riga, Latvia; kristaps.sarsuns@lu.lv

Introduction

Benperidol and droperidol are neuroleptic pharmaceuticals used as antipsychotics. Both compounds have very similar molecular structures – the two are only different by the order of C-C bond in the central ring (see below – piperidine ring in benperidol, tetrahydropyridine in droperidol).



Molecular structure of (a) droperidol and (b) benperidol

It is known that benperidol forms five polymorphs (^{B}I – ^{B}V) and eleven solvates (the most stable being $^{B}S_{Me}$, $^{B}S_{Et}$, $^{B}S_{ACN}$, ^{B}DH), but droperidol forms four polymorphs (^{D}I – ^{D}IV) and eleven solvates (the most stable being $^{D}S_{Me}$, $^{D}S_{Et}$, $^{D}S_{ACN}$, ^{D}DH) [1,2]. In previous research in cross-seeding experiments it was observed that it is possible to obtain droperidol phases isostructural to the benperidol phases, which suggest on solid solution formation between both compounds [3].

Aims

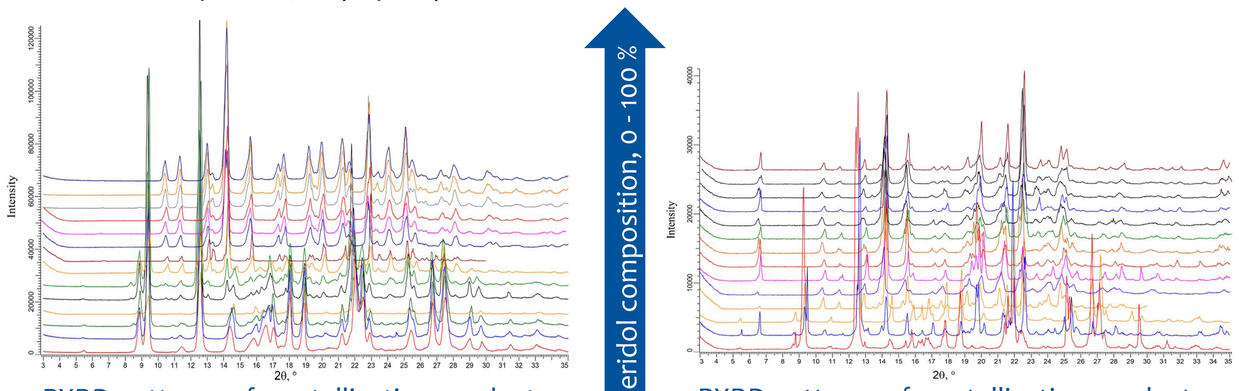
- ✓ To perfrom crystallization experiments between both compounds to check the possibillity for the formation of solid solutions
- ✓ To identify structural aspects responsible for differences observed in solid solution formation in different solid phases

Obtained crystalline phases

Experimentally obtained crystalline phases in benperidol – droperidol mixtures

Benperidol – droperidol proportion, %	Methanol solvate	Ethanol solvate	Acetonitrile solvate	Dihydrate	Ansolvate
100:0	$^{B}S_{Me}$	$^{B}S_{Et}$	$^{B}S_{ACN}$	^{B}DH	^{B}I
95:5	–	–	–	–	SS^{B}I
90:10	$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{B}S_{ACN}$	SS^{B}DH	SS^{B}II
80:20	$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{B}S_{ACN}$	SS^{B}DH	SS^{B}II
70:30	$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{B}S_{ACN}$	SS^{B}DH	SS^{B}II
60:40	$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$+$SS^{B}S_{ACN}$	SS^{D}DH+SS^{B}DH	SS^{B}II
50:50	$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$+$SS^{B}S_{ACN}$	SS^{D}DH+SS^{B}DH	SS^{B}II
40:60	$SS^{D}S_{Me}$+$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$+$SS^{B}S_{ACN}$	SS^{D}DH+SS^{B}DH	SS^{B}II
30:70	$SS^{D}S_{Me}$+$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$+$SS^{B}S_{ACN}$	SS^{D}DH+SS^{B}DH	SS^{B}II
20:80	$SS^{D}S_{Me}$+$SS^{B}S_{Me}$	$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$	SS^{D}DH+SS^{B}DH	SS^{B}II
10:90	$SS^{D}S_{Me}$	$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$	SS^{D}DH	SS^{D}II+SS^{B}II
5:95	$SS^{D}S_{Me}$	$SS^{D}S_{Et}$+$SS^{B}S_{Et}$	$SS^{D}S_{ACN}$	SS^{D}DH	SS^{D}II+SS^{B}II
0:100	$^{D}S_{Me}$	$^{D}S_{Et}$	$^{D}S_{ACN}$	^{D}DH	^{D}II

B – benperidol phase, **D** – droperidol phase, **S_{Me}** – methanol solvate, **S_{Et}** – ethanol solvate, **S_{ACN}** – acetonitrile solvate, **DH** – dihydrate, **I, II** – polymorphs, **SS** – solid solution



PXRD patterns of crystallization products from methanol

PXRD patterns of crystallization products from ethanol

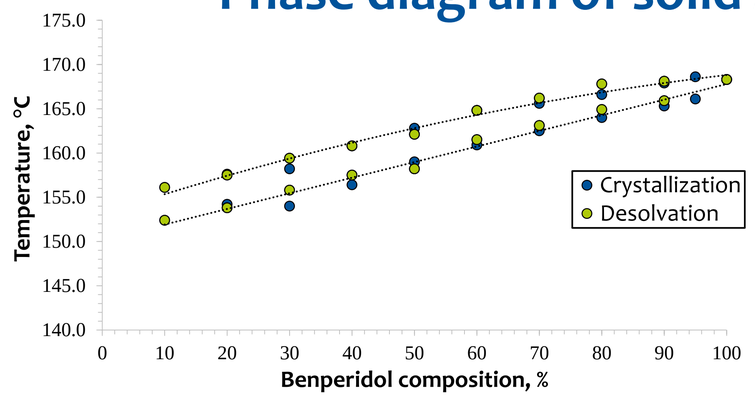
Preparation of solid solution SS^{B}II using desolvation

Crystalline phases before and after desolvation (80°C)

Benperidol – droperidol proportion, %	Methanol solvate		Ethanol solvate		Acetonitrile solvate		Dihydrate	
	Before desolvation	**After desolvation**	**Before desolvation**	**After desolvation**	**Before desolvation**	**After desolvation**	**Before desolvation**	**After desolvation**
100:0	$^{B}S_{Me}$	^{B}II	$^{B}S_{Et}$	^{B}II	$^{B}S_{ACN}$	^{B}II	^{B}DH	^{B}II
90:10	$SS^{B}S_{Me}$	SS^{B}II	$SS^{B}S_{Et}$	SS^{B}II	$SS^{B}S_{ACN}$	SS^{B}II	SS^{B}DH	SS^{B}II
70:30	$SS^{B}S_{Me}$	SS^{B}II	$SS^{B}S_{Et}$	SS^{B}II	$SS^{B}S_{ACN}$	SS^{B}II	SS^{B}DH	SS^{B}II
50:50	$SS^{B}S_{Me}$	SS^{B}II	$SS^{B}S_{Et}$	SS^{B}II	$SS^{D}S_{ACN}$+ $SS^{B}S_{ACN}$	SS^{B}II	SS^{D}DH+ SS^{B}DH	SS^{B}II
30:70	$SS^{B}S_{Me}$	SS^{B}II	$SS^{B}S_{Et}$	SS^{B}II	$SS^{D}S_{ACN}$+ $SS^{B}S_{ACN}$	SS^{B}II	SS^{D}DH+ SS^{B}DH	SS^{B}II
10:90	$SS^{D}S_{Me}$	SS^{B}II	$SS^{B}S_{Et}$	SS^{B}II	$SS^{D}S_{ACN}$	SS^{B}II	SS^{D}DH	SS^{B}II
0:100	$^{D}S_{Me}$	^{D}II	$^{D}S_{Et}$	^{D}II	$^{D}S_{ACN}$	^{D}II	^{D}DH	^{D}II

When solid solutions (such as ethanol solvate) and even when mixtures of solid solutions (in case of methanol and acetonitrile solvate and dihydrate) are formed, after desolvation, a solid solution which is isostructural to benperidol II crystalline form, is always formed.

Phase diagram of solid solution SS^{B}II



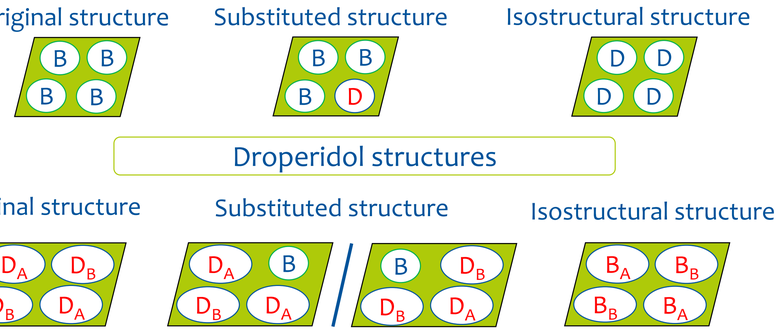
Combined phase diagram of crystallization and desolvation products

Graphically depicting melting temperatures depending on the benperidol composition and also including the maximum temperatures, a phase diagram is obtained, where maximum temperature is liquidus, while the melting point is solidus.

Combining the crystallization and desolvation products melting and maximum temperatures, can be observed to practically coincide with each other.

Characterisation of intermolecular interactions

Benperidol structures



Droperidol structures

Intermolecular interaction energies were calculated for original, isostructural and substituted structure solvates, as well as for dihydrate and polymorph.

In the case of droperidol energy of intermolecular interactions were calculated in two cases, because the molecules are not identical (and named as A and B respectively).

Computational calculations

Lattice energies of various solid forms of benperidol and droperidol (kJ/mol)

Phase	Structure					
	Benperidol			Droperidol		
	Original	Substituted	Isostructural	Original	Substituted	Isostructural
Methanol solvate	-159,1	-157,6 ▲	-160,0 ▼	-187,3	-183,1 ▲	-182,0 ▲
Ethanol solvate	-165,8	-164,0 ▲	-168,5 ▼	-189,6	-185,9 ▲	-184,7 ▲
Acetonitrile solvate	-144,2	-141,6 ▲	-146,0 ▼	-183,5	-180,6 ▲	-178,4 ▲
Dihydrate	-134,9	-132,3 ▲	-133,1 ▲	-134,5	-133,1 ▲	-131,3 ▲
Polymorph II	-244,7	-241,8 ▲	-245,4 ▼	-237,3	-231,9 ▲	-232,0 ▲

Intermolecular interaction energies of various solid forms of benperidol and droperidol (kJ/mol)

Phase	Structure					
	Benperidol			Droperidol		
	Original	Substituted	Isostructural	Original	Substituted	Isostructural
Methanol solvate	-114,0	-112,3 ▲	-115,3 ▼	-106,5	-104,9 ▲	-103,7 ▲
Ethanol solvate	-114,9	-115,4 ▼	-118,2 ▼	-105,9	-105,5 ▲	-103,0 ▲
Acetonitrile solvate	-110,1	-108,9 ▲	-109,6 ▲	-105,9	-105,4 ▲	-103,0 ▲
Dihydrate	-123,7	-123,2 ▲	-119,3 ▲	-119,9	-118,3 ▲	-121,4 ▼
Polymorph II	-245,7	-245,1 ▲	-233,7 ▲	-226,7	-220,5 ▲	-218,5 ▲

Lattice energies as well as intermolecular interaction energies were calculated in order to compare and find out likelihood of solid solution formation.

Notes and references

1. Bērziņš, A., Skarbulis, E., Rēķis, T., Actiņš, A. *Cryst. GrowthDes.* **2014**, *14*, 2654-2664.
2. Bērziņš, A., Skarbulis, E., Actiņš, A. *Cryst. GrowthDes.* **2015**, *15*, 2337-2351.
3. Bērziņš, A., Actiņš, A. *Cryst. GrowthDes.* **2016**, *16*, 1643-1653.

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Summary

- ✓ Crystallization of benperidol – droperidol mixtures from various solvents produced various crystalline structures, including various solvates, i.e., four solvated solid solutions and also a non-solvated solid solution
- ✓ Experimental observations of solid solution formation were supported by computational studies, as a result, it was concluded that the benperidol – droperidol system computational studies can be used to predict solid solution formation
- ✓ In case of benperidol ethanol solvate, both - isostructural structure and substituted structure, are more energy efficient than the original structure, indicating that the replacement of the ethanol solvate will occur easily and the solid solution will form all over the concentration range

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