

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

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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. Figure.1 - piperidine ring in benperidol, tetrahydropyridine in droperidol).

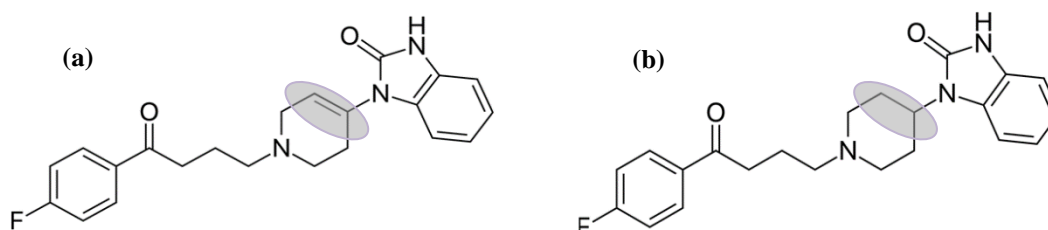


Figure 1. Molecular structure of (a) droperidol and (b) benperidol

It is known that benperidol forms five polymorphs (^{BI} – ^{BV}) and eleven solvates (the most stable being ^{BS_{Me}}, ^{BS_{Et}}, ^{BS_{ACN}}, ^{BDH}), but droperidol forms four polymorphs (^{DI} – ^{DIV}) and eleven solvates (the most stable being ^{DS_{Me}}, ^{DS_{Et}}, ^{DS_{ACN}}, ^{DDH}) [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].

In this research mixtures of both compounds were crystallized to test the solid solution formation (see Table 1) while computational calculations were carried out to identify structural aspects responsible for differences observed in solid solution formation in different phases.

Table 1. Experimentally obtained crystalline phases in benperidol – droperidol mixtures

Benperidol – droperidol proportion, %	Phase				
	Methanol solvate	Acetonitrile solvate	Ethanol solvate	Ansolvate	Dihydrate
0:100	^{DS_{Me}}	^{DS_{ACN}}	^{DS_{Et}}	^{DII}	^{DDH}
5:95	<i>SS^{DS_{Me}}</i>	<i>SS^{DS_{ACN}}</i>	<i>SS^{DS_{Et}}+SS^{BS_{Et}}</i>	<i>SS^{DII}+SS^{BII}</i>	<i>SS^{DDH}</i>
10:90	<i>SS^{DS_{Me}}</i>	<i>SS^{DS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{DII}+SS^{BII}</i>	<i>SS^{DDH}</i>
20:80	<i>SS^{DS_{Me}}+SS^{BS_{Me}}</i>	<i>SS^{DS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{DDH}+SS^{BDH}</i>
30:70	<i>SS^{DS_{Me}}+SS^{BS_{Me}}</i>	<i>SS^{DS_{ACN}}+SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{DDH}+SS^{BDH}</i>
40:60	<i>SS^{DS_{Me}}+SS^{BS_{Me}}</i>	<i>SS^{DS_{ACN}}+SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{DDH}+SS^{BDH}</i>
50:50	<i>SS^{BS_{Me}}</i>	<i>SS^{DS_{ACN}}+SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{DDH}+SS^{BDH}</i>
60:40	<i>SS^{BS_{Me}}</i>	<i>SS^{DS_{ACN}}+SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{DDH}+SS^{BDH}</i>
70:30	<i>SS^{BS_{Me}}</i>	<i>SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{BDH}</i>
80:20	<i>SS^{BS_{Me}}</i>	<i>SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{BDH}</i>
90:10	<i>SS^{BS_{Me}}</i>	<i>SS^{BS_{ACN}}</i>	<i>SS^{BS_{Et}}</i>	<i>SS^{BII}</i>	<i>SS^{BDH}</i>
95:5	–	–	–	<i>SS^{BI}</i>	–
100:0	^{BS_{Me}}	^{BS_{ACN}}	^{BS_{Et}}	^{BI}	^{BDH}

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

[1] Bērziņš, A.; Skarbulis, E.; Rēķis, T.; Actiņš, A. On the Formation of Droperidol Solvates: Characterization of Structure and Properties. *Crystal Growth & Design*. **2014**, *14*, 2654-2664.p.

[2] Bērziņš, A.; Skarbulis, E.; Actiņš, A. Structural Characterization and Rationalization of Formation, Stability, and Transformations of Benperidol Solvates. *Crystal Growth & Design*. **2015**, *15*, 2337-2351.p.

[3] Bērziņš, A.; Actiņš, A. Why Do Chemically Similar Pharmaceutical Molecules Crystallize in Different Structures: A Case of Droperidol and Benperidol. *Crystal Growth & Design*. **2016**, *16*, 1643-1653.p.