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A new polymorph of Bisacodyl

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A new polymorph structure of bisacodyl, (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate, was determined. The starting bisacodyl was extracted from suppositories with petroleum ether and the precipitate was recrystallized from acetone. The purity of the recrystallized product was verified with powder X-ray diffraction. The single crystal structure of bisacodyl shows that the compound crystallizes in a noncentrosymmetric manner in orthorhombic $P2_12_12_1$ space group, with unit cell parameters a = 8.06862(18) Å, b = 8.27567(18) Å, c = 28.3631(7) Å.

Keywords: bisacodyl, polymorph, single crystal, powder diffraction.

INTRODUCTION

Bisacodyl, (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate, [4-[(4-acetyloxyphenyl)-pyridin-2-ylmethyl]phenyl] acetate); is a stimulant laxative, widely used for the relief of occasional constipation [1, 2]. It is an over-the-counter drug sold under different brand names: Dulcolax, Correctol, Bisacolax, Bisac-Evac, Alophen, Feen-A-Mint. Bisacodyl is a white or almost white crystalline powder poorly adsorbed *in vivo* as it is practically insoluble in water. It is soluble in acetone, sparingly soluble in ethanol (96% *v/v*) and it dissolves in dilute mineral acids [3]. Bisacodyl mode of action requires its hydrolyzation by intestinal deacetylase enzymes to bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM) [4, 5]. BHPM is also the active metabolite of sodium picosulfate [6]. Bisacodyl can be administered orally or as suppositories. Though oral administration of Bisacodyl is easier the observed side effects (stomach or abdominal irritation, pains, vomiting) have forced the implementation of pharmaceutical approaches such as "controlled" pH-, time-, and enzyme-dependent release [4, 7]. Normally, new drug formulations are permitted only if they contain a particular polymorph (solid form), or a defined mixture of polymorphs (solid forms) [8], of the Active Pharmaceutical Ingredients. Consequently, it is important to control the crystallization conditions in order to allow the crystallization of only one particular solid form. In order to avoid problems linked with the crystallization of undesired solid forms (e.g. amorphous *vs* crystalline) or the crystallization of a new and unexpected crystal polymorph usually polymorphic screening is performed [9]. Up to now, data for only one crystal structure of Bisacodyl could be located in the databases (CCDC-CSD). The Bisacodyl structure was originally solved by powder diffraction ([10], **polymorph 1**) in $P\bar{1}$ space group (SG). In the present work we have identified and report the crystal structure a new polymorph (**polymorph 2**) of Bisacodyl (space group $P2_12_12_1$). Interestingly the crystals were grown from acetone, like those (space group $P\bar{1}$) structure reported in [10].

EXPERIMENTAL

Bisacodyl purification and preparation of solid form: 20 suppositories of bisacodyl (10 mg) were dissolved in 20 ml petroleum ether (b.p. 40–60 °C). After precipitation, the petroleum ether was decanted and the crude bisacodyl was washed with petroleum ether (2×10 ml). The bisacodyl precipitate was dried in air for 24 h and then recrystallized from acetone at room temperature which resulted in formation of colorless crystals.

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POWDER X-RAY DIFFRACTION (PXRD)

The PXRD investigations were performed on an X-ray powder diffractometer D2 Phaser (Bruker AXS) using Cu*K*α radiation, with a step size 0.02° 2θ and a collection time of 8 s per step. The simulated XRPD patterns were calculated with Mercury software (version 3.9) [11].

SINGLE CRYSTAL X-RAY ANALYSIS

A suitable single crystal of bisacodyl was selected and mounted on a glass capillary. All intensity and diffraction data were collected on an Agilent SupernovaDual diffractometer equipped with an Atlas CCD detector using micro-focus Cu Kα radiation (λ = 1.54184 Å) at 290 K. Collection and data reduction program was CrysAlisPro, Rigaku Oxford Diffraction, 2017, version 1.1.171.37.35 [12]. The crystal structure was solved by direct methods and refined by the full-matrix least-squares method on F^2 with ShelxS and ShelxL programs [13]. All non-hydrogen atoms were located successfully from Fourier maps and were refined anisotropically. Hydrogen atoms were placed at calculated positions using a riding scheme (Ueq = 1.2, aromatic C-H = 0.93 Å and Ueq =1.5, methyl C-H = 0.96 Å). The ORTEP [14] drawing of the molecule present in the asymmetric unit (ASU) and the most important crystallographic parameters from the data collection and refinement are shown in Figure 1 and Table 1 respectively. The figures concerning crystal structure description and comparison were prepared using Mercury software (version 3.9) [11].

Table 1. Most important crystallographic parameters for data collection and refinement of bisacodyl

Empirical formula	$C_{22}H_{19}NO_4$
Formula weight	361.38
Temperature/K	290
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	8.06862(18)
b/Å	8.27567(18)
c/Å	28.3631(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1893.90(8)
Z	4
ρ_{calc} g/cm^3	1.267
μ/mm^{-1}	0.714
F(000)	760.0
Crystal size/mm^3	0.25 × 0.2 × 0.2
Radiation	Cu *K*α (λ = 1.54184)
2*Θ* range for data collection/°	11.138 to 149.058
Index ranges	$-9 \le h \le 9, -9 \le k \le 4, -34 \le l \le 31$
Reflections collected/ Independent	6518/3717
R_{int} / R_{sigma}	0.0236/0.0289
Data/restraints/ parameters	3717/0/246
Goodness-of-fit on F^2	1.046
Final R indexes [*I* >= 2σ (*I*)]	R_1= 0.0386 *w*R_2= 0.0993
Final R indexes [all data]	R_1= 0.0435 *w*R_2= 0.1047
Largest diff. peak/hole / e Å^{-3}	0.12/–0.16
Flack parameter	–0.25(17)
CCDC number	1831419

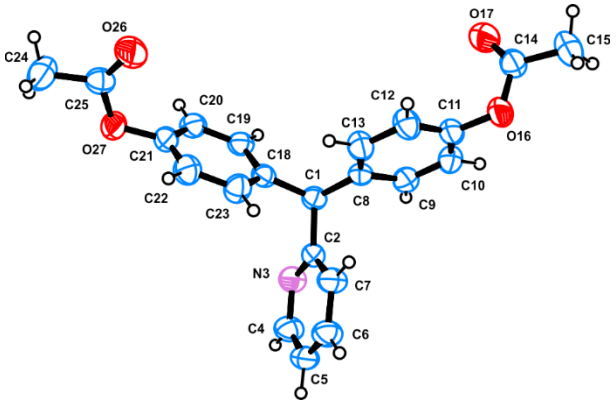

Fig. 1. ORTEP drawing of the molecule present in the asymmetric unit (atomic displacement parameters are at 50% probability); hydrogen atoms are shown as spheres with arbitrary radii.

RESULTS AND DISCUSSION

The comparison of the powder and the single crystal generated diffraction patterns clearly shows the existence of two polymorphic forms (Fig. 2). The assessment of the purity of the polymorph 1 from powder patterns of ref. [10] and this shown on Fig. 2 suggests that the employed purification procedure yields cleaner bisacodyl substance than that one purchased from Heowns Biochem Technologies LLC (considering the observed halo in the 5–15 2θ° region of [10]).

The new polymorph of Bisacodyl crystalizes in the orthorhombic $P2_12_12_1$ space group with one molecule in the ASU and four molecules in the unit cell (Z = 4) (Fig. 1). The values for the most bond lengths, angles and torsion angles (Table 2) are comparable with the other similar structures from the

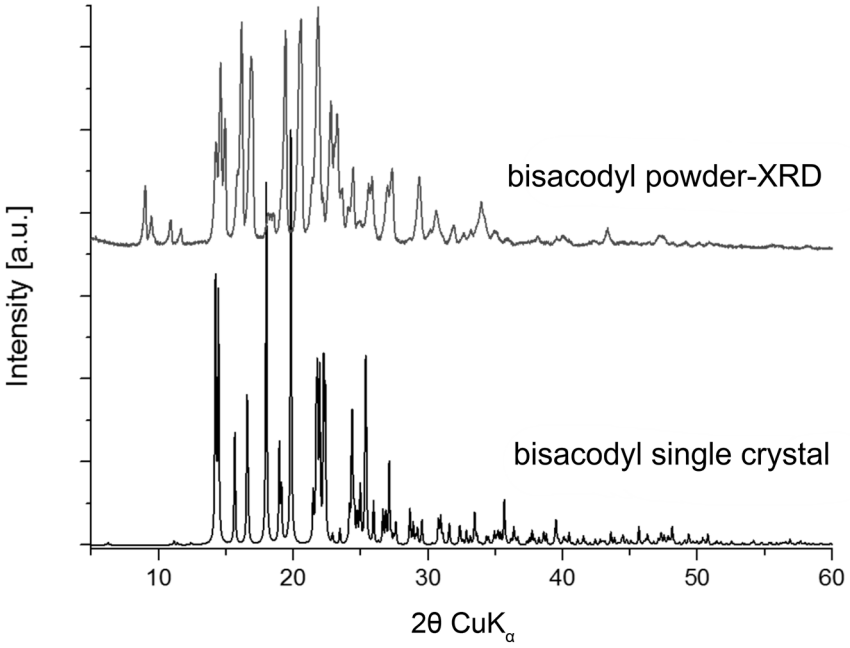

Fig. 2. Comparison between the powder and single crystal generated diffraction patterns of **polymorph 2**.

Table 2. Selected bond lengths, angles and torsion angles of the crystal structure of **polymorph 2**

Bond lengths	Å	Angles	°
N3—C2	1.335 (3)	C22—C21—O27	119.2 (3)
N3—C4	1.340 (4)	C25—O27—C21	118.4 (2)
C1—C8	1.523 (3)	C18—C1—C2	109.97 (18)
C1—C2	1.526 (3)	O17—C14—C15	126.4 (3)
C1—C18	1.525 (3)	O17—C14—O16	122.7 (2)
C11—O16	1.406 (3)	N3—C4—C5	124.3 (2)
O27—C21	1.411 (3)	O27—C25—C24	110.9 (2)
O16—C14	1.350 (3)	O26—C25—C24	126.3 (3)
O27—C25	1.337 (3)	Torsion angles	°
O17—C14	1.187 (3)	C21—O27—C25—O26	0.6 (5)
C25—O26	1.173 (3)	C2—C1—C8—C9	75.2 (3)

CSD-database 5.38 [10, 15–17]. A detailed comparison molecular packing similarity [18] of bisacodyl from **polymorph 1** [10] and **polymorph 2** shows an overall root mean square deviation (*rms*) of 1.017 and reveals that main difference is in the orientation of the acetate moieties (Fig. 3). Indeed the minimal variations of molecular geometry are the reason for the existence of the two polymorphic forms. The existence of a third polymorph form, which differs by the orientation of only one of the acetate moieties can be envisaged. The geometry around the –CH center is also interesting. Because of the two identical substituents (phenyl acetate) the C is not

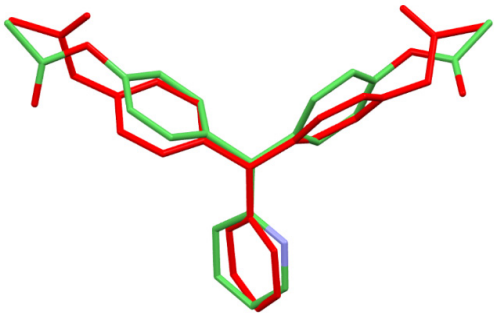

Fig. 3. Overlaid molecules [100] of **polymorph 1** (in green) [10] and **polymorph 2** (in red). The main difference between the forms is the torsion of the acetate moieties.

truly "chiral" and the polymorph in ref. [10] crystallizes in centrosymmetric SG $P\bar{1}$. Nevertheless the second polymorph crystallizes in a noncentrosymmetric manner (SG 19) with only one molecules in the ASU. Having in mind that the active metabolite of bisacodyl BHMP is hydrolyzed by intestinal enzymes one could expect that after the production of one –OH moiety the enzymes will continue to act only on the correct *R* or *S* 4-((4-hydroxyphenyl)(pyridin-2-yl)methyl)phenyl acetate. Thus for the reduction of the administered bisacodyl dose (e.g. by a factor of two) one should obtain the "correct" molecular orientation in the solid form.

Weak hydrogen bonding interactions (C—H···O) could be located in the structure (Table 3, Fig. 4). In both polymorphs the number of the weak interactions is two. However in the present structure the two C—H···O involve aromatic C-H (Fig. 4b) while in **polymorph 1** one of the detected interactions is obtained from a methyl group (Fig. 4a, e.g. $C\text{-}H_{methyl}$…O with H…*A* distance of 2.718 Å).

As the bisacodyl molecule features only classical hydrogen bond acceptors (2 × C=O), no hydrogen bond donors, and it is practically insoluble in water, the three dimensional crystal packing is governed by the network of weak interactions and the minimization of free spaces. Indeed the three dimensional packing of the bisacodyl molecules in **polymorph 2** shows a zig-zag orientation alongside *b*–axis and S-shaped orientation alongside *a*-axis (Fig. 5).

CONCLUSIONS

In this work, we describe the crystal structure and solid state behavior of a new bisacodyl polymorph. The single-crystals of the new polymorph form were obtained by a standard procedure followed by recrystallization from acetone. The single crystal structure data of **polymorph 2** showed a high molecular similarity with polymorph 1 with an overall *rm*s of 1.017 and only the orientation of the two acetate moieties is different. However, we found significant differences for **polymorph 2**: it crystallizes in a noncentrosymmetric manner ($P2_12_12_1$) and $C\text{-}H_{aromatic}$…O weak interactions stabilizing the three-dimensional packing are prefered over $C\text{-}H_{methyl}$…O ones. The existence of a third polymorph modification, differing by the orientation of only one acetate moiety should be envisaged.

Table 3. Weak intermolecular hydrogen bonding interactions of **polymorph 2**

D—H···A	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A (°)
C10—H10···O17i	0.93	2.623	3.333 (4)	134
C5—H5···O26ii	0.93	2.546	3.243 (3)	132

Symmetry codes: (i) −x+1, y−1/2, −z+1/2; (ii) x−1, y−1, z.

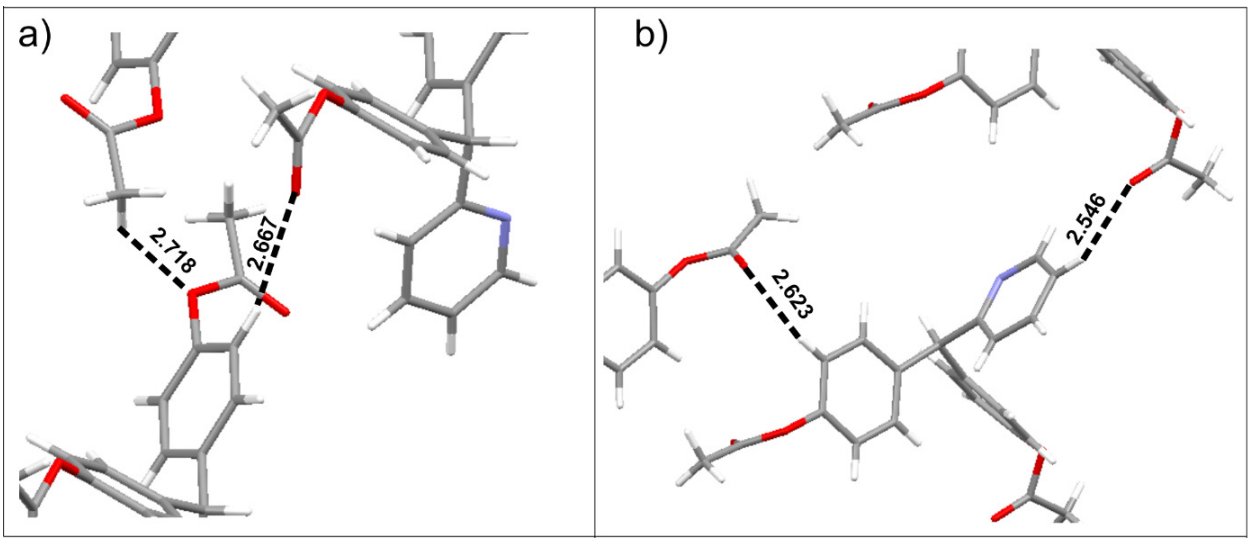

Fig. 4. Observed weak interactions in a) **polymorph 1** and b) **polymorph 2**

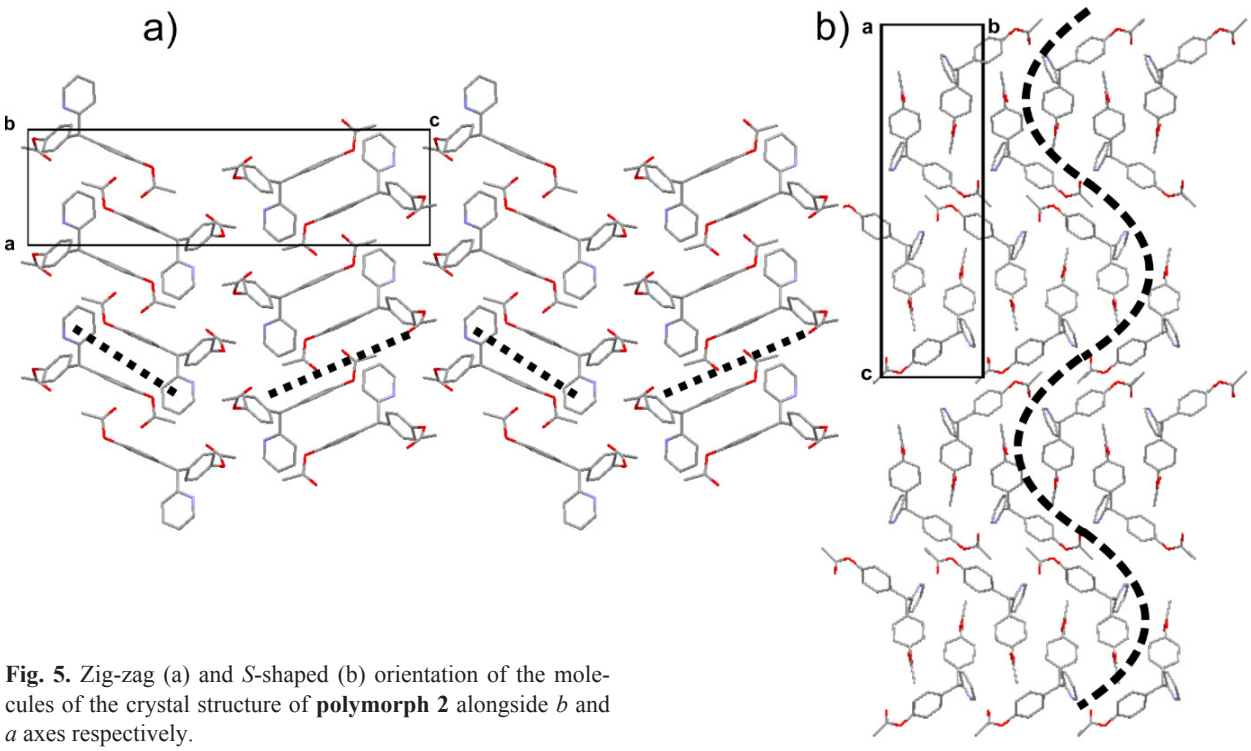

Fig. 5. Zig-zag (a) and *S*-shaped (b) orientation of the molecules of the crystal structure of **polymorph 2** alongside *b* and *a* axes respectively.

REFERENCES

1. E. M. H. Mathus-Vliegen, K. van der Vliet, I .J. W. der Storm, J. S. Stadwijk, *Diseases of the Colon & Rectum*, **61**, 2, 239 (2018).
2. G. Pala, G. Coppi, E. Crescenzi, *Arch Int Pharmacod T*, **164**, 2, 356 (1966).
3. European Pharmacopoeia Commission, Council of Europe, European pharmacopoeia 9-th edition, Maisonneuve, Sainte Ruffine, 2016.
4. H. J. Park, H. J. Jung, M. J. Ho, D. R. Lee, H. R. Cho, Y. S. Choi, J. Jun, M. Son, M. J. Kang, *European Journal of Pharmaceutical Sciences*, **102**, 172 (2017).
5. W. J. Adams, A. P. Meagher, D. Z. Lubowski, D. W. King, *Diseases of the Colon & Rectum*, **37**, 229 (1994).
6. [6] R. Jauch, R. Hankwitz, K. Beschke, H. Pelzer, *Arzneimittel-Forschung*, **25**, 1796 (1975).
7. D. R. Friend, *Advanced Drug Delivery Reviews*, **57**, 247 (2005).
8. W. Beckmann, *Engineering in Life Sciences*, **3**, 113 (2003).
9. [9] E. H. Lee, *Asian Journal of Pharmaceutical Sciences*, **9**, 163 (2014).
10. S. S. Li, X. Q. Wu, Q. Wang, P. X. Tang, H. Li, *Powder Diffraction*, **29**, 295, (2014).
11. C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P. A. Wood, *Journal of Applied Crystallography*, **41**, 466 (2008).
12. CrysAlis PRO, in: Agilent Technologies, UK Ltd, Yarnton, England, 2011.
13. G. M. Sheldrick, *Acta Crystallographica A*, **64**, 112 (2008).
14. L. Farrugia, *Journal of Applied Crystallography*, **45**, 849 (2012).
15. N. C. Habermehl, F. Mohr, D. J. Eisler, M. C. Jennings, R. J. Puddephatt, *Canadian Journal of Chemistry*, **84**, 111 (2006).
16. B. Nath, D. Kalita, J. B. Baruah, *Solid State Sciences*, **14**, 880 (2012).
17. R. J. Sarma, J. B. Baruah, *Chemistry – A European Journal*, **12**, 4994 (2006).
18. J. Rohlicek, E. Skorepova, M. Babor, J. Cejka, *Journal of Applied Crystallography*, **49**, 2172 (2016).

НОВ ПОЛИМОРФ НА БИЗАКОДИЛ

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(Резюме)

Определена е кристалната структура на нов полиморф на бизакодил. Изходният продукт е екстрахиран от супозитори с петролев етер, а преципитатът е прекристализиран с ацетон. Чистотата на прекристализирания продукт е проверена с помощта на прахов рентгенофазов анализ. Монокристалният рентгеноструктурен анализ показа, че молекулите на бизакодил кристализират по нецентросиметричен начин в орторомбичната $P2_12_12_1$ пространствена група, с параметри на елементарната клетка a = 8.06862(18) Å, b = 8.27567(18) Å, c = 28.3631(7) Å. Сравнението между праховата рентгенограма на пречистения бизакодил и на полиморфа, докладван от Li et al., навежда на мисълта, че приложената екстракция дава продукт с висока чистота.