

CRYSTAL STRUCTURES OF LARGE-VOLUME COMMERCIAL PHARMACEUTICALS

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As part of a continuing project, the challenging room-temperature crystal structures of six commercial pharmaceutical APIs have been solved by Monte Carlo simulated annealing techniques using synchrotron X-ray powder diffraction data (11-BM at APS), and optimized using density functional techniques. **Bisoprolol fumarate**, $(C_{18}H_{33}NO_4)_2(C_4H_2O_4)$, crystallizes in $P\bar{1}$, with $a = 8.16570(5)$, $b = 8.51639(12)$, $c = 16.75179(18)$ Å, $\alpha = 89.142(1)$, $\beta = 78.155(1)$, $\gamma = 81.763(1)^\circ$, $V = 1128.265(10)$ Å³, and $Z = 1$. The structure was difficult to solve because the two ends of the bisoprolol cation are similar but not identical. **Hyoscyamine sulfate monohydrate**, $(C_{17}H_{24}NO_3)_2(SO_4)(H_2O)$, (generally described as a dihydrate) crystallizes in $P2_1$ with $a = 6.60196(2)$, $b = 12.95496(3)$, $c = 20.93090(8)$ Å, $\beta = 94.8839(2)^\circ$, $V = 1783.680(5)$ Å³, and $Z = 2$. The multiple fragments led to a low success rate. **Atropine sulfate monohydrate**, $(C_{17}H_{24}NO_3)_2(SO_4)(H_2O)$, (racemic hyoscyamine) crystallizes in $P2_1/n$ with $a = 19.2948(5)$, $b = 6.9749(2)$, $c = 26.9036(5)$ Å, $\beta = 94.215(2)^\circ$, $V = 3610.86(9)$ Å³, and $Z = 4$. The success rate of solution using DASH was only 1%, and required Mogul Distribution Bias and {010} preferred orientation. Despite being apparently orthorhombic **cefprozil monohydrate**, $C_{18}H_{19}N_3O_5S(H_2O)$, crystallizes in $P2_1$ with $a = 11.26503(5)$, $b = 11.34017(4)$, $c = 14.72628(10)$ Å, $\beta = 90.1249(4)^\circ$, $V = 1881.24(2)$ Å³, and $Z = 4$. DFT calculations suggest that the carboxylic acid proton on one (but not the other) of the two independent cefprozil molecules is transferred to an amino group, forming a salt. This suggestion needs to be confirmed by spectroscopic experiments and calculations of the vibrational spectrum. Despite being apparently monoclinic, **metolazone**, $C_{16}H_{16}ClN_3O_7$, crystallizes in $P\bar{1}$ with $a = 8.1976(5)$, $b = 14.4615(69)$, $c = 16.0993(86)$ Å, $\alpha = 115.009(18)$, $\beta = 90.096(7)$, $\gamma = 106.264(4)^\circ$, $V = 1644.52(9)$ Å³, and $Z = 4$. The broad 02 $\bar{1}$ peak indicates stacking faults in the structure. **Linagliptin**, $(C_{25}H_{28}N_8O_2)_2(\text{solvent})(H_2O)$, crystallizes in $P2_12_12$ with $a = 24.85078(12)$, $b = 21.5691(8)$, $c = 9.74377(4)$ Å, $V = 5222.77(3)$ Å³, and $Z = 8$. The structure was solved by TEM electron tomography. Initial fit to the X-ray powder data was relatively poor, but the structure contains a channel, which is filled with water and solvent. Hydrogen bonding is important in all these crystal structures.