Polymorphism in Pharmaceutical Solids

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Preface

Since the middle of the last century
molecules can be obtained in more
property that became known as po
methods based on the diffraction of x-
the structures of crystalline substanc
extremely large number of molecule
phenomenon. In addition, numerous
other nonequivalent crystalline struct
vent molecules in the lattice.

It was also established that the s
pound upon crystallization would exe
state properties of that system. For a
conductivity, volume, density, visco
crystal hardness, crystal shape and co
conductivity, melting or sublimation
heat of solution, solubility, dissoluti

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Theory and Origi

David J. W. Grant

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I. INTRODUCTION

Many pharmaceutical solids exhi

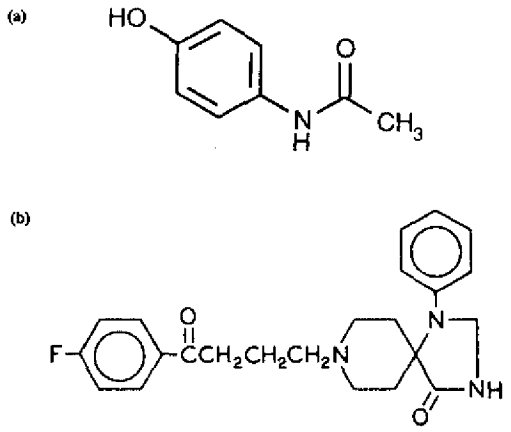


Fig. 1 Molecular structure of (a) acetaminophen and (b) spiperone.

ecules in the crystal lattice [1–3]. Thus, in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules. As a result, the polymorphic solids have different unit cells and hence display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial, and mechanical properties, as discussed below [1–3].

For example, acetaminophen (paracetamol, 4-acetamidophenol, 4-hydroxyacetanilide, shown in Fig. 1a) can exist as a monoclinic form, of space group $P2_1/n$ [4], which is thermodynamically stable under ambient conditions. The compound can also be obtained as a less stable orthorhombic form, of space group *Pbca*, and which has a higher density indicative of closer packing [5–7]. The unit cells of these two forms are compared in Fig. 2 and Table 1. The molecule of acetaminophen is rigid on account of resonance due to conjugation involving the hy-

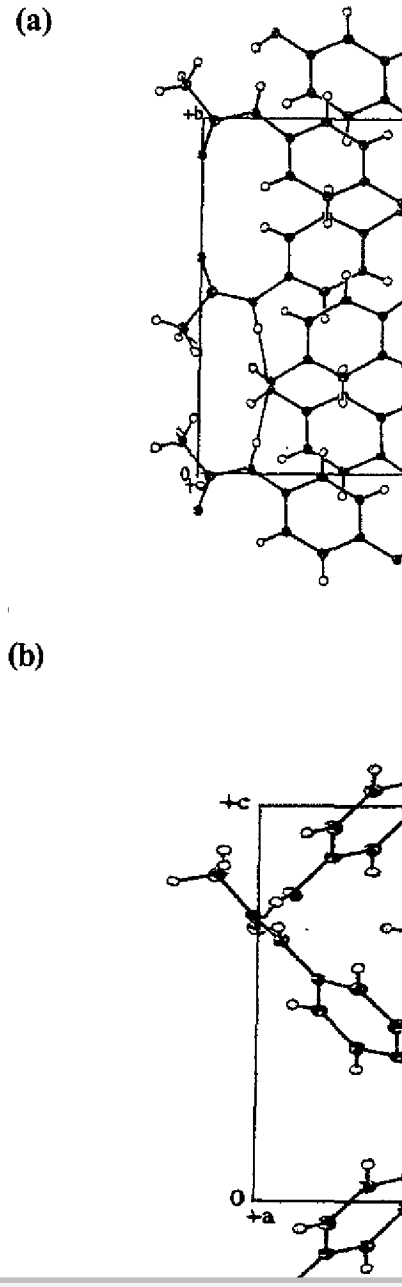


Fig. 2 View of the unit cell contents for two polymorphs of acetaminophen: (a) orthorhombic form (b) monoclinic form [4,5,7]. (Reproduced with permis-

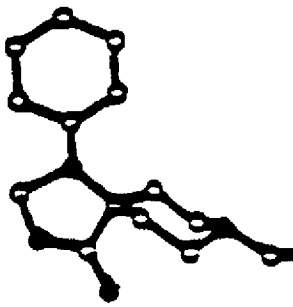
Table 1 Crystal Data for Two Polymorphs of Acetaminophen

Crystal data and structure refinement	Orthorhombic phase	Monoclinic phase
Empirical formula	$C_8H_9NO_2$	$C_8H_9NO_2$
Formula weight	151.16	151.16
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1/n$
Unit cell dimensions	a = 17.1657(12) Å	a = 7.0941(12) Å
	b = 11.7773(11) Å	b = 9.2322(11) Å
	c = 7.212(2) Å	c = 11.6196(10) Å
	α = 90.000°	α = 90.000°
	β = 90.000°	β = 97.821(10)°
	γ = 90.000°	γ = 90.000°
Volume	1458.1(4) Å^3	753.9(2) Å^3
Z	8	4
Density (calculated)	1.377 g/cm^3	1.332 g/cm^3
Crystal size	0.28 × 0.25 × 0.15 mm	0.30 × 0.30 × 0.15 mm
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Hydrogen bond lengths and angles		
H(5)O(2)	1.852(26) Å	1.772(20) Å
H(6)O(1)	2.072(28) Å	2.007(18) Å
O(1)—H(5)O(2)	170.80(2.35)°	166.15(1.75)°
N(1)—H(6)O(1)	163.52(2.19)°	163.93(1.51)°

Source: Refs. 4, 5, and 7. Reproduced with permission of the copyright owner, the American Crystallographic Association, Washington, DC.

droxyl group, the benzene ring, and the amido group. Therefore the conformation of the molecule is virtually identical in the two polymorphs of acetaminophen. On the other hand, the spiperone molecule (8-[3-(p-fluorobenzoyl)-propyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one, shown in Fig. 1b) contains a flexible -CH_2-CH_2-CH_2- chain and is therefore capable of existing in different molecular conformations [8]. Two such conformations, shown in Fig. 3, give rise to two different

Form I



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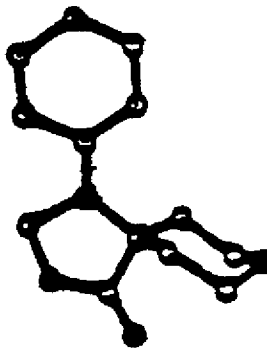

Fig. 3 The molecular conformatio
phic forms I and II [8]. (Reproduced
the American Pharmaceutical Assoc

though their space groups are the
as shown in Table 2 [8].

As mentioned above, the va
exhibit a variety of different phys

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