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Crystal polymorphism of pharmaceuticals

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Since the last review that one of the authors has done on the subject of polymorphism, there has been a mushrooming of papers on pharmaceutical substances which have exhibited crystal polymorphism. The present review is an effort to compile a listing of the various pharmaceutical substances which have reported having crystal polymorphism.

INTRODUCTION

Polymorphism is a technical term used both in biology and in crystallography, describing the fact that some natural substances can occur in different forms. In the following review the term is used to describe crystal polymorphism only. The ability of the same element or chemical compound to crystallize in more that one crystal arrangement is known as polymorphy or more often as polymorphism. White, red and black phosphorous or the diamond-graphite pair are examples of crystal polymorphism.

This phenomenon, although known for a long time, interested only crystallographers until the 1950's and was looked at as an expression of nature's richness. The discovery of polymorphism among pharmaceutical substances, however, initiated a growing interest in this field. The synthetic and analytic departments of leading pharmaceutical companies nowadays carry out systematic work to detect polymorphism of their drugs and to find intelligent applications of this phenomenon. Drug registration documents submitted by leading pharmaceutical companies to regulatory bodies will today, almost without exception, have a section on polymorphism when describing the physico-chemical properties of the active substance. The statement that the substance exhibits no polymorphism is equally important as exhibiting polymorphism. After discovery of the first cases of polymorphism with dramatic differences in biological activity betwen two forms of the same drug (*e. g.* chloramphenicol palmitate) no pharmaceutical manufacturer could neglect the problem. Lately even Groups of Polymorphism and Biovailability have been established as it is done at the Faculty of Pharmacy, Montpellier, France. While the scientific literature is rich in reports on polymorphism, only a

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few reviews (1—6) and the monograph by Kuhnert-Brandstätter deal with the role of polymorphism in the area of pharmaceuticals. Excellent aids in handling polymorphic crystals in the laboratory are the books of McCrone (8) and Nikolics (9) and naturally the old classic »Mikro-Methoden« by Kofler and Kofler (10).

ANALYTICAL METHODS

The analytical methods used to study polymorphism have not changed much in the past 10—15 years. These methods are reviewed in detail (1, 2, 11) and will only shortly be mentioned here.

Infra-red spectroscopy is still a sensitive, but not necessarily infallible, method in identifying polymorphs. There are cases of polymorphism as registered by X-ray diffraction methods or melting point anomalies without yielding different infrared spectra. On the other hand, X-ray diffraction methods on single crystals or powdered samples almost never fail due to their outstanding ability of detecting differences in crystal structures.

Polarized light microscopy, accompanied with a relatively inexpensive hot stage is the simplest, yet one of the most powerful methods of studying polymorphism. It is amazing how many substances were discovered exhibiting polymorphism by Kuhnert-Brandstätter and her co-workers using only thermomicroscopy, before the introduction of Differential Scanning Calorimetry (DSC) and Differential Thermal Analysis (DTA). These latter two methods yield computable data for calculating energy differences between polymorphs. This is especially true in the work of Burged (12, 13) where he used DSC to arrive at a mathematical-thermodynamical understanding of the essence of polymorphism.

Laser Raman spectroscopy has been applied by Bellows *et al.* (14) to study the various crystal forms and solvates of ampicillin and griseofulvin. Their interesting observation was that during solvate formation with chloroform the griseofulvin crystal lattice expanded to accept chloroform. Benzene, however, forces the crystal lattice into a new structure when forming solvate. Although laser Raman spectroscopy undoubtedly has potentials, it has not gained broader popularity for the time being.

High-resolution, solid state nuclear magnetic resonance (NMR) was applied by Hewitt *et al.* (15) to study amylodextrin and amylose polymorphs. Conventionally NMR spectroscopy is used to study molecules in solutions, which is of no use for crystal polymorphy-research. With the introduction of cross-polarization magic-angle-spinning (c. p.—m. a. s.) technique, a valuable new tool is available as demonstrated in the study of orientation of the glycosidic linkages in amylose in the solid phase.

LIST OF PHARMACEUTICALS

The goal of this article, unlike the previous review article by one of the authors (2) where all aspects of crystal polymorphism had been reviewed, is to compile a list of various pharmaceuticals which have reported crystal polymorphism. The authors are well aware that there are many other pharma-

ceuticals which do indeed exhibit polymorphism but have not been reported in the literature or have not been studied long enough to find if they exhibit polymorphism or not.

Pharmaceutical substances reporting crystal polymorphism

Substance	*Reference(s)*
Acebutolol hydrochloride,	16
Aceclidine hydrochloride	17
Acedapsone	17
Acemetacin	18
Acetamide	7, 19
Acetazolamide	13, 20, 21, 22, 23, 24
Acetohexamide	25
21-Acetoxypregneloolne	26
β-Acetyldigoxin	27, 28
DL-O-Acetylpantolacton	29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43
Acetylsalicylic acid (ASA)	7
Acetylsulfisoxazole	44, 45, 46
Adeps solidus (Lard)	47
Adiphenine hydrochloride	48
Ajmaline	—
Algedrate, see Aluminium hydroxide gel	49
Allantoin	7
Allobarbital	7
Allopregnane-3β, 20α-diol	7
3,20-Allopregnanedione	7
5-Allyl-5-(2-cyclopenten-1-yl)barbituric acid	7
5-Allyl-5-phenylbarbituric acid	7
Alprenolol hydrochloride	50
Aluminium hydroxide gel	51, 52, 53, 54
Amino acetic acid, see glycine	55
p-Aminobenzoic acid	56
6-(1-aminocyclohexanecarboxamido)--penicillanic acid	50
Amisometradine	57, 58, 59
Amitriptyline hydrochloride	7, 60
Amobarbital	61
Amphetamine sulfate	62, 63, 64, 65, 66
Ampicillin	67, 68
Amrinone	16
Amylodextrins	15
5α-Androstane-3β,17β-diol	69
Androstane-β,17β-diol	7, 70, 71
5α-Androstane-3α,17β-diol	71
Androstane-3,17-dione	7
Androstanolone	69
5-Androstene-3β,17-α-diol	69
Androstene-3β,17β-diol	7
4-Androstene-3,17-dione	72
Anilamate	73
Anthranilic acid	74
Aprindine hydrochloride	7, 60
Aprobarbital	75
Apronalide	76
Asparaginase	