Analytical Profiles of Drug Substances

Volume 8

Edited by

Klaus Florey

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New Brunswick, New Jersey

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PREFACE

Although the official compendia list tests and limits for drug substances related to identity, purity, and strength, they normally do not provide other physical or chemical data, nor do they list methods of synthesis or pathways of physical or biological degradation and metabolism. For drug substances important enough to be accorded monographs in the official compendia, such supplemental information should also be made readily available. To this end the Pharmaceutical Analysis and Control Section, Academy of Pharmaceutical Sciences, has undertaken a cooperative venture to compile and publish *Analytical Profiles of Drug Substances* in a series of volumes of which this is the seventh.

The concept of analytical profiles is taking hold not only for compendial drugs but, increasingly, in the industrial research laboratories. Analytical profiles are being prepared and periodically updated to provide physicochemical and analytical information of new drug substances during the consecutive stages of research and development. Hopefully, then, in the not too distant future, the publication of an analytical profile will require a minimum of effort whenever a new drug substance is selected for compendial status.

The cooperative spirit of our contributors has made this venture possible. All those who have found the profiles useful are requested to contribute a monograph of their own. The editors stand ready to receive such contributions.

Thanks to the dedicated efforts of Dr. Morton E. Goldberg, a long cherished dream has come to fruition with the publication of *Pharmacological and Biochemical Properties of Drug Substances*, M. E. Goldberg, editor, published by APhA Academy of Pharmaceutical Sciences. This new series supplements the comprehensive description of the physical, chemical, and analytical characteristics of drug substances covered in *Analytical Profiles of Drug Substances* with the equally important description of pharmacological and biochemical properties.

Drug substances appearing in the new series will be cross-referenced in the cumulative index.

The goal to cover all drug substances with comprehensive monographs is still a distant one. It is up to our perseverance to make it a reality.

Klaus Florey

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ASPIRIN

Klaus Florey

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1. Introduction

1.1 Foreword

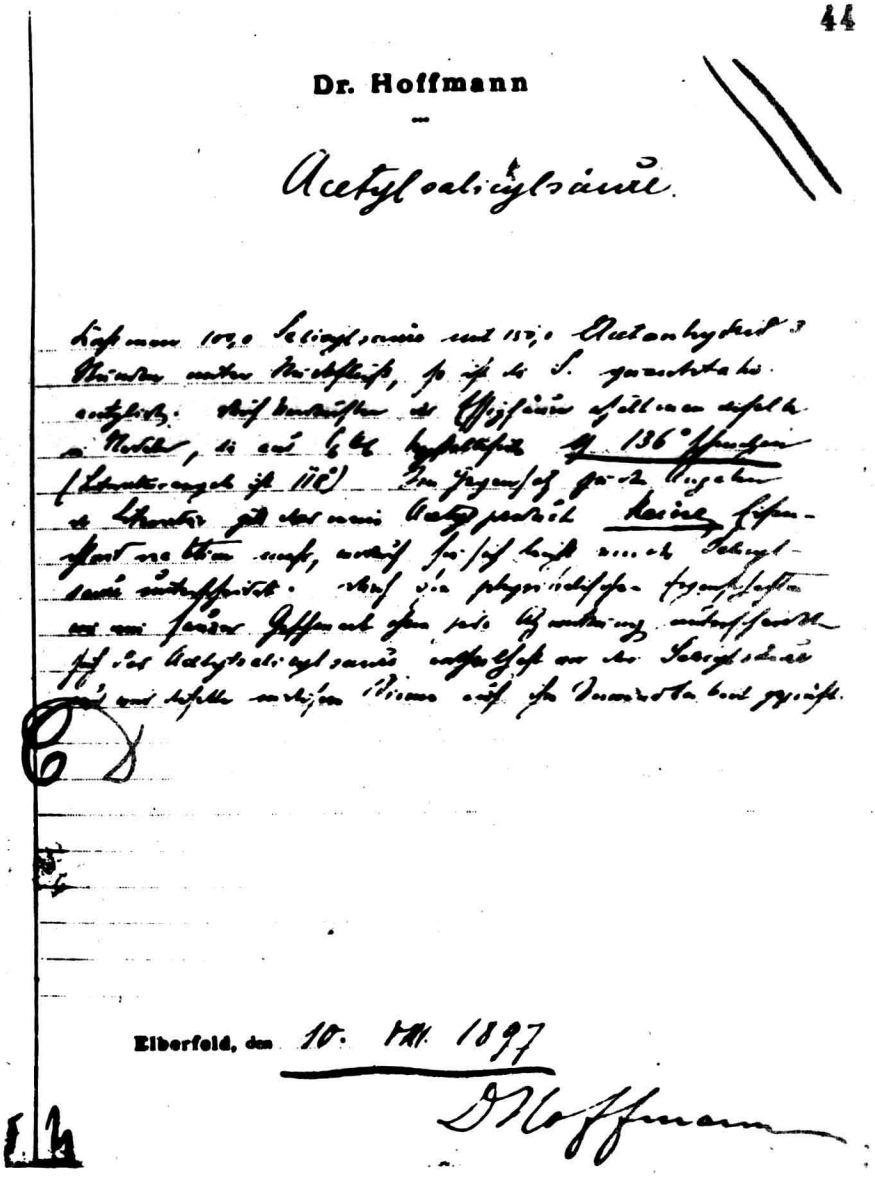
The writing of an analytical profile of aspirin, this drug of drugs, poses two major dilemmas. The first is in the name itself. There are many countries where Aspirin is still a trade-name of the German firm Bayer AG, and Acetylsalicylic Acid is used as the generic. Yet, I decided to use the former because it is the U.S.P. and B.P., the better known worldwide and the more elegant name.

Aspirin has now been available for close to 80 years, and its usefulness and popularity are undiminished. Consequently, the literature is voluminous and also undiminished. A complete coverage would be beyond the scope of an analytical profile. I have endeavored to cover the newer literature as comprehensibly as possible and have included only those older references which I found of historical interest. To all those who have labored in the vineyard of aspirin and who go unreferenced in this profile, I tender my sincere apologies.

1.2 History

The documented facts of the discovery of aspirin are quickly told. It was synthesized by the German chemist Felix Hoffmann (1868-1946) in the laboratories of Farbenfabriken Bayer, Elberfeld, Germany in 1897 (Fig. 1). The compound was tested pharmacologically by H. Dreser[1] and clinically among others by Wohlgemuth[2] and Witthauer[3] who documented the antirheumatic, antipyretic and analgesic properties free of the undesirable side effects of salicylic acid.

Apparently, there was some initial reluctance at Bayer to market the new compound since it was thought that the field was already crowded with new drugs. But opposition faded when the new drug got the support of Carl Duisberg, then the general manager of Bayer. Duisberg, of course, was the great chemist and industrialist who built Bayer into the chemical giant of world renown. After the inspired trade name Aspirin, a contraction of acetyl and "spirsäure" (salicylic acid), was coined in the offices of Bayer - Euspirin was also considered and fortunately discarded[4] - it was marketed in tablet form in 1899 and conquered the world.



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Dr. Hoffmann

—

Acetylsalicylsäure.

Elberfeld, den 10. VIII. 1897

D Hoffmann

Figure 1. Laboratory notebook entry of Felix Hoffmann, describing his first preparation of aspirin. The initials CD on the page are those of Carl Duisberg. (Courtesy of Bayer A.G., Leverkusen, Germany)

What motivated Hoffmann to undertake this momentous synthesis? Legend has it that he wanted to help his father who was suffering from rheumatism and who was no longer able to tolerate sodium salicylate, then widely used in rheumatic and arthritic diseases. Salicylic acid occurs naturally in several plants. The analgesic and antipyretic properties of willow bark were already known in antiquity to Hippocrates and the blossoms of spiraea ulmaria (meadow sweet) were used in the middle ages. Salicylic acid was crystallized from willow bark extracts in the early years of the last century, and Kolbe, in 1859, was able to synthesize it from sodium phenolate and carbon dioxide. His student von Heyden worked out a commercially feasible process and started a factory to produce salicylic acid which made possible its widespread use in rheumatic diseases. However, its bad taste, stomach irritation and other side effects were a strong incentive to search for derivatives which retained its efficacy without its disadvantages. Acetylation of the hydroxyl group was one of the logical modifications. Acetylated salicylic acid had already been described three times in the literature (see Section 3). Von Heyden and possibly also Merck, Darmstadt, are reputed to have experimented with aspirin without being able to produce the pure drug.

At the time when Felix Hoffmann prepared pure aspirin successfully in the Bayer laboratories, one of his colleagues was Arthur Eichengrün, who had been hired by Carl Duisberg in 1896, while Hoffmann had been hired in 1894. Eichengrün, as an old man, had to undergo the horrors of the infamous Nazi concentration camp in Theresienstadt which he survived. In 1949, Eichengrün published his memoirs relating to the invention of aspirin[5] which was then a half-century old. He claimed that it was he who told Hoffmann to prepare acetylsalicylic acid. Acetylation certainly was on Eichengrün's mind, since he had also experimented successfully with the acetylation of cellulose about the same time. He went on to fame as the inventor and developer of rayon and safety film. Eichengrün also claimed that another colleague of Bayer, the pharmacologist Dreser, opposed clinical trials. However, the memory of the 82 year-old Eichengrün must have been faulty when he

wrote these rather bitter reminiscences concerning Hoffmann's, Dreser's and his own role in the discovery of aspirin because, in 1913, Eichengrün wrote a chapter on "The Pharmaceutical Research Laboratory" in the book History and Development of Farbenfabriken Bayer, Vorm. Friedr. Bayer & Co., Elberfeld by F. Fischer, 1913[4], where he laid no paternity claim to aspirin and described Dreser's role correctly. The pertinent passage (p. 412) translates as follows: "Acetylsalicylic acid, prepared by Felix Hoffmann ..... rested unnoticed for 1½ years among the preparations rejected by the pharmacological laboratory until in 1898, during unrelated investigations, Dreser's attention was again drawn to it. On account of the observation that the acetyl compound was increasing cardiac activity in contrast to salicylic acid itself, he recommended a clinical trial of the product...."

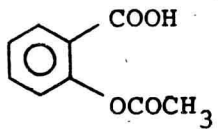
Felix Hoffmann did not publish his version of the discovery, nor did he obtain a German patent, since the synthesis had been previously described. Farbenfabriken Bayer did obtain a U.S. Patent[6] in 1900 which named him as the inventor. Chemical Abstracts reveal no subsequent publications by him, nor is there any record that he was publicly honored for his contribution. However, in 1899, he was appointed director of the pharmaceutical research and marketing division of Bayer. He retired in 1928[7].

In many ways, the story of the discovery of aspirin is typical for the way in which new drugs are invented and developed in pharmaceutical research laboratories, where many individuals have to make a contribution and where it is often difficult to fathom completely what thought processes, suggestions and interactions lead to a successful new drug.

2. Description

2.1 Name, Formula, Molecular Weight

Aspirin is acetylsalicylic acid, also salicylic acid acetate and 2-(acetyloxy)-benzoic acid (50-78-2). The last name is currently popular in Chemical Abstracts.



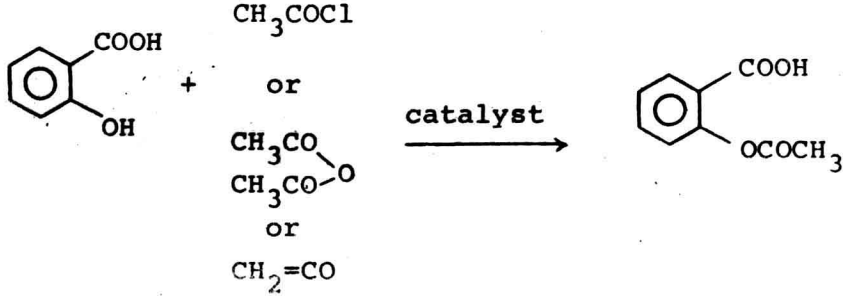
$C_9H_8O_4$ M.W. 180.16

2.2 Appearance, Color, Odor

Aspirin is a white, crystalline powder. It is odorless but might have a faint odor of acetic acid.

3. Synthesis

The first synthesis of aspirin is credited to Gerhardt[8] in 1853. Gerhardt was investigating mixed organic acid anhydrides and, among others, reacted acetylchloride with sodium salicylate. He obtained a solid product, undoubtedly impure acetylsalicylic acid, which immediately and without further characterization he hydrolyzed with aqueous sodium carbonate to salicylic and acetic acids. Next it was prepared by reaction of salicylic acid with acetylchloride by H. von Gilm[9] in 1859, who described a crystalline product. In 1869, K. Kraut[10] had a student, A. Prinzhorn, prepare acetylsalicylic acid by the methods of Gerhardt and von Gilm and obtained an identical product by both methods with a reported melting point of 118.5°. Kraut also correctly observed that the product is not an acid anhydride as assumed by Gerhardt but rather a phenolic ester. Felix Hoffmann[6] used acetic anhydride for its preparation.



Essentially, all methods of synthesis are variations of the reaction of acetylchloride, acetic anhydride or ketene[11] with salicylic acid using a variety of catalysts such as pyridine[12] or sulfuric acid[13] and reaction conditions (c.f. 14). The preparation of aspirin labeled with a ^{14}C-labeled acetyl group has also been reported.[15] Efforts to improve the commercial processes continue to the present day.

4. Physical Properties

4.1 Spectra

4.11 Infrared

The assignment of the KBr infrared spectrum (Figure 2) of aspirin (U.S.P. reference standard #0675-F-4) is summarized in Table 1.[16] It agrees essentially with a spectrum published previously.[17] A reflection spectrum has also been presented.[18]

TABLE 1

Infrared Spectrum Interpretation

Wavelength (cm^{-1})	Assignment
2300-2500	carboxyl OH
1760	vinyl ester C=O
1690	aromatic acid C=O
1610, 1580, 1490	aromatic C=C stretch
1220, 1190	=C-O (acid and ester)
760	ortho subst. phenyl C-H bending

4.12 Ultraviolet

Aspirin in 0.1N sulfuric acid[19] and in dilute trichloroacetic acid[20] exhibits maxima at 229 nm (E_1^1 484) and 276 nm (E_1^1 65.5). In chloroform a maximum was found at 277 nm (E_1^1 68).[21]

4.13 Fluorescence - Phosphorescence

The native fluorescence of aspirin, in contrast to salicylic acid, is a weak one and has been studied only recently.[22] Excitation wavelength maximum is at 280 nm and emission maximum is at 335 nm. Maxima for salicylic acid are at 308 and 450 nm respectively.