Analytical Profiles of Drug Substances

Volume 3

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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 third.

Reviews and comments received so far have reinforced our belief that the series fills a need and they have strengthened our determination to continue. The enthusiasm and cooperative spirit of our contributors have made these profiles possible. All those who have found the profiles useful are earnestly requested to contribute a monograph of their own. The editors stand ready to receive such contributions.

Beginning with Volume 2 a cumulative index has been added, to facilitate the correction of errors and to encourage the addition or relevant new information.

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 physico-chemical and analytical information on 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.

Klaus Florey

CONTENTS

ACETAMINOPHEN

John E. Fairbrother

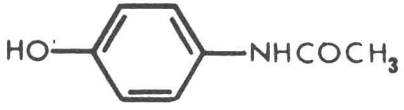
CONTENTS

1. Description

1.1 Name, Formula, Molecular Weight

Generic names - Acetaminophen[1], Paracetamol and Acetophenum[2].

Chemical names - 4' - Hydroxyacetanilide; p-hydroxyacetanilide; p-acetamidophenol; p-acetaminophenol; p-acetylaminophenol; N-acetyl-p-aminophenol.



$C_8H_9NO_2$ Mol. wt. 151.16

1.2 Appearance, Color, Odor, Taste

White, odorless, crystalline powder, possessing a bitter taste.

2. Physical Properties

2.1 Spectra

2.11 Infrared Spectrum

Infrared spectra of solid dispersions of acetaminophen in potassium bromide[3,7] and in Nujol[6], have been recorded. In the solid state[6] the carbonyl stretching band appears at 1659 cm^{-1} (1650 cm^{-1}; ref. 3), the N-H stretching band at 3326 cm^{-1} and a broad O-H stretching band at 3162 cm^{-1}. In solution the C=O,N-H and O-H stretching bands occur at higher frequencies.

Solvent	C=O Stretching Band	N-H Stretching Band	O-H Stretching Band
Chloroform	$1686cm^{-1}$ (9)		
Dichloro-methane	$1690cm^{-1}$ (6)	$3435cm^{-1}$ (6)	$3588cm^{-1}$ (6)
	$1700cm^{-1}$ (8)		
1,4-Dioxan	$1692cm^{-1}$ (8).		

Several other authors[10,11,12,15,16] report infrared spectra of acetaminophen. The infrared spectra of acetaminophen[14] in KBr and in a mineral oil mull are presented in figures 1 and 2[13].

2.12 Ultraviolet Spectrum

The u.v. spectrum of acetaminophen has been recorded in a number of solvents, showing two bands in each. The long wavelength band corresponds to the Alg → B2u transition while the short wavelength band corresponds to the $\pi_N \rightarrow \pi^*_{CO}$ transition[17].

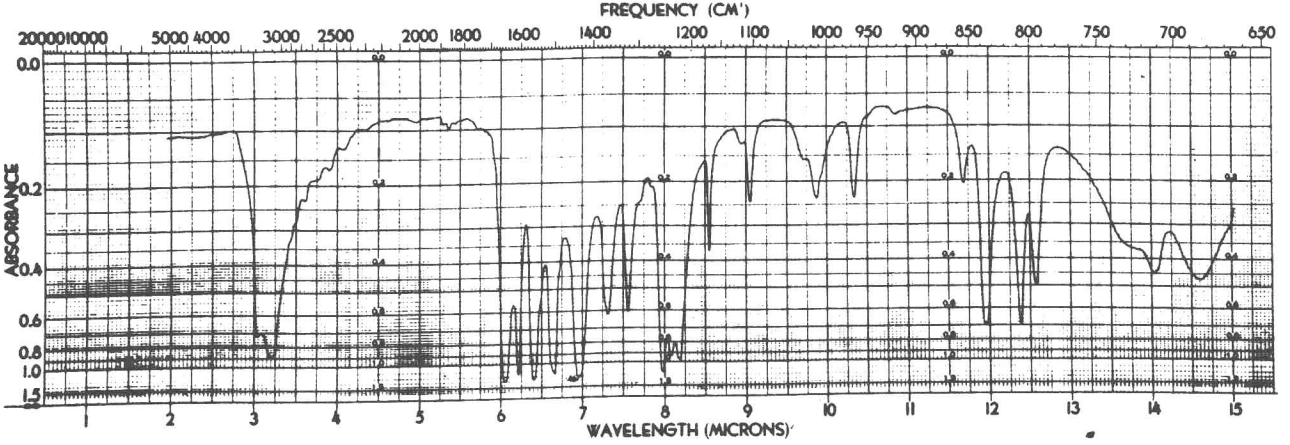


Fig. 1. Infrared spectrum of acetaminophen (KBr pellet)

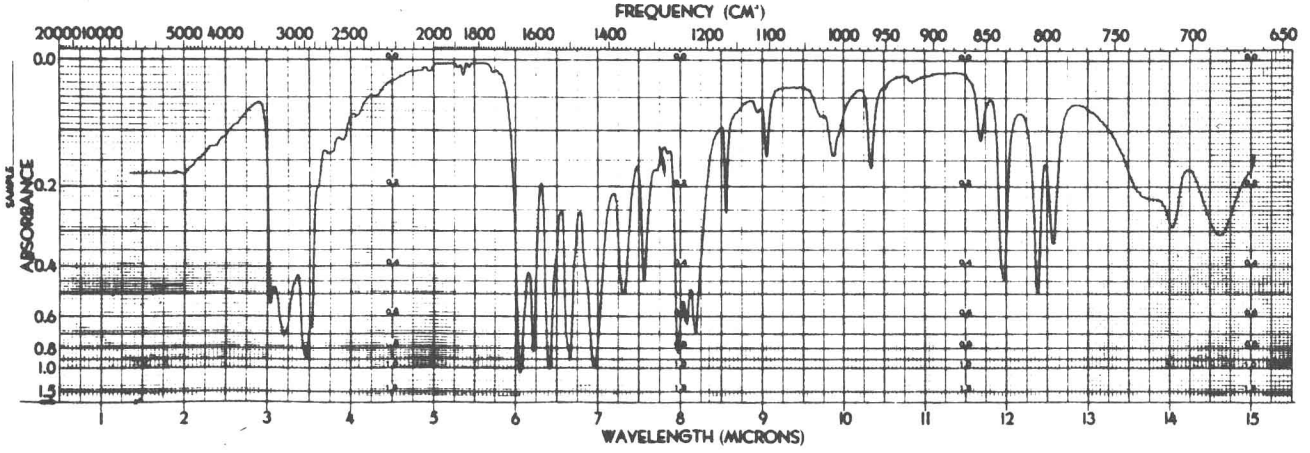


Fig. 2. Infrared spectrum of acetaminophem (Mineral Oil Mull)

TABLE 1
Absorption maxima of
acetaminophen in neutral solvents

Solvent	K band	B band	Reference
Methanol	248-249mμ.		3,18
Ethanol (abs.)	249-250mμ.	about 290mμ.	4, 8,19
n-Butanol	250mμ.		20
iso-Propanol	250mμ.		19
Cyclo-hexane	244-245mμ.		19
Cyclo-hexane	278mμ.		8 .
Ether	264mμ.		19
Ether(dry)	247mμ.	about 283mμ.	8
Water	242.5-243.5mμ.	about 283mμ.	8,19,23

The addition of acid to aqueous and alcoholic solutions does not give any observable change in the position of the maximum of the main band[7,16,18,19,21,22]. In 10^{-1} M caustic alkali acetaminophen ionises to give the p-acetamidophenolate ion and the maximum of the main band is shifted bathochromically, in aqueous solution from 243 mμ. to about 258 mμ.[19,20,22,23] and in methanolic solution from 248 mμ. to 262 mμ.[18].