Analytical Profiles of Drug Substances

Volume 4

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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 fourth.

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 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 had made this venture 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.

This volume of Analytical Profiles is dedicated to the memory of David E. Guttman, an enthusiastic member of the Editorial Board until his tragic and untimely death in 1974.

Klaus Florey

CONTENTS

CEFAZOLIN

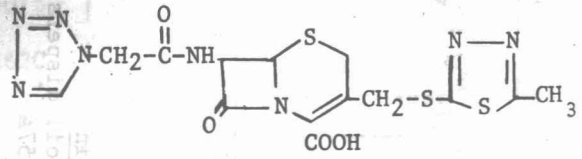
Alfred F. Zappala, Walter W. Holl, and Alex Post

Contents

1. Description

1.1 Name, Formula, Molecular Weight

Cefazolin is 3-[[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]methyl]8-oxo-7-[2-(1H-tetrazol-1-yl)acetomido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. It also exists as the sodium salt. Parenteral products are known as Ancef and Kefzol.



$C_{14}H_{14}N_8O_4S_3$ (Na, -H)

Mol. wt. 454.512 (acid)
476.495 (salt)

1.2 Appearance, Color, Odor

White to slightly off white, odorless.

2. Physical Properties

2.1 Infrared Spectrum

The infrared spectrum of cefazolin is presented in Figure 1. The spectrum taken was that of a mineral oil dispersion of the standard using a Perkin-Elmer 457A Grating IR Spectrophotometer. A list of the assignments made for some of the characteristic bands is given in Table I (1).

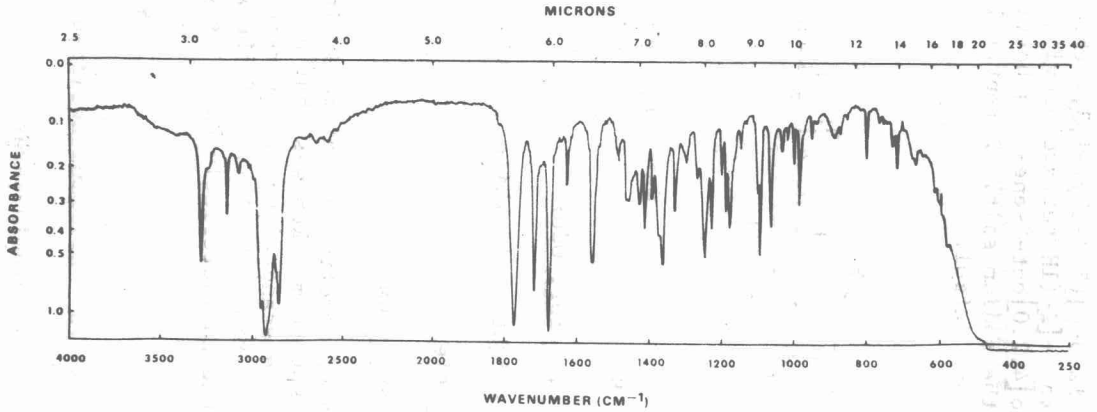


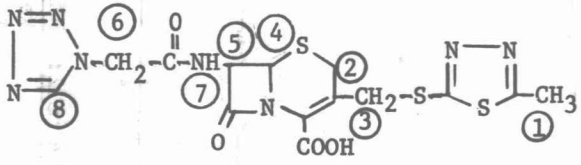
Figure 1: Infrared Spectrum of Cefazolin
Reference Standard, mineral oil dispersion.
Instrument: Perkin-Elmer 457A

Table I - IR Spectral Assignments for Cefazolin

Frequency (cm^{-1})	Characteristic of	
3280	-NH-	
3140	-N=N-	tetrazole ring
3075	-C=N-	tetrazole ring
2620	-OH, bonded, -COOH	
2580	-OH, bonded, -COOH	
1770	>C=O	lactam
1715	>C=O	acid
1670	>C=O	amide I
1555	>C=O	amide II

2.2 Nuclear Magnetic Resonance Spectrum

The 60 MHz NMR spectrum of cefazolin presented in Figure 2 was obtained in trifluoroacetic acid at a concentration of about 100 mg/ml and tetramethylsilane as internal standard. The spectral assignments are listed in Table II (1).



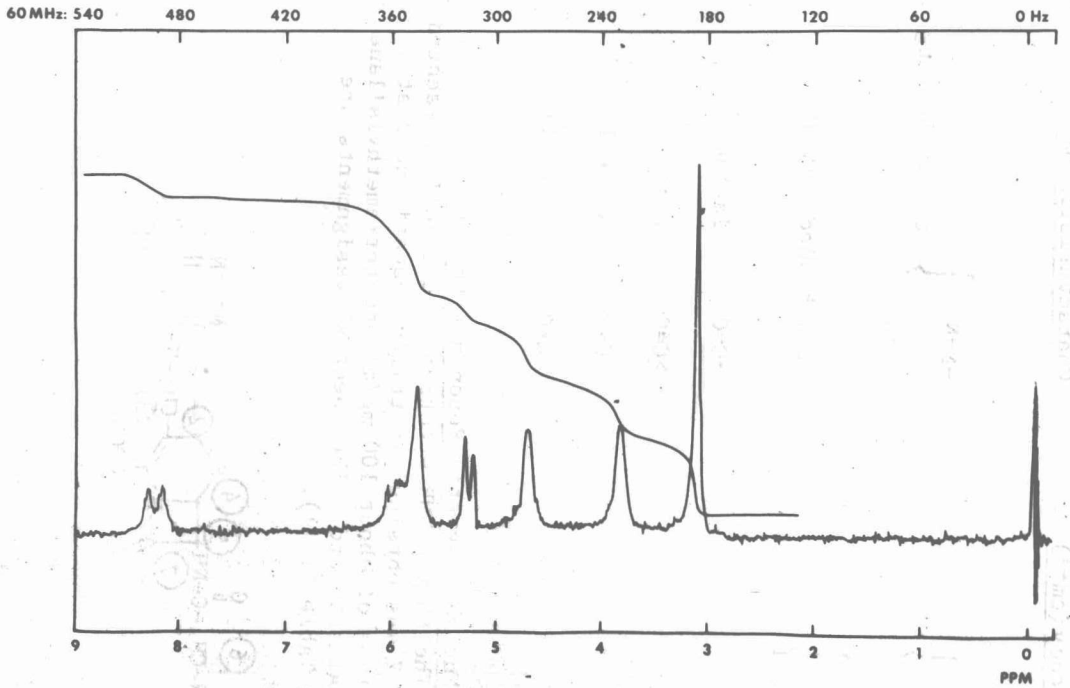


Figure 2: NMR Spectrum of Cefazolin
Reference Standard, in TFA with TMS as internal standard.
Instrument: JEOL Co., Model JNM-C-60H

Table II - NMR Spectral Assignments for Cefazolin

Chemical Shift (ppm)	Multiplicity	Characteristic of	Integration of No. of Protons
3.11	singlet	protons at 1	3
3.85	singlet	protons at 2	2
4.71	singlet	protons at 3	2
5.40	doublet	protons at 4	1
5.75	overlapping singlet & doublet	protons at 5 and 6	3
8.21	doublet	protons at 7	1

proton at 8 is beyond 9 ppm; however, it is masked by the solvent

2.3 Ultraviolet Spectrum

The ultraviolet absorption spectrum of cefazolin in 0.1M $NaHCO_3$ is shown in Figure 3. When scanned between 350 and 220 nm, cefazolin exhibits a single band with an absorption maximum at 270 - 272 nm (ε = 13,100).

2.4 Optical Rotation

The specific rotation of a 5% solution of cefazolin in 0.1M $NaHCO_3$ when measured at 25°C in a 1 decimeter tube is -17° ± 7°.

2.5 Melting Range

Cefazolin starts to decompose at about 190°C under USP conditions for Class I substances (2).

2.6 Differential Thermal Analysis

A differential thermal analysis was performed on cefazolin and the thermogram is presented in Figure 4. The typical melting endotherm is absent and only the decomposition exotherm at about 205°C is present.

2.7 Solubility

The approximate solubilities obtained for cefazolin at room temperature (25°C ± 1°C) are listed in Table III.

Table III - Approximate Solubilities of Cefazolin

Solvent	mg Cefazolin/ml
acetone	5.7
acetone:water (4:1 v:v)	21.2
chloroform	0.02
95% ethanol	1.1
ethyl acetate	0.24
isobutylacetate	0.05
isopropyl alcohol	0.21
methanol	1.7
methylene chloride	0.02
methylisobutylketone	0.25
sodium chloride, half-saturated	0.83
sodium chloride, saturated	0.44
water	1.1