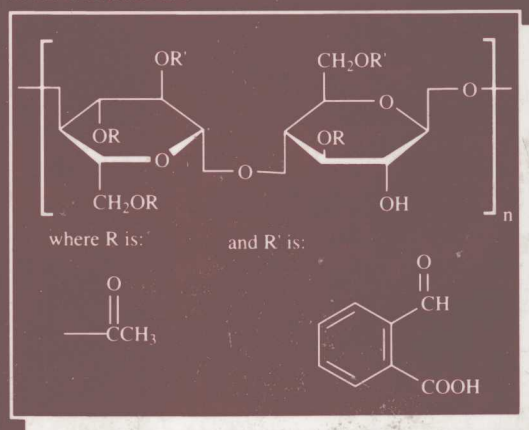


# Pharmaceutical Excipients

Characterization by IR, Raman,  
and NMR Spectroscopy

Structure:



David E. Bugay  
W. Paul Findlay

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Characterization by IR, Raman,  
and NMR Spectroscopy

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DEB dedicates this book to his wife, Terri, and children, Chris, Ryley, and  
Kyle.

Your love and support made this book possible.

Additionally, DEB dedicates this book to his parents for all their love,  
support, and sacrifice given over the years.



WPF dedicates this book to his parents, for their constant support and  
encouragement, and to his co-workers, for all their understanding.

## Preface

It is ironic to think that although the vast majority of pharmaceutical dosage forms are solids, a systematic approach to the complete physical characterization of pharmaceutical solids has arisen only within the last decade or two. In part, this is due to the rapid advancement in physical analytical techniques, but we like to think it is also the result of a drive for a better understanding of pharmaceutical solids. Typically, when one considers a pharmaceutical solid, the active drug substance comes first to mind, but in the majority of cases the major components within a solid dosage form are excipients. Therefore, it is equally important to physically characterize excipients as well as bulk drug substances.

In the Materials Science laboratories at Bristol-Myers Squibb, we have taken a systematic approach to the physical characterization of pharmaceutical solids. The characteristics of solids may be classified at three levels: (1) *molecular*—properties associated with individual molecules, (2) *particulate*—properties pertaining to individual solid particles, and (3) *bulk*—properties associated with an assembly of particulate species. At the molecular level, characterization of a pharmaceutical solid can involve simple chemical identification of the material, or physical characterization of a specific crystalline form (polymorphism or pseudopolymorphism). To this end, molecular spectroscopy techniques such as vibrational (including infrared (IR) and Raman) and nuclear magnetic resonance (NMR) spectroscopy are ideally suited. It must be kept in mind that solid-state sampling procedures are utilized.

Over the past five to ten years, we have found that molecular spectroscopy has been an invaluable tool for the physical characterization of pharmaceutical solids, including bulk drug substances, bulk excipients, physical blends, and final solid dosage forms. It has also become apparent that our construction of spectral libraries of excipients and bulk drug substances has been invaluable. The use of spectral libraries in the field of vibrational spectroscopy is very common. Typically, spectral libraries can be used for the identification of materials, investigative studies, and problem-solving activities. In our drug development efforts, the *Handbook of Pharmaceutical Excipients* continues to be an invaluable resource, but the volume contains no molecular spectroscopy information. We have also discovered that no complete IR, Raman, or NMR spectral library exists for pharmaceutical excipients. This is what prompted us to produce this volume.

There are three key aspects of this volume: (1) a textbook with an explanation of the

## Preface

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three molecular spectroscopy techniques, (2) a compendium of IR, Raman, and NMR spectra of pharmaceutical excipients for reference use, and (3) an accompanying electronic spectral library (IR and Raman only) for use on personal computer systems. The electronic spectral library is available through Nicolet Instruments, Inc., Madison, Wisconsin. If you are interested in the electronic spectral data, please contact Nicolet directly by telephone at (608) 276-6100 or at the following address:

Nicolet Instrument Corporation  
5225 Verona Road  
P.O. Box 44451  
Madison, Wisconsin 53744-4451

The most commonly used excipients have been presented in this first volume. If this book proves useful to the individuals involved in pharmaceutical development, additional volumes will be published in which the complete array of pharmaceutical excipients will be presented. We welcome your suggestions and hope to incorporate these in future volumes.

*David E. Bugay  
W. Paul Findlay*

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# 1

## Vibrational Spectroscopy

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### I. INTRODUCTION

Chemists usually think of infrared (IR) spectroscopy as the only form of vibrational analysis for a molecular entity. Typically, IR is utilized as an identification assay for various intermediates and final bulk drug products, but is also used as a quantitative technique for solution phase studies. The complete vibrational analysis of a molecule must also include Raman spectroscopy. Although IR and Raman spectroscopy are complementary techniques, widespread use of the Raman technique in pharmaceutical investigations has been limited. In the past, experimental difficulties tended to limit the use of Raman spectroscopy. However, with the advent of Fourier transform techniques, instrumentation development, and laser improvements, the last 20 years has seen a renaissance of the Raman technique.

Today, the complete characterization of pharmaceutical solids (including bulk drug, excipients, physical mixtures, formulated product, and placebo) is a

requirement for the consistent, reliable, and safe development of drug products. One stage of the characterization of pharmaceutical solids must be at the molecular level. Ideally suited for this task are the various forms of molecular spectroscopy techniques such as infrared, Raman, and nuclear magnetic resonance (NMR). Infrared and Raman analysis provide a complete vibrational motion analysis of the molecule, whereas NMR provides insight to the local environment of each NMR active atom. In this chapter, the theory of vibrational spectroscopy is presented in the context of identification of pharmaceutical excipients. The next chapter provides insight into the use of solid-state NMR techniques. Together, these forms of spectroscopy can provide a complete characterization of pharmaceutical solids at the molecular level.

The general experimental details of vibrational spectroscopy have been intentionally omitted from this volume. The reader is referred to a number of other literary works for fundamental details of vibrational spectroscopy instrumentation [1] and practical sampling techniques [2]. Chapter 3 provides information about the instrumentation, sample preparation techniques, and data acquisition parameters used to develop this compendium.

## II. VIBRATIONAL SPECTROSCOPY THEORY

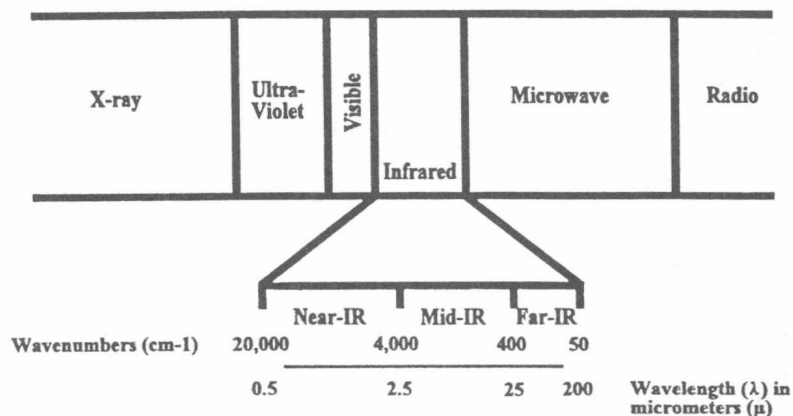
A brief description of IR and Raman theory will be presented so that a common understanding of the techniques is available to the reader. A complete description of the underlying theory to IR and Raman spectroscopy is outside the scope of this chapter, but can be obtained from the literature [3–7].

### A. Infrared

All molecules of pharmaceutical interest absorb some form of electromagnetic radiation. Within the electromagnetic spectrum (Figure 1), infrared energy is a small portion that is typically divided into three regions, the near-, mid-, and far-IR regions with their respective energy/frequency limits. In IR spectroscopy, the energy unit wavenumber ( $\text{cm}^{-1}$ ) is typically used. Wavenumber is the reciprocal of the IR wavelength expressed in centimeters.

When a broad band source of IR energy irradiates a sample, the absorption of IR energy by the sample results in molecular vibrational and rotational energy level transitions. A vibrational transition may be approximated by treating two atoms bonded together within a molecule as a harmonic oscillator. Based upon Hooke's law, the vibrational frequency between these two atoms may be approximated as:

$$\nu = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \quad (1)$$



**Figure 1** A segment of the electromagnetic spectrum comparing infrared energy to other forms of radiation.

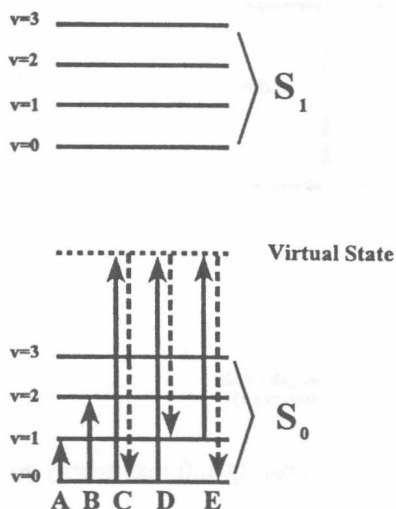
where  $\mu$  is the reduced mass of the two atoms:  $\mu = (m_1 m_2) / (m_1 + m_2)$  and  $k$  is the force constant of the bond (dynes/cm). Quantum mechanical analysis of the harmonic oscillator reveals a series of equally spaced vibrational energy levels that are expressed as:

$$E_n = \left(n + \frac{1}{2}\right) h \nu_0 \quad (2)$$

where  $E_n$  is the energy of the  $n^{\text{th}}$  level,  $h$  is Planck's constant, and  $\nu_0$  is the fundamental vibrational frequency. These energy levels may be graphically described in a Jablonski energy level diagram (Figure 2). It must be noted that the fundamental vibrational frequencies in a polyatomic molecule do not necessarily correspond to the vibrations of single pairs of atoms, rather from a group of atoms. The absorption of IR energy by a molecule corresponds to approximately 2–10 kcal/mole, which in turn equals the stretching and bending vibrational frequencies of most bonds in covalently bonded molecules. Thus, the correlation between IR spectroscopy and the ability to probe the vibrational motion of a molecule.

The number of fundamental vibrational modes of a molecule is equal to the number of degrees of vibrational freedom. For a non-linear molecule of  $N$  atoms,  $3N-6$  degrees of vibrational freedom exist. Hence,  $3N-6$  fundamental vibrational modes. Six degrees of freedom are subtracted from a non-linear molecule since: a) three coordinates are required to locate the molecule in space, and b) an additional three coordinates are required to describe the orientation of the molecule based upon the three coordinates defining the position of the molecule in space. For a linear molecule,  $3N-5$  fundamental vibrational modes are





**Figure 2** Jablonski energy level diagram illustrating possible transitions. Solid lines represent absorption processes and dotted lines represent scattering processes. (A) IR absorption; (B) near-IR absorption of an overtone; (C) Rayleigh scattering; (D) Stokes Raman transition; and (E) anti-Stokes Raman transition.  $S_0$  is the singlet ground state,  $S_1$  the lowest singlet excited state, and  $v$  represents vibrational energy levels within each electronic state.

possible since only  $2^\circ$  of rotational freedom exist. Thus, in a total vibrational analysis of a molecule by complementary IR and Raman techniques,  $3N-6$  or  $3N-5$  vibrational frequencies should be observed. It must be kept in mind that the fundamental modes of vibration of a molecule are described as transitions from one vibration state (energy level) to another ( $n = 1$  in Equation 2, Figure 2). Sometimes, additional vibrational frequencies are detected in an IR and/or Raman spectrum. These additional absorption bands are due to forbidden transitions that occur and are described in the section on near-IR theory. Additionally, not all vibrational bands may be observed since some fundamental vibrations may be too weak to observe or give rise to overtone and/or combination bands (*vide infra*).

For a fundamental vibrational mode to be IR active, a change in the molecular dipole must take place during the molecular vibration. This is described as the IR selection rule. Atoms which possess different electronegativity and are chemically bonded change the net dipole of a molecule during normal molecular vibrations. Typically, asymmetric vibrational modes and vibrations due to polar groups are more likely to exhibit prominent IR absorption bands.

A transmission IR spectrum may be calculated by Equation 3:

$$\text{Transmission (T)} = \frac{I}{I_0} \quad (3)$$