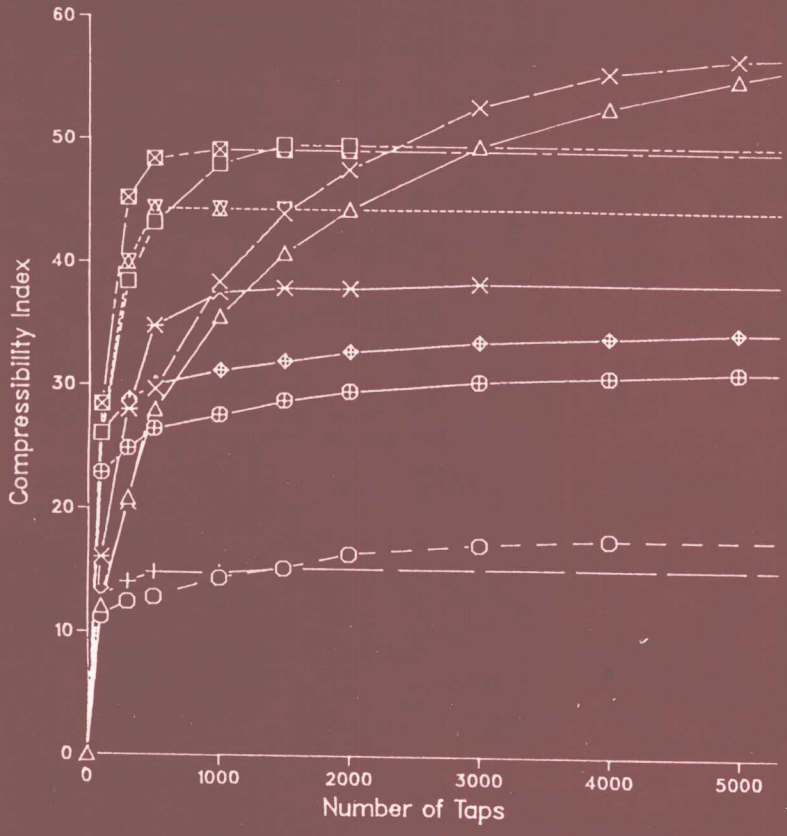
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 70

Physical Characterization of Pharmaceutical Solids



edited by
Harry G. Brittain

Physical Characterization of Pharmaceutical Solids

edited by
Harry G. Brittain

Ohmeda, Inc.
Murray Hill, New Jersey

Marcel Dekker, Inc. New York • Basel • Hong Kong

Library of Congress Cataloging-in-Publication Data

Physical characterization of pharmaceutical solids / edited by Harry G. Brittain.

p. cm. — (Drugs and the pharmaceutical sciences ; 70)

Includes bibliographical references and index.

ISBN 0-8247-9372-2 (hardcover : alk.paper)

1. Solid dosage forms. 2. Pharmaceutical chemistry.

I. Brittain, H. G. II. Series: Drugs and the pharmaceutical sciences ; v. 70.

[DNLM: 1. Chemistry, Pharmaceutical—methods. 2. Chemistry, Physical—methods. 3. Powders—chemistry. 4. Tables—chemistry. W1 DR893B v.70 1995 / QV 744 P5779 1995]

RS201.S57P49 1995

615'.19—dc20

DNLM/DLC

for Library of Congress

95-4852

CIP

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the address below.

This book is printed on acid-free paper.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Preface

It is evident even to the casual observer that the vast majority of pharmaceutical products are administered as solid dosage forms, which are in turn produced by the formulation and processing of powdered solids. All too often characterization of raw materials and products has centered on aspects of chemical purity, with only passing attention being given to the physical properties of the solids. However, every pharmaceutical scientist knows of at least one instance in which a crisis arose due to some variation in the physical properties of input materials, and in which better characterization would have prevented the problem.

The continued refinement of manufacturing processes results in increasing degrees of automation. In this streamlined operation style, raw materials are mixed, granulated, dried, tableted, coated, and packaged in a continuous operation. The key requirement associated with these manufacturing procedures is that all ingredients be totally characterized, since an unattended operation functions only if its materials fall within a specified range of material properties. Any lot-to-lot variation in physical properties has to be detected before the material is used, or else the entire manufacturing run is compromised.

The pharmaceutical community is rapidly becoming aware of the need to obtain proper physical characterization of raw materials, drug substances, and formulated products. The present volume seeks to address these concerns by outlining a comprehensive program for this work. The modern and highly regulated industry cannot tolerate the inconsistent practices of the past, when the only physical properties documented were those that a particular lab knew how

to determine. Proper physical characterization must be systematic in its approach, and it should follow a protocol that is rationally designed to obtain all needed information.

In the present work, such a systematic approach to the physical characterization of pharmaceutical solids is outlined. Techniques available for the study of physical properties are classified as being associated with the *molecular* level (properties associated with individual molecules), the *particulate* level (properties pertaining to individual solid particles), and the *bulk* level (properties associated with an ensemble of particulates). Acquisition of this range of physical information yields a total profile of the pharmaceutical solid in question, whether it is an active drug, an excipient, or a blend of these. The development of a total profile is a requirement for successful manufacture of any solid dosage form.

Each author has provided an introduction that serves to initiate the reader into the topic. Where appropriate, a brief exposition of associated theory is presented, but the essence of each chapter lies in the practical examples used to illustrate each topic. It is anticipated that even though the range of presented examples is not necessarily comprehensive, sufficient information is given to allow the reader to understand the strengths, advantages, and limitations of each technique. It is important that workers in the field have a good feel for what a given method cannot yield, as well as what it can provide.

Harry G. Brittain

Contributors

Gregory E. Amidon, Ph.D. Senior Scientist, Drug Delivery R&D—Pharmaceutics, The Upjohn Company, Kalamazoo, Michigan

Harry G. Brittain, Ph.D. Director, Pharmaceutical Development, Pharmaceutical Products Division, Ohmeda, Inc., Murray Hill, New Jersey

David E. Bugay, Ph.D. Senior Research Investigator II, Analytical R&D, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey

David J. W. Grant, M.A., D.Phil., D.Sc. Professor of Pharmaceutics, Department of Pharmaceutics, University of Minnesota, Minneapolis, Minnesota

Mark J. Kontny, Ph.D. Associate Director, Pharmaceutics Department, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut

James A. McCauley, Ph.D. Senior Investigator, Analytical Research, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey

Ann W. Newman, Ph.D. Senior Research Investigator, Materials Science Group, Analytical R&D, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey

Cynthia S. Randall, Ph.D. Senior Investigator, Pharmaceutical Technologies, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania

Raj Suryanarayanan, Ph.D. Associate Professor and Director of Graduate Studies, Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota

Adrian C. Williams, Ph.D. Lecturer in Pharmaceutical Technology, School of Pharmacy, University of Bradford, Bradford, West Yorkshire, United Kingdom

George Zografi, Ph.D. Professor of Pharmaceutics, School of Pharmacy, Univeristy of Wisconsin—Madison, Madison, Wisconsin

Contents

1

Overview of Physical Characterization Methodology

Harry G. Brittain
Ohmeda, Inc., Murray Hill, New Jersey

I. INTRODUCTION

The normal route of administration for the majority of pharmaceutically active therapeutic agents is through solid dosage forms [1], and these units are conventionally produced by the formulation and processing of powdered solids [2]. The priority of regulatory bodies has always been to focus primarily on concerns of safety and efficacy, which in turn has led to an almost total emphasis on aspects of chemical purity. This consideration has resulted in the situation that often only passing attention is given to the physical properties of the solids that comprise a dosage form.

Ignoring the physical aspects of a given formulation can be disastrous, since the stability of the drug entity can be strongly affected by its matrix [3]. A wide variety of reactions are known to take place in the solid state [4], the pathway of which can be dramatically different when compared with how the same reaction would proceed in the liquid or gaseous phase [5].

It is assumed during the course of drug development that any concerns related to the physical properties of the substances being formulated will be adequately researched at the appropriate moment. Unfortunately, this work is often not conducted until a crisis situation develops due to some variability in the physical properties of input materials. It is perhaps a truism that most of these problems could have been avoided had the materials received more balanced characterization. The economics of drug development, however, often interferes with the desire of the formulator to fully understand his system, and performance of the proper background work can become a casualty.

Nevertheless, the acquisition of a sufficiently detailed body of physical information can allow a formulator to go far beyond the mere ability to cope with crises when they develop at unexpected times. For a well-understood system, it is theoretically possible to design an automated or semi-automated manufacturing scheme for which the processing variables would be appropriately controlled so as to minimize the possibility of batch failure. Materials passing the hurdles of physical test specifications would be totally predictable in their performance, and they could therefore be blended, granulated, dried, compressed, and delivered into containers without operator intervention.

The need for physical characterization becomes even more crucial for the use of excipients in formulations. These materials have historically been characterized solely by the criteria of the National Formulary, which only rarely includes any mention of physical testing. Every formulation scientist knows that the present situation allows for the existence of wide variability in excipient properties, and such lot-to-lot variations can often be the cause of significant processing difficulties. To avoid problems during drug development, the physical characterization of bulk drugs, excipients, and blends of these should become part of the normal process. The degree of physical testing would necessarily vary

with the particular formulation, but it would include any and all test methods deemed appropriate.

It may be envisioned that a protocol for the complete physical characterization of a solid material could easily be developed. At the early stages in drug development, each lot of active drug, excipients, and formulated blends would be characterized as fully as possible. A feedback loop would be established after each formulation run, in which the physical characteristics of the input materials were correlated with the quality of formulated product. Out of these studies would come an understanding of what particular properties were essential to the production of an acceptable formulation.

As the maturity of the process increased, only the key parameters would require continued monitoring. Ultimately, the data collected on these properties would permit the generation of material specifications. If the work had been performed properly, then it would be possible to specify limits for the appropriate bulk drugs and raw materials that would ensure that the final product always was satisfactory. These guidelines would naturally apply only to the specific formulation, but their implementation would enable manufacturers to deliver their products with a greater degree of security than is now possible.

With these concerns in mind, it is appropriate to outline a comprehensive program for the physical characterization of pharmaceutical solids. A modern industry cannot tolerate the inconsistent practices of the past, where the only physical properties that might be documented were those that could be conveniently measured. It is of extreme importance that investigators measure the parameters that need to be measured and not merely collect the type of data that is convenient to obtain. Proper physical characterization must be systematic in its approach, and it should follow a protocol that is rationally designed to obtain all needed information.

A systematic approach to the physical characterization of pharmaceutical solids has been outlined [6], and it will be filled out in significantly more depth in the chapters of the present work. Within this system, physical properties are classified as being associated with the *molecular* level (those associated with individual molecules), the *particulate* level (those pertaining to individual solid particles), or the *bulk* level (those associated with an assembly of particulate species).

II. PROPERTIES ASSOCIATED WITH THE MOLECULAR LEVEL

Molecular properties may be defined as those material characteristics which theoretically could be measured for a small ensemble of individual molecules. Due to the minimal sample requirements, molecular properties can be determined at the earliest stages of drug development. Though the molecular level techniques

are all spectroscopic in nature, substantial information of great use to formulators can be obtained from appropriately designed experiments. For example, a screening of stressed materials can be carried out on the microgram level using infrared microscopy [7], and the results of such work would aid the preformulation characterization of a new chemical entity.

A. Ultraviolet/Visible Diffuse Reflectance Spectroscopy

With the exception of single-crystal transmission work, most solids are too opaque to permit the conventional use of ultraviolet/visible (UV/VIS) electronic spectroscopy. As a result, such work must be performed through the use of diffuse reflection techniques [8–10]. Important work has been conducted in which UV/VIS spectroscopy has been used to study the reaction pathways of various solid state reactions. Other applications have been made in the fields of color measurement and color matching, areas which can be of considerable importance when applied to the coloring agents used in formulations.

It was recognized some time ago that diffuse reflectance spectroscopy would be a very useful tool for the study of interactions among various formulation components, and the technique has been successfully used in the characterization of many solid state reactions [11]. Investigations conducted under appropriately designed stress conditions have been useful in the study of drug–excipient interactions, drug degradation pathways, and alterations in bioavailability owing to chemisorption of the drug onto other components in the formulation.

Connors and Jozwiakowski have used diffuse reflectance spectroscopy to study the adsorption of spiropyrans onto pharmaceutically relevant solids [12]. The particular adsorbants studied were interesting in that the spectral characteristics of the binary system depended strongly on the amount of material bound. As an example of this behavior, selected reflectance spectra obtained for the adsorption of indolinonaphthospiropyran onto silica gel are shown in Fig. 1. At low concentrations, the pyran sorbant exhibited its main absorption band around 550 nm. As the degree of coverage was increased the 550 nm band was still observed, but a much more intense absorption band at 470 nm became prominent. This secondary effect is most likely due to the presence of pyran–pyran interactions, which become more important as the concentration of sorbant is increased.

The perception of color is subjectively developed in the mind of an individual, and consequently different people can perceive a given color in various ways. Such variability in interpretation causes great difficulty in the evaluation of color-related phenomena, leading to problems in making objective judgements. The development of quantitative methods for color determination was undertaken to eliminate the subjectivity associated with visual interpretative measurements.

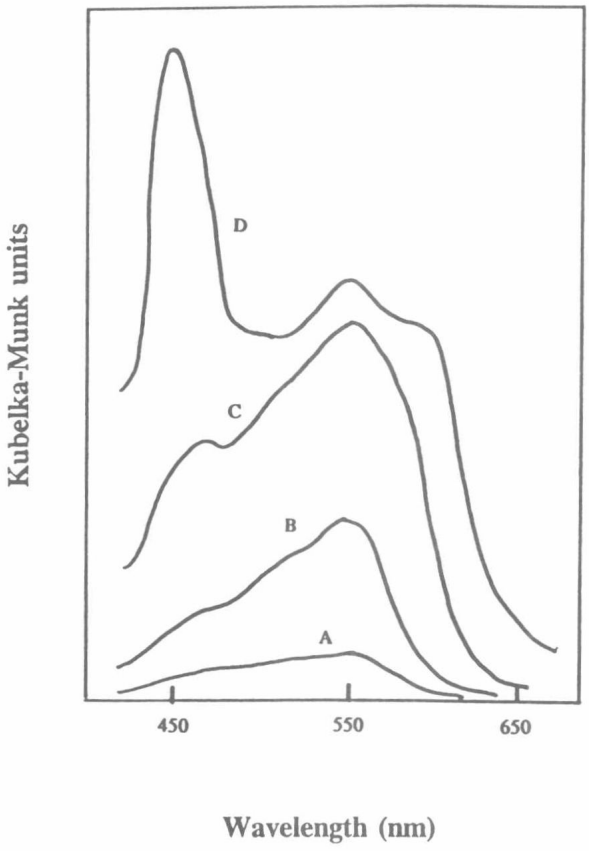


Fig. 1 Absorption spectra, obtained through the Kubelka–Munk transformation of diffuse reflectance spectra, of indolinonaphthospiropyran adsorbed onto silica gel. Spectra are shown for coverages of (A) 2.35, (B) 9.49, (C) 34.2, and (D) 46.7 $\mu g/m^2$. (Data adapted from Ref. 12.)

The most successful quantitative expression of color is that known as the CIE (Commission Internationale de l'Éclairage) system [13]. This methodology assumes that color may be expressed as the summation of selected spectral components (blue, green, and red hues) in a three-dimensional manner. The CIE system is based on the fact that human sight is trichromatic in its color perception, and that two stimuli will produce the same color if each of the three tristimulus values (X, Y, and Z) are equal for the two. Detailed summaries of the CIE and other quantitative systems for color measurement are available [14,15].

In a recent application, the appearance testing of tablets through measurement of color changes has been automated through the use of fiber optic probes

and factor analysis of the data [16]. Good correlation between measured chromaticity parameters and visual subjective judgment was demonstrated, with samples of differing degrees of whiteness being used to develop the correlation. The methodology was complicated since surface defects on the analyzed materials could compromise the quality of the correlation.

B. Vibrational Spectroscopy

Infrared (IR) spectroscopy, especially when measured by means of the Fourier transform method (FTIR), is another powerful technique for the physical characterization of pharmaceutical solids [17]. In the IR method, the vibrational modes of a molecule are used to deduce structural information. When studied in the solid, these same vibrations normally are affected by the nature of the structural details of the analyte, thus yielding information useful to the formulation scientist. The FTIR spectra are often used to evaluate the type of polymorphism existing in a drug substance, and they can be very useful in studies of the water contained within a hydrate species. With modern instrumentation, it is straightforward to obtain FTIR spectra of micrometer-sized particles through the use of a microscope fitted with suitable optics.

The FTIR method makes simultaneous use of all the frequencies produced by the source, thus providing a large enhancement of the signal-to-noise ratio when compared with that of a dispersive instrument. Infrared spectra are best obtained on powdered solids through the use the diffuse reflectance method, and interpreted through the conventional group frequency compilations [18]. Three different spectral intervals are commonly identified: far-IR (100–400 cm^{-1}), mid-IR (400–4000 cm^{-1}), and near-IR (4000–14,000 cm^{-1}) regions, although most applications have been made in the mid-IR or near-IR regions.

When the vibrational modes of a compound are affected by fine details of molecular structure (i.e., polymorphism), the diffuse reflectance IR spectra of the polymorphs can be used for study of this behavior. For example, fosinopril sodium contains three carbonyl groups, the stretching frequencies of two of which are essentially equivalent (1600 versus 1598 cm^{-1}, and 1622 versus 1621 cm^{-1}) in the two known polymorphs [19]. This finding would suggest that the sidechains containing these groups are also equivalent in the two polymorphic structures. The stretching frequency of the third carbonyl group was found to be significantly different (1759 versus 1753 cm^{-1}) in the two forms, suggesting in turn that the polymorphism of fosinopril sodium was conformational in nature and associated with modified packing arrangements of the acetal sidechain [19].

Another technique of vibrational spectroscopy suited for the characterization of solids is that of Raman spectroscopy. In this methodology, the sample is irradiated with monochromatic laser radiation, and the inelastic scattering of the source energy is used to obtain a vibrational spectrum of the analyte [20]. Since

most compounds of pharmaceutical interest are of low symmetry, the Raman spectrum will generally produce spectra equivalent to those obtained using the FTIR method. Differences in peak intensity can be observed, however, which may in turn provide details into the structural composition of the analyte and its host matrix.

In one application, Raman spectroscopy was used to identify and quantitate various drugs present in polymer matrices [21]. In Fig. 2, Raman spectra obtained within the fingerprint region for diclofenac, sodium alginate, and a 20% dispersion of diclofenac in sodium alginate are shown. It is evident in the spectra

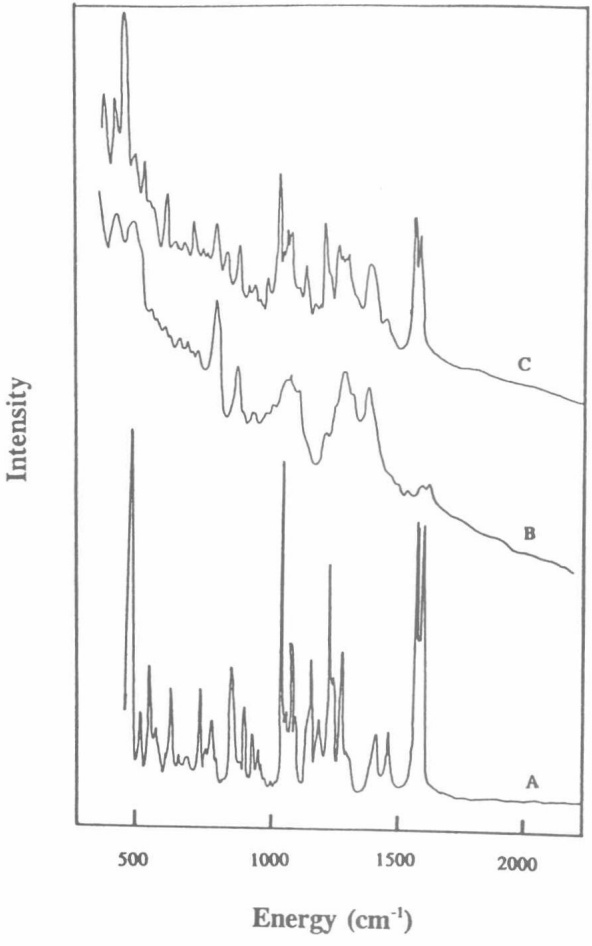


Fig. 2 Raman spectra obtained for (A) diclofenac sodium, (B) sodium alginate, and (C) a 20% dispersion of diclofenac sodium in sodium alginate. (Data adapted from Ref. 21.)

that the vibrational spectrum of the solute is easily distinguished in the mixture. The authors were able to perform a spectral subtraction of the data to reproduce the Raman spectra of the drug itself. In addition, they found that the bands at 1578 and 1603 cm^{-1} could be used to develop a quantitative method for the levels of drug in the polymer matrix.

The range of applications possible when using near-IR spectroscopy are numerous, but the range of problems addressable by this methodology are quite different than those just described [22]. Near-infrared spectra consist of overtone transitions of fundamental vibrational modes, and they therefore are not generally useful for identity purposes without the use of multicomponent analysis. The spectral features are of greatest utility in the detection and determination of functional groups that contain unique hydrogen atoms. For example, studies of water in solids can be easily performed through systematic characterization of the characteristic OH band, usually observed around 5170 cm^{-1}. The determination of hydrate species in an anhydrous matrix can easily be performed using near-IR analysis.

The near-IR technique has been used very successfully for moisture determination, whole tablet assay, and blending validation [23]. These methods are typically easy to develop and validate, and far easier to run than more traditional assay methods. Using the overtone and combination bands of water, it was possible to develop near-IR methods whose accuracy was equivalent to that obtained using Karl–Fischer titration. The distinction among tablets of differing potencies could be performed very easily and, unlike HPLC methods, did not require destruction of the analyte materials to obtain a result.

C. Magnetic Resonance Spectrometry

Yet another spectroscopic characterization tool that can be used to probe the solid state is that of nuclear magnetic resonance (NMR). The combination of magic-angle spinning and cross-polarization techniques now permit NMR spectra to be obtained in the solid state with only moderate difficulty relative to analogous solution-phase studies [24]. Although any NMR-active nucleus can be studied in the solid state, most of the work has focused on ^{13}C investigations. As was the case for FTIR spectroscopy, extensive compilations of ^{13}C resonances for various functional groups are available [25].

When the crystallography of compounds related by polymorphism is such that nuclei in the two structures are magnetically nonequivalent, it will follow that the resonances of these nuclei will not be equivalent. Since it is normally not difficult to assign organic functional groups to observed resonances, solid state NMR spectra can be used to deduce the nature of polymorphic variations, especially when the polymorphism is conformational in nature. Such information is extremely valuable at the early states of drug development when solved single crystal structures for each polymorph or solvate species may not yet be available.