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Review

Physical Characterization of Pharmaceutical Solids

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A general review of the methods available for the physical characterization of pharmaceutical solids is presented. The techniques are classified as being on the molecular level (properties capable of being detected in an ensemble of individual molecules), the particulate level (properties which can be detected through the analysis of an ensemble of particles), and the bulk level (properties which can be measured only using a relatively large amount of material). The molecular-level properties discussed are infrared spectroscopy and nuclear magnetic resonance spectrometry, the particulate-level properties discussed are particle morphology, particle size distribution, powder X-ray diffraction, and thermal methods of analysis, and the bulk-level properties discussed are surface area, porosity and pore size distribution, and powder flow characteristics. Full physical characterization of three modifications of lactose (hydrous, anhydrous, and Fast-Flo) is presented to illustrate the type of information which can be obtained using each of the techniques discussed.

KEY WORDS: solid pharmaceuticals; physical characterization; infrared spectroscopy; nuclear magnetic resonance; particle morphology; powder X-ray diffraction; thermal analysis; lactose.

INTRODUCTION

The majority of pharmaceutically active therapeutic agents are administered as solid dosage forms (1), produced by the formulation and processing of powdered solids (2). 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. It is not surprising that instances arise where a crisis situation develops due to variability in the physical properties of input materials, which could have been avoided had these been better characterized (3).

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 which might be documented were those which could be conveniently measured. Proper physical characterization must be systematic in its approach and should follow a protocol which is rationally designed to obtain all needed information.

In the present article, such a systematic approach to the physical characterization of pharmaceutical solids is outlined. 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), or the *bulk* level (properties associated with an assembly of particulate species). The total profiling of a material would require study at each stage, the extent of which would depend on the quantity of compound available at the time.

To illustrate this systematic approach, full physical data have been obtained on three modifications of lactose: anhydrous, hydrous, and Fast-Flo. These results are used at appropriate places to feature the type of information available for each technique discussed.

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. Substantial information of great use to formulators can be obtained from appropriately designed experiments. For instance, a screening of stressed materials can be carried out on the microgram level using infrared microscopy (4), and the results of such work would aid the preformulation characterization of a new chemical entity.

Infrared Spectroscopy

An extremely powerful method for study of a pharmaceutical solid is Fourier transform infrared (FTIR) spectroscopy, with the vibrational modes of a compound being used for a variety of investigational purposes (5). Most workers are familiar with the use of mid-IR spectra for identity purposes, since the pattern of absorption bands is usually diagnostic for a given compound. The acquisition of high-quality

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infrared spectra on solid materials is possible only with the FTIR method, since transmission and beam attenuation problems are minimized. FTIR spectra are often used to evaluate the relative polymorphism of a substance crystallized from different solvents. Since FTIR spectra can be obtained through a suitable IR microscope, the technique can be used to characterize extremely minute quantities of substance. IR spectra can also be used to study the water of hydration contained in a crystal lattice.

The FTIR method makes use of all frequencies from the source simultaneously (rather than sequentially as in a scanning instrument) and, therefore, provides an immediate increase in the signal-to-noise ratio. The infrared spectra can be obtained in the solid state by means of diffuse reflectance, and extensive compilations of group vibrational frequencies exist which allow the ready assignment of observed bands (5). Useful data may be obtained either in the mid-infrared (400–4000 cm^{-1}) or near-infrared (4000–14,000 cm^{-1}) regions of the spectrum, depending on the requirement of the study.

Essentially all FTIR spectrometers use a Michelson interferometer. Radiation entering the interferometer is split into two beams by means of a beam splitter. Beam A follows a path of fixed distance before being reflected back into the beam splitter, while beam B travels a variable distance before being recombined with beam A. The recombination of these two beams yields an interference pattern. The detector is placed so that radiation in the central image of the interference pattern will be incident upon it, and therefore intensity variations in the recombined beam are manifest as phase differences.

Since the incoming radiation is polychromatic, it follows that the interferometer has the effect of transforming each frequency component so that a detector output wave of unique frequency is produced for each component. The overall detector output as a function of time is termed an *interferogram* and is the sum of all the waves for each frequency component. The digitized interferogram contains all the information associated with a conventional spectrum (i.e., a display of absorption intensity against wavelength). The frequency domain spectrum is obtained from the interferogram by performing the mathematical operation called Fourier transformation (FT).

Since an interferometer does not require narrow slits to achieve spectral resolution (entrance apertures can be typically 1 cm or more in diameter), the energy throughput of a Fourier transform spectrometer is quite large when compared to that of a conventional dispersive spectrometer. This feature is extremely important to the measurement of FTIR spectra of solids, since this technique requires the detection of diffuse reflectance off the solid surface (6). The sample is basically contained within an integrating sphere, which permits collection of all the very weak infrared radiation reflected by the solid surface. The inefficiency of the diffuse reflectance process normally requires the use of more sensitive detectors.

The diffuse reflectance technique sometimes requires dilution of the sample with a powdered alkali halide (normally KBr or KCl) and therefore a background spectrum of the stock alkali halide is required. The spectrum of the dilute sample is recorded next, and the reflectance spectrum obtained as the ratio of the sample to the reference spectrum. Since the theory for diffuse reflectance at scattering layers was proposed by Kubelka and Munk (7), the arbitrary units obtained for diffuse reflectance spectra are termed Kubelka-Munk units and displayed as such. The best spectra are obtained when the samples are ground into uniform, fine powders. In that case, the Kubelka-Munk theory predicts a linear relationship between the molar absorption coefficient and the value of the ratioed spectrum. The latter feature can permit the use of diffuse reflectance as a quantitative tool, under appropriately controlled sample conditions.

Mid-IR spectra, obtained using diffuse reflectance, for hydrous, anhydrous, and Fast-Flo lactose, are shown in Fig. 1. As would be anticipated from the existence of differing crystal structures, the IR spectra exhibit significant differences in the observed vibrational transitions. An absorption due to bound crystalline water is clearly observed at 3524 cm^{-1} in hydrous lactose but is lacking in the anhydrous phase. The existence of some crystalline water is clearly evident in the IR spectrum of Fast-Flo lactose, which also exhibits an absorption band at 3524 cm^{-1}.

The near-IR spectra obtained for the three modifications of lactose are shown in Fig. 2. Near-IR spectra normally consist of overtone absorptions of fundamental vibrational modes and are, therefore, not very useful for identity purposes. Near-IR spectral features are of greatest utility in the detection and determination of functional groups that contain unique hydrogen atoms. For instance, both hydrous and

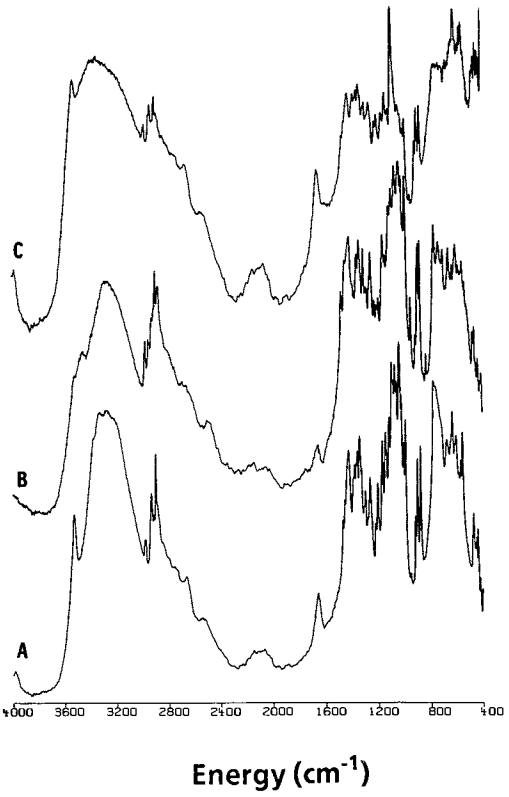

Fig. 1. Diffuse reflectance spectra obtained in the mid-IR region for (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

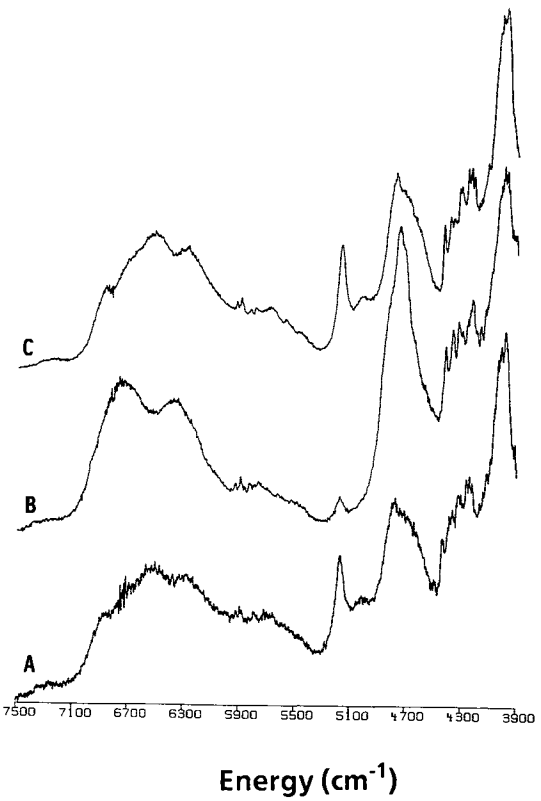

Fig. 2. Diffuse reflectance spectra obtained in the near-IR region for (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

Fast-Flo lactose exhibited a significant water band at 5168 cm^{-1}, whereas only a very small absorption band was observable for the anhydrous lactose. The water detected in the anhydrous lactose material probably was absorbed during sample preparation. Since the water absorption band is often very evident in a near-IR spectrum, this particular spectral region is extremely useful for spectroscopic determinations of water content (8).

Nuclear Magnetic Resonance Spectroscopy

The ultimate characterization of a pharmaceutical material concerns the chemical environment of each atom in the compound, and this information is best obtained through the use of nuclear magnetic resonance (NMR) spectroscopy. With recent advances in instrumentation and computer pulse sequences, these studies can now be carried out in the solid state (9). Although any nucleus which can be studied in the solution phase can also be studied in the solid state, most of the work has focused on ^{13}C studies. As in the case for FTIR, extensive compilations of ^{13}C resonances for various functional groups are available in the literature (10).

^{1}H NMR remains an extremely difficult measurement in the solid state, and the data obtained from such work can be obtained only at medium resolution. Since protons are abundantly present in organic compounds, the removal of dipolar interactions is necessary to obtain high-resolution ^{1}H spectra in solids. Although this is possible, the resulting ^{1}H NMR spectra are still inferior to those obtained in the solution phase. The primary reason for this is that ^{1}H NMR has one of the smallest isotropic chemical shift ranges (12 ppm), but with peak-broadening effects that can span 8–10 ppm in magnitude. Other nuclei yield far better data, with ^{13}C and ^{31}P solid-state NMR studies being very useful to the physical characterization of all pharmaceutical solids.

The random molecular motions which take place in the liquid phase result in an averaging of the effects which would broaden NMR resonance lines. Spinning the sample at an angle of 54°44′ (the so-called "magic angle") with respect to the direction of the applied magnetic field results in an averaging of the chemical shift anisotropy. Since it is this anisotropy that is primarily responsible for the spectral broadening associated with ^{13}C samples, magic-angle spinning makes it possible to obtain high-resolution ^{13}C NMR spectra of solid materials. In a solid sample, the anisotropy reflects the chemical shift dependence of chemically identical nuclei on their spatial arrangement with respect to the applied field. High-power proton decoupling is also used simultaneously to eliminate additional line broadening effects due to ^{13}C–^{1}H dipolar interactions.

Even though high-resolution spectra can be obtained on solids using the MAS technique, the data acquisition time is lengthy due to the low sensitivity of the nuclei and the long relaxation times exhibited by the nuclei. This problem has been circumvented through the use of cross polarization (CP), which involves the transfer of spin polarization from the high-abundance, high-frequency nucleus (^{1}H) to the rare, low-frequency nucleus (^{13}C). This process results in a more efficient buildup of ^{13}C magnetization and, thus, shortens the waiting periods between pulses. The CP experiment also allows the measurement of several relaxation parameters that can be used to study the dynamic properties of the solid under investigation.

It is ordinarily observed that the NMR spectra of compound polymorphs or pseudopolymorphs are nonequivalent. This effect arises since the differing crystal structures of the various types can perturb the chemical environment of each nucleus under investigation. In considering the NMR spectra of polymorphs, it is commonly observed that certain resonance bands are observed at identical chemical shifts, while others are significantly shifted (10). 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. Such information is extremely valuable at the early stages in drug development when solved single crystal structures for each polymorph or pseudopolymorph may be unavailable.

The solid-state ^{13}C CP/MAS NMR spectra for hydrous, anhydrous, and Fast-Flo lactose are shown in Fig. 3. Analogous to the mid-IR spectra, the solid-state NMR spectra display differing resonant bands for the differing crystal structures. Essentially identical NMR spectra were obtained for the Fast-Flo and hydrous lactose materials, indicating nearly identical crystal structures for these two forms. The NMR data also indicate that many of the nuclei in anhydrous lactose are not equivalent to the analogous nuclei in hydrous lactose. The resonances in the anhydrous lactose spectrum that do not correlate with the hydrous sample are due to the magnetically nonequivalent nuclei of the anhydrous crystal structure.

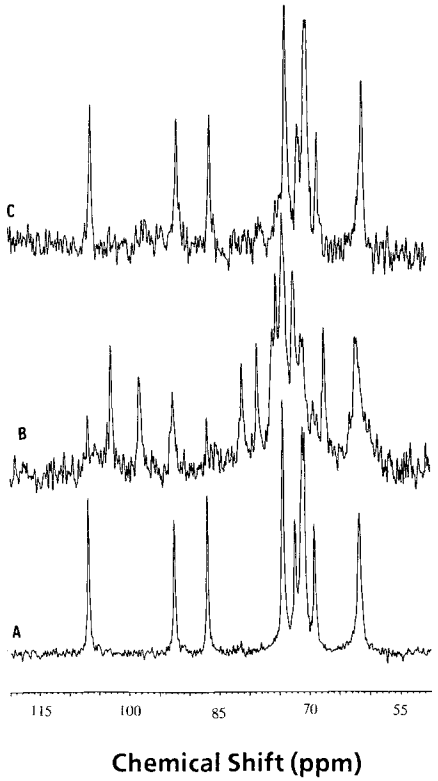

Fig. 3. CP/MAS solid-state ^{13}C NMR spectra of (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

PROPERTIES ASSOCIATED WITH THE PARTICULATE LEVEL

Particulate properties are defined as material characteristics which theoretically can be determined by the analysis of one or a few particles. Since the sample requirements are extremely modest, these properties can be investigated as soon as a drug candidate is available in milligram quantities.

Particle Morphology

Most pure pharmaceutical materials consist of small microcrystals aggregated into much larger composite structures. Microscopy is the best method for study of such aggregate species, and both optical and electron microscopies are the methods of choice for such work (11). The nature of aggregate species can be quickly determined, and preliminary estimates regarding average particle sizes can be obtained. The flowability of a given powder is related to the particle size and shape, and such information is easily obtained through a microscopic examination of the solid.

Since the stability of a drug candidate will be related to the degree of crystallinity, it is important to identify all the possible crystalline forms of the compound which may be encountered. When small amounts of material are available, crystallization from a variety of solvents is effected and a microscopic examination used to observe any possible differences in crystal habit. Should a compound be capable of existing in more than one crystalline state, it is crucial to identify the most stable polymorph. It is also equally important to study the physical interconvertibility of the various crystal structures, so that there would be no unexpected forms arising either during the course of scale-up in manufacture or during a stability study.

Different crystal polymorphs will generally feature different melting points, with the highest melting form being regarded as the most stable polymorph. The interconversion of these is classified as being either enantiotropic or monotropic, according to whether the transformation of one modification into the other is reversible or not. Enantiotropic modifications interchange reversibly at the transformation point, and each form is characterized by having its own stability range of temperature. Monotropic substances are characterized by a hypothetical transition temperature, which is predicted to be higher than the melting points of both polymorphs. Monotropic polymorphs are characterized by the fact that one form is stable at all temperatures below its melting point, while the second form is metastable at all temperatures. Monotropy is more commonly encountered than enantiotropy.

According to the law of successive reactions, the polymorph which crystallizes out of either a supercooled liquid or a supersaturated solution is not necessarily the most stable form (12). The polymorph which is obtained under a given set of crystallization conditions is the one which can be attained with the minimum loss of free energy. This will ordinarily be the metastable form, and therefore uncontrolled crystallization from supercooled liquids or supersaturated solutions is to be avoided. Crystallization of the most stable polymorph (the pharmaceutically desirable form) can be obtained under conditions for which equilibrium is established between the dissolved and crystallized solute.

Optical microscopy can be easily used to determine whether compound polymorphs are either enantiotropic or monotropic in their relation to each other (13). These experiments are carried out using the combination of a variable-temperature hot stage and polarizing optics. Should the less stable polymorph of a solid be heated past its transition temperature, the transformation into the more stable polymorph is observed. The change is recognized by the development of turbidity in clear crystals and changes in color when viewing the crystals through crossed polarizers. After the solids are melted, the stage can be allowed to cool and the crystallization monitored. With polarizing optics it is usually not difficult to determine whether the birefringence of the newly crystallized solid is equivalent to that which existed prior to melting.

Determination of crystal habit by SEM examination enables a description to be made regarding the outer appearance of the intrinsic microcrystals making up a solid. The surface is scanned by a focused electron beam, and the intensity of secondary electrons is monitored. The output from the secondary electron detector modulates the raster of a cathode-ray tube, which is scanned in synchronization with the focused electron beam. Each point on the cathode-ray tube raster corresponds to a point on the surface of the sample, and the strength of the image at each point varies according to the production of secondary electrons on the surface. The SEM images typically contain wide ranges of contrast and depth of focus. As a result, electron microscopy is able to give the investigator an excellent picture of the details of the sample surface.

As an example of the use of electron microscopy, typical photomicrographs of anhydrous, hydrous, and Fast-Flo lactose are shown in Fig. 4. The differences between the three forms are striking when viewed on the particulate level. Anhydrous lactose is seen to consist of particles which are aggregates of extremely small, needle-like microcrystals. Hydrous lactose particles appear to be discrete crystals, often of banded layers. Both the anhydrous and the hydrous lactose samples illustrated consisted of a wide range of particle sizes. In contrast, Fast-Flo lactose is seen to consist of aggregates composed of the layering and cementing of smaller crystals. These aggregated species are invariably rounded and essentially homogeneous in particle size distribution. It is undoubtably the latter characteristics which give Fast-Flo lactose its desirable handling properties.

Particle Size Distribution

The particle size distributions of drugs and excipients will exert profound effects on mixing phenomena and on possible segregation in mixed materials (14). It is generally accepted that in the absence of electrostatic effects, it is easiest to produce homogeneously mixed powders if the individual components are of equivalent particle size. The distribution of particle sizes in a powdered material can affect the bioavailability of certain active drugs and exerts a major effect on powder flowability. All pharmaceutical dosage forms must be produced in uniform units, and good content uniformity will be possible only when the particle size of the active component is carefully controlled.

A variety of methods is available for the determination of the particle size distribution of powdered solids (15). These are optical microscopy (usually combined with image analysis), laser light scattering of particles suspended in inert solvents, electrical zone sensing, or sieve analysis. Each method is most appropriately used in conjunction with a given application. Since the light scattering and electrical zone sensing are normally carried out on solids dispersed in an inert solvent medium, they are most suited for determinations of suspended particle size. Due to the suspension process, the size distributions obtained by these methods reflect what exists in the suspending medium, and not necessarily what existed in the original powder sample. Microscopy and sieving are normally carried out on dry powders and are, therefore, useful as true indicators of the actual particle size of a powdered solid.

In principle, sieve analysis represents the simplest method for the determination of particle sizes (16). Particles are allowed to pass through a series of screens (typically wire mesh), and the amount of material retained on each screen is determined. The smaller particles which pass through a screen are termed the fines, while the larger particles remaining on the screen are the coarse particles. When using multiple screens, the intermediate-sized particles which pass through one or more screens (but which are retained on a subsequent screen) are called the medium fraction. Most sieving machines use vibration to enable the particles to pass through the various screens, but some devices pulse air through the sieves to prevent blinding of the screen openings. A good size determination requires the use of five or six sieves, whose sizes are selected to obtain approximately equal amounts of powder on each screen and past the smallest sieve. The data are most commonly displayed as the percentage of material retained on each sieve, the cumulative percentage of sample retained, and the percentage of sample passing each sieve.

It is known that if a nonconducting particle is suspended in a conducting medium and allowed to pass between two electrodes, the resistance between the electrodes is momentarily increased. The magnitude of this increase in resistance can be related to the diameter of the particles, and accurate results can be obtained which are not highly sensitive toward the shape or nature of the particles. This electrical zone sensing method is based on the Coulter principle, in which the detection is continuous, but entails the measurement of electrical pulses caused by passage of particles through the

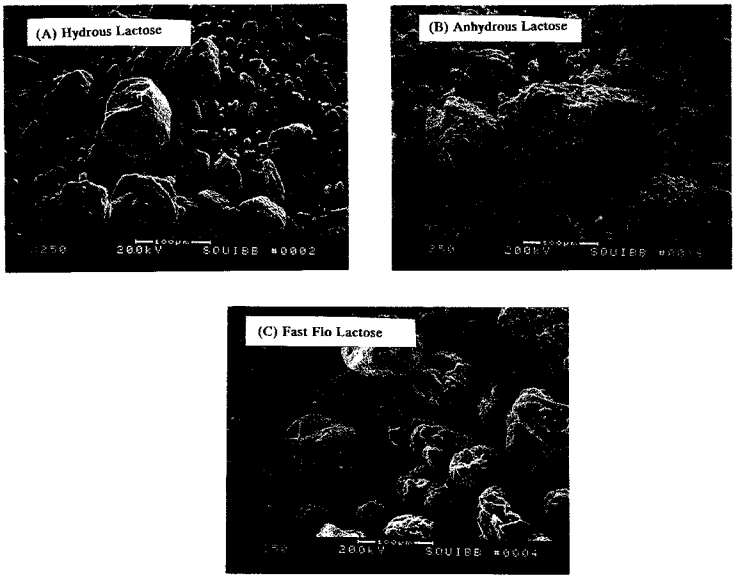

Fig. 4. Scanning electron microscope photos obtained for (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

sensing zone (17). The magnitudes of the pulse sizes are proportional to the particle volumes. One drawback to the Coulter method is that calibration using monodispersed particles of known diameter is required to assign the particle sizes of unknown species. The lowest size limits which may be measured are limited by thermal and electrical noise and by the ability of the discrimination electronics to distinguish true signal pulses from the background.

For particles larger than 1 μm, Fraunhofer diffraction can be used to obtain particle size distributions (18). The laser source is expanded, collimated, and allowed to pass through a suspension of particles in some medium. The diffracted and transmitted light is focused onto the detector, which is in the focal place of the focusing lens. The detector is typically a 16-element, concentric, light-sensitive ring detector with a hole in the center. Behind the hole is a photodiode, which is used for alignment and measuring the ratio of transmitted to initial light intensities. Data are obtained by sweeping all 16 rings many times and averaging to improve the signal-to-noise ratio. At the end of the experiment, the average background is subtracted from the average signal, and each successive pair of ring data is averaged. The 15 data points are normalized and represent 15 size fractions. The magnitude of the particle size ranges is determined by the focal length of the lens used. Calibration is not necessary, since the method does not require the use of standards for the conversion of signal response into a size distribution. The data are normally displayed as a volume distribution, with the percentages present in each size band being tabulated.

The only direct or absolute method of particle size determination is that of microscopy, combined with some form of image analysis (19). Calibration of observed image is easily effected with the use of stage micrometers, and a given set of optics does not require recalibration. The optical microscopic determination of particle size has been made even more effective through the use of image analysis. In this method, the microscope parameters are adjusted so as to optimize the contrast between the background and the particles to be sized. A video image of the powder is transmitted into a computer system, which then counts the number of pixels which make up a particle. The size of each pixel is easily converted to micrometers, and the data analyzed as to any property desired. Average particle sizes, full weight distributions, or shape information can be generated. The advantage of the optical microscope method is that it provides direct and absolute information on the particles under characterization. Its chief disadvantage is that it can provide data only on the particles on the slide and can, therefore, be biased by the method preparing the slide.

As an example of the situation which can arise when an inappropriate method of particle size measurement is used, data obtained on Fast-Flo lactose are collected in Table I. Using the optical microscopic method combined with image analysis, an average particle size of 39.9 × 59.3 μm was obtained. This result may be rounded to an effective spherical size of approximately 50 μm, which is consistent with the observations made using electron microscopy. When suspended in methanol, the same Fast-Flo lactose sample exhibited average particle sizes which ranged from 86 to 49 μm, depending upon the amount of time the solid remained dispersed in the suspension solvent. Examination of the particle size ranges indicates that the lactose sample aggregated upon suspension and slowly deaggregated upon standing. Since the deduced particle size evidently represents the state of deaggregation, it is clear that this characterization of suspended particle (required for either the light scattering or the conductiometric method) would not be the method of choice for these powdered solids.

X-Ray Diffraction

The diffraction of X rays by crystalline substances is of great analytical interest, since no two compounds would be expected to form crystals in which the three-dimensional spacing of planes is totally identical in all directions. In most instances, a powdered sample will present all possible crystal faces at a given interface, and the diffraction off this powdered surface will therefore provide information on all possible atomic spacings (the crystal lattice) (20). The powder pattern consists of a series of peaks detected at various scattering angles. These angles, and their relative intensities, are correlated with computed d-spacings to provide a full crystallographic characterization of the powdered sample. After indexing all the scattered lines it is possible to derive unit cell dimensions from the powder pattern of a substance.

Table I. Particle Size Distributions Obtained for Fast-Flow Lactose: Light Scattering and Optical Microscopic Methods

Band size, upper limit (μm)	Light scattering method Percentage in band (at elapsed time)					Optical microscopic method
	$t = 0$	$t = 4$	$t = 9$	$t = 15$	$t = 20$	
9.3	11.2	13.3	13.0	11.3	10.3	7.6
20.4	10.3	10.4	10.4	10.9	11.9	12.6
27.9	1.9	3.6	4.7	5.3	5.9	13.6
41.8	7.0	9.2	10.7	12.4	13.7	18.2
54.9	8.1	9.3	11.2	13.4	14.3	9.3
80.0	2.7	9.9	15.0	18.4	19.1	12.9
118.4	58.9	44.3	35.1	28.2	25.0	11.9
	Average particle size (μm)					
	85.9	65.6	55.1	51.6	49.4	39.9

The existence of drug polymorphism (or pseudopolymorphism) is best characterized by means of powder X-ray diffraction (XRD). Such measurements represent a specification of the internal structure within a crystal and an evaluation of its lattice type. Given that many drugs and excipients are capable of existing in more than one crystal state, and that the physical properties of these can vary significantly, it is crucial to verify the structure of all materials as influenced by changes in the manufacturing process. Since dissolution and subsequent drying can sometimes yield an undesired structure, it is also important to confirm crystal structures at each formulation stage during the beginning of the development process.

The technique is based on Bragg's law, which describes the diffraction of a monochromatic X-ray beam impinging on a plane of atoms (21). Parallel incident rays strike the crystal planes at an angle θ and are then diffracted at the same angle θ. These angles are correlated to the spacings between planes of molecules in the lattice, using Bragg's law:

$$n\lambda = 2d \sin \theta \quad (1)$$

where

n = order of the diffraction pattern
λ = wavelength of the incident beam
d = distance between the planes in the crystal
θ = angle of beam diffraction

To measure a powder pattern, a randomly oriented powdered sample is prepared so as to expose all the planes of a sample. The angle θ is determined by slowly rotating the sample and measuring the angle of diffracted X rays (with a scintillation counter) with respect to the angle of the incident beam. Alternatively, the angle between sample and source can be kept fixed, while moving the detector to determine the angles of the scattered radiation. Knowing the wavelength of the incident beam, the spacing between the planes (identified as the d-spacings) is calculated using Bragg's law.

A very useful complement to ordinary powder X-ray diffraction is variable-temperature XRD. In this method, the sample is contained on a stage which can be heated to any desired temperature. The method is extremely useful in the study of thermally induced phenomena and is seen as a complement to thermal methods of analysis.

As shown in Fig. 5, the XRD powder patterns of hydrous and Fast-Flo lactose are extremely similar, while the powder pattern of anhydrous lactose is quite different from these two. These findings are consistent with those obtained using solid-state NMR and FTIR spectroscopies and clearly indicate that both the hydrous and the Fast-Flo forms of lactose consist largely of the α-lactose monohydrate phase. The anhydrous lactose is normally obtained from commercial sources as the β-lactose phase and has a completely different crystal structure.

Variable-temperature XRD studies carried out on the hydrous and Fast-Flo modifications of lactose also indicate the similarity of the two materials. After dehydration (150°C for 30 min), the powder patterns of the two materials were still found to be similar, and equivalent to that of the anhydrous α-phase of lactose. The difference in crystal structure between anhydrous α-lactose and β-lactose was clearly evident from the differences between their powder patterns. Heating the anhydrous β-phase of lactose did not yield any measurable changes upon heating.

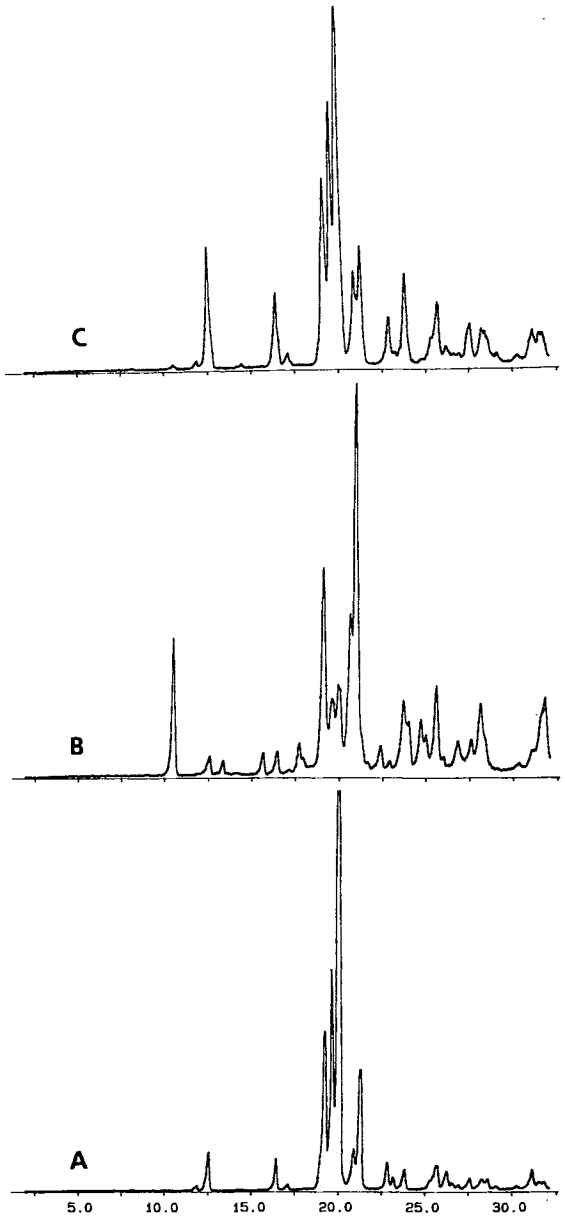

Fig. 5. Powder X-ray diffraction patterns obtained for (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

Thermal Methods of Analysis

Thermal analysis methods are defined as those techniques in which a property of the analyte is determined as a function of an externally applied temperature (22). The sample temperature is dynamically ramped, while the property in question is evaluated on a continuous basis. These methods are used to characterize compound purity, polymor-

phism, solvation, degradation, and excipient compatibility (23). Thermal analysis methods are normally used to monitor endothermic processes (melting, boiling, sublimation, vaporization, desolvation, solid-solid phase transitions, and chemical degradation) as well as exothermic processes (crystallization and oxidative decomposition). Thermal methods can be extremely useful in preformulation studies, since the carefully planned studies can be used to indicate the existence of possible drug–excipient interactions in a prototype formulation.

Differential thermal analysis (DTA) is the monitoring of the difference in temperature between a sample and a reference as a function of temperature (24). Differences in temperature between the sample and the reference are observed when changes occur which require a finite heat of reaction. If ΔH is positive (endothermic reaction), the temperature of the sample will lag behind that of the reference. If the ΔH is negative (exothermic reaction), the temperature of the sample will exceed that of the reference. DTA analysis is not normally used for quantitative work but, instead, is used to deduce temperatures associated with thermal events.

Differential scanning calorimetry (DSC) is similar to DTA and is the most widely used method of thermal analysis. In the DSC method, the sample and reference are kept at the same temperature and the heat flow required to maintain the equality in temperature is measured (25). This is achieved by placing separate heating elements in the sample and reference cells, with the rate of heating by these elements being controlled and measured. DSC plots are obtained as the differential rate of heating (in units of W/sec, cal/sec, or J/sec) against temperature. The area under a DSC peak is directly proportional to the heat absorbed or evolved by the thermal event, and integration of these peak areas yields the heat of reaction (in units of cal/sec · g or J/sec · g).

When a compound is observed to melt without decomposition, DSC analysis can be used to determine the absolute purity (26). If the impurities are soluble in the melt of the major component, the van't Hoff equation applies:

$$T_s = T_o - \{R(T_o)^2 X_i\} / \{F \Delta H_f\} \quad (2)$$

In Eq. (2), T_s is the sample temperature, T_o is the melting point of the pure major component, X_i is the mole fraction of the impurity, F is the fraction of solid melted, and ΔH_f is the enthalpy of fusion of the pure component. A plot of T_s against $1/F$ should yield a straight line, whose slope is proportional to X_i. This method can therefore be used to evaluate the absolute purity of a given compound without reference to a standard, with purities being obtained in terms of mole percent. The method is limited to reasonably pure compounds which melt without decomposition. The assumptions justifying Eq. (2) fail when the compound purity is below approximately 97 mol%, and the method cannot be used in such instances (26).

Thermogravimetry (TG) is a measure of the thermally induced weight loss of a material as a function of the applied temperature (27). TG analysis is restricted to studies which involve either a mass gain or a mass loss and is most commonly used to study desolvation processes and compound decomposition. The major use of TG analysis is in the quantitative determination of the total volatile content of a solid. When a solid can decompose by means of several discrete, sequential reactions, the magnitude of each step can be separately evaluated. TG analysis of compound decomposition can also be used to compare the stability of similar compounds. The higher the decomposition temperature of a given compound, the more positive would be the ΔG value and therefore the greater would be the stability.

As is evident in Fig. 6, the DSC thermograms of hydrous and Fast-Flo lactose are extremely similar. Each features a dehydration endotherm at 147°C and a decomposition endotherm at 218–219°C. The TG weight losses (attributed to water loss) were observed to be 4.9% for the hydrous lactose and 5.0% for the Fast-Flo modification. The theoretical weight loss for lactose monohydrate is calculated to be 5.0%. The DSC thermogram for anhydrous lactose consisted mainly of the decomposition endotherm at 237°C and a very minor dehydration endotherm at 135°C. The TG weight loss for this sample was found to be only 0.6%, probably indicating the pickup of a small amount of adventitious water. However, the observation of some water in the anhydrous material explains the small features assigned to crystalline water and noted in the NMR and FTIR work. The higher decomposition temperature associated with anhydrous lactose implies that this form would be more stable than the monohydrate phase, which is known to be the case (28).

PROPERTIES ASSOCIATED WITH THE BULK LEVEL

Bulk material properties may be conveniently defined as those characteristics of a solid which require a large assembly of particles for measurement. Once a solid formulation has reached the bulk manufacturing stage, these bulk physical properties are certainly of the highest importance.

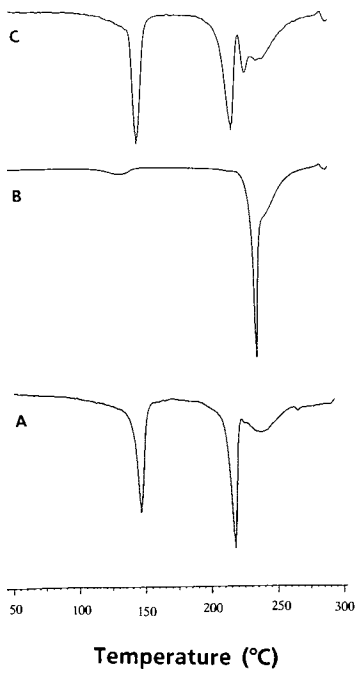

Fig. 6. Differential scanning calorimetry thermograms obtained for (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

Surface Area

The surface area of a solid material is important in that it provides information on the available void spaces on the surfaces of individual particles or aggregates of particles (29). In addition, the dissolution rate of a solid is partially determined by its surface area. The surface area of a solid is obtained by first adsorbing a monolayer of inert gas onto the solid surface at reduced temperature and then desorbing this gas at room temperature. The sorption isotherms obtained in this technique are interpreted using the equations developed by Brunauer, Emmett, and Teller, and therefore the technique is referred to as the BET method (30). The surface area is obtained in units of square meters of surface per gram of material.

Any condensable inert gas can be used for BET measurements, but the preferred gases are nitrogen and krypton. Nitrogen is used for most samples exhibiting surface areas of 2 m^2/g or greater, but materials with smaller surface areas should be measured using krypton. The gas to be adsorbed (the adsorbate) is mixed with an inert, noncondensable, carrier gas (usually helium). A range of 5 to 30% adsorbate in carrier gas is commonly used. The use of multiple adsorbate gas levels in a BET determination is recommended.

Surface areas are calculated using the following equation:

$$\frac{P}{V(P_o - P)} = \frac{1}{V_m C} + \frac{(C-1)P}{V_m C P_o} \tag{3}$$

where

V = volume of gas adsorbed at pressure P
P = partial pressure of adsorbate
V_m = volume of gas adsorbed in monolayer
P_o = saturation pressure of adsorbate at experimental temperature
C = a constant exponentially relating the heats of adsorption and condensation of the adsorbate

Using various concentrations of adsorbate, a graph of $P/V(P_o - P)$ against P/P_o yields a straight line. The value of V_m is obtained as the reciprocal of the sum of the slope and intercept. The total surface area of the sample is calculated using

$$S_t = \{V_m N_o A_{cs}\} / M \tag{4}$$

where

S_t = total surface area
N_o = Avogadro's number
A_{cs} = cross-sectional area of the adsorbate

The specific surface area is finally obtained by dividing S_t by the sample mass taken.

The adsorption and desorption isotherms obtained for the three modifications of lactose studied in the present work were found to be equivalent and indicated no existence of hystersis. All isotherms were of the Type III described by Brunauer (31), which are typical for powdered, relatively nonporous solids. The low surface areas measured (0.38 m^2/g for anhydrous lactose, 0.53 m^2/g for hydrous lactose, and 0.34 m^2/g for Fast-Flo lactose) are consistent with the observations made by electron microscopy which indicate little surface detail.

Porosity and Pore Size Distribution

Although a variety of methods is available to characterize the interstitial voids of a solid, the most useful of these is mercury intrusion porosimetry (32). This method is widely used to determine the pore size distribution of a porous material and the void size of tablets and compacts. The method is based on the capillary rise phenomenon in which excess pressure is required to force a nonwetting liquid into a narrow volume. Mercury, with its contact angle on glass of approximately 140°, is most commonly used as the intrusion fluid. The mercury is forced into the pores of the sample using an externally applied pressure, with the smallest pores requiring the highest pressures to effect the filling.

For a circular pore opening, the Washburn equation gives the relation between the pressure applied and the pore size opening (32):

$$\Delta P = -(2\gamma/r)\cos\theta \tag{5}$$

where

ΔP = pressure difference across the interface
γ = surface tension of the liquid
θ = contact angle of the liquid
r = pore radius

To perform the analysis the powdered material is weighed into the sample cell, which consists of a piece containing the sample and a cap with a precision bore tube (the dilatometer). The sample is degassed, and mercury introduced into the sample chamber until the sample is completely covered. The pressure in the chamber is raised in small increments until the limit is reached (this can be as high as 60,000 psi). The amount of mercury intruded into the pores is measured (V, in units of mL/g) at each pressure value. If the pressure P is in psi, then the pore size radius, r, is calculated in μm using

$$r = 89.5/P \tag{6}$$

The plot of volume intruded against pressure is known as the pressurizing curve, and this is converted into a plot of intruded volume vs pore radius using Eq. (6). The relative distribution of pore sizes in a solid is obtained by differentiating this cumulative curve ($\Delta V/\Delta r$).

Plots of the pore number fractions against pore radius are shown in Fig. 7. For all three materials, a significant amount of the pores was found to be smaller than 5 μm. An alteration in material properties was most evident when comparing the data obtained for hydrous and Fast-Flo lactose. Although both materials have been shown to be composed of the same lactose pseudopolymorph, the Fast-Flo material exhibits very well-defined pores having an average radius of approximately 20 μm. The Fast-Flo modification of lactose is also significantly more porous than either anhydrous or hydrous lactose. It is concluded that the processing of lactose to produce the Fast-Flo modification leads to the

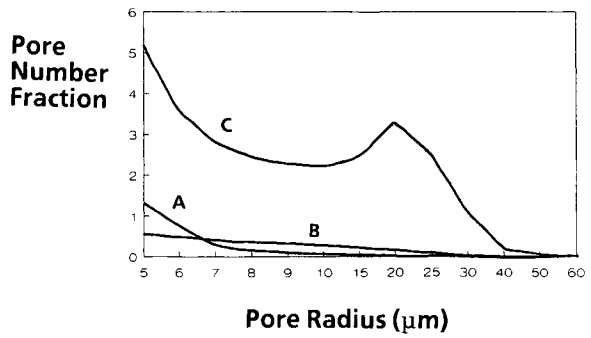

Fig. 7. Dependence of the pore number fraction on pore radius for (A) hydrous, (B) anhydrous, and (C) Fast-Flo lactose.

production of the particular 20-μm pore and the general porous nature. The well-defined pore could be useful in the generation of an ordered mix of drug and excipient, if the drug particle size was reduced to 20 μm or less. The overall porous nature of the Fast-Flo lactose could also be exploited in a variety of ways.

Powder Flow Characteristics

One of the more important parameters of interest to formulators is the flowability of the powdered solid material (34). This becomes especially important when tablets are to be compressed using a high-speed press, since the efficiency of the machine will be high only if the powder feed can be delivered at a sufficiently high rate. When powders flow, they do so in either a steady controlled fashion or an uncontrollable gushing manner. Since many pharmaceutical compounds are cohesive in nature, their flow characteristics tend to be undesirable. One of the aims of granulation is reduce the cohesive nature of the active component, producing materials whose physical properties are more suitable for processing. The flowability of a given granulation is an exceedingly important characteristic, which should be maximized to permit use in high speed tabletting machines.

Carr (35) has described a method which is extremely useful in the evaluation of the flowability of powdered solids. In this approach, a number of parameters related to flow are measured and scored according to a weighting system. Powder flowability is evaluated using the angle of repose (defined as the angle formed when a cone of powder is poured onto a flat surface), the angle of spatula (defined as the angle formed when material is raised on a flat surface out of a bulk pile), compressibility (obtained from measurement of the bulk and tapped material densities), and cohesion (relating to the attractive forces which exist on particle surfaces). The overall summation of these permits deductions regarding the degree of powder flowability and the possible necessity of bridge-breaking measures.

When powders flow, they do so either in a steady controlled fashion (as in the case of dry sand) or in an uncontrolled gushing manner (as would damp sand, for which the entire bulk tries to move in a solid mass). The latter condition is termed floodable flow and is most characteristic of the flow of cohesive, sticky powders. The floodability of a powder is determined by its flowability, angle of fall (obtained as the new repose angle when the powder cone is mechanically shocked), dispersibility (ability of a given powder to become fluidized), and angle of difference (obtained as the numerical difference between the angle of fall and the angle of repose). Carr has also detailed the method whereby indices are obtained for each floodability parameter, and the summation of these indicates the tendency of a powder to exhibit floodable flow (35).

The full range of physical characteristics needed to characterize powder flow is summarized in Table II for anhydrous, hydrous, and Fast-Flo lactose. As indicated by the mass flow rates, the hydrous lactose sample was characterized by very poor flow, while the Fast-Flo sample exhibited excellent flow rates. These trends are evident in the Carr flowability indices, which follow the same general classification. The reason for the superior flow rates of the Fast-Flo lactose is its consistently larger particle size and lack of fines in the particle size distribution. These properties are manifest in the cohesion and compressibility parameters, which are highest for the hydrous lactose sample and lowest for the Fast-Flo modification. All other parameters appear to be roughly consistent, suggesting that the flowability of lactose materials is dictated by the particle cohesion and compressibility.

SUMMARY

It may be envisioned that a protocol for the complete physical characterization of a solid material could be easily developed following the approach just outlined. 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 were correlated with the quality of produced product. Out of these studies would come an understanding of what particular properties were essential to the production of a given formulation.

As the maturity of the process increases, 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 raw material properties which would ensure that final product will always turn out satisfactory. These guidelines

Table II. Flowability and Floodability Data: Anhydrous, Hydrous, and Fast-Flo Lactose

Property	Anhydrous	Hydrous	Fast-Flo
Angle of repose	49°	53°	41°
Angle of spatula	58°	81°	58°
Compressibility	21%	44%	12%
Cohesion	31	50	17
Angle of fall	28°	25°	20°
Dispersibility	10%	18%	23%
Angle of difference	21°	28°	21°
Flowability index	50	34	73
Floodability index	66	66	83
Mass flow rate (g/sec)	1.5	0.17	6.2

would naturally apply only to the specific formulation, but through continued use of the systematic materials science approach the more general trends would become apparent.

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