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RAW MATERIALS

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ABSTRACT

The goal of materials science in the pharmaceutical industry is to develop specifications which enable product to be manufactured so that lot failure would never take place. At the present time, all raw materials (either active drugs, excipients, or formulated products) are fully characterized as to their chemical characteristics, but insufficient attention has been paid to physical characterization. A wide range of methods are available for physical testing (primarily bulk and particulate properties), and these will be discussed and illustrated.

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INTRODUCTION

The manufacture of any pharmaceutical product must necessarily begin with raw materials, and the quality of these will ultimately determine the value of any finished product. The chemical purity of bulk drugs is controlled by stringent specifications, and the purity of excipients on the accepted list is usually subject only to minor verification. However, the physical properties of both bulk drugs and excipients is not normally examined in great detail, and lot-to-lot variation in these properties is considered normal. Formulators will process their materials extensively (e.g., through granulation) in an attempt to reduce the physical properties to a semi-uniform level which they feel will form acceptable product.

In spite of all the precautions, every pharmaceutical scientist is aware of disasters which have resulted from incomplete specification of the physical properties of either a bulk drug or an excipient. At this point, a crisis mentality ensues and much work is expended on trying to find a solution to the problem. Eventually, active minds will deduce the critical parameter(s) which determine the quality of the formulation, and take corrective steps based on this information. It would be much more rational to know at the beginning of development what these key parameters are, and perhaps even how they should be controlled.

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The goal of a materials scientist in pharmaceutics is to develop the specifications which would enable product to be manufactured so that lot failure would never take place. Raw materials which were found to pass these testing standards would behave in a predictable manner and would yield reproducible, uniform product. The ultimate aim of this approach would then be an implementation of totally automated manufacturing procedures, where characterized raw materials would be blended, granulated, dried, tabletted, and delivered into containers without the need of intervention. The only tests which would be performed would evaluate the final quality of the product. If the materials scientist has developed appropriate specifications for the raw materials, then no product should ever fail if its ingredients passed their initial screens.

If the chemical quality of raw materials is assured (or determined by a suitable chromatographic procedure), then the bulk of raw material testing centers around physical characterization. The properties of importance to formulators fall into two main categories, the relative importance of which is directly related to stages in the development process. At the beginning of formulation development, all properties are equally important. As the manufacture scale increases, the material bulk properties assume an increasingly greater importance.

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EXPERIMENTAL

Scanning electron microscopy studies were performed on an Amray model 1820T digital SEM. Samples were sputter coated with Au/Pd to reduce charging, and were imaged using a 20kV electron beam. Magnifications between 50x and 2000x were used for characterization purposes. Optical microscopic investigations were performed on a Nikon Microphot system, at magnification values between 100x and 200x. For particle size analysis, the optical microscope image (as detected by a video camera) was passed into the image analysis system produced by Image Technology. This system permits automatic measurement of particle widths, lengths, cross sectional areas, and perimeters, and then provides average values and standard deviations in each property. The particle size distributions were obtained by transferring the raw data over to a relational data base program, and then sorting these according to the desired size fractions.

Powder surface areas were obtained on the Quantachrome Autosorb-1 system. Data were typically obtained using five concentrations of nitrogen adsorbent, and the results were analyzed using a multi-point B.E.T. equation. Pore size distributions were obtained using mercury intrusion porosimetry, using the Quantachrome Autoscan porosimeter system. With the

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range of accessible pressures, pore sizes as small as 5 angstroms are easily detected.

Flowability and floodability determinations were obtained on the Powder Characteristics Tester, manufactured by Hosowaka Micron. The device permits measurement of the angle of repose, angle of spatula, compressibility, cohesion, angle of fall, dispersibility, and angle of difference for a given powder system. Each parameter is given a numerical index, and these indices used to evaluate the overall characteristics of the powder.

Powder x-ray diffraction patterns were obtained using a Philips model APD 3720 powder diffraction system, equipped with a vertical goniometer in the theta/2-theta geometry. The x-ray generator (Philips model XRG 31000) was operated at 45 kV and 40 ma, using the K-alpha line of copper at 1.544056 A as the radiation source. Each sample was scanned between 2 and 50 degrees 2-theta, at a scan rate of 0.04 degrees 2-theta/sec, and in step sizes of 0.04 degrees 2-theta.

Measurements of differential scanning calorimetry and thermogravimetry were obtained on the DuPont model 9900 thermal analysis system. Approximately 1.5 mg samples were accurately weighed into a DSC pan, the pans hermetically sealed, and a pinhole punched into the pan lid. The use of the pinhole allows for pressure

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release, but still ensures that the thermal reactions proceed under controlled conditions. For TG determinations, approximately 10 mg of sample was placed on the pan, and inserted in the TG furnace. For either measurement, the samples were heated at a rate of 10°C/min, up to a final temperature of 200°C.

RESULTS AND DISCUSSION

Bulk material properties may be defined as those characteristics which require a relatively large amount of material for measurement. Studies of particle aggregation, particle size distribution, surface area, porosity, and flowability all fall within this category.

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 few techniques are better suited for the study of particle aggregates than scanning electron microscopy (SEM) [1]. The nature of the aggregate species can be quickly determined, and preliminary estimates regarding average particle sizes can be obtained. It the aggregates are seen to be loosely held together, then they might be broken (and made more suitable for subsequent blending) in a simple mixing step. If, however, the microcrystals in the aggregates appear to be strongly cemented together, then

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milling might be the only way to produce suitable material. A good materials scientist will make microscopic studies his first characterization tool.

The particle size distributions of drugs and excipients will exert profound effects on mixing phenomena, and on possible segregation in mixed materials [2]. 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 size distribution can affect the bioavailability of certain active drugs, and exerts a major effect on powder flowability. The two most important methods for determination of particle size use either laser light scattering of particles suspended in inert solvents, or optical microscopy combined with image analysis. The latter method is the most preferable since it yields data free from particle morphology assumptions, and is free from solvent-induced aggregation effects.

The particle size distribution of a given sample is often a function of its processing history and handling. In Table I, size distributions obtained on the same lot of compressible starch are shown. As received, the material consisted mainly of particles smaller than 500 μm, but with aggregate species ranging as large as 1200 μm. The sample was then tumbled in its container for

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Table I

Particle Size Distribution Data, Compressible Starch

Band Size (micrometers)	Material As Received	Tumbled	Sieved (30 mesh)
0 - 100	7.5	1.0	52.7
100 - 200	7.0	1.1	13.4
200 - 300	13.1	9.6	17.6
300 - 400	19.5	3.5	9.8
400 - 500	15.3	4.9	3.7
500 - 600	8.4	9.5	2.8
600 - 700	6.7	0.0	0.0
700 - 800	5.5	13.0	0.0
800 - 900	5.0	16.2	0.0
900 - 1000	4.3	15.5	0.0
1000 - 1100	3.8	12.0	0.0
1100 - 1200	3.9	13.7	0.0
1200 - 1300	0.0	0.0	0.0
1300 - 1400	0.0	0.0	0.0

Note: No particles larger than 1200 micrometers were observed in any material, regardless of its handling history.

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approximately 48 hours, and it was then observed that 70% of the particles had been transformed into aggregate species between 700 and 1200 μm in diameter. Passage of this aggregated sample through a 30 mesh screen destroyed all aggregate species, and over 50% of the material was now smaller than 100 μm. Any situation might represent material received for characterization, but it is evident that the experimentally determined size distribution would be strongly influenced on the handling of the material prior to its analysis.

The surface area and porosity of aggregated particles are important quantities in that they provide information on the available void spaces on the surfaces of the aggregates [3]. The surface area is obtained in units of square meters of surface area per gram of material, and is best measured through quantitation of the amount of inert gas (e.g., nitrogen) adsorbed onto the particle surfaces. The equation developed by Brunauer, Emmett, and Teller for the analysis of adsorption data is the most widely used. The use of multi-point B.E.T. determinations is recommended, since accurate surface area results require the use of at least three concentrations of nitrogen adsorbent in an inert carrier. The interstitial voids of a solid can be measured using mercury adsorption porosimetry, which ultimately yields a determination of the pore size distribution at the particle surface.

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Table II

Average Particle Size, Surface Area, and Average Pore Radius Obtained on Various Lots of Magnesium Stearate

Source	Particle Size (micrometers)	Surface Area (m^2/g)	Pore Radius (Angstroms)
U.S.	1.5 x 3.2	13.4	50
Gt. Britain	2.1 x 5.2	12.2	68
Germany	4.1 x 6.9	7.4	61
Italy	5.5 x 9.1	4.2	36

Average particle sizes, surface areas, and average pore radii are shown in Table II for four samples of magnesium stearate obtained from different international sources. The two lots which exhibit the smallest particle size also were found to exhibit the largest intrinsic surface areas. The average pore radii were found to be substantial, and more indicative of interstitial void volumes between aggregated particles. The relation of these properties to material performance as a lubricant would be the next logical step in the materials research process.

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One of the more important parameters of interest to formulators is the flowability of the powdered solids with which they are working [4]. For any product to be successful, it must be manufactured on a large scale. This requires movement of hundreds of kilograms of material at each stage of the process, and materials capable of flowing well will greatly aid the manufacturing scheme.

Following the characterization scheme proposed by Carr [5], the best estimation of the ability of a given powder to flow requires measurement of four parameters. These are the angle of repose (defined as the angle between the horizontal and the slope of a pile of material), 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). Using Carr's method, indices are computed for each parameter, and 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 a uncontrolled gushing manner (as would wet sand, for

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which the entire bulk moves in a solid mass). This 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 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.

Flowability and floodability data obtained on anhydrous and Fast-Flo lactose are collected in Table III. It is evident that the superior flow characteristics of the Fast-Flo lactose are reflected in the higher values observed for the Carr indices. The most important factors contributing to the increased flowability of the Fast-Flo lactose are its lower degree of compressibility, lower cohesion, and higher dispersibility.

Particulate properties are defined as material characteristics which can theoretically be determined by the analysis of a one or a few particles. This area would include studies of particle morphology, crystallography, and thermal analysis.

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Table III

Flowability and Floodability Data Obtained on Anhydrous and Fast-Flo Lactose

Parameter	Anhydrous Lactose	Fast-Flo Lactose
Angle of Repose	45°	42°
Angle of Spatula	64°	54°
Compressibility	31%	16%
Cohesion	44%	35%
Angle of Fall	38°	25°
Angle of Difference	7°	17°
Dispersibility	15%	23%
Flowability Index	44	68
Floodability Index	49	82

Electron and optical microscopies are the most important method for study of the morphology of individual particles [1]. Materials may not exhibit their intended function if their morphology is not correct. If highly flowable powders or granulations are

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required, then the generation of sharp angular crystals should be avoided. If a drug or excipient forms as needles, then it would be prudent to process the material until rounded particles predominate. Determination of crystal habit by SEM examination enables a description of the outer appearance of the intrinsic microcrystals making up a solid.

As an example of how individual particle morphologies can affect the performance of a material, consider the two lots of stearic acid whose optical microscopic images are shown in Figure 1. Both materials were found to be equivalent in chemical properties, and most physical properties (including particle size). In spite of their similarities, the Canadian stearic acid did not function as a lubricant. The microscopic examination revealed that the U.S. sourced material existed as spherical particles, while the Canadian source material was obtained as angular flakes. Evidently, the spherical particles were better able to migrate in the compression mixture, and be present at the punch and die faces in sufficient quantity to lubricate the surfaces.

The existence of drug polymorphism (or pseudopolymorphism) and its possible effects on bioavailability and compound stability require monitoring [6]. This characterization is performed by means of powder x-ray

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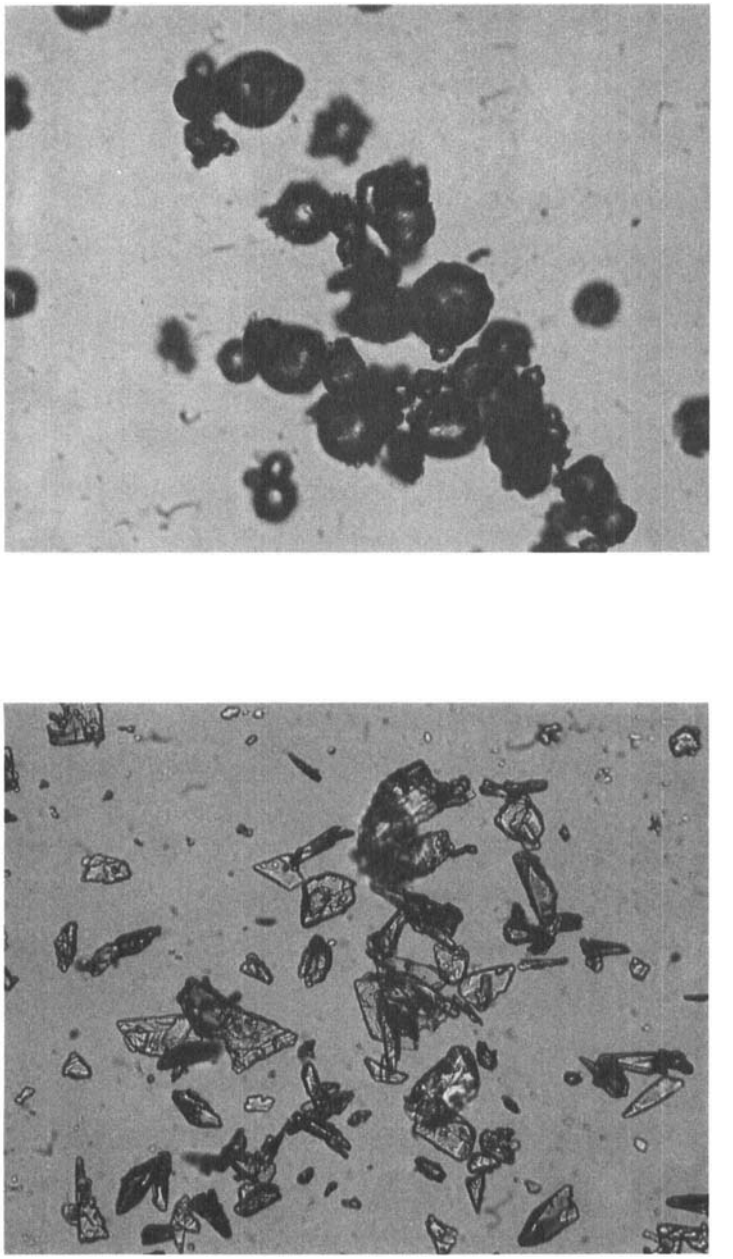

Figure 1. Optical microscope photographs taken at 200x magnification for stearic acid. The upper photo was taken on U.S. sourced material, while the lower photo was taken on Canadian sourced material.

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diffraction (XRD), and represents a specification of the internal structure within a crystal. Other parameters affected by the crystal structure include melting point, density, and hardness. 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 processed during every state of manufacture. 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 powder x-ray diffraction patterns obtained for the four internationally sourced magnesium stearate samples are shown in Figure 2. Comparison of the XRD powder patterns indicates that while the crystal structures of the U.S. and Gt. Britain sources materials were comparable, material obtained from the German source appears to contain significant amounts of one of the other pseudopolymorphs. Material obtained from Italy was found to be amorphous, and did not function nearly as effectively as a lubricant.

Thermal analysis methods have been used to characterize compound purity, polymorphism, solvation, degradation, and excipient compatibility [7].

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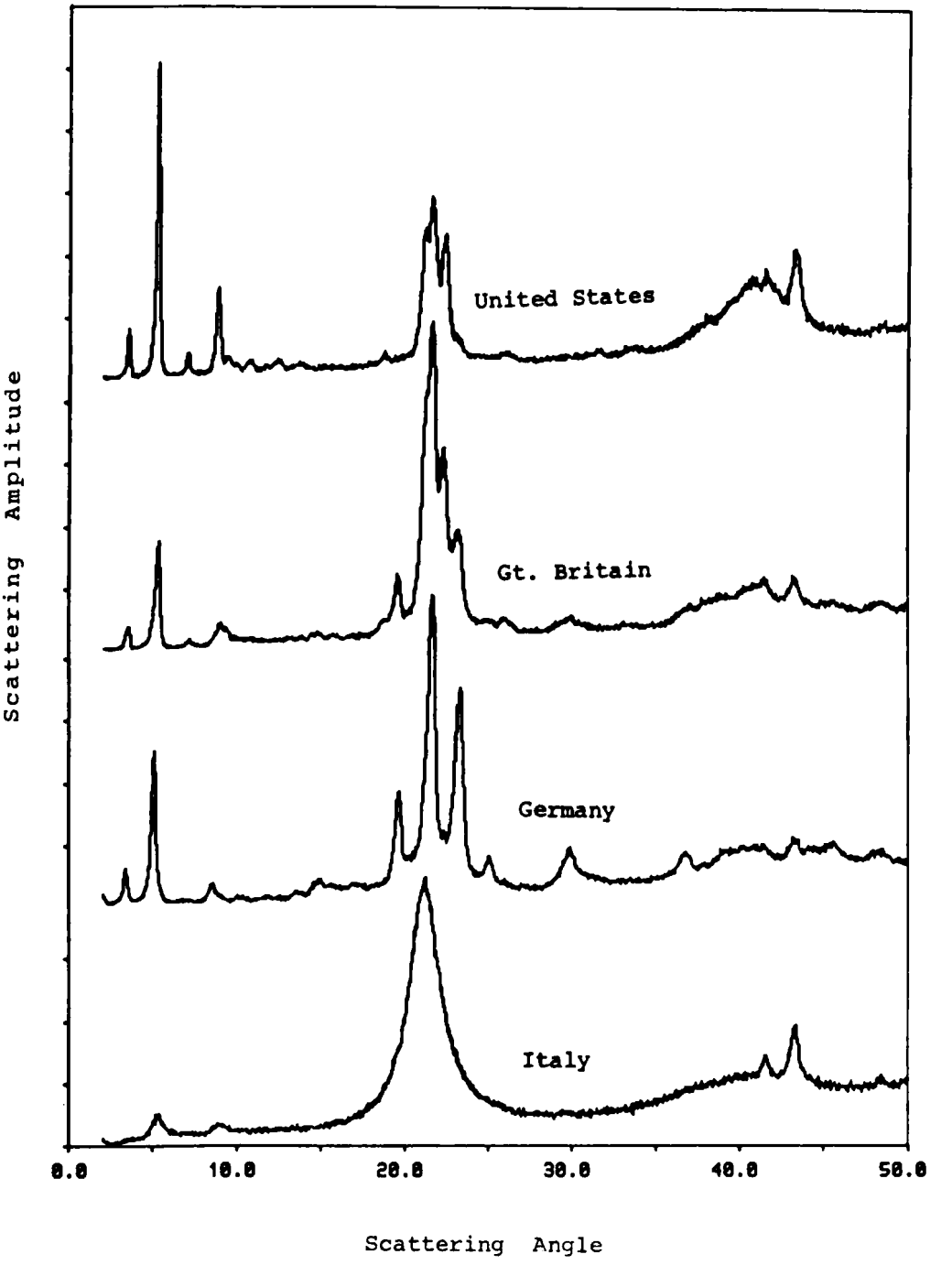

Figure 2. Powder x-ray diffraction patterns obtained on magnesium stearate, obtained from different international sources. Each trace is identified by its country of origin.

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Differential scanning calorimetry (DSC) can be 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). Thermogravimetry (TG) is a measure of the thermally induced weight loss of a material as a function of the applied temperature. TG analysis is most commonly used to study desolvation processes and compound decomposition.

Differential scanning calorimetry thermograms obtained for the four internationally sourced magnesium stearate samples are shown in Figure 3, and it is clearly evident that all four samples are quite different in their thermal characteristics. Each contains one or several dehydration endotherms, for which definite TG weight loss can be recorded. Carstensen [8] has classified magnesium stearate materials on the basis of their DSC behavior, and his scheme permits partial understanding of the samples illustrated in Figure 3. The U.S. sourced material is seen as pure type B. The Gt. Britain sourced material consists of type A plus an unclassified species (evident in the 75°C endotherm). The German sourced material consists of type C plus the same unclassified species, while the Italian sourced material cannot be classified due to its amorphous character.

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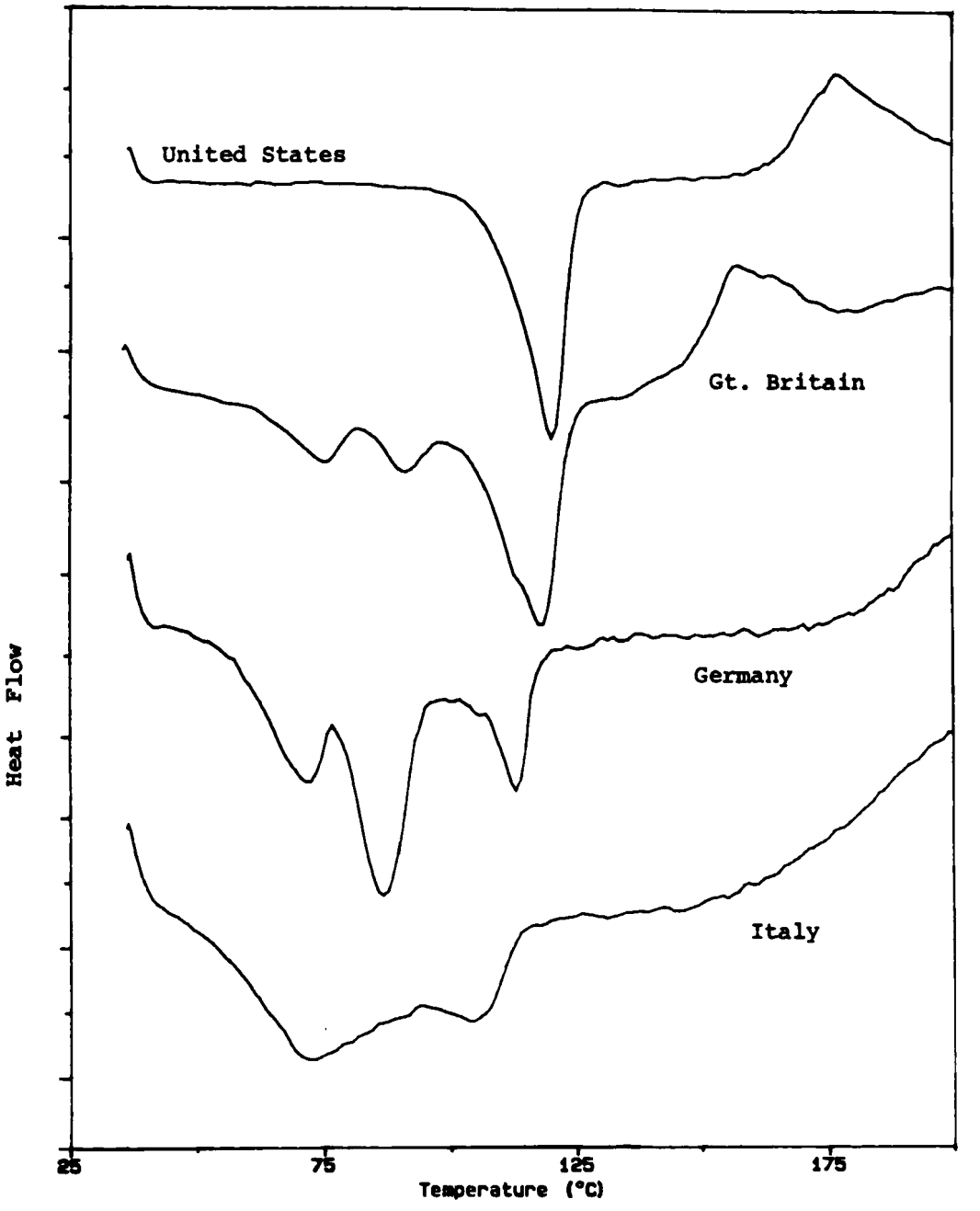

Figure 3. Differential scanning calorimetry thermograms obtained on magnesium stearate, obtained from different international sources. Each trace is identified by its country of origin.

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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 should be characterized as fully as possible. A feedback loop should be established after each formulation run in which the physical characteristics are correlated with the quality of the product. 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 has been performed properly, then it should be possible to specify limits for raw material properties which ensure that final product will always turn out satisfactory.

CONCLUSIONS

Early in drug development, each lot of active drug, excipients, and formulated blends should be physically characterized as fully as possible to set up a material property data base. The quality of product produced from each formulated blend should be correlated with the raw material properties. Key parameters should be identified which appear to determine the quality of

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the final product, and these should then be monitored throughout all development phases. After sufficient lot production has taken place, it should be possible to generate tight raw material specifications so that acceptable product would invariably result after manufacture with approved raw materials. If these goals can be attained, then automated manufacturing with zero product failure rate should be possible.

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