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EFFECTS OF PARTICLE MORPHOLOGY IN SELECTING PHARMACEUTICAL EXCIPIENTS

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ABSTRACT

Knowledge of the morphic features of solid excipients used in drug formulation, is important to validate the quality of raw materials and to identify changes in the production line. This paper describes a quantitative method for the characterization of solid excipients based on the analysis of individual particles and quantifying the particle shape. The study suggests that Fourier descriptors determined from the particle image data offer valuable and more definitive preformulation parameters. As a consequence, deviation in the performance of the pharmaceutical excipient could be predicted if the particle signature changed.

INTRODUCTION

Fundamental parameters like size, size distribution, surface area and chemical composition are measured quantitatively, in a routine manner, during the quality control of raw materials. These parameters are directly corrolated with numerous bulk properties of the excipient. Several relevant examples include flowability[1], setteling properties[2] and surface reactivity[3].

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The behavior of excipients as bulk solids is also strongly influenced by the shape of the particle. Powders with identical size and size distribution, density and chemical composition, may behave quite differently as result of the particle morphology[4]. Morphological characteristics are known to modify, to great extent the rheology of suspension[5], adhesion on solid surfaces[6], and solid-solid mixing[7]. Because excipients are prepared by variable processes such as: crystallization, size reduction, screening and spray drying etc, the characteristic shape of the solid particles can be dramatically influenced by these processes. Grant[8] reported that modification of crystal habit of adipic acid by deliberate addition of trace amounts of impurities during crystallization can facilitate the production of an excipient of different properties.
Meloy[4] demonstrated that size reduction of large particles produce more large particles which are round and less elongate than the smaller particles that are complex and have more points and more edge length. The increasingly complex shape with decreasing particle size continues to micrometer size particles. Within the pharmaceutical industry, there are increasing needs for improved methods for rapidly characterising and validating solid excipients used in drug and cosmetic formulations. Such methods will be of great help in identifying occasional variation in the manufacturing process, and predicting any change in the production line.

The present study was designed to show that morphological characterization of solid excipients could be quantitatively and routinely determined and the results could be corrolated with changes in the physical behavior of the bulk solid.

MATERIALS

Materials used in this study are pharmaceutical excipients frequently used in tablet making: lactose monohydrate, sorbitol, corn starch and talc. The excipients are USP grade of known particle size and each excipient was obtained from different sources. Table 1 summarizes the source, the size characteristics and reported differences in physical behavior.

TABLE I

EXCIPIENTS FROM DIFFERENT SOURCES AND THEIR REPORTED VARIATIONS

EXCIPIENT	SOURCE	SIZE CHARACTERISTICS	REPORTED VARIATION	REF.
Corn starch 1 Corn starch 2 Corn starch 3	CPC - lot AH22 St.Lawrence lot 3L792 Staley lot: G32361	The difference between the three samples is insignificant (S.E.M.)	Starch 1 gives better uniformity of weight in capsules than starch 2 and 3	14
Lactose monohydrate 1 Lactose monohydrate 2	Glaxo Canada lot 69300 Glaxo Canada lot. 73796	Mean volume diameter 75 μm Mean volume diameter 50 μm (Coulter Counter)	Flow and packing characteristics in capsules	13
Talc 1 Talc 2	Biopharm. Mtl. lot 108139	The difference between the two samples is insignificant. (Coulter Counter)	Talc 1 has more hiding power than talc 2.	15
Sorbitol A Sorbitol B	E. Merck Darmstadt lot M673640 Neosorb 20/60 Roquette Fr. Lille-France	B.E.T. Surface Area 0.96m^2/g B.E.T. Surface Area 0.77m^2/g	Adsorbs 6% vit.B_1 in solid-solid mixing Adsorbs 2% vit.B_1	7

METHODS

Many particle shape characterization methods rely on imaging individuals particles in powder and measuring particle shape. Based on the image analysis of individual particles in a sample, Beddow and Philip[9], Erlich and Weinberg[10] and Meloy[11] independently developed a quantitative method called Fourier grain or Morphological analysis of measuring the shape of individual particles. In this work, Fourier descriptors were determined by the digitalization of the particle image by obtaining the (x, y) coordinates of the particle boundary following the work of Nguyen[12]. These coordinates were represented in complex form as $\mu(\ell) = x(\ell)\, iy(\ell)$ and are calculated in terms of Fourier Series as:

$$\mu(\ell) = \sum_{n=-p}^{p} C_n \, e^{i2\pi n\ell/L}$$

$$Cn = \frac{1}{L} \int_{0}^{L} \mu(\ell)\, e^{-i2\pi n\ell/L} \, d\ell$$

Cn = the n^{th} Fourier coefficient
n = the harmonic number
ℓ = the path length along the particle boundary
L = the perimeter of the particle
i = the complex value equal $\sqrt{-1}$
p = maximum harmonic number considered

To obtain the size invariance, we compute the Fourier coefficient normalized by the amplitude of the first coefficient.

$$a_n = C_n / (| C_1 | + | C_{-1} |)$$

Thus, the normalized amplitude of each coefficient is $| a_n | + | a_{-n} |$.

Figure 1 shows schematic diagram of the components of the system selected for use in digitizing and extracting features from the image data. Fourier descriptors were obtained using a special com-

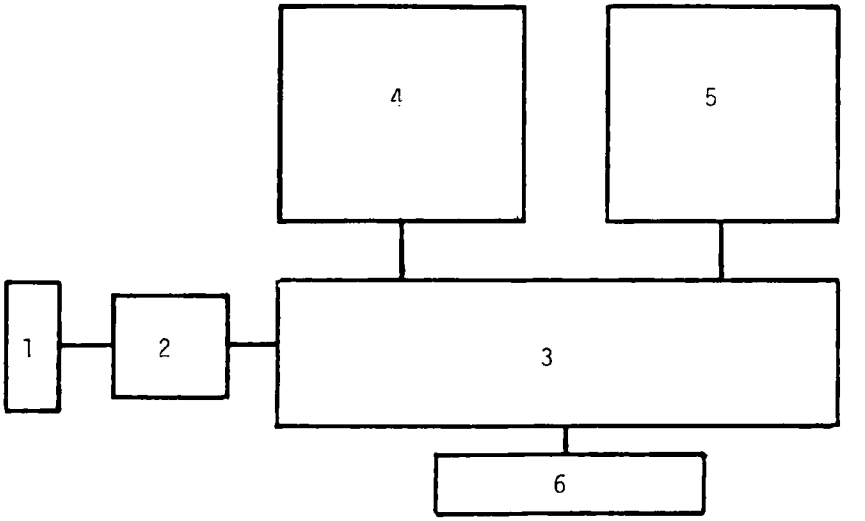

FIGURE 1

Schematic diagram of the components of the system used for the digital processing of the particle image

1- Hitachi camera
2- Video Vangoch digitizer
3- Computer (IBM PCXT)
4- Monitor Amdex for text and graphic display
5- Monitor Hitachi for image display
6- Printer

puter program written in Fortran and assembler that can determine the amplitude of the Fourier coefficients at different harmonics and represent graphically the computed data.

RESULTS AND DISCUSSION

Figure 2 shows the particle signature of the three samples of corn starch. The morphological analysis is represented by three different curves. Each curve shows the average normalised Fourier coefficient as a function of the harmonic number. Taking the second harmonic, as an example, the samples are further separated and characterized by the shape frequency distribution (see Fig. 3 and Table 2).

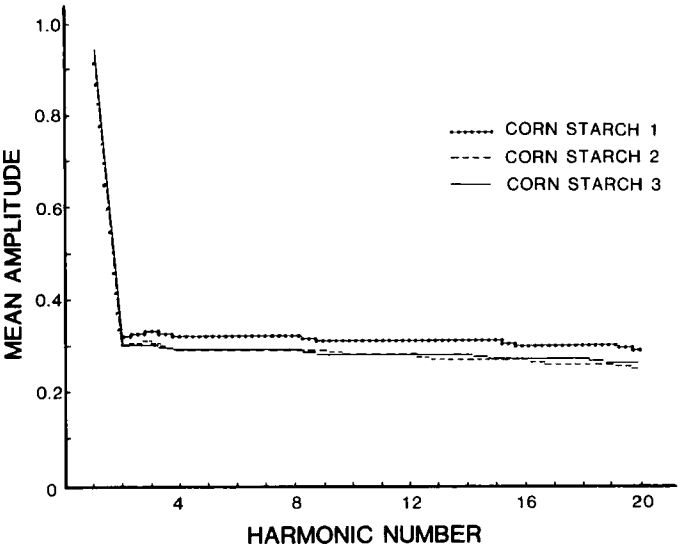

FIGURE 2 - Morphological analysis (particle signature) of three samples of corn starch using Fourier descriptors.

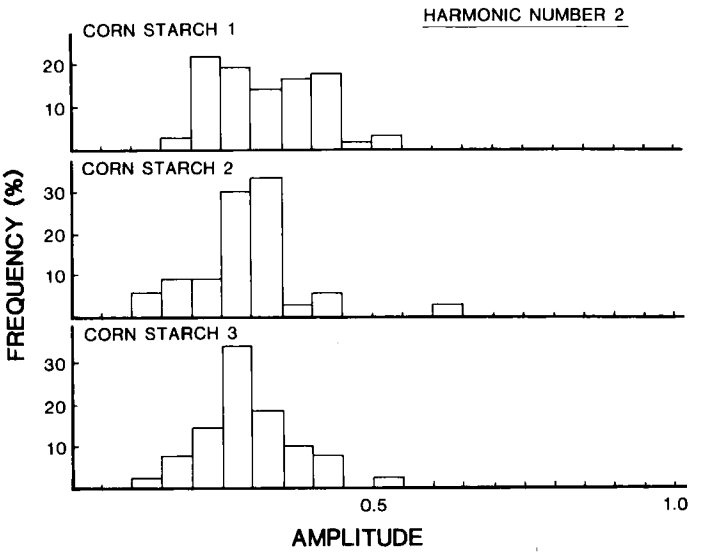

FIGURE 3 - Shape frequency distribution of the three samples of corn starch at Harmonic number 2.

TABLE 2 - Example of Fourier descriptors of starch 1, combuted from the particle image data (number of particles 116)

Harmonic number	Average normalised Fourier coefficient	Varriance
1	1.00000000	0
2	0.32341980	7.393503E-03
3	0.33420920	7.083054E-03
4	0.32322460	7.402792E-03
5	0.32109470	7.194605E-03
6	0.31861060	6.991024E-03
7	0.31849050	7.295637E-03
8	0.31653910	7.137814E-03
9	0.31460060	7.114658E-03
10	0.31398920	7.138977E-03
11	0.31159670	7.005301E-03
12	0.30986900	7.149782E-03
13	0.30945520	7.107048E-03
14	0.30699640	7.100059E-03
15	0.30674410	6.996468E-03
16	0.30325610	7.097861E-03
17	0.30145110	6.841717E-03
18	0.29913580	6.774137E-03
19	0.29547230	6.818438E-03
20	0.29468230	6.687784E-03

Since there is no significant difference in size and size distribution of three samples of starch, it appears that their morphological characteristics can offer an explanation for the variation notices in the behavior of the bulk solid. Starch 1, which gives a better weight uniformity in capsules, is clearly characterised by it particle signature. It shows clearly a narrower and more uniform shape distribution than the other samples.

In case of lactose monohydrate, the two samples are characterized by the particle signature in Fig. 4. The reported difference in their packing characteristics can probably by attributed to the difference in particle size. However, the difference in morphological characteristics could be equally important, contributing to change in the packing characteristics of the two samples (Fig. 5).

In the case of talc, Fig. 6 and 7, show the difference in particle shape signature and the frequency of particle shape at Harmonic 2. Although there is no significant difference in the

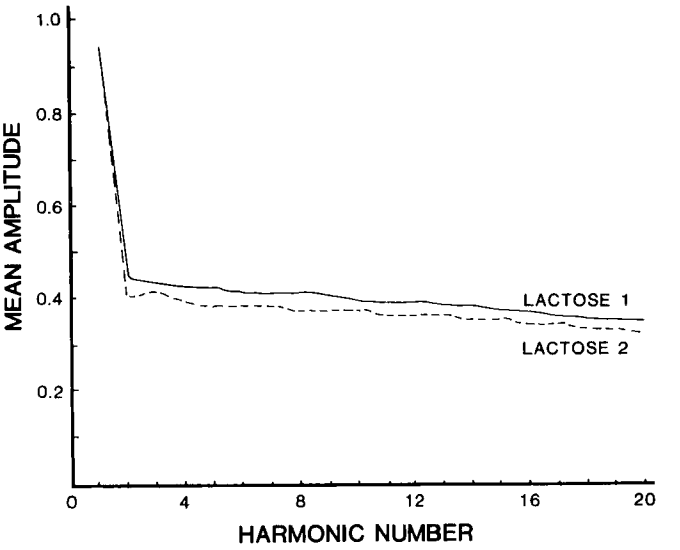

FIGURE 4 - Morphological analysis of lactose monohydrate 1 and 2.

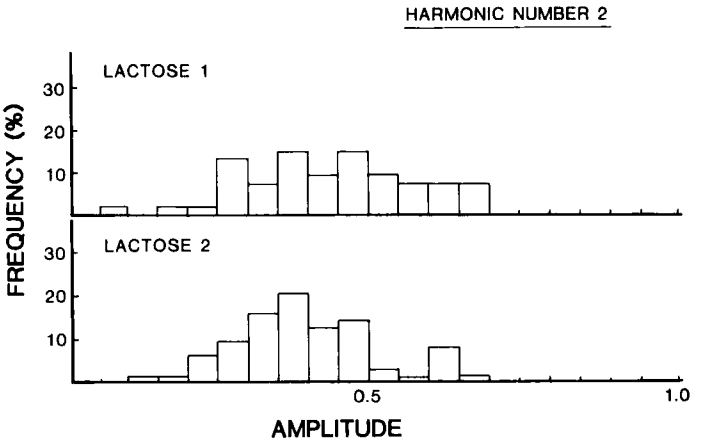

FIGURE 5 - Shape frequency distribution of lactose monohydrate at harmonic number 2.

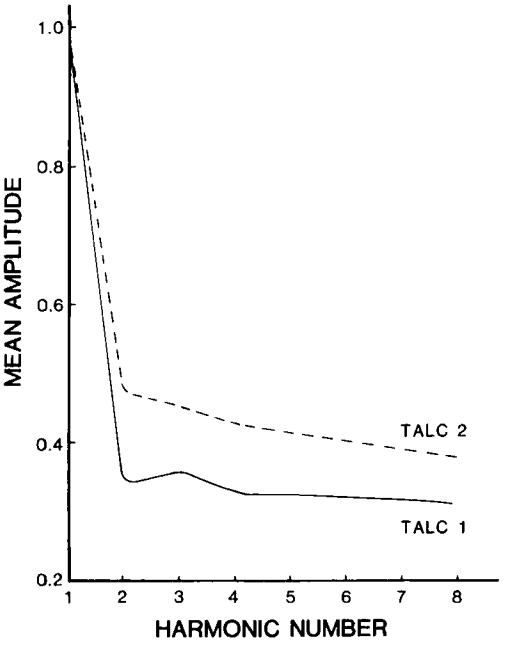

FIGURE 6 - Morphological analysis of talc 1 and talc 2.

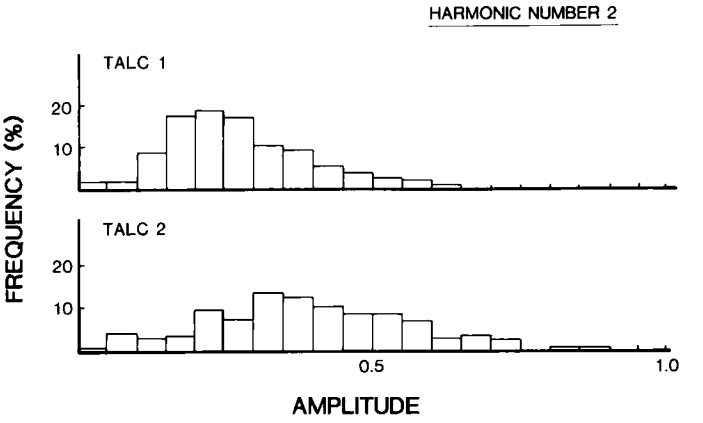

FIGURE 7 - Particle shape frequency distribution of talc at harmonic number 2.

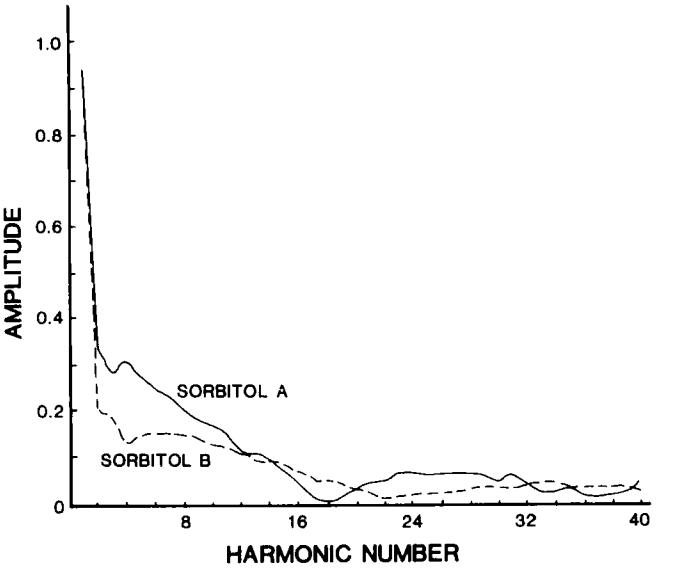

FIGURE 8 - Morphological analysis of sorbitol A and sorbitol B particles.

particle size and particle size distribution, the two samples demonstrated significant difference in their hiding powder[15]. The study of shape frequency distribution indicates that talc 1 has more particles of elliptical shape and less multimodel particles and of smoother boundaries than talc 2.

The shape analysis of sorbitol A and sorbitol B particles (Fig. 8) confirm the recent findings of Schmidt and Benke[7] on the use of sorbitol as carrier for drugs in direct compression. Surface area measurements of the two excipients cannot explain why sorbitol A adsorbs 3 times more vitamin B_1. The morphological analysis of the 2 particles shows clearly the difference in shape.

It is important to point out,at this stage, that from large particles to subsieve range and from granules to microcapsules, morphic features can significantly influence the behavior of the bulk solids. The quantification of these parameters is important in pharmaceutical research.

New emerging techniques offer powerful tools for performing shape analysis of individual to particles. A precise and difinitive shape descriptors could be computed from the image analysis of the

particle boundary and the digital processing of the data. This in no way reduces the value of sizing techniques and other standard testing procedures used in quality control departments, rather, it complements the definition of specifications. The system described in this paper could be further developed in the future to make the computor a cybernetic system capable to recognize the shape of the drug or excipient particle, by cross-corrolation of the signature against a memory bank of stored particle signatures. This approach could help not only to avoid undesirable properties related to the morphic features of excipient particles but also to provide basis for future experimentation in excipient selection.

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