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RESEARCH PAPER

Compaction Force Analysis: Research Tool for Assessing Mass-Produced Acetaminophen Granulations

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ABSTRACT

The aim of this research is to define a suitable method for comparing the compressibility of acetaminophen granulations. This paper focuses on the derivation of the method and how it will be applied in a large-scale production environment. This new tool will also aid in the analysis of new formulations on a smaller scale in a lab environment. The result is the use of the Leuenberger model for consolidation, which accurately describes the ease of compaction.

INTRODUCTION

In order to produce quality tablets, a good-quality granulation must be manufactured. The objective is to produce a granulation that, when compressed, will consolidate with minimal effort. However, there are many aspects of a granulation to analyze, and describing how well a powder consolidates is difficult.

The purpose of compaction force analysis (CFA) is to be able to accurately assess the compressibility of a granulation. This research tool is expected to become an in-house standard in evaluating new formulations of existing products in terms of compactibility, as well as in assessing the performance of new products in compression. One other use of CFA is to log the current granulations being mass produced and to determine optimum granulation conditions by correlating the CFA test results with the granulator parameters.

The distinct advantage of CFA is its ability to analyze the samples using "shop floor" technology. All of the apparatus used is standard production equipment (i.e., instrumented tablet press, scale, hardness tester).

Producing granulations that compact with minimal effort enables operators to run the tablet presses at higher speeds because of the decreased amount of "dwell time" necessary to produce a stable tablet. This results in higher production capacity. As well, there is less wear on the presses and tooling if lower forces are required

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to produce the tablets. If optimum granulations can be produced, less down time in production results, since fewer compaction problems arise. This is a definite asset to the production environment.

MATERIALS AND METHOD

Sample Preparation

Currently, the CFA process starts by obtaining a 2- to 3-kg sample of the acetaminophen-based granulation that is fully blended and lubricated. The laboratory Manesty BB4 27 station Rotary Tablet Press is set to a speed of 1400 tablets/min, using a one-third or nine-station setup. The tooling used is a flat-faced 15/32-in. round tablet. The tablet weight is set to 500 mg/tablet and the press is started. Using the PressVision Data Acquisition and Analysis System, the compaction load is carefully monitored. The load is read by a strain gauge mounted on the tie rod of the pressure roll assembly. The strain gauge is interpreted by a Manesty Compaction Force Monitor. Although the readout of this monitor is averaged over several punches, and it will not function properly with a nine-station setup, a port in the rear of the unit will output the load signal in real time. This step is important in assuring the proper load readings. In addition, this type of analysis is not limited to the laboratory BB4 press, as any instrumented tablet press is most likely equipped with similar compaction force monitors.

A sample of tablets is taken at the first compaction load, which is usually 0.5 (UK) tons (where 1 UK ton ≈ 2240 lb). The compaction load is increased and the process is repeated. The samples are then tested for average weight, thickness, and friability. In general, it is commonly known that tablet hardness increases over time (2). Therefore for CFA testing, the tablets are permitted to equalize for 1.5 hr and are then tested for average hardness.

The granulation is again sampled and a tapped density test is performed. This is accomplished by filling a graduated cylinder with 100 ml of granulation and tapping the sample with a Vanderkamp Tap Density Tester for 50 taps. The weight of the sample over the final volume gives the tapped density.

Modeling the Data

The next task is to find a suitable model for the system to be able to identify and compare the compaction characteristics. The first attempt was to devise a new formula that encompasses the important attributes of the compressed material.

The first function, called the consolidation efficiency index, or CEI, attempted to account for tablet weight variation, as well as hardness and thickness. The function is:

$$CEI = \frac{W_a \cdot H}{\ln(t) \cdot W_t} \quad (1)$$

where W_a is the actual average tablet weight (milligrams), W_t is the theoretical weight as set by the tablet press (milligrams), H is the average tablet hardness (kilograms), and t is the average thickness (millimeters). This empirical equation is based on the assumption that a good tablet will have minimum weight variation as well as maximum hardness with minimum thickness. The compaction profiles are a plot of the compaction load versus the CEI, at compaction loads ranging from 0.5 to 4.0 (UK) tons in half-ton increments. Unfortunately, this index turned out to be a scaled hardness parameter as the term

$$\frac{W_a}{\ln(t) \cdot W_t}$$

remained reasonably constant through all batches. Therefore this index was not suitable.

Subsequently, a new formula was proposed, similarly named the consolidation index (CI):

$$CI = \frac{H}{(t-5)\sqrt{F_r}} \quad (2)$$

where F_r is the average friability of the sample, in percent weight loss. This equation used the available data for the CEI and attempted to model the granulation based on several stipulations. First, a 10% change in CI is deemed significant. This 10% is caused by a 10% change in hardness, a 1% change in thickness, and a 20% change in friability. The $(t - 5)$ term in the denominator increases the function's sensitivity to thickness. Since the tablets produced typically range in thickness from 5.5 to 5.9 mm, subtracting 5 from the thickness means that it only takes a small change in thickness to affect the index. In the same respect, taking the root of the friability increases the function's sensitivity to friability.

Difficulty arose with this function when it was observed that the friability values did not seem to be repeatable. After some investigation, it was noted that the percent weight loss varied by as much as 15% for a single sample. This incorporated too much variability for a useful index.

With two failed attempts at inventing an appropriate index, other sources were sought. Upon discovery of a published relationship, this new model was tested for its potential. Leuenberger's model (1) is now the focus of CFA:

$$T = T_{max} [1 - \exp(-\gamma DP)] \quad (3)$$

where T is the tensile strength in kilograms/square centimeter, T_{max} is the theoretical maximum obtainable tensile strength in kilograms/square centimeter, γ is defined as the compression susceptibility in reciprocal megapascals, D is the relative density, and P is the pressure applied by the tablet press in megapascals.

With the new model in mind, the sampling takes place at loads of 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, and 2.25 (UK) tons. About 0.5 tons is the bare minimum amount of force required to produce a stable tablet that will not crumble when handled. At loads greater than 2.25 tons, the tablets no longer fracture upon hardness testing in the correct manner (i.e., diametrically) as they tend to laminate or cap (2). The tensile strength parameter is only applicable to tablets that fracture along the diameter in a compression hardness test.

Leuenberger Model Evaluation

The tensile strength of the tablet is calculated using the equation:

$$T = \frac{2H}{\pi dt} \quad (4)$$

where H is the tablet hardness in kilograms, t is the tablet thickness in centimeters, and d is the tablet diameter in centimeters (1).

The density of the tablet is also calculated by dividing the average weight of the sample by the average volume:

$$D_{\text{Tablet}} = \frac{W}{\frac{\pi}{4} d^2 t} \quad (5)$$

The relative density is defined as the ratio of the tapped granulation density (as described earlier) to the density of the tablet (1).

The consolidation of the tablet theoretically behaves according to the Leuenberger relationship, which will be used to obtain the consolidation parameters, T_{max} and γ.

The unknown Leuenberger parameters in Eq. (3) are to be used to describe the compression capability of the granulation. This is accomplished by curve fitting the Leuenberger relationship to the measured data using a least squares method (3,4) in the computer program CURVEFIT, which is a program designed in-house to accomplish the least squares calculations.

One final note is that the above equations are modeled for *tablet* production. For application on the "shop floor," a standardized set of tablet tooling is advisable for granulation-to-granulation comparison. However, if caplet tooling is to be used, then Eq. (5) could be altered to calculate the volume of a caplet, and this analysis could still be applied.

RESULTS AND DISCUSSION

Samples of granulations were removed from production for eight different lots and were analyzed in the lab. The results of plotting relative density × compaction pressure versus tensile strength are shown in Fig. 1. All of the granulations are of the same product and seem to have a similar profile, except for one outlier. This eighth granulation was selected because of a deviation from the normal granulating procedure during the production run. Of the seven batches grouped together, minor differences in consolidation are noted, mainly in the regions at the right-hand side of the graph. These differences are assumed to be normal process variation. The eighth sample shows a poorly consolidating granulation, due to a change in the production method for this batch. Although it was possible to compress tablets from

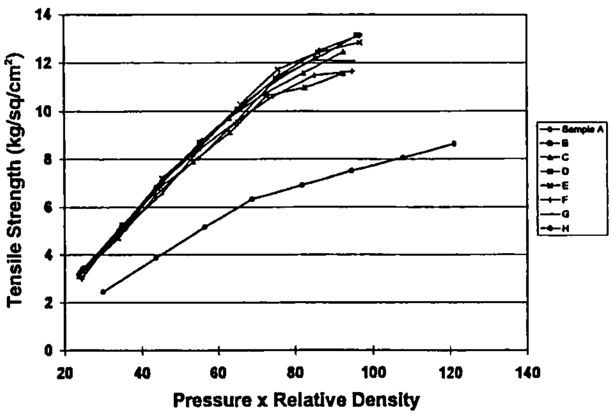

Figure 1. Compaction profiles of several batches of a single product.

this granulation that did meet the required specifications, this is clearly not the optimum way of producing reliable granulations.

All of the data from this chart have been processed through the program CURVEFIT and the results are listed in Table 1. This table also includes the correlation coefficient, *r*, which indicates how representative the curve is of the data, with the calculated T_{max} and γ factors. With $r = 1.0$ being a perfect fit, note that all *r* values are greater than 0.99, indicating that the data follow the theoretical Leuenberger relationship quite accurately.

The important observation from this data is not to analyze *why* there are differences between the granulations, but that the method has the ability to differentiate between good- and poor-quality batches. Again, the focus of this project was to define the method for identifying and ranking consolidation characteristics of granulations. The Leuenberger parameters are a good indicator of how well a sample performed in compression. A large T_{max} is favorable as this indicates a high theoretical maximum hardness. In addition, a low γ value is an indication that the hardness continues to increase as the compaction loads increase and does not level out. Granulation sample H is an example of a less then ideal granulation, as it has a low T_{max} and a larger γ, in comparison to the rest of the samples.

The other application of CFA is in correlation analysis. This involves correlating the data obtained from Leuenberger's model with granulation parameters. An example of this could be in trying to find the optimum final moisture of a granulation. The T_{max} values from several granulation batches could be plotted versus the final moisture of each batch and from this, trends would be easily identifiable. If these data produced an inverted parabolic trend, the vertex of the parabola would indicate the optimum final moisture and the corresponding maximum theoretical T_{max} value. This would indicate that this specification for final moisture would produce the most compressible granulations. This is just an analysis of a single granulation parameter, but multiple parameters could be analyzed and correlated at the same time. Here, the analysis becomes increasingly complex.

Table 1

Leuenberger Parameters for Granulation Samples

Sample	T_{max} (kg/cm^2)	γ (MPa^{-1})	*r*
A	44.99	0.00374	0.994
B	41.58	0.00409	0.994
C	35.84	0.00477	0.995
D	31.21	0.00529	0.994
E	38.53	0.00448	0.993
F	27.65	0.00619	0.992
G	37.02	0.00451	0.992
H	14.98	0.00730	0.992

SUMMARY AND CONCLUSIONS

From what has been said, the Leuenberger relation seems to be the most appropriate function available for the CFA process. It produces two factors, T_{max} and γ, which identify how well a granulation performs in compression. This method of producing tablet samples, collecting data, and curve fitting has become significantly streamlined within the laboratory and is to be used extensively for all projects where the compaction capabilities of a granulation need to be investigated. The largest benefit of compaction force analysis is that it provides fast, accurate results, with very little specialized, high-cost lab equipment necessary to complete the testing.

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