esters. Corresponding results have also been evident when electron-withdrawing groups were placed on the salicylate ring (13). The doubly halogenated salicylate derivatives of methylenecitric acid have activating groups both on the aromatic rings and on the middle carbon of the five-carbon bridge so that hydrolytic instabilities are magnified. Even in the solid state, traces of moisture lead to slow cleavage of these esters. Thus, as has been emphasized previously (11, 12) a careful balance between stability and reactivity is essential for optimal activity of the double-headed aspirins.

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COMMUNICATIONS

Computer-Interfaced Capacitive Sensor for Monitoring the Granulation Process

Keyphrases □ Granulation—computer-interfaced capacitive sensor, high-intensity mixer, moisture measurement, instrumentation, process control

To the Editor:

Wet granulation of powders is a fundamental process in pharmaceutical technology. The phenomenon of granulation, however, is not well understood because of the many variables involved in the process. The need for a better understanding and control of wet granulation has increased in recent years because greater utilization of high-intensity mixers has dramatically reduced the total time required to reach or exceed a proper granulation end point. Several workers have reported results from studies of the granulation process using instrumented mixers (1–8). These studies have shown that measurements of power consumption by the mixer, torque on the mixer shaft, change in rotation-rate of the mixer shaft, or the force with which granules deflect a strain-gauged beam, provided insight into the changes that occur as a powder is massed.

We wish to report a new approach to study the dynamics of wet granulation, which uses a computer-interfaced capacitive sensor that has been designed in our laboratories. The sensor is constructed from a polytetrafluoroethylene cylinder 1.5 cm in diameter, to which two insulated stainless steel electrodes are attached. The sensor is threaded to fit the existing thermocouple port in the wall of a high-intensity mixer[1]. The sensor extends into the mixer a distance of 5 cm and is 12 cm below the mixer center, with the distal 3 cm of each electrode exposed.

The two electrical leads from the sensor are connected to a moisture analyzer[2] which acts as the interface to the computer. The electronics of the moisture analyzer have been modified to filter signal noise caused by the rotation of the mixer plowshares and to allow for initial baseline adjustments. The moisture analyzer with sensor operates on the principle of power loss from a tuned radio-frequency (R/F) circuit as the dielectric of the medium surrounding the sensor changes. The analog DC voltage output of the moisture analyzer is converted to a digital value by an A/D converter and is fed to a 16-bit microprocessor[3] which is used for data processing and system control. System software is stored in a nonvolatile form in an onboard, programmable, read-only memory and allows for operator control of data sampling rate and text information for hard-copy output. Each data point, taken at 4-s intervals, is the average of 5000 A/D conversions.

Granulations were prepared by charging the mixer with 20 kg of lactose powder and using only the plowshare mixing action. Figure 1 shows the resulting voltage *versus* mixing time profile as incremental additions of water were made to the lactose[4]. The decreases in voltage are the result of rapid moisture distribution throughout the powder after each addition. The plateau reached between each addition is an equilibrium voltage value that is a function of the amount of water in the moist powder. The granules formed with this simple lactose water system, however, were not of good quality.

Figure 2 shows the voltage response when 2.5 kg of a 4% w/w methylcellulose 15 cps[5] aqueous solution was added to 20 kg of lactose at time zero. A similar voltage response

[1] Model FM-50, Littleford-Lödige, Florence, Ky.

[2] Moisture Register Model G8R, Moisture Register Co., Berwind Instruments Group, North Hollywood, Calif.

[3] iSBC 88/25, Intel Inc., Santa Clara, Calif.

[4] Lactose Hydrous USP, No. 80M, Sheffield Products, Memphis, Tenn.

[5] Methocel A 15 Premium, The Dow Chemical Co., Midland, Mich.

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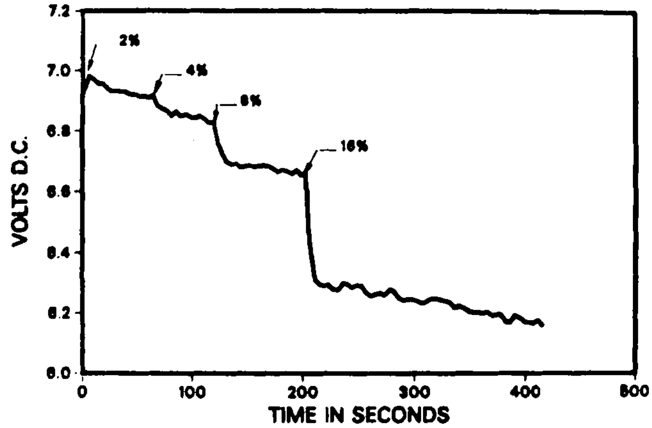

Figure 1—*Voltage response curve when water is added in incremental portions to 20 kg of lactose. Amount of water is shown as cumulative percent based on the weight of lactose.*

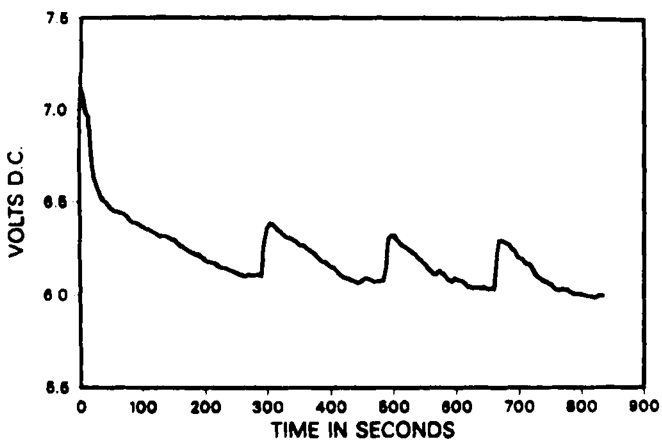

Figure 2—*Voltage response curve when 2.5 kg of an aqueous methylcellulose (4% w/w) granulating solution is added at time zero to 20 kg of lactose.*

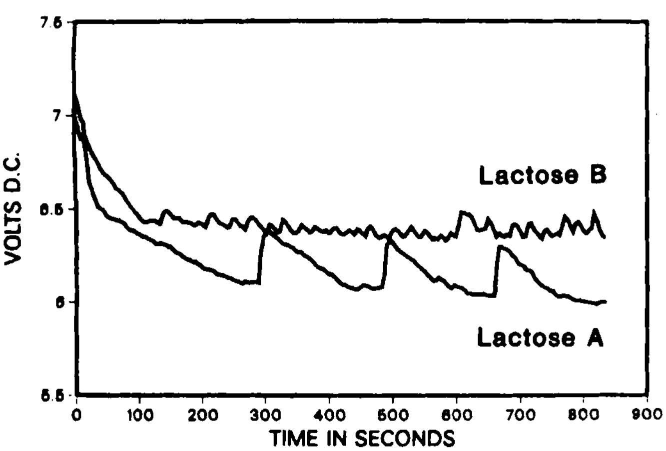

Figure 3—*Voltage response curves for smaller particle lactose A and larger particle lactose B when 20 kg of each is granulated with 2.5 kg of an aqueous methylcellulose (4% w/w) solution added at time zero.*

is seen; however, after the initial distribution phase, periodic voltage increases are observed. The difference in voltage response when a granulating agent is used in place of water indicates that the system, as designed, is sensing granule formation as well as moisture distribution. These voltage fluctuations have also been observed with other granulating agents when granules are formed. The height and periodicity of these voltage spikes seem to be associated with granule quality. The favored explanation for these observations is that the apparent density of the moist powder bed fluctuates in a periodic manner as agglomeration and deagglomeration occur during the mixing process. The changes in bed porosity around the sensor are reflected in a greater or lesser power-loss from the tuned R/F circuit.

Table I—Sieve Analysis Comparison of Lactose from Two Sources

	Lactose A[a]	Lactose B[b]
Weight % > 200 mesh	16.2	41.8
Weight % on 325 mesh	33.9	35.5
Weight % < 325 mesh	49.9	22.7

[a] Lactose hydrous USP, No. 80M, Sheffield Products, Memphis, Tenn. [b] Lactose hydrous USP, 310/Regular Grind, Foremost-McKesson, Inc., San Francisco, Calif.

Figure 3 illustrates the difference in sensor response when two lots of lactose having different particle sizes are granulated using the identical procedure described above for Fig. 2. The lower curve is the granulation response seen with fine particle lactose, while the upper curve is that observed with a more coarse lactose. A comparison of results from sieve analyses[6] conducted on the two lots of lactose is given in Table I. It is hypothesized that the finer lactose, because of its smaller particle diameter, forms more stable agglomerates that tend to deagglomerate less readily; therefore, the voltage spikes are fewer and more widely spaced. Conversely, the coarser lactose does not agglomerate as well and tends to deagglomerate rather quickly as indicated by the smaller and more closely spaced voltage spikes. Moreover, the granulation produced from the finer lactose was of better quality than that produced from the coarser lactose.

The dynamic granulation monitor using a computer-interfaced capacitive sensor shows promise both as a research tool to gain better understanding of the granulation phenomenon and as a control system to obtain better reproduction of granulations made in high-intensity mixers. In future communications, we will discuss the system and its applications in greater detail.

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