Noninvasive Dissolution Measurement Using Perturbed Angular Correlation

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Abstract □ A novel noninvasive technique was developed to measure dissolution of the water-soluble component of a solid dosage form using indium 111 and perturbed angular correlation. The method involves time-delayed coincidence counting of two cascading γ-rays that exhibit angular correlation. This angular correlation can be perturbed if the intermediate excited state of the nucleus is reoriented due to an interaction with its environment. When such an interaction occurs, as in a phase change (solid to liquid), the perturbation changes can be shown by anisotropy. A highly perturbed condition in the solid state results in low values (0.02–0.04), while increasing values of anisotropy indicate dissolution. Anisotropy values reach 0.14–0.15 when the total unperturbed physical state (liquid) exists. The worth of this technique was demonstrated by both *in vitro* and *in vivo* determinations of dissolution rates.

Keyphrases □ Perturbed angular correlation—noninvasive dissolution measurement *in vivo* and *in vitro* □ Dissolution—noninvasive measurement *in vivo* and *in vitro* using perturbed angular correlation, solid dosage forms □ Noninvasive dissolution measurement—of solid dosage forms using perturbed angular correlation, *in vivo* and *in vitro*

Radionuclides with simple decay schemes have been widely utilized as labels for following drug absorption, metabolism, and excretion. External scintigraphy was used to follow labeled solid dosage forms while their behavior in the human stomach was monitored (1). Some radionuclides, following radioactive decay, emit two or more γ-rays in cascade; those γ-rays emitted following an initial one are released immediately or are delayed for some very predictable time unique to that nucleus.

BACKGROUND

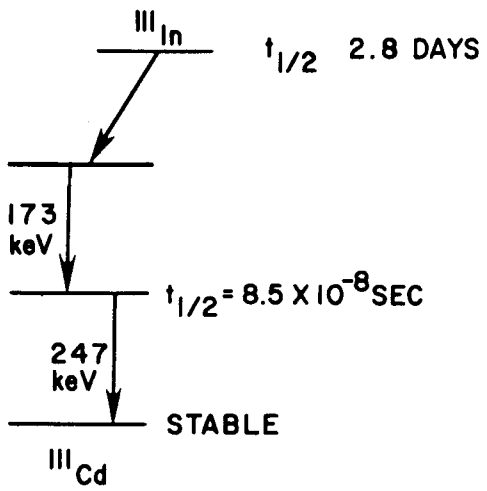
Indium 111 is a radionuclide with a delay during its γ-cascade (Scheme I). Occasionally, for some radionuclides the γ-rays may exhibit an angular correlation since the directional emission of a γ-ray depends on the orientation of the magnetic moment of the nucleus involved. For indium 111, this angular correlation can be perturbed if the intermediate excited state of the nucleus is reoriented due to an interaction with its environment. The major perturbing influence on the emission angular correlation is the interaction of external gradients of the quadrupole moment of the nucleus (2). The theory of perturbed angular correlation was thoroughly reviewed by Steffen and Frauenfelder (3, 4).

Some recent investigations used indium 111 and perturbed angular correlation measurements to monitor the structural and rotational behavior of biological macromolecules (5–7). It also was reported that inhibition of nuclear rotational properties of indium 111 by chemical binding, temperature reduction, and increased viscosity can be observed (8, 9).

The purposes of this work were to measure the conversion of one distinct state of nuclei to another, illustrating a phase change from solid indium chloride to liquid indium chloride, and to illustrate a noninvasive technique for measuring a phase change from solid to liquid in a solid dosage form using indium chloride (indium 111) and perturbed angular correlation.

EXPERIMENTAL

Dosage Form Preparation—Three different formulations of solid dosage forms were prepared with commercially available excipients: Formulation 1, lactose (89%), microcrystalline cellulose (10%), and magnesium stearate (1%), (by weight); Formulation 2, dibasic calcium phosphate (89%), microcrystalline cellulose (10%), and magnesium stearate (1%); and Formulation 3, only sucrose. Each formulation was prepared in bulk for convenient storage. Several grams of each mixture was placed in separate round-bottom flasks, and 95% ethanol was added to allow a satisfactory suspension.



Scheme I—Indium 111 decay scheme illustrating the γ-ray cascade with the delayed intermediate nuclear state following the first gamma emission.

Indium 111 in the chloride[1] form was pipetted into each flask to an activity concentration of 20 μCi/200 mg of formulation powder. Indium 111 has a half-life of 2.8 days, and it decays by electron capture and γ-emission with energies of 173 and 247 kev (Scheme I). The ethanol was evaporated in a flask evaporator until dryness was achieved. The powder was removed by scraping, pulverized using a mortar and pestle, and then compressed into 200-mg tablets.

A representative number of tablets were counted for indium 111 activity using a γ-ray scintillation detector for homogeneity testing. Several tablets of each formulation were used for a disintegration time determination[2], and some were used to test for hardness[3].

Instrumentation—Three sodium iodide γ-ray detectors were positioned in a flat plane on three sides of a beaker in which the dosage form was tested (Fig. 1). The 12.7 × 7.62-cm detectors were positioned 20 cm from the geometric center of the beaker containing the tablet. For electronic clarity, the detectors were labeled 1, 2, and 3 such that Detector 2 was positioned 90° to Detector 1 and Detector 3 was positioned 180° to Detector 1 (Fig. 1).

The γ-ray spectrometry equipment[4] consisted of a single high voltage power supply for the three detectors, three preamplifiers, three linear amplifiers, and three pulse height analyzers designated 1, 2, and 3 (Fig. 1). There were two time-to-pulse height converters (TPC) for coincidence counting (designated A and B), two additional pulse height analyzers for selecting differential or integrated coincidence delay times, and two count scalers for recording the coincidence counts from Converters A and B (Fig. 1).

Pulse height Analyzer 1 was energy calibrated for counting the 173-kev

[1] Medi-physics, Emeryville, Calif.
[2] USP basket disintegration test.
[3] Erweka, 20 Broadway, New York, N.Y.
[4] ORTEC, Oak Ridge, Tenn.

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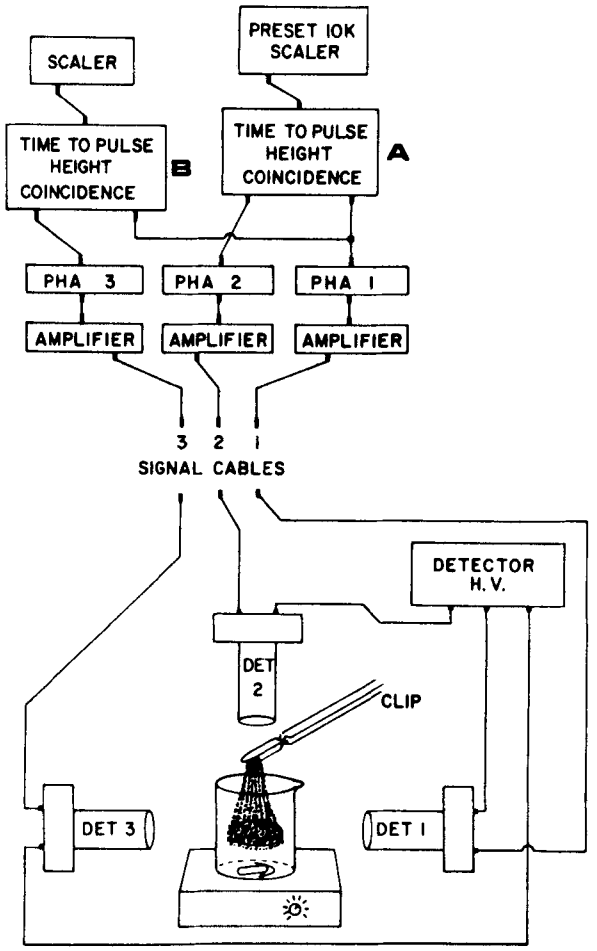

Figure 1—*Apparatus assembly illustrating the positioning of the radiation detectors in a flat plane around the tablet for an* in vitro *dissolution experiment using perturbed angular correlation. The schematic of electronic equipment required for coincidence counting between Detectors 1 and 2 (90°) and 1 and 3 (180°) is illustrated. A cotton gauze sheet containing the solid dosage form was suspended 6 cm from the bottom and in the center of a glass beaker containing the dissolution medium (see* Experimental*). Three pulse height analyzers (PHA) were utilized.*

γ-ray while Analyzers 2 and 3 were calibrated for the 247-kev emission. Converters A and B were calibrated to accept coincidence delay times between 70 and 100 nsec.

Procedure—The apparatus used for the experimental determination of dissolution consisted of a 10 × 10-cm single-layer cotton gauze sheet with a mesh size sufficiently small to prevent the tablet and larger particles from falling through. The gauze containing the solid dosage form was suspended 6 cm from the bottom and in the center of a 1000-ml glass beaker containing 700 ml of hydrochloric acid–water (Fig. 1). A hemostat clamped to the gauze and a ring stand held the dosage form in place. The aqueous dissolution medium was stirred with a magnetic stirring bar at ~100 rpm and remained at 25–26°.

Immediately after the tablet was immersed and positioned, serial coincident counting on the scalers was begun, which continued until the completion of the experiment. Throughout the experiment, 0.5-ml samples were removed using a 1-ml tuberculine syringe fitted with a 0.22-μm filter to prevent particles from being collected. These samples, removed at appropriate time intervals, were transferred to sample vials and counted in a well γ-counter.

RESULTS AND DISCUSSION

Assessment of dosage form homogeneity was performed when tablets within a batch of each preparation were counted. Results indicate the tablets were prepared with a homogeneous distribution of indium 111 since they varied by only 2%.

The two γ-rays emitted during the indium 111 to cadmium 111 decay are illustrated in Scheme I. The 247 kev γ-ray is delayed by 85 nsec. The probability that it will be emitted at some time t and at some angle θ to the direction of the 173-kev γ-ray is given by:

$$\omega(\theta, t) = \frac{1}{\tau} e - \frac{t}{\tau}\left[1 + A_2\left(\frac{3\cos^2\theta - 1}{2}\right)\right] \qquad \text{(Eq. 1)}$$

where τ is the mean life of the intermediate nuclear state (1.21×10^{-7} sec), t is the interval of time between the two γ-rays, and A_2 is a coefficient −0.18. This numerical value of A_2 may vary with the solid angle subtended by the γ-ray detectors used. If τ is long enough and the magnitude of the electric field gradients at the nucleus from the environment are great enough, then the angular correlation of the two cascading γ-rays can be perturbed. When a perturbation factor $G_2(t)$ is inserted into the second term of Eq. 1, its approximate behavior can be shown by anisotropy to be:

$$A \simeq -\frac{3}{2} A_2 G_2(t) \qquad \text{(Eq. 2a)}$$

and:

$$A = 1 - \frac{\omega\,(180°, t)}{\omega\,(90°, t)} \qquad \text{(Eq. 2b)}$$

where $\omega(180°, t)$ and $\omega(90°, t)$ are coincident count rates in each of the two selected angles, 180 and 90°.

The coincidence counts from either the 180 or 90° detector are those counts of the 247-kev γ-ray that are detected within 70–100 nsec following the Detector 1 observation of the 173-kev γ-ray. The 173-kev γ-ray initiates a constant-rise time pulse in each A and B time-to-pulse height converter. When the 180 and 90° detectors count a 247-kev γ-ray, the rising pulse is stopped in Converter A or B, and its magnitude is analyzed with a differential window corresponding to 70–100-nsec delays. These coincidence counts were recorded on each of two scalers.

Since the perturbation factor $G_2(t)$ behavior can be shown by anisotropy (A), the coincidence counts $\omega\,(180°, t)$ from the 180° detector and those counts $[\omega\,(90°, t)]$ from the 90° detector were substituted into the relation $A = 1 - \omega\,(180°, t)/\omega\,(90°, t)$ for computation. For anisotropy (A) calibration, a maximum perturbed dry solid dosage form was counted. Then a sample of liquid [^{111}In]chloride was counted. The calculation of anisotropy (A) resulted in values of 0.02–0.04 for the perturbed state (dry) and of 0.14–0.15 for the unperturbed state (liquid), a mean increase of 4.8-fold.

To illustrate the changing of anisotropy values during a dissolution experiment, a sucrose tablet was prepared with [^{111}In]chloride as previously described. After it was placed in the apparatus, coincidence data were collected and calculated. The results from a typical experiment are shown in Fig. 2. The experiment ran for 26 min, with nine data points collected for the calculation of anisotropy. Initially, the anisotropy value was 0.02, representing the dry perturbed state; then, after ~24 min, the values of 0.14 for anisotropy were calculated, illustrating the unperturbed liquid state. Those intermediate anisotropy values represent varying numbers of indium 111 atoms in transition from the dry to the liquid state. By simply observing the graph in Fig. 2, the percent dissolution of the radionuclide from the solid form for any desired time can be found. After ~13 min, 50% of the indium 111 was in solution, which was verified by liquid sample removal and counting the indium 111 in a well scintil-

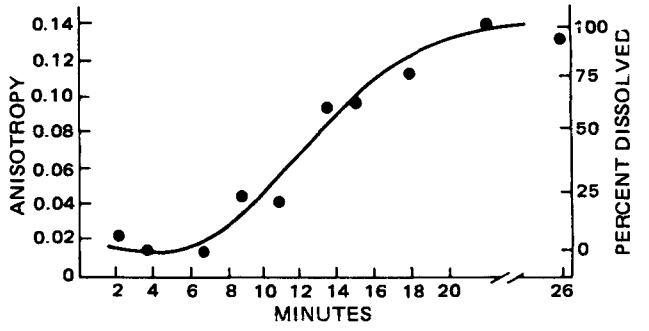

Figure 2—*Anisotropy* versus *time for a [^{111}In]chloride-labeled sucrose tablet measured* in vitro *using perturbed angular correlation, illustrating the progressive change of anisotropy corresponding to that quantity of the [^{111}In]chloride dissolved.*

Table I—Summary of Perturbed Angular Correlation Dissolution Times [a] and Concomitant Sampling Verification *In Vitro* along with Physical Parameters of Each Dosage Form Tested

Tablet	Perturbed Angular Correlation Method Time[a], min[b]	Sampling Method Time[a], min[b]	Revolutions per Minute	Hardness	USP Disintegration Time, min[b]
Sucrose[c]	10.8 ± 3.3	11.3 ± 3.4	100	NA	NA
Lactose[d]	5.8 ± 2.4	6.6 ± 2.6	100	9	6
Dical[e] (Run 1)	76 ± 9.0	80 ± 8.9	100	11	13
Dical[e] (Run 2)	60 ± 7.0	58 ± 7.6	400	11	13

[a] Time to achieve 50% dissolution. [b] Average of three determinations. [c] Sucrose (100%) and [^{111}In]chloride. [d] Lactose (89%), microcrystalline cellulose (10%), magnesium stearate (1%), and [^{111}In]chloride. [e] Dicalcium phosphate (89%), microcrystalline cellulose (10%), magnesium stearate (1%), and [^{111}In]chloride.

lation counter. All other experiments had samples removed for corroborative measurements.

Results for this and similar experiments indicate a time delay prior to the onset of tablet dissolution. The delay in the sucrose formulation was ~6 min (Fig. 2). Presumably, this observed delay was due to continued nuclear perturbation in the viscous stagnate layer from the highly structured aqueous conditions existing therein. As the [^{111}In]chloride escaped into the unstructured water of the media, the exhibition of free nuclear motion was evident in the notable change of the anisotropy values.

Two additional formulations were prepared, one (called "dical tablet") containing dibasic calcium phosphate (89%), microcrystalline cellulose (10%), and magnesium stearate (1%), and the other (called "lactose tablet") containing lactose (89%), microcrystalline cellulose (10%), and magnesium stearate (1%). Each formulation contained [^{111}In]chloride. Hardness and USP disintegration tests were conducted on these formulations. Perturbed angular correlation and sampling measurements were performed from the beginning of the dissolution experiment through completion (Table I). Table I shows that in all experiments there was good agreement between perturbed angular correlation measurements and the indium 111 sampling method for the determination of percent dissolution *in vitro* as a function of time.

Included in Table I are the results of perturbed angular correlation and sampling measurements for the dical tablet at two different stirring rates. Run 1 was stirred at 100 rpm, and Run 2 was stirred vigorously at ~400 rpm. When the stirring rate increased, the dissolution rate increased, indicated by both perturbed angular correlation and sampling measurements (Table I). The reduction in time was from 76 to 60 min using the perturbed angular correlation technique and from 80 to 58 min using the sampling method.

After the *in vitro* dissolution measurements using perturbed angular correlation were shown to be successful, an *in vivo* measurement on the lactose formulation was attempted on one subject to illustrate its *in vivo* applicability. Three detectors were positioned to view the anterior, posterior, and left lateral sides of the volunteer. It was estimated that they were equidistant from the stomach where the tablet would be located.

The calculated anisotropy values were not expected to be the same as those in the *in vitro* experiments, but their changing values would nevertheless reflect the physical state of the solid dosage form. The *in vivo* dissolution data are illustrated in Fig. 3. The anisotropy behavior is quite similar to that in the *in vitro* experiments, differing only in actual anisotropy values, including the delays of onset of dissolution.

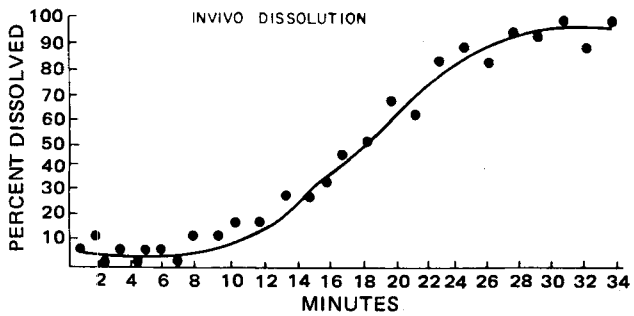

Figure 3—*Dissolution* versus *time for a lactose tablet measured in a human subject indium 111 and perturbed angular correlation. Graph shows an 8-min delay for onset of dissolution of the radionuclide, which was complete by 28 min.*

Figure 3 shows that 50% dissolution of [^{111}In]chloride from a lactose tablet was achieved in the stomach of the human subject in ~17 min, while the *in vitro* data on the identical dosage form (Table I) showed a dissolution in 5.8 min (perturbed angular correlation) and 6.6 min (sampling method). With a hardness value of 9, the USP disintegration test demonstrated a 6-min disintegration time for the lactose formulation. When the same volunteer with an identical lactose tablet was studied by a previously developed external scintigraphy technique (1), the tablet exhibited a disintegration time of 21 min. These results indicate that there is no good correlation between *in vitro* and *in vivo* measurements for the lactose formulation since they differ so widely in the times of disintegration and dissolution.

The dibasic calcium phosphate formulation was also tested with the same human volunteer. Table I shows that the dical formulation with a hardness of 11 disintegrated[2] in 13 min and that the times for 50% dissolution measured using perturbed angular correlation and sampling were 76 and 80 min, respectively. When the *in vivo* measurement using perturbed angular correlation was performed on this dibasic calcium phosphate formulation, there was evidence that ~40% dissolution had occurred over 30 min. No further dissolution was observed as illustrated by unchanging anisotropy values.

An identical dosage form was then examined *in vivo* by external scintigraphy (1) to gain insight into the dissolution of this dosage form by monitoring its disintegration behavior. The *in vivo* disintegration results showed the dosage form remained motionless in the lower stomach near the duodenal bulb for ~11 min and then began to disintegrate partially until 25 min. During this time, the loss of radioactivity from the original tablet was ~31%. The remaining core of the tablet was then expelled through the pyloric valve and proceeded to move through the small bowel, changing locations repeatedly. This main core of the tablet remained intact throughout the additional period of observation of 52 min.

The data obtained with the perturbed angular correlation method show that this technique, when coupled with external scintigraphy (1), may permit the *in vitro* and *in vivo* study of the disintegration behavior of a solid dosage form. This technique follows the dissolution pattern of the radionuclide and does not provide information on the dissolution of any particular component of the solid dosage form. The technique might prove useful in comparative studies in which various solid dosage formulations could be compared for their disintegration properties.

One further experiment was performed to assess the effects of the physical geometry of the source when acquiring perturbed angular correlation data. A drop of liquid [^{111}In]chloride was placed as a source in the bottom of a 150-ml glass beaker, yielding an anisotropy value of 0.13. When the bottom of the beaker was covered with a dilute solution of hydrochloric acid, the resulting anisotropy was 0.15. When the beaker was filled 25%, the anisotropy value was 0.17; when it was 50% filled, the anisotropy value was 0.15; and when it was 75% filled, the anisotropy value was 0.15. These results indicate no significant problem in detecting an unperturbed liquid state of indium 111 with varying geometric configurations.

CONCLUSION

In the present study, a chemical phase change was observed in solid dosage forms using indium 111 and a perturbed angular correlation measurement. When this novel technique is performed in conjunction with a previously described external scintigraphy method (1), the study of the *in vivo* dissolution and disintegration behavior of a solid dosage form can be accomplished in a qualitative and quantitative manner. The technique monitors the extent of dissolution of the dosage form as a function of solubilization of the radionuclide from the solid dosage form.

The method does not measure dissolution of a pharmacologically active ingredient or any other ingredient in the solid dosage form.

With minor detector modifications, this method should contribute significantly in the evaluation of viscosity gradients and sedimentation rates in heterogeneous dosage forms.

REFERENCES

(1) D. L. Casey, R. M. Beihn, G. A. Digenis, and M. B. Shambhu, *J. Pharm. Sci.*, **65**, 1412 (1976).

(2) "Table of Isotopes," C. M. Lederer, J. M. Hollander, and J. Perlman, Eds., Wiley, New York, N.Y., 1968, p. 252.

(3) R. M. Steffen and H. Frauenfelder, in "Perturbed Angular K. Correlations," E. Karlsson, E. Matthias, and R. Siegbahn, Eds., North-Holland, Amsterdam, The Netherlands, 1964.

(4) H. Frauenfelder and R. M. Steffen, in "Alpha, Beta, and Gamma-Ray Spectroscopy," K. Siegbahn, Ed., North-Holland, Amsterdam, The Netherlands, 1965.

(5) T. K. Leipeat, J. D. Baldeschwieler, and D. A. Shirley, *Nature*, **220**, 907 (1968).

(6) A. G. Marshall, L. G. Werbelow, and C. F. Meares, *J. Chem. Phys.*, **57**, 364 (1972).

(7) D. A. Goodwin, C. F. Mears, and C. H. Song, *Radiology*, **105**, 699 (1972).

(8) C. F. Mears, R. G. Bryant, J. D. Baldeschwieler, and D. A. Shirley, *Proc. Natl. Acad. Sci. USA*, **64**, 155 (1969).

(9) P. B. Hemmig and R. M. Steffen, *Phys. Rev.*, **92**, 832 (1953).

Interaction of Tablet Disintegrants and Magnesium Stearate during Mixing I: Effect on Tablet Disintegration

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Abstract □ The effect of magnesium stearate on the disintegration of tablets was studied. Three different preblends, containing a slightly or a strongly swelling disintegrant, were mixed before compression with magnesium stearate for different time periods. The results show that a strongly swelling disintegrant, such as sodium starch glycolate in contrast to potato starch, can reduce the deteriorating effect of hydrophobic lubricants on tablet disintegration. However, the interaction between magnesium stearate and potato starch or sodium starch glycolate and the resulting differences in disintegration characteristics can be masked by the use of disks in the USP disintegration apparatus.

Keyphrases □ Tablets—disintegration, effect of magnesium stearate during mixing □ Magnesium stearate—effect on tablet disintegration during mixing □ Disintegration—tablets, effect of magnesium stearate during mixing

Previous work (1, 2) showed that magnesium stearate can have a strong negative effect on binding properties of tablet excipients. The phenomenon of decreasing crushing strength with increasing mixing time is caused by the formation of a lubricant film interfering with particle binding. The lubricant film is a result of adhesion to the substrate of magnesium stearate molecules, which are sheared off mechanically from the magnesium crystals during mixing (1–4). The formation of such a hydrophobic film can dramatically decrease the wettability of a powder mix, as was shown for sodium chloride–magnesium stearate blends (4). Thus, the deteriorating effect of hydrophobic lubricants on tablet disintegration is not only dependent on the nature and concentration of the lubricant used (5–11) but also on the mixing intensity of the tablet ingredients with the lubricants (12, 13).

The present study concerned the effect of magnesium stearate on tablet disintegration. Three different preblends, containing a slightly or a strongly swelling disintegrant, were mixed before compression with magnesium stearate for different time periods. Particular attention was focused on the effect of disks in the USP disintegration apparatus.

EXPERIMENTAL

Materials—The disintegrants used were dried potato starch[1] (moisture content ~8%) and sodium starch glycolate[2] NF XV. The other excipients were unmilled dibasic calcium phosphate dihydrate[3], extra-fine crystalline lactose[4], aspirin[5] (crystalline acetylsalicylic acid), and magnesium stearate[6].

Methods—*Mixing*—Preblends of filler and disintegrants were prepared by mixing[7] the excipients for 15 min, using glass vessels with a loading of ~20%. If not stated otherwise, the rotation speed was 90 rpm. After addition of 0.5% magnesium stearate, mixing was continued for a specified period.

Tablet Compression—Tablets were prepared by introducing manually 520.8 mg of the blend containing sodium starch glycolate or 625 mg of the blend containing potato starch into a prelubricated 13-mm die of a compression device mounted between the plattens of an instrumented hydraulic press[8]. The samples were compressed at a compression force of 20 kN with a loading rate of 2 kN/sec.

Crushing Strength—The crushing strength of the tablets was determined immediately after compression using a motorized instrument[9]. The data given are the means of at least five tablets.

Disintegration time—The disintegration time of the tablets was determined using the USP XIX apparatus. If not stated otherwise, the test was performed without disks. The data given are the means of the dis-

[1] Avebe G. A., Veendam, The Netherlands.
[2] Primojel, Avebe G. A., Veendam, The Netherlands.
[3] Emcompress, Edward Mendell Co., New York, N.Y.
[4] Lactose EFC, N. V. Hollandse Melksuikerfabriek, Uitgeest, The Netherlands.
[5] Feinkristallin (40-mesh USP), Bayer, Leverkusen, West Germany.
[6] Ph. Ned. grade, Lamers en Indemans's-Hertogenbosch, The Netherlands.
[7] Turbula mixer model 2P, W.A. Bachofen, Basel, Switzerland.
[8] Hydro Mooi, Appingedam, The Netherlands.
[9] Heberlein model WTP-3, Dr. K. Schleuniger, Zürich, Switzerland.

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