Effect of Intensity of Agitation on Disintegration Time of Tablets

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Abstract □ The effect of the intensity of agitation on the disintegration time of tablets was studied. Preliminary results obtained using tablets fabricated under controlled conditions and selected commercial tablets revealed that the intensity of agitation produced in the test apparatus was not reproducible with fixed geometry for successive runs when the settings were maintained constant. The disintegration times increased at a lower intensity of agitation. The intertablet range values obtained were rather large at the start and increased with a corresponding decrease in the intensity of agitation. The results showed that the measurement of disintegration times with the existing apparatus may not serve as a guide to the pharmaceutical formulator in the preparation of optimal dosage forms of drugs for clinical trial and may not ensure lot-to-lot uniformity of the pharmaceutical product.

Keyphrases □ Tablets—disintegration time, effect of intensity of agitation, specially fabricated and commercial formulations □ Disintegration time—tablets, specially fabricated and commercial, effect of intensity of agitation □ Agitation intensity—effect on disintegration time of specially fabricated and commercial tablets □ Dosage forms—tablets, specially fabricated and commercial, effect of intensity of agitation on disintegration time

The disintegration test is an essential attribute of tablets intended for oral administration, except those intended to exhibit extended release of their active ingredient(s). The rate at which a drug dissolves from its fragmented dosage form in the human GI tract often partially or completely controls the rate at which the drug appears in the blood (1). Therefore, measurement of disintegration time not only serves as a guide to the pharmaceutical formulator in the preparation of optimal dosage forms of drugs for clinical trial but also ensures that a given pharmaceutical product is essentially uniform from lot to lot.

The tablet disintegration apparatus has been official since USP IX and consists of a basket-rack assembly attached to a device for raising and lowering the basket in the immersion fluid through a distance of 5.5 ± 0.5 cm and at a constant frequency rate of 30 ± 2 complete cycles/min (cpm) (2, 3).

Some drawbacks of the disintegration test apparatus include:

1. The intensity of agitation produced in the apparatus is relatively much higher than that produced in the stomach. Therefore, the *in vivo* disintegration times may be much greater than the *in vitro* results (4).
2. The primary agitation intensity produced in the apparatus results from the turbulence of fluid flowing through the basket chamber, making the apparatus incapable of reproducing a given intensity of agitation with fixed geometry for successive runs when the settings are maintained constant.
3. The apparatus has only one speed, and the high degree of agitation introduced in the test may make it difficult to discriminate between a physiologically available product and a physiologically unavailable product[1] (5, 6).
4. The apparatus fails to simulate *in vivo* conditions (7).

While it may be difficult, if not impossible, to simulate *in vivo* conditions, the other drawbacks are primarily related to the single-speed agitation of the apparatus. This investigation reports the effect of agitation intensity on the disintegration time of tablets.

Table I—Tablet Formulations

Ingredient, % (w/w)	Formulation I	II	III	IV
Sodium salicylate	20	20	—	—
Magnesium trisilicate	—	—	20	20
Corn starch	5	5	5	5
Magnesium stearate	0.75	0.75	0.75	0.75
Lactose	74.25	—	74.25	—
Dibasic calcium phosphate	—	74.25	—	74.25

EXPERIMENTAL

Fabrication of Tablets—The tablets used in the preliminary investigation were made by direct compression using a water-insoluble and a water-soluble active ingredient, each incorporated into a water-soluble and water-insoluble matrix. Table I shows the composition of the formulations studied.

The active ingredient and the diluent were mixed in a planetary type mixer[2] for 5 min. Then the mixture was passed through a No. 30 bolting cloth and remixed for 5 min in the same mixer. The disintegrant (corn starch) was then passed through a No. 60 bolting cloth, added to the mixture, and blended for 5 min with a twin-shell V blender[3].

The lubricant (magnesium stearate) was passed through a No. 60 bolting cloth and sprinkled directly on the mixture, which had been spread as a thin layer on a waxed paper. The mixture then was blended for 3 min using the twin-shell V blender. The blends were then compressed into tablets on a single-punch press[4] equipped with a round, flat-faced punch and operated at a speed to produce 60 tablets/min. The characteristics of the tablets obtained were: weight, 500 ± 10 mg; hardness, 8.0 ± 0.5 kg; friability, <2.5%; and thickness, sufficient to give desired hardness.

Determination of Disintegration Time—The disintegration times were determined with the official test apparatus[5] (2, 3); water, maintained at 37 ± 1°, was the immersion fluid.

Effect of Intensity of Agitation—The effect of the intensity of agitation on the disintegration time of the tablets was determined by replacing the constant-speed motor used in the official test apparatus with similar constant-speed motors[6] having frequencies of 4 and 12 cpm. Thus, the basket-rack assembly could be raised and lowered in the immersion fluid at a constant frequency of 4, 12, or 30 cpm.

RESULTS AND DISCUSSION

Fabrication of Tablets—To eliminate the influence of unknown excipients, the investigation was restricted initially to the tablets fabri-

[1] P. L. Madan, unpublished results.
[2] Model 80 N, Hobart Manufacturing Co., Troy, Ohio.
[3] Patterson Kelley Co., East Stroudsburg, Pa.
[4] Model A-3, Stokes Division, Pennwalt Corp., Philadelphia, Pa.
[5] Van-Kel Industries, Chatham, N.J.
[6] Merkle-Korff Gear Co., Chicago, Ill.

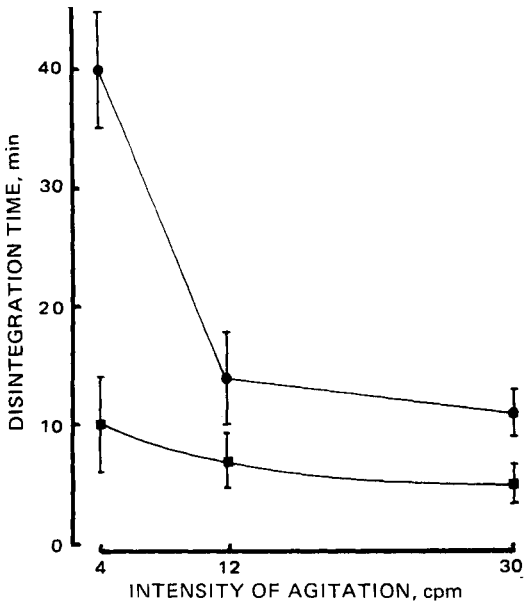

Figure 1—*Disintegration time of sodium salicylate tablets as a function of the intensity of agitation. Key: ●, Formulation II; and ■, Formulation I.*

cated under controlled conditions. The tablets were fabricated using a single-punch machine under conditions that would ensure minimum intertablet variability in the disintegration times due to manufacturing variables (*e.g.*, type and concentration of excipients and compression force employed).

Formulations—Two formulations, both known to compress directly into tablets, were selected. The basic difference between the two formulations was in terms of their water-solubility characteristics. One formulation was made primarily of lactose and was, therefore, considered essentially water soluble. The other formulation was made primarily of dibasic calcium phosphate and thus considered essentially water insoluble.

Since the active ingredient may influence disintegration, especially when present in a significant proportion, two types of active ingredients were selected for incorporation into each of the two formulations: water-soluble sodium salicylate and water-insoluble magnesium trisilicate.

Determination of Disintegration Time—The disintegration times were determined at three speeds: 4, 12, and 30 cpm. Figure 1 shows the disintegration times and the range values obtained with the water-soluble sodium salicylate in each of the two matrixes at the three agitation intensities. As expected, the disintegration times obtained at the lower speeds were higher than those obtained at 30 cpm. However, in spite of fabricating the tablets under controlled conditions, the intertablet range values obtained at 30 cpm were rather large. This result suggests the lack of reproducibility of the intensity of agitation produced in the apparatus at the speed specified in the official compendia (2, 3).

Even at less than half the speed specified in the official compendia, the agitation intensity was not reproducible (Fig. 1). The disintegration times as well as the range values obtained at 12 cpm were higher than those obtained at 30 cpm. A further reduction in the intensity of agitation apparently worsened the situation since there was a significant increase in the disintegration times as well as in the intertablet range values at 4 cpm.

The disintegration times as well as the intertablet range values were lower for tablets made with the water-soluble matrix. One possible explanation for this difference may be the hydrophilic character of the lactose used in the water-soluble matrix. Apparently, the immersion fluid penetrated the water-soluble matrix somewhat rapidly and, in doing so, it dissolved in part the matrix as well as the water-soluble drug contained within the tablet. Due to the dissolution of portions of the tablet, its entire structure would weaken and it would tend to fall apart even in the absence of agitation.

To test this hypothesis, an experiment was conducted using an aqueous solution of a water-soluble dye as the tracer. The tablets were soaked in the dye solution, and the migration of the dye in the tablets was examined. Tablets soaked in the dye solution for short time periods were completely covered with the dye externally but exhibited a spotty appearance when examined sectionally. The spots were located only near the periphery of the tablet and appeared dense at some points.

An increase in the soaking time increased not only the number and the density but also the distance of the spots from the surface of the tablets. Further increases in the soaking time resulted in the erosion of portions of the tablets, both externally and internally. However, the tablets were not completely spotted on the inside. An attempt was made to soak the tablets for longer periods to achieve spottiness throughout the inside, but such efforts were not very successful. The tablets became soft and soggy, and any attempt to obtain a section of the tablets only resulted in their being crushed.

The experiments were repeated using harder tablets, and the sequence of results obtained was identical to that found with the experimental ones.

It is, therefore, reasonable to assume that the disintegration of the hydrophilic tablets was due to the rapid penetration and dissolution of the tablet components. Thus, in the presence of agitation, the dissolution process of the water-soluble components of the tablets will be hastened and, at the same time, the disintegration of the tablet will be accelerated. Depending on the characteristics of the tablet formulation, the effect of the intensity of agitation on both the disintegration time and the range values could vary from negligible to enormous.

Apparently, the characteristics of the lactose-based tablets used in this study were such that the immersion fluid penetrated the tablets easily, weakening the tablet structure and causing disintegration soon thereafter. This result would also explain the similarity in the range values observed at 12 and 30 cpm. It is possible that the penetration of the immersion fluid resulting in the weakening of the tablet structure was a function of the agitation intensity, but the extent of weakening was more or less similar. At 4 cpm, however, the intensity of agitation was much slower and, therefore, accounted for an increase in the range values at this speed.

For tablets made with the water-insoluble matrix, the disintegration times as well as the range values increased at the lower speed of agitation. While the increase in the disintegration time was significantly higher at 4 cpm than at 12 cpm, the increase in the range values at these two speeds was only modest and more or less similar. Apparently, the hydrophobic nature of the dibasic calcium phosphate retarded the penetration of the immersion fluid through the tablet, thus resulting in increased disintegration times, the effect being more pronounced at the lower intensity of agitation.

However, once the immersion fluid penetrated the tablets and contacted the hydrophilic components, the tablet structure began to weaken and the tablet started to disintegrate. Apparently the disintegration of the water-insoluble based tablet was a function of the weakening of the tablet structure (Fig. 1). Thus, a reduction in the speed of agitation only increased the time of weakening of the tablet structure but did not significantly affect the range values.

Figure 2 shows the disintegration times and the range values obtained with the tablets containing the hydrophobic active ingredient, magnesium trisilicate. The results are similar to those found for tablets containing sodium salicylate, except that the disintegration times as well as the range values were somewhat higher. These results were even more apparent for tablets made with the water-insoluble matrix than for those made with the water-soluble matrix, supporting the view that the penetration of the immersion fluid was slower through the water-insoluble matrix, thus resulting in not only delayed disintegration but also in higher range values. For the tablets made with the water-soluble matrix, although the active ingredient was hydrophobic, the hydrophilic nature of the matrix may have aided in the penetration of the immersion fluid through the tablet, resulting in relatively faster disintegration and thus giving relatively lower disintegration times and lower range values.

It has been argued that the lack of reproducibility of the intensity of agitation in the disintegration apparatus may result from the turbulance of the fluid flowing through the basket chamber when the apparatus is operated at 30 cpm (8). If such is the case, then reducing the speed should reduce the turbulance, which, in turn, should produce a relatively reproducible intensity of agitation. Reducing the speed of the apparatus apparently did not result in a corresponding reduction of the turbulance (Figs. 1 and 2). Possibly there was some reduction in the degree of turbulance, but it was not sufficient to cause appreciable reproducibility in the intensity of agitation.

The coefficient of variation of the disintegration times (Fig. 3) was largest for the essentially water-soluble tablet (Formulation I) at all three speeds but was smaller for the three formulations that contained one or more hydrophobic components. At 30 cpm, the coefficients of variation followed the order: Formulation I > Formulation III > Formulation II > Formulation IV. At 12 cpm, the order was: Formulation I > Formula-

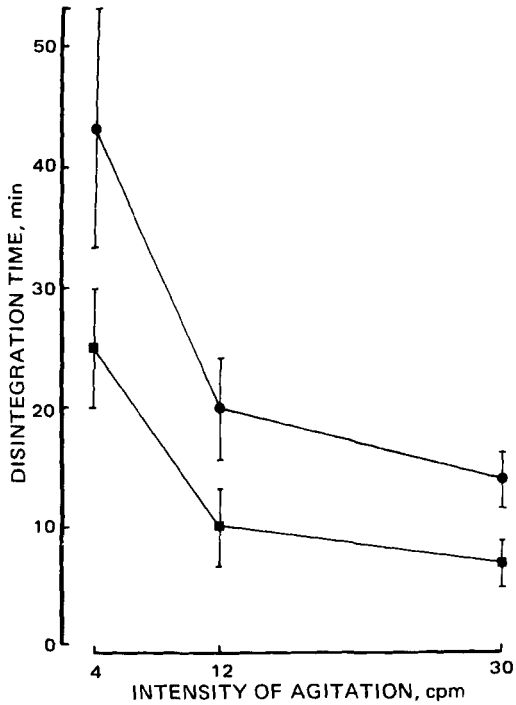

Figure 2—*Disintegration time of magnesium trisilicate tablets as a function of intensity of agitation. Key: ●, Formulation IV; and ■, Formulation III.*

tion III ≈ Formulation II > Formulation IV. And at 4 cpm, the order was: Formulation I > Formulation IV > Formulation III > Formulation II.

The rank order shows some similarity at the two higher speeds but lacks consistency at the lowest speed. However, it is interesting to note the linear relationship between the coefficient of variation and the intensity of agitation for the essentially water-insoluble tablet (Formulation IV) and the lack of such a relationship for the three formulations containing one or more water-soluble components.

These results suggest that a reduction in the speed of agitation apparently did not correspondingly reduce the turbulance in the apparatus. Had such been the case, the water-soluble components of the formulations would have been affected by the disintegration fluid relative to the speed of agitation and the results would have been reversed. That is, there would have been a direct relationship between the coefficient of variation and the speed of agitation for the formulations containing the water-soluble components but not for the formulations containing the water-insoluble components; the penetration of the disintegrating fluid in the tablets and the dissolution of the water-soluble components would have been a function of the intensity of agitation produced in the apparatus.

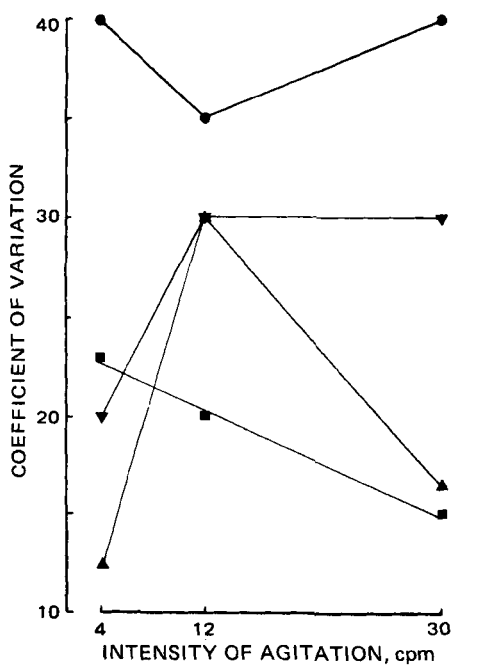

Figure 3—*Coefficient of variation as a function of intensity of agitation. Key: ●, Formulation I; ▲, Formulation II; ▼, Formulation III; and ■, Formulation IV.*

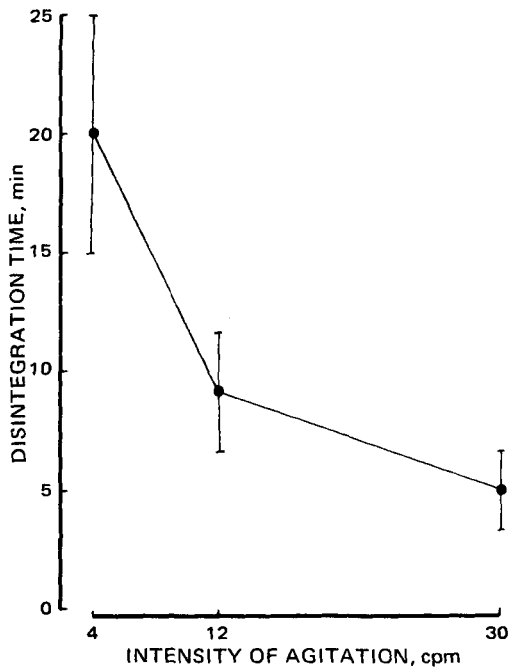

Figure 4—*Disintegration time of a commercial formulation as a function of the intensity of agitation.*

To determine the effect of the intensity of agitation on commercial formulations, several of them were studied at the three disintegration speeds. In most cases, the results showed that the disintegration times followed the order: 30 < 12 < 4 cpm. The intertablet range values increased significantly at lower speeds. Figure 4 shows the results obtained with a typical commercial formulation.

In the few cases where the commercial tablet formulations did not show

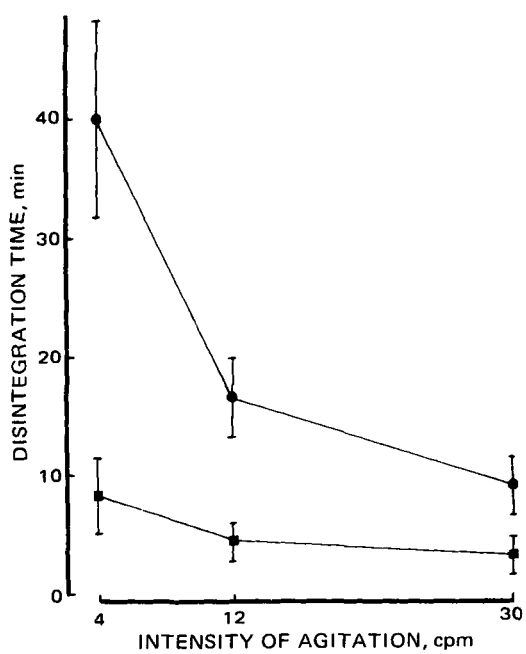

Figure 5—*Effect of disks on the disintegration time of tablets. Key: ●, Formulation IV; and ■, Formulation I.*

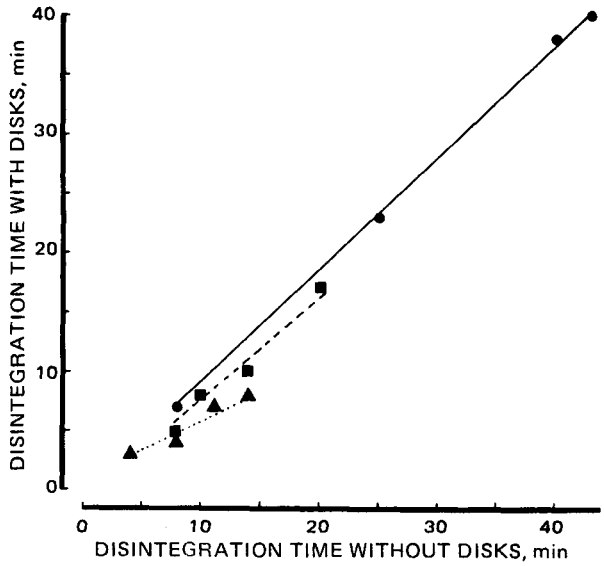

Figure 6—*Disintegration time with disks as a function of the disintegration time without disks. Key: ●, 4 cpm; ■, 12 cpm; and ▲, 30 cpm.*

significant variations in the disintegration times and the intertablet range values at the three agitation intensities, their disintegration time was less than 2 min. These tablets appeared to start breaking apart as soon as they were placed in the immersion fluid. In contrast, tablets that gave higher disintegration times did not exhibit any disintegration sign during the first few minutes. After a lapse of time, which varied from one brand to the other, the tablets started to disintegrate slowly. Visual observation indicated that the rate of disintegration of the slow-disintegrating tablets appeared to slow down as the disintegration process progressed. That is, the rate of breakdown of the tablet into larger fragments was faster than the rate of breakdown of the larger fragments into smaller particles.

Possibly, the commercial formulations that did not show variations in the disintegration times and intertablet range values at the three agitation intensities may have contained a component that approximated an erupting type of a disintegrant. In such a case, the agitation intensity would be expected to have little, if any, effect on the disintegration time. To test the validity of this hypothesis, the disintegration times of these formulations were determined in the absence of any externally applied agitation, and the results approximated the disintegration times obtained at 4, 12, and 30 cpm.

Effect of Disks—Disks are used in the disintegration apparatus to prevent the tablets from floating in the assembly (2, 3). It has been reported that the presence of disks causes a high degree of abrasion, resulting in rapid tablet disintegration (9).

The effect of disks on the disintegration time of the tablets is shown in Fig. 5. The disintegration times as well as the intertablet range values obtained at the three speeds were indeed reduced in the presence of disks. However, the reduction in the disintegration time was greater at 12 or 30 cpm than at 4 cpm. This result may be due to an increased degree of abrasion caused at the higher speed of agitation because of the more frequent abrasive contact of the disks with the tablets.

Visual observation during disintegration experimentation showed that the movement of disks in the apparatus at 4 cpm was relatively negligible; the disks appeared to be stationary most of the time. Even if the disks did have any abrasive action, it was only negligible. This view is supported by the excellent correlation found between the disintegration times obtained in the presence and absence of disks (Fig. 6).

Table II—Parameters of Correlation between Disintegration Times in the Presence and Absence of Disks

Intensity of Agitation, cpm	Correlation Coefficient[a]	Slope	Equation of Straight Line
4	0.99895	0.9535	$y = 0.9535x - 0.6516$
12	0.9700	0.8334	$y = 0.8334x - 0.8342$
30	0.9874	0.5346	$y = 0.5346x + 0.6886$

[a] Theoretical value at a probability level of 0.05 = 0.95.

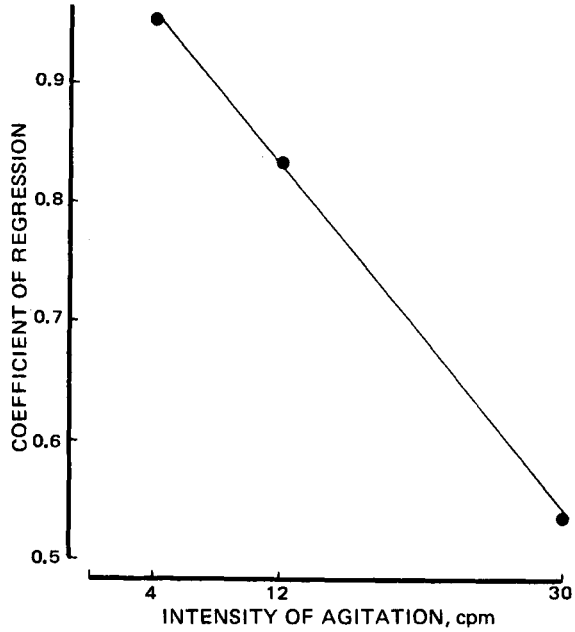

Figure 7—*Coefficient of regression as a function of the intensity of agitation.*

The results shown in Fig. 6 are summarized in Table II. These results indicate that the correlation between the disintegration times in the presence and absence of the disks followed the order 4 > 30 > 12 cpm. Apparently, the abrasive action of the disks was minimal at 4 cpm and, therefore, the value of the correlation coefficient was closest to unity. At 30 cpm, the abrasive action was much greater, and the disintegration times of all formulations studied appear to have been affected more or less similarly.

At 12 cpm, however, the correlation coefficient was the lowest of the three values, probably because the presence of disks affected different formulations differently at this intensity of agitation. This result may have been due to the nonreproducibility of the agitation intensity in successive runs because of the unpredictable nature of the turbulance, resulting in the smaller value of the correlation coefficient. However, at all three speeds, the calculated values of the correlation coefficient were greater than 0.95, the theoretical value of the correlation coefficient at a probability level of 0.05, indicating that the correlation between the disintegration times obtained in the presence and absence of disks was significant.

The three equations in Table II indicate that the straight lines do not pass through the origin. In all cases, the magnitude of the y-intercept was small (less than 1 min) and deviated from zero in the order 4 < 30 < 12 cpm. The rank order observed here was similar to that observed for the correlation coefficients.

The slope (coefficient of regression) followed the order 4 > 12 > 30 cpm (Table II), indicating that the influence of the disks on the disintegration times of the tablets was a function of the intensity of agitation. The coefficient of regression was closest to unity at the lowest intensity of agitation and declined sharply with an increasing intensity of agitation. That the coefficient of regression was directly related to the intensity of agitation is evidenced by the linear plot shown in Fig. 7.

Extrapolation of the linear plot yields a value of 63 cpm for the regression coefficient to be 0, *i.e.*, no correlation between the disintegration times in the presence and absence of disks. For the coefficient of regression to be unity, the graph in Fig. 7 predicts a value of 1.5 cpm, apparently the minimum intensity of agitation needed to keep the disks afloat but not sufficiently turbulant to have any abrasive action.

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Microsealed Drug Delivery Systems I: *In Vitro–In Vivo* Correlation on Subcutaneous Release of Desoxycorticosterone Acetate and Prolonged Hypertensive Animal Model for Cardiovascular Studies

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Abstract □ A new generation drug delivery system, named the Microsealed Drug Delivery (MDD) system, was developed. Subcutaneous implantation of MDD's in rats for up to 129 days resulted in a constant release profile of desoxycorticosterone acetate. Three formulations were examined. An excellent *in vitro–in vivo* correlation was established on both the mechanism and the rate of controlled release of desoxycorticosterone acetate from MDD's. A significant degree of hypertension was reproducibly produced within 21 days after implantation and successfully sustained through Day 98. Comparative studies were conducted on MDD's and a previously developed matrix-type silicone device. The elevation of systolic blood pressure initiated by either MDD's or the matrix-type silicone device was essentially the same in pattern, and the difference in the hypertensive responses between these polymeric drug delivery systems was statistically insignificant, although a higher dose, which is time dependent, was administered to rats through the matrix-type silicone device than through MDD's. The bioavailability of desoxycorticosterone acetate and its dose–response relationship apparently were accomplished more effectively *via* the constant drug delivery mechanism of MDD's.

Keyphrases □ Drug delivery systems, microsealed—subcutaneous release of desoxycorticosterone acetate in rats, *in vitro–in vivo* correlation, *compared to matrix-type silicone device* □ Desoxycorticosterone acetate—subcutaneous release from microsealed drug delivery system in rats, *in vitro–in vivo* correlation, compared to matrix-type silicone device □ Dosage forms—microsealed drug delivery system, subcutaneous release of desoxycorticosterone acetate in rats, *in vitro–in vivo* correlation, compared to matrix-type silicone device □ Adrenocortical steroids—desoxycorticosterone acetate, subcutaneous release from microsealed drug delivery system in rats, *in vitro–in vivo* correlation, compared to matrix-type silicone device

Metacorticoid hypertension, induced by the chronic administration of desoxycorticosterone acetate to rats in conjunction with saline loading, simulates, both pathologically and physiologically, the syndrome of essential hypertension in humans (1). A close relationship was observed between salt metabolism and many forms of experimental and clinical hypertension. An increase in total sodium, due in large part to an increase in intracellular sodium, and a fall in intracellular potassium, were reported to occur during the development of hypertension induced by desoxycorticosterone acetate (2).

Induction of experimental hypertension in rats to evaluate the antihypertensive activity of various drugs requires either daily injections of a desoxycorticosterone acetate suspension or implantation of a desoxycorticosterone acetate-containing wax pellet (3) while the rats are maintained on saline. The first technique consistently initiates onset of metacorticoid hypertension within 21–28 days, but the required daily injections are time consuming and may be hazardous for the animals. The second technique, because of inconsistent release rates of desoxycorticosterone acetate from the wax matrix, results in wide variations in hypertensive onset.

Recent reports (4, 5) demonstrated that experimental hypertension could be reproducibly induced in rats and successfully maintained for a prolonged period of time, *e.g.*, 100 days, by subcutaneous delivery of desoxycorticosterone acetate through a long-acting matrix-type silicone device. The release of desoxycorticosterone acetate was substantially prolonged by homogeneously impregnating the desoxycorticosterone acetate in a silicone polymer matrix. The same drug delivery system was also applied for the intravaginal administration of ethynodiol diacetate to rabbits for sustained contraceptive activity (6). Both the *in vitro* and *in vivo* releases of desoxycorticosterone acetate from silicone devices followed a matrix-controlled process, as defined by Q *versus* $t^{1/2}$ release kinetics (4, 6–11). The release profile of a drug from the matrix-type polymeric devices is high initially and then decreases with time.

In this investigation, a new generation drug delivery system, named the Microsealed Drug Delivery (MDD) system (12), was developed to provide a means for the constant (zero-order) release of desoxycorticosterone acetate. Both the *in vitro–in vivo* release profiles of desoxycorticosterone acetate from MDD's were studied, and their relationship was analyzed. The differences between MDD's and matrix-type silicone devices on the modes of desoxycorticosterone acetate release were examined. The time courses for the production of metacorticoid hypertension in rats also were explored.