planation may be that the receptor for the benzodioxans will not accommodate the larger naphthodioxan.

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Influence of Particle Size on Rectal Absorption of Aspirin

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Abstract □ The rectal absorption of aspirin from theobroma oil suppositories was studied in seven human subjects using urinary excretion measurements. The effect of particle size on the excretion rate and cumulative amount of total salicylate excreted was demonstrated by the administration of a 600-mg dose as powdered aspirin and as aspirin disks having 0.023 as much surface as powdered aspirin. *In vitro* dissolution profiles of aspirin from the suppositories were studied. By the NF XIII Method II, the time required for 50% of the aspirin to dissolve from the suppository was 50 and 100 min for the powdered aspirin and the aspirin disks, respectively. In the bioavailability study, the diffusion equilibrium was attained at approximately 4–5 and 9–10 hr after the rectal administration of powdered aspirin and aspirin disks, respectively. No correlation was found between bioavailability and the dissolution profiles as determined by the USP XVIII dissolution method.

Keyphrases □ Aspirin—absorption from theobroma oil suppositories, effect of particle size □ Dissolution—aspirin from suppositories, effect of particle size □ Bioavailability—aspirin, effect of particle size, correlation with *in vitro* dissolution profiles □ Particle-size effect—aspirin absorption from suppositories □ Absorption, rectal—effect of particle size on aspirin absorption from suppositories

Since early studies (1, 2), numerous investigations have demonstrated the influence of particle size on bioavailability from oral dosage forms. For poorly soluble drugs, it is widely recognized that a smaller particle size (greater surface) brings about more rapid dissolution and more rapid GI absorption. If absorption is rate limited by slow dissolution so that the drug is not completely absorbed from a solid dosage form, the more rapid absorption obtained by increasing the surface may also cause an increase in the total amount of the drug absorbed from a given dose (3–6).

The purpose of this investigation was to demonstrate that the particle size of aspirin incorporated in a rectal suppository could influence absorption. As shown by plasma salicylate concentration (7) and urinary salicylate excretion (8), rectal administration of aspirin is as effective as oral administration. Wagner

(9) cited certain general conclusions regarding absorption of drugs following rectal administration in humans. The emphasis in investigating suppositories has been on physical characteristics (10, 11), the influence of the base (12–14), and the *in vitro* release of the drug (15). By use of a simple aspirin and theobroma oil suppository, which melted at body temperature, the effect on absorption of approximately a 40-fold difference in surface area of the aspirin was studied.

EXPERIMENTAL

Protocol—Six healthy male and one healthy female subjects, 25–49 years of age and 60–82 kg, participated. Subjects were ambulatory and permitted to ingest food and fluids as desired. Urine samples were collected at hourly intervals after rectal insertion of the suppository. Volumes of the urine samples were measured, and aliquots were retained for analysis. Although the pH of each sample was measured, no attempt was made to control the pH. The formulations were coded, and a crossover technique was used with an interval of 1 week between bioavailability studies.

Preparation of Suppositories—When using mineral oil in the pycnometer, the density of powdered aspirin[1] was 1.40 g/cm³. An 80–100-mesh fraction of the powdered aspirin was separated by a sieve shaker[2]. The average size of the fraction was assumed to be 163 μm. Aspirin powder of 163-μm size was quantitatively mixed with theobroma oil[3], placed in a suppository machine[4], and pressed into a suppository containing 600 mg of aspirin and 475 mg of theobroma oil.

Disks of aspirin were made by compressing the powdered aspirin with a 0.3175-cm (0.125-in.) flat-faced punch and die set. The length and diameter of each disk were measured using an optical micrometer[5]. Disks were selected so that 13 disks weighed 600 mg.

Suppositories containing the disks were prepared by the fusion method. The cavity of the mold was approximately one-third filled with melted theobroma oil, several disks were added, and the mass was allowed to congeal. This procedure was repeated until all disks had been added and the cavity was filled. The mold was immediately placed in a refrigerator so that the disks were not in contact

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[1] USP, fine crystal, J. T. Baker Chemical Co.
[2] Allen-Bradley sonic sifter.
[3] Cocoa butter.
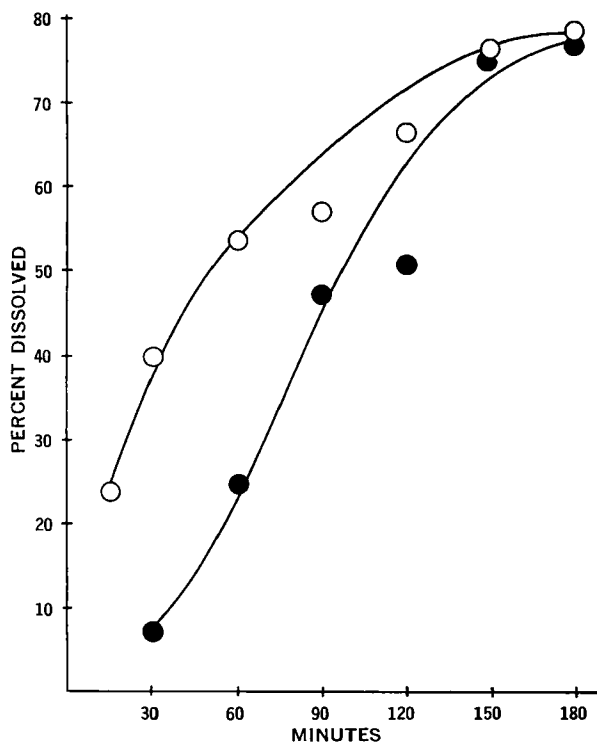[4] Armstrong suppository machine No. 3.
[5] Gaertner Scientific Corp.

Figure 1—*Dissolution profile of aspirin from theobroma oil suppository using the NF Method II. Key: O, powdered; and ●, disks.*

Table I—Mean Rate of Total Salicylate Excretion (Milligrams per Hour ± SE) after the Administration of a Rectal Suppository Containing 600 mg of Aspirin in Seven Human Subjects

Collection Interval, hr	Powdered Aspirin, Surface = 320 cm²	Disks of Aspirin, Surface = 7.5 cm²
0–1	5.45 ± 1.87	1.67 ± 0.61
1–2	16.11 ± 4.22	4.36 ± 1.08
2–3	20.64 ± 5.83	5.79 ± 1.66
3–4	18.60 ± 5.51	7.55 ± 1.52
4–5	18.61 ± 4.54	10.35 ± 1.92
5–6	19.79 ± 5.15	11.38 ± 1.22
6–7	16.03 ± 3.75	13.09 ± 2.02
7–8	18.70 ± 5.18	14.91 ± 2.14
8–9	16.64 ± 3.86	15.28 ± 1.72
9–10	15.69 ± 3.68	16.16 ± 2.19
10–11	14.94 ± 4.30	14.62 ± 3.30
11–12	11.66 ± 3.06	15.28 ± 2.00

the 12-hr period, the total salicylate excreted after the administration of the suppository containing the powdered aspirin was 1.5 times that excreted after the administration of the suppository containing the aspirin disks. The data show that the particle size of aspirin incorporated in the theobroma oil influences the rectal absorption of aspirin.

In small doses of aspirin, the overall salicylate elimination proceeds by apparent first-order kinetics after the attainment of diffusion equilibrium. The rate of excretion (dC/dt) may be defined by (20):

$$\log\,(dC/dt) = -k_u t/2.3 + K \qquad (\text{Eq. 1})$$

where t is time, and k_u is the specific velocity constant for elimina-

with the molten theobroma oil for more than 5 min. To determine if this brief exposure to the molten theobroma oil would alter the dimensions of the disk, disks were exposed to molten theobroma oil at 40° for 20 min and the dimensions were measured with an optical micrometer. No change in the diameter of the disk was detected. Each suppository contained 0.600 g of aspirin in the form of 13 disks and 1.50 g of theobroma oil.

All suppositories were stored in a refrigerator for 1 week before use.

Analytical Methods—The analysis of the urine samples for total salicylate was conducted by the method of Chiou and Onyemelukwe (16). For the measurement of dissolution from the suppository, an aliquot of the dissolution medium was subjected to alkaline hydrolysis. This solution was then acidified, appropriately diluted with 0.1 N hydrochloric acid, and assayed spectrophotometrically in terms of salicylic acid (17).

Dissolution—The percent of aspirin dissolved from the suppository was determined using 900 ml of distilled water at 37° in the NF Method II dissolution apparatus (18). Samples were removed by a pipet fitted with a filter, and the fluid was replenished with the same volume of distilled water. The samples were analyzed, and the percent dissolved at each interval of time was calculated (Fig. 1).

Similarly, the percent of aspirin dissolved from the suppository was determined using the USP dissolution apparatus (19) at 50, 100, and 200 rpm (Fig. 2).

RESULTS AND DISCUSSION

Bioavailability—The mean rates (±SE) of excretion of total salicylate for seven subjects are given in Table I. The initial excretion rates were greater for the aspirin powder with a surface of 320 cm² than for the aspirin disks with a surface of 7.5 cm², although both were incorporated in a theobroma oil base.

Even with the limited fluid available in the rectal canal, the suppository in which the aspirin had the greater surface dissolved at a faster rate and, consequently, this aspirin was absorbed and excreted more rapidly than the aspirin with approximately 0.023 as much surface.

Figure 3 shows the mean cumulative amount of total salicylate excreted as a function of time following rectal administration. In
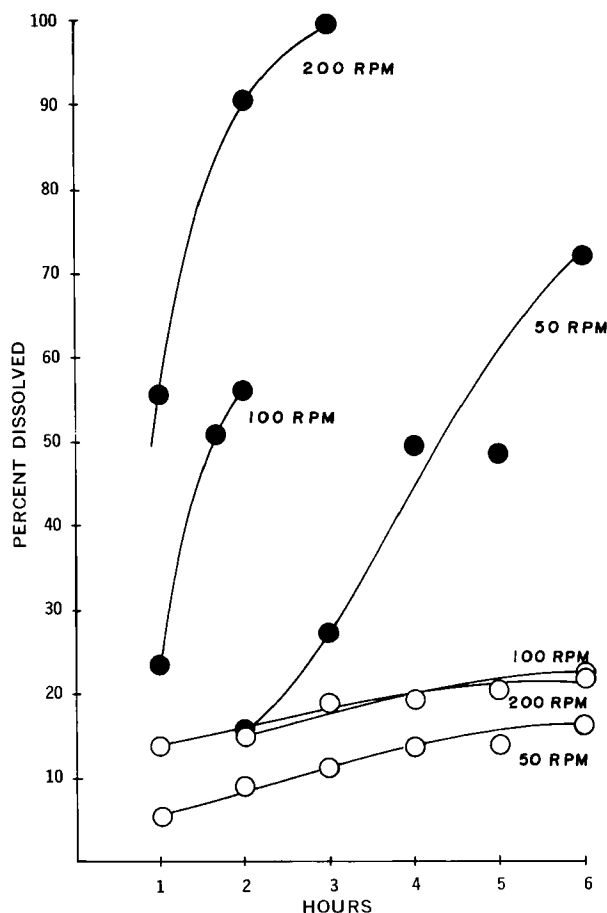

Figure 2—*Dissolution profile of aspirin from theobroma oil suppository using USP dissolution apparatus at 50, 100, and 200 rpm. Key: O, powdered; and ●, disks.*
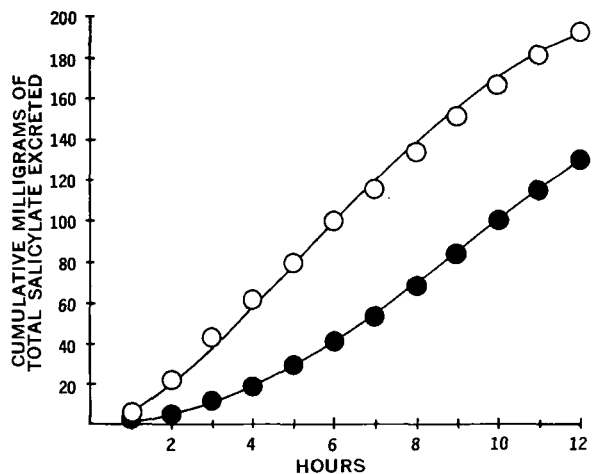
Figure 3—*Effect of particle size on the mean cumulative amounts of total salicylate excreted after the rectal administration of 600 mg of aspirin in seven human subjects. Key:* O, *powdered; and* ●, *disks.*

tion of the drug based on urinary data. The biological half-life $(t_{1/2})_u$ based on urinary data is:

$$(t_{1/2})_u = 0.693/k_u \qquad \text{(Eq. 2)}$$

If the dose of aspirin is small, the half-life of salicylate elimination is from 4 to 6 hr (8, 21).

A semilogarithmic plot of the excretion rate against time according to Eq. 1 is shown in Fig. 4. The linear portion of the curve represents a $(t_{1/2})_u$ of 6 hr. With the powdered aspirin, the diffusion equilibrium is attained at approximately 4–5 hr; but with the aspirin disks having a limited surface, the diffusion equilibrium is not
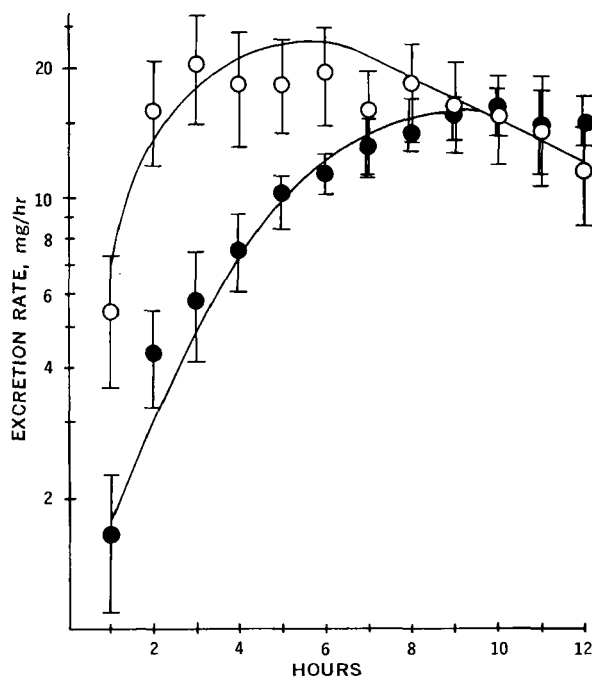

Figure 4—*Mean urinary excretion of total salicylates after rectal administration of 600 mg of aspirin in seven human subjects. Vertical bars represent standard error of the mean. Key:* O, *powdered; and* ●, *disks.*

attained until approximately twice as much time has elapsed. Thus, the limited surface of the disks prolongs dissolution and aspirin is still being absorbed at 9–10 hr.

Dissolution—The usefulness of dissolution profiles for tablets has been demonstrated by the inclusion of dissolution specifications and methods in the USP and NF. It is interesting to apply these methods to other dosage forms such as the suppository. The dissolution profiles from suppositories containing powdered aspirin and aspirin disks are shown in Fig. 1 as determined by the NF XIII Method II. The time $(t_{50\%})$ required for 50% of the aspirin to dissolve from the suppository containing the powdered aspirin is one-half the $t_{50\%}$ for the suppository containing the aspirin disks. This *in vitro* comparison of the release from powdered aspirin and aspirin disks is similar to the ratio of *in vivo* attainment of the diffusion equilibrium from powdered aspirin and aspirin disks at 4–5 and 9–10 hr, respectively.

The USP dissolution apparatus was used similarly to show the effect of speed on the $t_{50\%}$. At 37°, the suppository melted within 5 min. The disks remained on the bottom of the basket and appeared to be free of theobroma oil. After the suppository containing the powdered aspirin melted, an oily mass of aspirin and theobroma oil remained on the bottom of the basket. If the apparatus was allowed to cool, the mass congealed to a brittle solid that was oily to the touch. Aspirin was very slowly released from the mass; at the speeds used, the $t_{50\%}$ was not reached after 7 hr in the apparatus. Obviously, the USP dissolution apparatus was not applicable to the evaluation of the suppository, while it appears that the NF Method II might be useful.

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