Influence of Various Starches on Dissolution Rate of Salicylic Acid from Tablets

THELMA W. UNDERWOOD and DONALD E. CADWALLADER▲

Abstract □ The effect of various starches (corn, potato, rice, arrowroot, and a compressible starch) on the rate of dissolution of salicylic acid from tablets (prepared by double compression) was investigated. Dissolution rate determinations were carried out using three different test methods: USP–NF Method Types I and II and a modified flask method. In all instances, the dissolution of the drug was fastest from tablets containing a compressible starch, whereas the rank order of the dissolution times of the other starch formulations depended on the dissolution test method. Dissolution rates for starch formulations determined by the stirring agitation-type test methods were potato > corn > arrowroot > rice, and the rates determined by an oscillating agitation-type test were corn > rice > arrowroot = potato.

Keyphrases □ Dissolution rates, salicylic acid tablets—effect of starch formulation □ Salicylic acid tablets—effect of starch excipient on dissolution rate □ Starches, various, in salicylic acid tablets—effect on dissolution rate

Considerable interest has developed in the past 10 years concerning the influence of dissolution rate on the availability of the drug in the absorption process (1, 2). It is now well recognized that the dissolution rate of solid drugs can be the rate-limiting step in the absorption process when drugs in this form are introduced into the body. In a number of instances, poor tablet formulation has been shown to cause significant reduction of physiologic availability of the active ingredient and impairment of clinical response (3, 4). Jacob and Plein (5) studied the effects of binder concentration and tablet hardness on the dissolution rate of phenobarbital tablets. They found that an increase in binder concentration and hardness of compression resulted in a decrease in the dissolution rates.

Solvang and Finholt (6) studied the effects of different binders and the influence of particle size on the dissolution rate of phenobarbital. They also investigated the effect of granulation and tableting processes on the dissolution rate of phenobarbital, sodium phenobarbital, phenacetin, and prednisone in human gastric juice. It was found that the granulation process and the compression of the granules may greatly influence the rate of dissolution. Levy and Gumtow (7) investigated the effect of tablet lubricants on the dissolution rate of salicylic acid tablets. They found that a hydrophobic tablet lubricant (magnesium stearate) retarded dissolution, while a water-soluble, surface-active lubricant (sodium lauryl sulfate) enhanced the dissolution rate. Varley (8) showed that varying the amount of disintegrating agent in the formulation of tolbutamide tablets resulted in an increase in disintegration time and dissolution rate of the tablet. Both formulations met the USP requirements, but a small change in the amount of one ingredient resulted in a product that was less available for absorption and provided less therapeutic usefulness to the patient.

Starch is an important adjuvant used in tablet formulation. It is widely used as a tablet disintegrator, as a diluent, and as a binder. Levy *et al.* (9) investigated the effect of granule size, compression pressure, and starch concentration on the dissolution rate of salicylic acid from granules prepared by double compression. It was found that the dissolution rate increased with decreasing granule size, with increasing precompression pressure, and with increasing starch content. Commons *et al.* (10) studied the influence of starch concentration on the disintegration time of tolbutamide tablets. They reported that disintegration times did not decrease with increasing concentrations of starch, as might be expected, but there appeared to be a critical starch concentration for different granule sizes of tolbutamide.

The purpose of this investigation was to study the effect of different starches (corn, rice, potato, arrowroot, and a directly compressible starch) on the dissolution rate of a model drug (salicylic acid) in a compressed tablet. Dissolution rates were determined using three different methods: the two USP–NF official dissolution methods, Types I and II, and a modified flask method.

EXPERIMENTAL

Materials—Salicylic acid USP[1] was separated into the desired size fraction by sieving. The powder used was passed through a U. S. Standard 60-mesh screen and retained on a 80-mesh screen (60/80-mesh powder). Cornstarch USP[2], potato starch[2], rice starch[3], arrowroot starch[2], and a directly compressible starch[4] were used as received.

Preparation of Tablets—Compressed tablets were made by double compression with a hydraulic press[5] using a conventional set of flat-faced punches and die, 2.7 cm. in diameter. Slugs were compressed at 1430 kg./cm.^{2} using a premixed powder containing 11.25 g. of salicylic acid and 1.25 g. of starch. The slugs were subsequently broken into granules with a mortar and pestle. The granules were separated into the desired size fraction (20/40) by sieving. A 361-mg. amount of the granules (containing 325 mg. of salicylic acid) was accurately weighed and compressed at 526 kg./cm.^{2} using a 0.95-cm. (0.375-in.) shallow concave punch and die set.

Preparation of tablets and dissolution rate determinations were carried out the same day. The preparation of the granules was done on the preceding day.

All tablets disintegrated within 1–2 min. in distilled water using the official disintegration test (11).

Aging—Granules containing each type of starch were kept in 30-ml. (1-oz.) powder jars with Bakelite screw-on caps at ambient temperature for 9 months and were tested at the end of the storage

[1] Merck & Co.
[2] Fisher Scientific Co.
[3] S. B. Penick & Co.
[4] Marketed as STA-Rx-1500, A. E. Staley Mfg. Co., Decatur, Ill.
[5] Carver model B.

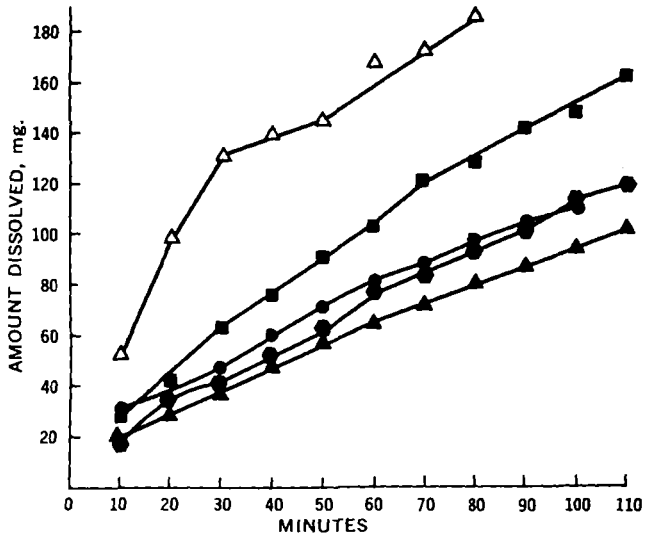

Figure 1—*Dissolution rates of salicylic acid from tablets containing various starches using the flask method (59 r.p.m.) at 37°. Key: ●, cornstarch; ■, potato starch; ▲, rice starch; ⬢, arrowroot starch; and △, compressible starch.*

period. The granules were compressed into tablets as already described, and disintegration times and dissolution studies were carried out that same day.

Dissolution Rate Determinations—Three different methods were used to determine the dissolution rates of various tablet formulations. The flask method consisted of a 500-ml. three-necked round-bottom flask, which was modified by cutting a 6-cm. diameter center opening to accommodate the entrance of a 5-cm. propeller. The dissolution medium used was 350 ml. of distilled water. A three-

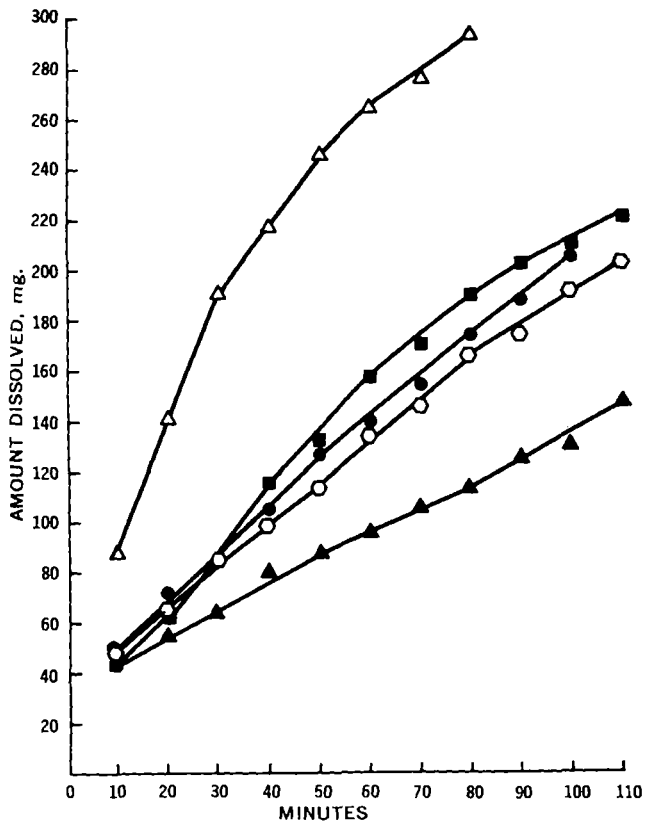

Figure 2—*Dissolution rates of salicylic acid from tablets containing various starches using the USP–NF Method Type I (basket, 100 r.p.m.) at 37°. Key: ●, cornstarch; ■, potato starch; ▲, rice starch; ○, arrowroot starch; and △, compressible starch.*

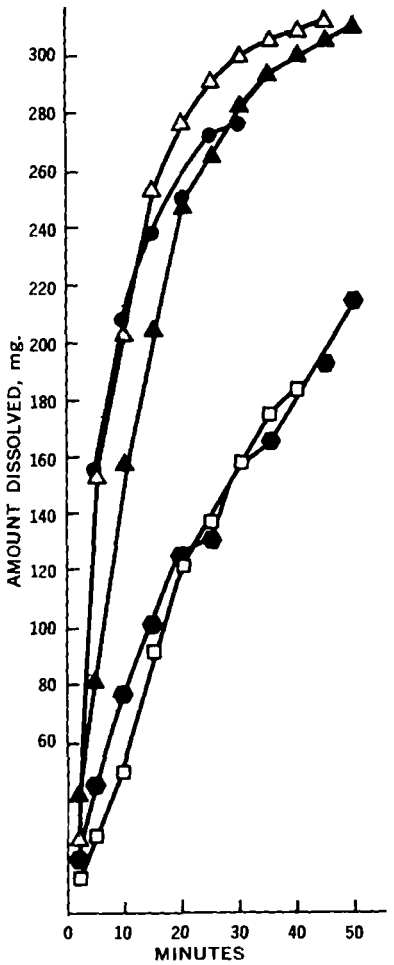

Figure 3—*Dissolution rates of salicylic acid from tablets containing various starches using the USP–NF Method Type II at 37°. Key: ●, cornstarch; □, potato starch; ▲, rice starch; ⬢, arrowroot starch; and △, compressible starch.*

blade, 5-cm. diameter, stainless steel propeller was inserted through the center opening of the flask and immersed in the dissolution medium to a depth of 27 mm. The propeller was centered and used at a stirring rate of 59 r.p.m. using an electronically controlled stirrer[6]. The tablet was dropped into the dissolution medium through one of the openings and came to rest under the propeller. The USP–NF Dissolution Method I (12) was used at a rotation speed of 100 r.p.m., and 900 ml. of distilled water was used as the dissolution medium. The third method was Method II of NF XIII (13), using 900 ml. of distilled water as the dissolution medium.

All dissolution studies were carried out at 37 ± 0.5°. At appropriate intervals, samples of the dissolution medium were withdrawn and filtered through a millipore filter unit containing a 0.22-μ filter. An equal amount of distilled water was used to replace the dissolution medium removed as a sample.

Six experiments were carried out on the cornstarch formulations, and a minimum of three to four runs was carried out on each of the other starch formulations.

Analytical Method—A 1.0-ml. sample was diluted with distilled water to an appropriate strength, and the solution was read on a spectrophotometer[7] at a wavelength of 297 nm. Distilled water was used as the blank. The spectrophotometer readings were compared to a Beer–Lambert standard curve, and the milligrams of salicylic acid dissolved were determined.

Any possible interference from the starch in solution was ascertained by the following method. A mixture was prepared by adding 25 mg. of starch to 100 ml. of distilled water and was gently

[6] Heller Electronic Controller model GT-21 laboratory mixer.
[7] Beckman DU-2.

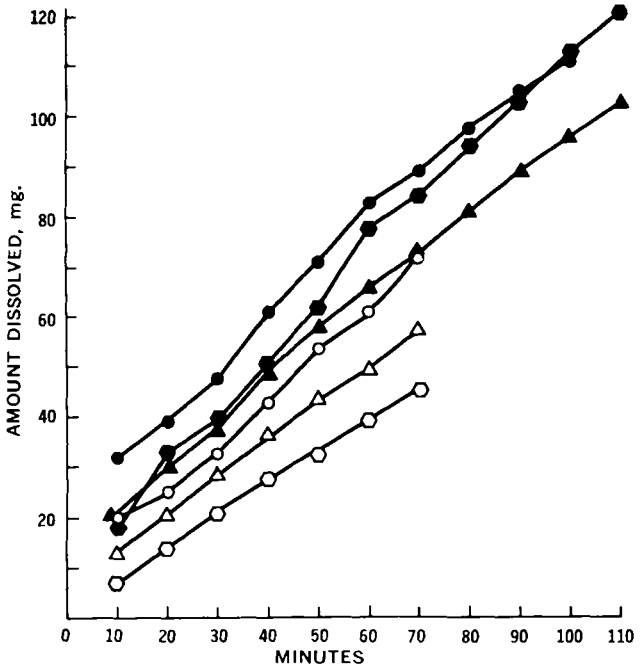

Figure 4—*Effect of aging of granules (9 months at room temperature) on dissolution rates of salicylic acid from tablets containing various starches using the flask method (59 r.p.m.). Key: ●, corn, initial; ○, corn, aged; ▲, rice, initial; △, rice, aged; ■, arrowroot, initial; and □, arrowroot, aged.*

agitated for 1 hr. Then a 3-ml. sample was filtered through a millipore filter assembly containing a 0.22-μ filter and scanned on a spectrophotometer[8] in the range of 200–400 nm. There was no absorption by any of the starches at the wavelength used in the assay of salicylic acid.

Chiou and Smith (14) reported that salicylic acid is adsorbed on millipore filter disks (17.5 mm. o.d.) after a 30-sec. passthrough time. To determine if any significant error might be introduced during the filtering step, samples of salicylic acid solution (2, 5, 10, and 20 mcg./ml.) were forced through (2–3 sec. passthrough time) millipore filter disks (13 mm. o.d.). No significant loss of salicylic acid was detected under the conditions of these studies; this finding probably can be attributed to the small surface area of the filter and the rapid passthrough time.

The pH of the starch solution was read on a pH meter[9]. The pH of the starches ranged from 7 to 7.1. There was no significant difference in the pH of the various starches in distilled water.

RESULTS AND DISCUSSION

Effect of Starches—The experimental results depicted in Figs. 1–3 show dissolution rate profiles determined by three different methods for tablets containing various starches. From these data, it can be seen that the type of starch used as a disintegrant did significantly affect the rate of dissolution of salicylic acid from a tablet dosage form. Figure 1 shows that dissolution of the drug was considerably faster from tablets formulated with a compressible starch, while the dissolution rates from tablets containing other starches were potato > corn > arrowroot > rice. As seen in Fig. 2, the same rank order for the starches was obtained; however, all the dissolution rates were much faster than the rates determined by the flask method. These increases in rates of dissolution were probably due to the different hydrodynamics of the system and the higher agitation (100 r.p.m.) used in the USP–NF Method Type I dissolution test.

Figure 3 shows a change in rank order of the rate of dissolution of the active ingredient based on type of starch contained in the tablets. The use of compressible starch resulted in the fastest dissolution rate; however, the order of the other starch formulations

[8] Perkin-Elmer 202.
[9] Corning model 7.

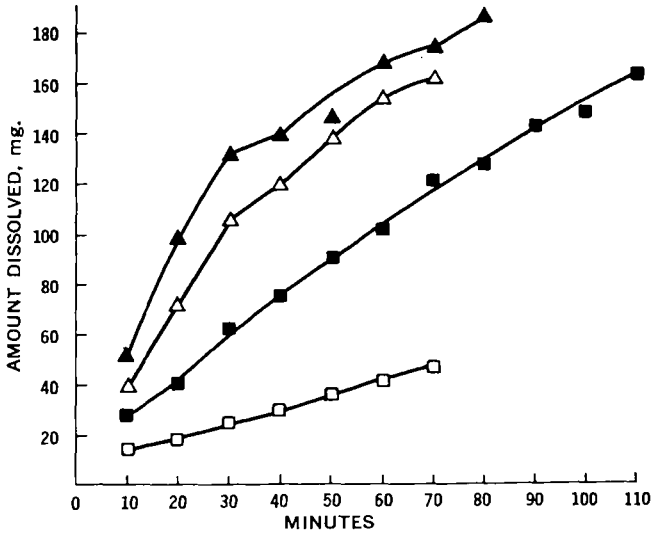

Figure 5—*Effect of aging of granules (9 months at room temperature) on dissolution rates of salicylic acid from tablets containing various starches using the flask method (59 r.p.m.). Key: ■, potato, initial; □, potato, aged; ▲, compressible starch, initial; and △, compressible starch, aged.*

was corn > rice > potato = arrowroot. Due to the oscillating agitation of the USP–NF Method Type II dissolution method, the dissolution rates were much faster than those with the other two test methods. The rapid dissolution times made it difficult to delineate clearly between the various formulations.

Manudhane *et al.* (15) showed that compressible starch appears to have many advantages over starch USP because it is much more effective as a dry binder yet gives equivalent or faster disintegration and dissolution times. In the present study, a compressible starch had the fastest dissolution rate by each testing method, regardless of the agitation intensity. Of the five starches studied, the compres-

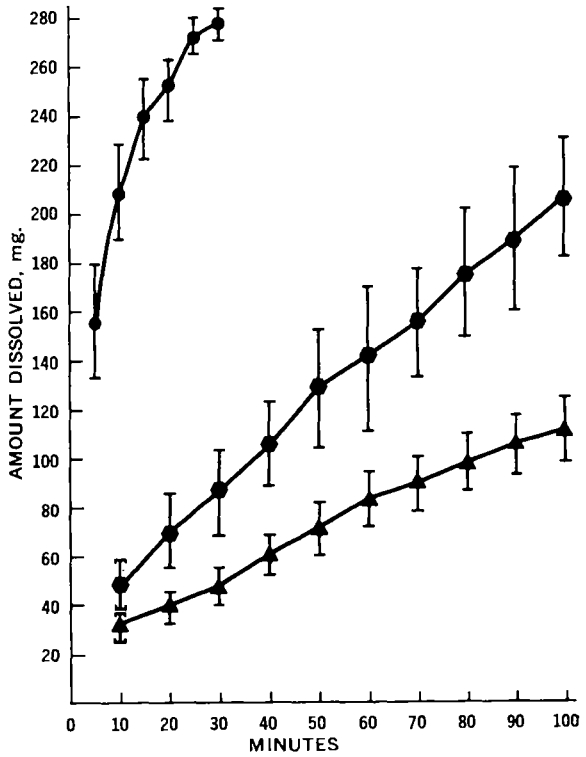

Figure 6—*Dissolution rates of salicylic acid from tablets containing cornstarch using different dissolution methods at 37°. Key: ▲, flask method; ■, USP–NF Method Type I; and ●, USP–NF Method Type II. Bars mark off one standard deviation on either side of the average.*

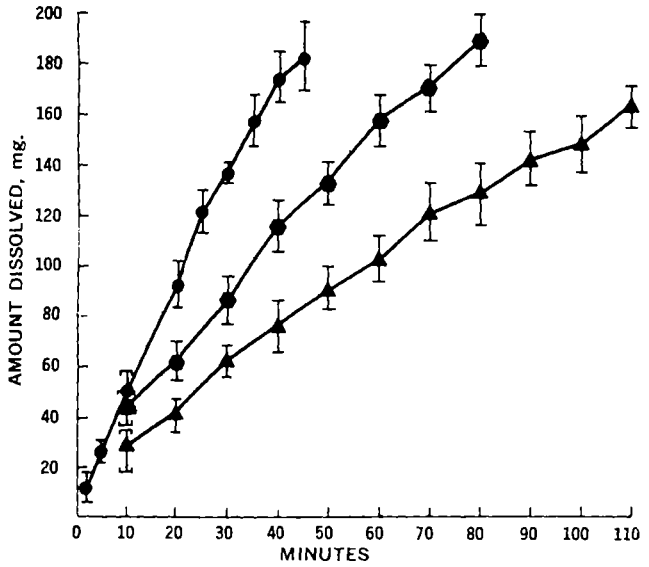

Figure 7—*Dissolution rates of salicylic acid from tablets containing potato starch using different dissolution methods at 37°. Key: ▲, flask method; ●, USP–NF Method Type I; and ●, USP–NF Method Type II. Bars mark off one standard deviation on either side of the average.*

sible starch was the only one that contained a relatively high amount (12%) of cold water solubles (14), and this physical property could be a possible reason for the faster dissolution of salicylic acid in distilled water.

The granule size of the four regular starches used in this study varied in average size: potato (33 μ) > arrowroot (25 μ) > corn (12.5 μ) > rice (5 μ)[10]; these sizes are in good agreement with published data (16). The potato starch contained many large irregular-shaped granules, while the other starches were more uniform in size. In the flask method and the USP–NF Method Type I, the tablet disintegrates and settles as a mound at the bottom of either the round-bottom flask or the wire basket. A possible explanation of the faster dissolution rate of drug from tablets containing potato starch when these two stirrer methods are used to test dissolution is that the potato starch, containing many large granules, allows a more porous and loose mound network to form, enabling the dissolution medium to circulate easily through the mound. The slower dissolution rate of rice starch formulation could be due to a more compact mound, as a result of the much smaller granule size of rice starch. The compact mound would make it more difficult for the dissolution medium to traverse and circulate.

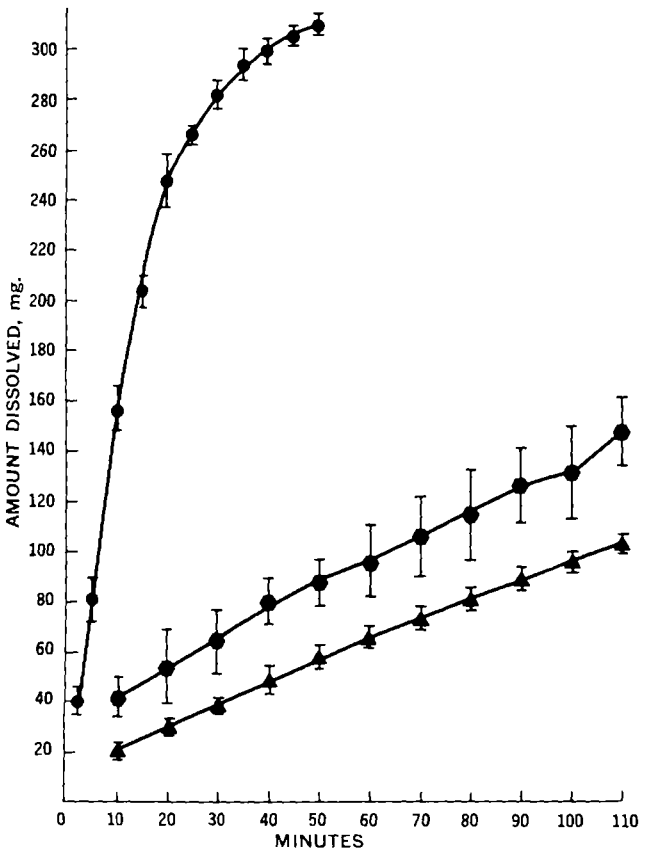

Figure 8—*Dissolution rates of salicylic acid from tablets containing rice starch using different dissolution methods at 37°. Key: ▲, flask method; ●, USP–NF Method Type I; and ●, USP–NF Method Type II. Bars mark off one standard deviation on either side of the average.*

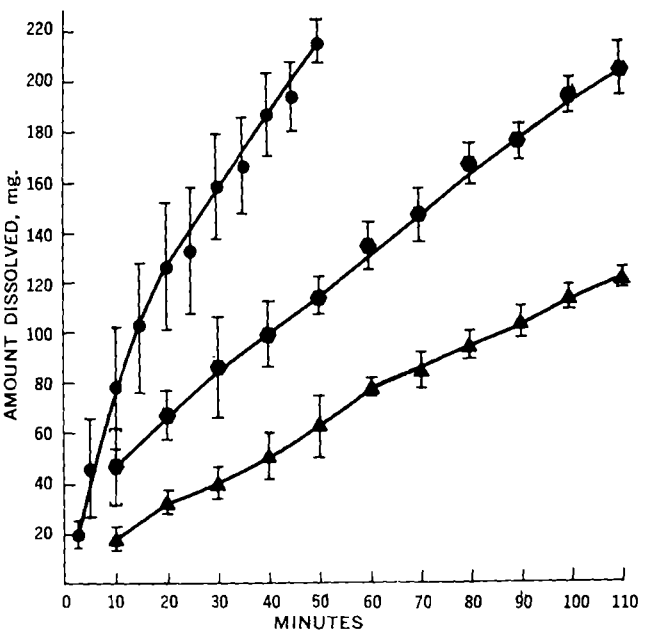

Figure 9—*Dissolution rates of salicylic acid from tablets containing arrowroot starch using different dissolution methods at 37°. Key: ▲, flask method; ●, USP–NF Method Type I; and ●, USP–NF Method Type II. Bars mark off one standard deviation on either side of the average.*

When the dissolution testing was carried out by the USP–NF Method Type II, the reverse happened; the formulations containing starch with smaller granules (rice and corn) had a faster dissolution rate than those containing larger granules (arrowroot and potato). The oscillating action of this test method caused rapid and complete dispersion of the tablet components throughout the dissolution medium. An explanation for difference in rank order might be that tablets containing a starch with large granules have a smaller starch particle to salicylic acid particle ratio (less starch separating individual salicylic acid particles) so that aggregates of salicylic acid may form. On the other hand, starches with the small granule size separate the salicylic acid particles and do not allow as much aggregate formation. The smaller particles dissolve faster when they are dispersed throughout the dissolution medium.

Effect of Aging—Figures 4 and 5 show the effect of aged granules on the dissolution rate of salicylic acid tablets containing corn, rice, arrowroot, potato, and a compressible starch. The aging of granules caused a decrease in dissolution rate of each tablet formulation. The compressible starch had the smallest decline, whereas arrowroot and potato formulations had the largest decline. Part of the decreased dissolution times can be attributed to increased disintegration times, since times of the aged formulations (potato, 18 min.; corn, 2–5 min.; arrowroot, 30 min.; and rice, 2–5 min.) were longer

[10] Microscopic examination 430× was made using dry powder samples. A 100 count was made for each sample. Particle-size ranges for each starch were potato (16–50 μ), arrowroot (20–30 μ), corn (10–15 μ), and rice (4–6 μ).

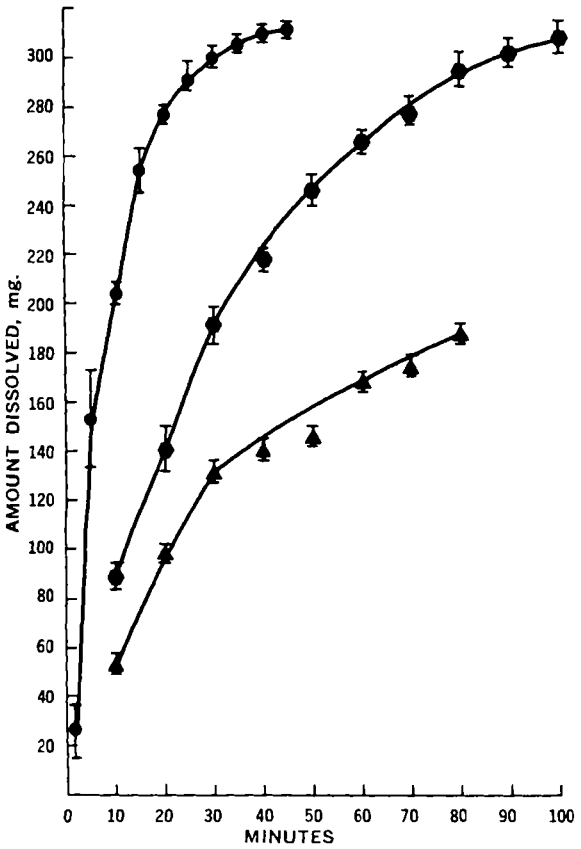

Figure 10—*Dissolution rates of salicylic acid from tablets containing a compressible starch using different dissolution methods at 37°. Key: ▲, beaker method; ⬬, USP–NF Method Type I; and ●, USP–NF Method Type II. Bars mark off one standard deviation on either side of the average.*

than unaged tablets (1–2 min.). Higuchi *et al.* (17) reported that granulations prepared at different times may exhibit differences in properties, and Levy *et al.* (9) showed that aging of granules significantly changes the dissolution rate of salicylic acid tablets containing starch.

Dissolution Methodology—Figures 6–10 show dissolution rates using three different dissolution methods. In all cases the rank order for rate of dissolution of tablets containing various starches was the same for each method of dissolution and can be directly attributed to the degree of agitation associated with each method. The oscillating action of the USP–NF Method Type II gave considerably faster dissolution times than the other two methods. Of the three dissolution testing methods used, the modified flask method appears to be the most reproducible.

An important point brought out in these studies was the fact that the rank order of dissolution rates of salicylic acid from various starch formulations changed depending on whether the dissolution method was a stirring agitation type or an oscillating action type. It appears that qualitative dissolution relationships between different formulations can be significantly changed depending on the methodology used for testing.

SUMMARY

1. The effect of various starches (corn, potato, arrowroot, rice, and a compressible starch) on the dissolution rate of salicylic acid in a tablet dosage form was determined.

2. Three methods of dissolution were used in this study: the USP–NF official dissolution Methods Types I and II and a modified flask method. The modified flask method appeared to be the most reproducible of the methods used.

3. Different types of starch did have an effect on the dissolution rate of salicylic acid from tablets prepared by dry granulation. The compressible starch formulation had the fastest dissolution rate in all instances.

4. The rate of dissolution of the active ingredient from tablets determined using the flask method and USP–NF Method I was a compressible starch > potato > corn > arrowroot > rice.

5. The rate of dissolution of the salicylic acid determined using the USP–NF Method II was a compressible starch > corn > rice > arrowroot = potato.

6. Aging of the granules resulted in slower dissolution rates for all tablet formulations.

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▲To whom inquiries should be directed.