Correlation Between the Rate of Dissolution and Absorption of Salicylamide from Tablet and Suspension Dosage Forms

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Abstract □ The *in vivo* absorption and the *in vitro* dissolution characteristics of a commercial suspension, a commercial tablet, and an experimental tablet formulation of the analgesic-antipyretic drug salicylamide were compared. The results of the study demonstrated that the absorption of this drug is dissolution rate-dependent and that the initial *in vitro* dissolution rate in 0.1 *N* HCl correlates well with the initial absorption rates of the test dosage forms in human subjects.

Keyphrases □ Salicylamide dosage forms—absorption-dissolution rates, correlation □ Dissolution rates—salicylamide dosage forms □ Absorption rates—salicylamide dosage forms □ Colorimetric analysis—spectrophotometer

Salicylamide, the amide of salicylic acid, is a moderately strong analgetic-antipyretic. It is usually administered orally in either a compressed tablet or suspension dosage form, alone or in combination with other analgetic-antipyretic drugs (*e.g.*, aspirin and *N*-acetyl-*p*-aminophenol).

The pharmacokinetics of salicylamide elimination in man has been reported by Levy and Matsuzawa (1). These investigators found that the metabolic fate of this drug, which appears to be eliminated from the body by competing apparent zero- and first-order processes, is dose and dosage form dependent.

The relatively low aqueous solubility of this drug and its fairly high pKa value of 8.2 suggested that its absorption across the gastrointestinal mucosa would exhibit a dissolution rate-limited dependence. This communication reports the results of a study designed to ascertain whether a correlation existed between the *in vitro* dissolution rate and the *in vivo* absorption rate of salicylamide following its oral administration, in tablet and suspension dosage form, to human subjects. The importance of such correlations is well recognized (2–6) since they may permit the prediction of the rate of absorption of drugs contained in dosage forms from suitable *in vitro* methods.

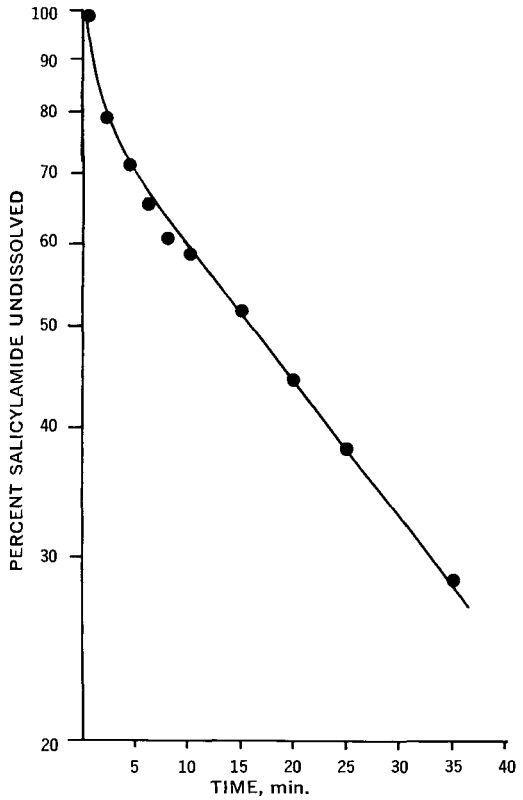

Figure 1—*Dissolution rate of salicylamide from a commercial suspension dosage form in 0.1* N *HCl at 37°. Agitation intensity, 70 r.p.m.*

EXPERIMENTAL

Reagents—Hydrochloric acid, nitric acid, ferric nitrate, ethylene dichloride, and salicylamide were of analytical reagent grade.

Dosage Forms—The salicylamide test preparations consisted of a commercially available suspension and tablet formulation and an experimental tablet formulation prepared by slugging the drug with 1% magnesium stearate as a lubricant. The dissolution characteristics of these dosage forms were investigated as well as their *in vivo* absorption rates. An aqueous solution of salicylamide was also included in the *in vivo* absorption studies.

Dissolution Apparatus—The apparatus consisted of a 500-ml. three-neck round-bottom flask immersed in a constant-temperature bath maintained at 37 ± 0.2°. A constant agitation intensity was provided by means of a 70-mm. diameter Teflon stirring propeller and shaft connected to a stirring motor controlled by a Servodyne constant torque unit.

Dissolution Procedure—Three hundred and fifty milliliters of 0.1 *N* HCl were placed in the flask and allowed to equilibrate to 37°. The stirring blade was introduced through the center neck of the flask, centered, and immersed into the dissolution medium to a depth of 20 mm. The agitation intensity employed in these studies was 70 r.p.m. One tablet or a weight of suspension corresponding to 0.3 g. of salicylamide was added to the agitated dissolution medium. At appropriate time intervals a 1-ml. sample was withdrawn from the vessel with the aid of a 1-ml. pipet fitted with a glass wool prefilter and immediately replaced with an equivalent volume of dissolution medium. Following suitable dilution of the sample, a 1-ml. quantity of diluted sample was added to 5 ml. of a $Fe(NO_3)_3$ color reagent (4% ferric nitrate in 0.12 *M* HCl) and assayed colorimetrically at 525 mμ using a Bausch & Lomb Spectronic 20. The salicylamide-iron colored complex was found to obey the Beer's

Table I—Initial Dissolution Rates of Salicylamide Preparations in 0.1 *N* HCl at 37°

Time, min.	Salicylamide Dissolved, %—Commercial Suspension	Commercial Tablet	Experimental Tablet
2.0	21.0	—	0.7
5.0	31.0	1.4	2.2
10.0	41.6	6.8	3.7
15.0	48.4	13.6	5.1
20.0	55.8	22.3	6.8
25.0	61.7	35.2	8.0
30.0	67.2	44.9	9.6

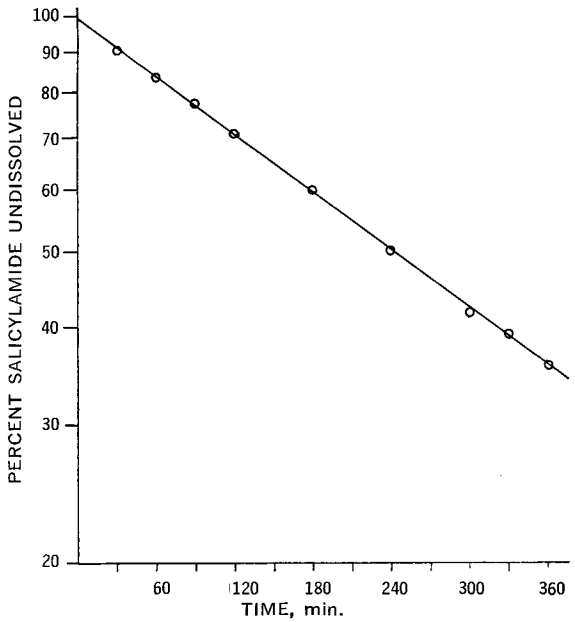

Figure 2—*Dissolution rate of salicylamide from an experimental tablet dosage form in 0.1* N *HCl at 37°. Agitation intensity, 70 r.p.m.*

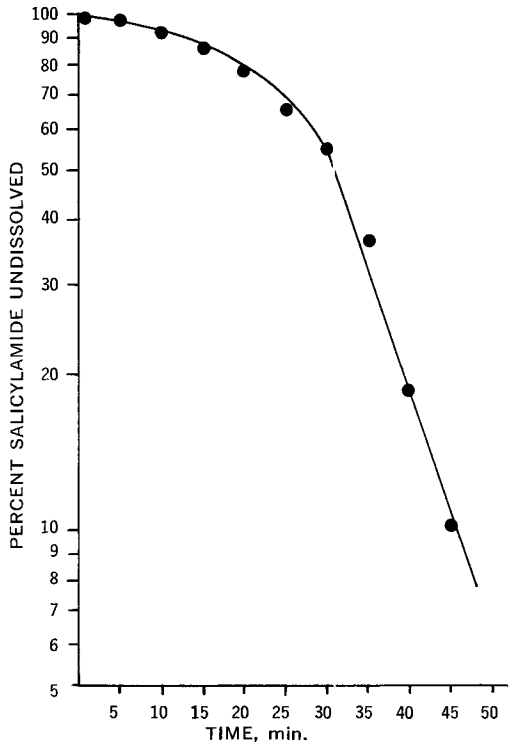

Figure 3—*Dissolution rate of salicylamide from a commercial tablet dosage form in 0.1* N *HCl at 37°. Agitation intensity, 70 r.p.m.*

law relationship. The amount of salicylamide in solution at each time was suitably corrected to account for the previously removed samples (7). The dissolution runs were performed at least in duplicate.

Absorption Testing Procedure—Four healthy adult male subjects were instructed to fast for a period of not less than 8 hr. prior to and for 2 hr. following the oral administration of the test dosage forms. The subjects were also informed not to ingest any form of salicylate or salicylamide-containing products for 72 hr. prior to the *in vivo* test. The absorption of salicylamide was studied using the urinary excretion method.

On the morning of the experiment the subjects voided their bladders of overnight urine and an hour later collected urine blanks. The subjects then swallowed two 0.3-g. salicylamide tablets or a weight of suspension equivalent to 0.6 g. of salicylamide, with the aid of exactly 250 ml. of water. A solution of 0.6 g. of drug in 250 ml. of water served as a control test preparation. Urine samples were collected at hourly intervals for 8 hr. following drug administration and at convenient time intervals thereafter for a total of 36 hr. The urine specimens were refrigerated until assayed for drug content.

Total salicylamide in the urine was determined by the colorimetric method of Levy and Matsuzawa (1), which essentially involves the acid hydrolysis of all the metabolites of salicylamide to salicylic acid, at 100°; extraction of the salicylic acid with ethylene dichloride and subsequent extraction of the salicylic acid-ethylene dichloride phase with a 0.05% $Fe(NO_3)_3$ in 0.0035 *N* HNO_3 reagent solution. The purple-colored complex formed between salicylic acid and the reagent was found to obey the Beer's law relationship at a wave length of 530 mμ. The total amounts of salicylamide equivalents excreted in the urine at each collection period were suitably corrected for the blank urine values.

The apparent relative availability of the test preparations were calculated from the following relationship:

$$\% \text{ physiological or biological availability} = \frac{\% \text{ of dose excreted from the test preparation}}{\% \text{ of dose excreted from the control preparation}} \times 100$$

RESULTS AND DISCUSSION

The initial dissolution rates of the three salicylamide-containing test dosage forms in 0.1 *N* HCl, represented as the percent salicylamide dissolved at various time periods, are listed in Table I. It is apparent from these results that the rate of solution of the test preparations decreases in the following order:

$$\text{commercial suspension} \gg \text{commercial tablet} > \text{experimental tablet}$$

Figures 1–3, represent plots of the logarithm of the percent salicylamide undissolved *versus* time for the test dosage forms. The initial rapid dissolution of salicylamide from the suspension dosage form (Fig. 1), probably involves the dissolution of the smaller salicylamide particles in the suspended state. It can be seen from these plots that both the suspension (Fig. 1) and the experimental tablet (Fig. 2) dosage forms appear to follow first-order dissolution kinetics. In the case of the commercial tablet formulation (Fig. 3) apparent first-order kinetics were not followed until less than 50% of the salicylamide contained therein remained undissolved. The significant lag in the dissolution characteristics of salicylamide from this dosage form probably reflects the influence of the nature of the inactive ingredients employed in the manufacture of the tablet dosage form on the dissolution process. It was observed that when the tablet was exposed to the dissolution medium it possessed poor disintegration characteristics, maintaining its shape during the greater portion of the dissolution run.

The dissolution half-lives ($T_{50\%}$), expressed as the time required for 50% of the salicylamide to be dissolved in 0.1 *N* HCl, were found to be 16, 31, and 240 min. for the commercial suspension, commercial tablet, and experimental tablet formulation, respectively.

The mean cumulative percent of dose of apparent salicylamide excreted in the urine by the four test subjects over a period of 36 hr. following the oral administration of the four test preparations was used to determine the *apparent* biological availabilities listed in Table II. Also shown in this table are the percentages excreted one hour following drug administration. It is readily apparent from these results that significant differences exist in the initial absorption rates of salicylamide from the test preparations, as are reflected by the total amounts of drug excreted in the urine during the first hour. The data indicate that salicylamide is most rapidly absorbed from the solution test preparation, followed by the commercial suspension, commercial tablet, and experimental tablet. Only in the case of the experimental tablet was there a marked reduction in *apparent* physiological or biological availability (*i.e.*, only about

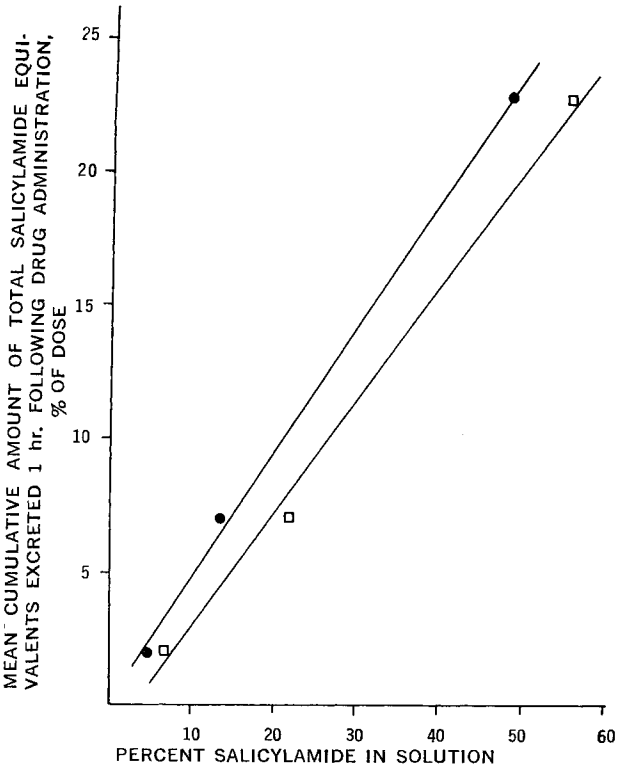

Figure 4—*Correlation between percent salicylamide in solution after 15 min.* (●) *and 20 min.* (□) *and the mean cumulative percent of apparent salicylamide excreted in the urine 1 hr. after administration of the three dosage forms.*

50% of the dose is apparently available to the body from this dosage form).

In Fig. 4, the mean quantities (% dose) of apparent salicylamide excreted 1 hr. after the oral administration of 0.6 g. of drug in the three test dosage forms are plotted against their *in vitro* dissolution rate, expressed as the amount (%) of salicylamide in solution after 15 min. (upper curve) or after 20 min. (lower curve). The equations for the two regression lines were determined to be:

$$y = 0.472\,x + 0.0744 \qquad \text{(upper curve)}$$

and

$$y = 0.432\,x - 1.63 \qquad \text{(lower curve)}$$

A significant *in vivo–in vitro* correlation was obtained using either the 15-min. dissolution rate data ($r = 0.99$) or the 20-min. dissolution data ($r = 0.99$).

However, it should be emphasized that the metabolism of salicylamide is quite complex. As has been suggested by Barr (8) and Levy and Matsuzawa (1) it is highly probable that a significant amount of salicylamide is capable of being metabolized during its initial transport from the fluids of the gastrointestinal lumen into the blood. This saturable biotransformation, which takes place during absorption, is both dose- and dosage form-dependent and

Table II—Effect of Dosage Form on the Cumulative Amount Excreted and the Relative Biological Availability of Salicylamide

Dosage Form	Cumulative Amount of Salicylamide Equivalents Excreted in 1 hr., %[a] — Subject[b] A	B	C	D	Mean	Apparent Relative Biological Availability, %[c] Mean
Aqueous solution	43.0	34.2	33.3	29.8	35.1	100.0
Commercial suspension	24.0	24.2	16.9	26.1	22.8	97.3
Commercial tablet	9.0	5.0	4.9	9.6	7.1	91.5
Experimental tablet	1.7	1.9	2.7	1.8	2.0	55.5

[a] Expressed as percentage of 0.6 g.-dose excreted in all forms. [b] Subject (age, weight in lbs.): A (24, 185), B (39, 163), C (21, 183), and D (20, 140). [c] Expressed as the ratio of the percent of the dose of salicylamide excreted in all forms from the test preparation to that from a control, aqueous solution of the drug, times 100.

can have a pronounced effect on the plasma levels of intact, pharmacologically active drug. As a result, the biological availabilities reported in the present communication are *apparent* values and should not be construed as meaning that one test dosage form of the drug is more therapeutically efficacious than another. The results obtained in this study do, however, demonstrate that the absorption of total salicylamide, and presumably intact drug (8), is dissolution rate-limited and that it is possible to correlate the initial absorption and dissolution rates of markedly different dosage forms of this drug.

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