Relative Bioavailability of Aspirin Gum

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Received July 28, 1980, from the *College of Pharmacy, Rutgers University, New Brunswick, NJ 08854, and the ‡Drug Concentration Laboratory, University of Massachusetts Medical Center, Worcester, MA 01605. Accepted for publication April 8, 1981.

Abstract □ The bioavailability of aspirin gum relative to unbuffered aspirin tablets was determined in six normal volunteers. Twenty-four hours following the administration of two aspirin tablets, 91.2 ± 1.7 % (*SE*) of the 648-mg dose was recovered in the urine. The relative bioavailability of aspirin gum was 69.5 ± 3.4 % (*SE*), based on cumulative 24-hr urinary excretion of total salicylate after the chewing of three gum tablets for 15 min. The chewed gum was analyzed for total salicylate and contained an average of 37.8% of the administered dose. When added to the cumulative amount of total salicylate excreted in the urine at 24 hr after dosing, the salicylate contained in the chewed gum accounted for essentially 100% of the dose administered. Chewing aspirin gum for up to 30 min did not significantly ($p > 0.05$) reduce the amount of salicylate entrapped in the gum base when compared to chewing times of 5, 10, and 15 min. Based on the results of this study, four pieces of aspirin gum would be needed to provide the same amount of salicylate to the general circulation as two 324-mg aspirin tablets.

Keyphrases □ Aspirin gum—relative bioavailability compared to unbuffered aspirin tablets in six normal volunteers □ Bioavailability—aspirin gum compared to unbuffered aspirin tablets in six normal volunteers □ Dosage forms—comparison of salicylate availability from aspirin gum and unbuffered aspirin tablets

Aspirin is the most frequently used nonprescription analgesic, and selection of an aspirin product should be based on formulation preference and proven efficacy (1). Bioavailability studies have been conducted on many dosage forms of aspirin including aqueous solutions (2, 3), compressed tablets (4, 5), effervescent tablets (6, 7), controlled-release tablets (8), enteric-coated tablets (9–11), and rectal suppositories (12). These studies have shown that the bioavailability differences between products apparently are related to formulation factors. Recognizing the potential for therapeutic inequivalence, the American Pharmaceutical Association published a bioavailability monograph for aspirin (13).

One aspirin product omitted from this bioavailability monograph was aspirin chewing gum[1]. There have been no reported investigations in humans of the relative bioavailability of aspirin from gum formulations. Aspirin gum was introduced commercially in 1924; in 1976, the total sale of aspirin gum was nearly 80 million gum pieces[2]. The label claims for aspirin gum include "for the temporary relief of minor sore throat pain, headache, aches and pains of colds and flu and muscular aches and pains." The efficacy of aspirin gum as a systemic analgesic is dependent on the rate and extent of aspirin bioavailability.

This investigation evaluated the relative bioavailability of aspirin gum by comparing the urinary excretion of total salicylate after dosing with aspirin gum and regular aspirin tablets.

EXPERIMENTAL

Subjects—Six male volunteers, 18–31 years of age (27.3 ± 1.5 years, mean ± *SE*) were selected. The study was approved by the institutional human studies review committee and valid, written, informed consent was obtained from each volunteer prior to his entering the study. The mean (±*SE*) body weight of the volunteers was 72.9 (±5.6) kg, and each volunteer was within 10% of his ideal body weight for his height and build (14). Each volunteer was determined to be in good physical health with no history of aspirin allergy, GI tract ulcers, or cardiac, hepatic, or renal disease.

The volunteers were instructed to refrain from taking any medication for at least 7 days prior to the study and to abstain from alcoholic beverages for 24 hr prior to dosing. All volunteers fasted, with the exception of water, for 12 hr prior to dosing, and fasting was continued for 4 hr after dosing. On the evening before each study day, the volunteers were instructed to empty their bladders and to drink 180 ml of water. Upon arising, the volunteers again emptied their bladders and drank 180 ml of water at 1 and 0.5 hr prior to dosing.

Drug Administration—On the 1st study day, the volunteers were assigned at random either the aspirin gum[3] or the aspirin tablets[4]; on the 2nd study day, the volunteers received the alternate formulation. The 2 study days were separated by a washout period of 7 days. At 8 am on each study day, the volunteers assigned the gum chewed three pieces (226.8 mg of aspirin/gum piece; total aspirin dose of 680.4 mg) for 15 min, swallowing saliva and any fragments of coating loosened by the chewing process. After chewing was completed, the gum was expectorated into a plastic vial and frozen at −20° for later salicylate analysis, and the volunteers were instructed to drink 120 ml of water. The volunteers assigned the aspirin tablets swallowed two tablets (324 mg of aspirin/tablet; total aspirin dose of 648 mg) with 120 ml of water. Previous replicate analysis for potency showed the gum and tablet to contain 98 and 105% of the label claim, respectively. To promote adequate urine flow, all volunteers were instructed to drink 180 ml of water 2 hr following the administration of each dosage form.

Urine Collection—Immediately before dosing, the volunteers emptied their bladders completely and an aliquot of the blank urine was collected and frozen at −20°. After dosing, urine was collected by complete voiding at 1, 2, 3, 4, 6, 8, 10, 12, and 24 hr. The volume and pH of voided urine were measured at each collection time, and an aliquot was frozen at −20° for salicylate analysis.

Effect of Chewing Time—Four of the six volunteers included in the bioavailability study were instructed to chew three aspirin gum pieces for 5, 10, 15, or 30 min, respectively, on 4 separate days. After chewing, the gum was expectorated into a plastic vial and the amount of salicylate remaining in the chewed gum was measured to determine if chewing time influenced salicylate release from the gum.

Assay of Total Salicylate in Urine—The total amount of salicylate in the urine samples was measured using the procedure of Chiou and Onyemelukwe (15). Briefly, 3.0 ml of urine and 2.0 ml of concentrated hydrochloric acid were added to a 50-ml culture tube, which was then incubated at 100° for 17 hr. After cooling to room temperature, 6.0 ml of chloroform was added to the tube and the mixture was shaken mechanically for 10 min. Following centrifugation, 3.0 ml of the chloroform was added to 6.0 ml of Trinders reagent (without mercuric chloride). After vortex mixing, the absorbance of the upper, aqueous phase was measured at 540 nm[5].

The concentration of salicylate in the urine sample was determined from a standard curve prepared by measuring the absorbance of sodium salicylate solutions of known concentrations after subjecting them to the described procedure. Each urine sample was analyzed in duplicate, and the average value was used to calculate the amount of total salicylate excreted during each collection interval. Urine blanks, urine standards spiked with known amounts of sodium salicylate, and aqueous sodium salicylate standard solutions were assayed with each batch of the vol-

[1] Aspergum, Plough, Memphis, TN 38151.
[2] Mr. McGee, personal communication, Plough, Memphis, TN 38151.
[3] Aspergum, lot 6060.
[4] Bayer aspirin tablets, lot 6L176, Glenbrook Laboratories, Division of Sterling Drug Inc., New York, NY 10016.
[5] DBGT spectrophotometer, Beckman Instruments, Irvine, Calif.

0022-3549/81/1200-1341$01.00/0

Table I—Mean ± *SE* Cumulative Amounts of Total Salicylate (Expressed as Milligrams of Aspirin Equivalents) Excreted in the Urine after Administration of Aspirin Gum or Tablets

Hours	Aspirin Excreted, mg: Gum (680.4-mg Dose)	Aspirin Excreted, mg: Tablet (648-mg Dose)
1	30.7 ± 4.0	23.1 ± 3.9
2	66.3 ± 8.0	63.7 ± 6.2
3	114.0 ± 11.1	111.6 ± 7.2
4	166.0 ± 16.2	153.8 ± 11.6
6	244.0 ± 23.1	242.1 ± 17.9
8	296.8 ± 24.1	324.8 ± 25.1
10	347.0 ± 25.9	387.6 ± 28.1
12	385.3 ± 25.8	462.9 ± 28.0
24	433.6 ± 19.8	592.6 ± 11.1

unteer's urine samples as a quality control check. The total salicylate measured in the urine samples was converted to milligrams of aspirin by multiplying by 1.125.

Assay of Total Salicylate in Chewed Gum—The amount of salicylate contained in chewed gum was determined as follows. The chewed gum was placed in a flask containing 50 ml of 1 *N* HCl, heated to 100°, and stirred for 1 hr. After cooling to room temperature, the mixture was centrifuged and the hydrochloric acid was removed and diluted to 100 ml with 1 *N* HCl. This solution was diluted 1:100, and the absorbance of this diluted solution was measured spectrophotometrically at 240 nm. The concentration of salicylate in the solution was determined from a standard curve constructed by subjecting sodium salicylate solutions of known concentration to the same procedure previously described.

The absorbance spectrum of the salicylate solution obtained from the gum analysis was compared to the absorbance spectrum of a standard solution of sodium salicylate. There were no differences between the spectra in the general shape of the curves or the wavelengths where maxima and minima occurred, indicating that the observed absorbance was due to salicylate. The amount of salicylate recovered from the gum was converted to milligrams of aspirin by multiplying by 1.125.

Bioavailability Calculations—The relative bioavailability of aspirin gum (F_{rel}) was calculated as the percentage of aspirin equivalent eliminated in the urine in the 24 hr (U_∞) following the administration of each dosage form after correcting for the dose (D) of aspirin administered:

$$F_{rel}(\%) = \left[\frac{U_\infty \text{ (gum)}}{U_\infty \text{ (tablet)}}\right]\left[\frac{D \text{ (tablet)}}{D \text{ (gum)}}\right] \times 100 \qquad \text{(Eq. 1)}$$

Statistical Analysis—A paired t test was used to determine the significance of differences in the mean total aspirin bioavailability between the gum and the tablet, respectively. A one-way analysis of variance was used to determine the significance of the effect of chewing time on the amount of aspirin recovered from chewed gum.

RESULTS AND DISCUSSION

Table I lists the mean ± *SE* amounts of total salicylate (in terms of equivalent aspirin) excreted in the urine at various intervals up to 24 hr following dosing. After tablet administration, a mean ± *SE* of 91.2 ± 1.7% of the aspirin dose was recovered in the urine. This percentage of dose recovered is consistent with the values reported by other investigators (16, 17) who recovered virtually 100% of the aspirin dose as metabolites in the urine. The analytical method used in this study to measure total salicylate in urine accounts for aspirin, salicylic acid, and all other metabolities. Collection of total urine for 24 hr also provides enough time for recovery of essentially all of the dose based on a plasma elimination half-life of salicylate of 3 hr after a single dose of ~650 mg (18). When aspirin gum was chewed, only 63.5 ± 2.9% (mean ± *SE*) of the dose was recovered.

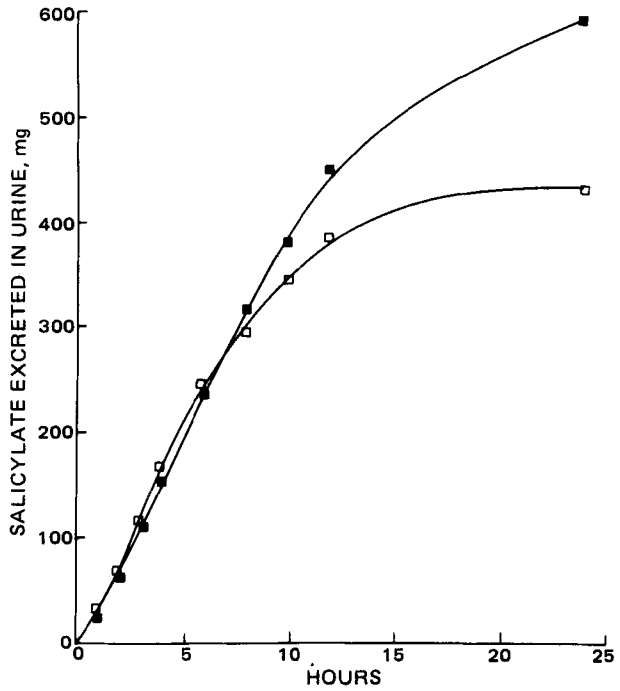

Figure 1—*Mean cumulative urinary salicylate (expressed as milligrams of aspirin) excretion curves for six subjects following administration of three aspirin gum pieces (680.4 mg) (□) or two aspirin tablets (648 mg) (■).*

Figure 1 shows the mean cumulative urinary excretion curves for six subjects following administration of gum and tablet dosage forms. Differences in the rate and extent of bioavailability are reflected in the shape of the curves. For up to 6 hr following dosing, the curves are practically superimposable, so it may be concluded that the dosage forms are bioequivalent in terms of bioavailability rate. However, beyond 6 hr, both curves begin to diverge and approach different asymptotic values. The total amounts (mean ± *SE*) of aspirin equivalent excreted in the urine 24 hr following the administration of the tablets and the gum were 592.6 ± 11.2 and 433.6 ±19.8 mg, respectively. The difference between dosage forms in the total amount of salicylate excreted shows that the extent of aspirin gum bioavailability was less than that of aspirin tablets.

The individual cumulative amount of total salicylate recovered in the urine at 24 hr following dosing and the relative bioavailability of aspirin gum are shown in Table II. The differences in total salicylate recovered in the urine were significant ($p < 0.05$), and the bioavailability of aspirin gum ranged from 61.0 to 81.0% (mean ± *SE* of 69.5 ± 3.4%). Since the renal clearance of free salicylate is pH dependent, urine pH possibly may influence the excretion pattern of aspirin metabolites and affect the evaluation of aspirin bioavailability. The pH of each urine sample col-

Table II—Individual Cumulative Amounts of Total Salicylate (Expressed as Milligrams of Aspirin Equivalents) Excreted in the Urine 24 hr after Administration of Gum and Tablets and the Relative Bioavailability of Aspirin Gum

Subject	U_∞, Gum[a], mg	U_∞, Tablet[b], mg	F_{rel}, %
A	410.8	587.7	67.6
B	497.2	586.7	81.0
C	460.1	565.1	77.1
D	369.0	572.2	61.0
E	466.1	634.7	69.5
F	398.4	618.2	61.0
Mean	433.6	592.6	69.5
±*SE*	19.8	11.2	3.4

[a] Oral dose, 680.4 mg. [b] Oral dose, 648 mg.

Table III—Total Amount of Salicylate (in Milligrams of Aspirin) Recovered in the Chewed Gum and Cumulative 24-hr Urine Collection after Administration of Three Aspirin Gum Pieces (680.4)

Subject	Gum, mg	Urine, mg	Total, mg
A	263.3	410.8	674.1
B	249.8	497.2	747.0
C	222.4	460.1	682.5
D	345.2	369.0	714.2
E	204.5	466.1	670.6
F	259.5	398.4	657.9
Mean	257.5	433.6	691.1
±*SE*	±19.8	±19.8	±13.6

Table IV—Amount of Salicylate (in Milligrams of Aspirin) Remaining in Chewed Aspirin Gum after the Chewing of Three Gum Pieces (680.4 mg) by Four Volunteers

Chewing time, min	Volunteer				Mean ± *SE*
	A	B	C	D	
5	195.4	280.7	301.7	385.4	290.8 ± 39.0
10	250.0	177.1	279.7	216.8	230.9 ± 22.0
15	213.6	261.9	276.5	202.2	238.6 ± 18.2
30	170.4	209.5	217.0	242.1	209.8 ± 14.9

lected during the study was recorded, and average pH values of all urine samples collected following administration of the tablet and gum were 6.1 and 6.3, respectively. The differences in urine pH between the two sets of urine samples were not significant ($p > 0.05$) using a paired t test, and it was concluded that urine pH did not influence the determination of relative bioavailability.

The amounts of salicylate remaining in the gum for each individual volunteer after chewing for 15 min are listed in Table III. The average amount of salicylate remaining in the gum represents 37.8% of the dose administered. When added to the 24-hr urinary recovery of salicylate, the amount of total salicylate in the chewed gum mass accounted for 101.6 ± 2.0% (mean ± *SE*) of the administered dose. Therefore, it may be concluded that the difference in the extent of bioavailability between aspirin gum and tablets is due to salicylate becoming entrapped or bound to the gum base during chewing.

Table IV shows the effect of chewing time on the amount of salicylate retained in the gum base. After 5 min, the average amount of salicylate in the chewed gum was equivalent to 42.7% of the administered dose. For chewing times of 10, 15, and 30 min, the average percentages of dose remaining in the gum between 5 min and the other chewing times were not significant ($p > 0.05$); therefore, the use of a 15-min chewing time in the bioavailability study did not influence the determination of relative bioavailability.

In aspirin bioavailability studies where single doses in excess of ~500 mg are used, consideration must be given to the possible effects of dose-dependent kinetics on the determination of relative bioavailability. This is particularly crucial in bioavailability studies based on the measurement of serum salicylate concentrations where dose-dependent kinetics may influence the shape of the serum concentration–time curve and possibly bias bioavailability calculations. In this study, total aspirin bioavailability for the gum and tablet was determined in terms of salicylate by analysis of total salicylate recovery in the urine for up to 24 hr. This type of bioavailability study design for aspirin eliminates any bias due to dose-dependent kinetics. In addition, measurement of total salicylate in the urine provides the most accurate estimation of total bioavailability because it masks intra- and interpatient variability in rates of salicylate absorption and metabolism which may affect the size and shape of a serum salicylate–time curve (19).

Since few studies have correlated relative bioavailability with relative therapeutic efficacy, the clinical significance of the inferior bioavailability of aspirin gum is unclear. However, many studies have shown aspirin to be superior to placebo in the treatment of pain, and it is generally thought that the onset and magnitude of pain relief are a function of the rate and extent of aspirin bioavailability from its dosage form. No published studies document the effectiveness of aspirin gum as a systemic analgesic, and, based on the data presented in this report, it may be concluded that two 324-mg aspirin tablets will provide as much salicylate to the general circulation as four 227-mg aspirin gums. Furthermore, the usual recommended adult dose of aspirin gum which is two pieces, is less than the minimum therapeutic dose of 324 mg.

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ACKNOWLEDGMENTS

Presented at the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Kansas City Meeting, November 1979.

Abstracted in part from a thesis submitted by D. W. Woodford to the Massachusetts College of Pharmacy in partial fulfillment of the Master of Science degree requirements.

The assistance of the Word Processing Center in the preparation of the manuscript is gratefully acknowledged.