# *In Vivo* Drug Release Rate from Hard Gelatin Capsules

By JOHN H. WOOD

**Serum salicylate levels were utilized to evaluate the relative release rate of aspirin from a commercial aspirin tablet and from a hard gelatin capsule. Although a few subjects obtained rapid release from the capsules, the majority had an appreciable delay relative to tablets. The population distribution of levels is markedly different between capsules and tablets at the times studied. The median delay for significant levels is approximately 15 min.**

THE USE of hard gelatin capsules is almost axiomatic in the preliminary pharmacologic study of a new drug before any technological study is even contemplated. Although *in vitro* disintegration testing may be examined by many procedures, "The National Formulary" XII (1) states, "Disintegration time limits are not specified for capsules, since the shell dissolves rapidly in the gastrointestinal tract." There is very little literature on capsule performance (2, 3), even *in vitro*.

Although many clinical references may be found in which tablets and capsules were used, the time intervals chosen do not permit a comparative evaluation of the initial release pattern.

For this reason, it seemed of interest to determine the *in vivo* release characteristics of commercial hard gelatin capsules relative to fast disintegrating, rapidly dissolving tablets.

## EXPERIMENTAL

Five grains of acetylsalicylic acid (powdered U.S.P.) were loaded into No. 1 commercial clear gelatin capsules (Eli Lilly Co., Indianapolis, Ind.). Two capsules were administered to each of 50 persons. Total salicylate serum levels were determined by the modified method of Brodie (4, 5). This determines the sum of both salicylic and acetylsalicylic acids present. For a reference comparison, the same persons received two tablets of a leading commercial 5 gr. aspirin–starch tablet. Anticipating a delay in release for the capsules, capsule plasma times were chosen as 15, 30, and 45 min. and tablet times as 10 and 20 min.

The data obtained are summarized in Table I. The nature of the distributions is shown in Fig. 1. The significance of these distributions has already been discussed (6, 7).

The median data are shown graphically in Fig. 2. In the latter, for comparison purposes, published data on the same commercial tablet (7, 8) are shown also, implying that the spectrum of subjects used was normal in both cases.

Standard deviations are not given because of the extremely broad capsule distribution. The shape of the distribution curves is more significant.

## DISCUSSION

The shapes of the serum level distributions are quite different between the capsules and the tablets, showing an unduly high percentage of low levels for the capsules.

It is apparent that the release rate from capsules is somewhat irregular. Indeed, a few capsules apparently released while being swallowed, while several were quite delayed, over 45 min., in opening. From the median behavior shown in Fig. 2, there is a median delay of approximately 15 min. between the release of a commercial hard gelatin capsule and a good commercial compressed fast disintegrating tablet.

Thus, in pharmacologic testing of relative response times or of time of onset of a given response, the release pattern from the dosage form can be of importance. The possible differences between capsules and tablets must, therefore, be taken into consideration.

TABLE I.—TOTAL SERUM SALICYLATE LEVELS OBTAINED

| Prepn. | Time, min. | Av. Level, mcg./ml. | Median Level, mcg./ml. |
|---|---|---|---|
| Tablets | 10 | 5.9 | 5 |
| | 20 | 14.0 | 14 |
| Capsules | 15 | 5.0 | 2 |
| | 30 | 15.1 | 8 |
| | 45 | 24.9 | 22 |

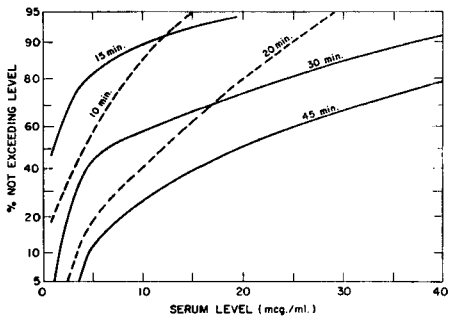


Fig. 1.—Cumulative per cent plot on probability scale of serum salicylate levels obtained at times as shown. Key: ---, tablets; ——, capsules

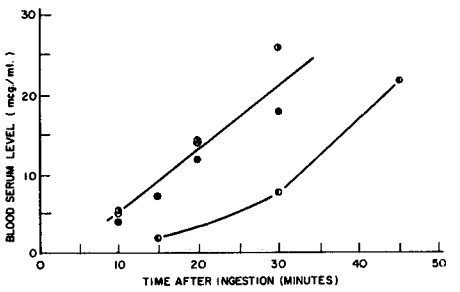


Fig. 2.—Median serum salicylate levels obtained as a function of time. Key:, ○, tablets (this study); ◑, *Reference 6;* ●, *Reference 7;* ◐, capsules (this study).

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# Investigation of the Saluretic and Kaliuretic Properties of a Diuretic Agent in Swine by *In Vivo* Whole Body Counting

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**A simple and concise analytical technique was developed for the determination of the kaliuretic and saluretic properties of diuretic agents in large animals. Whole body liquid scintillation counting, in conjunction with the radioactive isotopes $^{24}Na$ and $^{42}K$, was utilized to determine directly the retention of the isotopes in swine during control and diuretic treatment. A radioactive tracer was orally administered and allowed to equilibrate in the animals, and control or drug treatment was initiated. Animals were counted at selected time intervals. The per cent retention of the radioactive isotope was calculated for each whole body tracer determination. Control and treated data were compared for the loss of sodium and potassium due to diuretic action. The diuretic agent, furosemide, was found to exhibit a marked saluretic activity in swine, while causing a small loss in potassium.**

MANY BIOLOGICAL testing methods have been devised to evaluate diuretics. The measurement of urine volume, employing rats and dogs as test animals, is commonly used to indicate diuretic activity (1–5). Sodium excretion in the urine is used as an index of diuretic activity (6–8). In the biological comparison of the effectiveness of various diuretic compounds, as well as the determination of their effect on electrolyte balance, the Van Arman method or modifications (9–12) may be employed for dogs, while in rats the Lipschitz method or modifications may be used (1, 10, 13–16). Generally, the animals are fasted, hydrated, and dosed; the urine is collected, volume measured, and the urine analyzed by flame photometry for ionic content.

The development of large volume liquid scintillation counters has made possible whole body measurement of minute amounts of $\gamma$-emitting radioisotopes. The pharmacological action of diuretic agents upon the excretion of sodium and potassium by the rat has been investigated by small animal whole body liquid scintillation counting (17, 18). Microcurie amounts of the electrolyte studied were administered to the experimental animals. Following equilibration of the isotope with normal body electrolyte, whole body radioactivity was determined, and subsequent measurements were made during drug or control treatment. Direct comparison of radioisotope retention in treated and in control animals allowed the evaluation of drug action upon the excretion of the ion of interest.

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Although small animals, such as rats, are important in the study and evaluation of diuretic agents, larger animals, such as the dog, are commonly employed. This investigation was undertaken to study the utilization of a large animal whole body liquid scintillation counter for the determination of the saluretic and kaliuretic properties of a diuretic compound in large animals. Small swine were chosen as the experimental animal because of the biological similarity of swine to man.

## EXPERIMENTAL

The investigation was divided into two parts. Initially, radioactive potassium, $^{42}K$, was utilized to study the effect of the diuretic agent furosemide[1] upon whole body potassium retention. This procedure was followed by the study of the effect of the diuretic upon whole body sodium retention with radioactive sodium, $^{24}Na$. A total of nine swine, weighing from 9.1–17.3 Kg., was employed in the investigation. Five animals were utilized in the $^{42}K$ study and four in the $^{24}Na$ study. The animals served as their own controls, with drug treatment following the control study immediately after the decay of the radioactive isotope (5–10 days).

Swine were housed individually in dog metabolism cages. Food was removed 12 hr. before radioactive isotope determinations were initiated. Fasting was continued for the duration of the experiment. Distilled water was given *ad libitum*. Urine was collected, and the volume was measured throughout each experimental period. Animals were weighed at various time intervals during each study.

Radioactive isotopes were obtained as the chloride in an aqueous stock solution.[2] An accurately meas-

[1] Furosemide is 4-chloro-*N*-(2-furylmethyl)-5-sulfamoylanthranilic acid. This compound was supplied by Lloyd Brothers, Inc., Cincinnati, Ohio, and has the trade name of Lasix.
[2] Oak Ridge National Laboratory, Oak Ridge, Ten