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Method for Monitoring Hard Gelatin Capsule Disintegration Times in Humans Using External Scintigraphy

Keyphrases □ Gelatin capsules, hard—disintegration and drug release times *in vivo* monitored by external scintigraphy using technetium Tc 99m □ Disintegration time—hard gelatin capsules *in vivo*, monitored by external scintigraphy □ Drug release time—hard gelatin capsules *in vivo*, monitored by external scintigraphy □ Technetium Tc 99m—used in scintigraphic monitoring of disintegration and drug release times of gelatin capsules *in vivo* □ Scintigraphy, external—disintegration and drug release times of gelatin capsules monitored

To the Editor:

We wish to report a noninvasive and novel approach for monitoring disintegration and drug release times from a gelatin capsule in humans. The method involves the utilization of a short-lived radionuclide coupled with external scintigraphy.

Two separate formulations were used to fill identical hard gelatin capsules[1]. Formulation A consisted of 150 mg of a totally water-insoluble polystyrene resin (40–100 mesh) bearing polyamine functions which chelated the radionuclide, technetium Tc 99m, in an irreversible manner (1). Formulation B was water soluble, consisting of 145 mg of lactose and 5.9 mg of the soluble chelating agent etidronate disodium[2] labeled with technetium Tc 99m.

In a typical experiment, the subject ingested a gelatin capsule[1] filled with an appropriate material labeled with 20 mCi of technetium Tc 99m. Technetium Tc 99m is a γ-ray-emitting radionuclide (half-life = 6 hr) with an energy of 140 kev. The low energy and short half-life of this radionuclide make it suitable for external scintigraphic studies involving humans, and the radiation dose is minimal.

Following oral administration with 100 ml of water, the normal subject was placed in a supine position on a hard top stretcher for general body immobilization. The abdomen was then positioned beneath the collimated detector of a multicrystal scintillation camera[3]. Data were accumulated for up to 200 min, when necessary, at 1-min intervals. These 1-min count integrations were stored on the computer magnetic tape for future retrieval.

During data collection, scintiphotos were taken. These scintiphotos (Fig. 1) showed the release of radioactivity from the capsule region to the other portions of the stomach as a function of time. The pictures also illustrated the lack of capsule movement within the stomach, the swelling of the capsule, and, finally, the release and dispersion of the capsule contents to other stomach regions (Fig. 1).

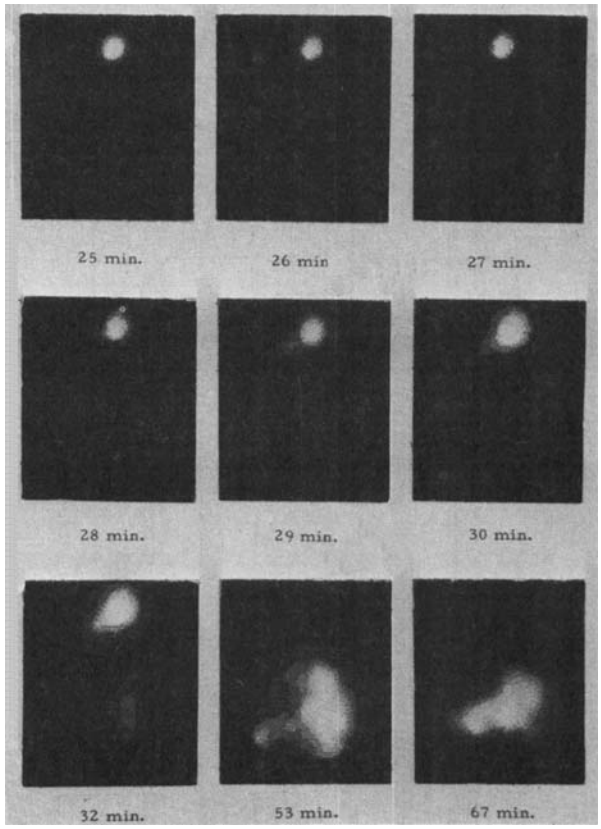

Figure 1—*Sequential scintiphotos of intermittent phases of the* in vivo *collapse of a gelatin capsule using Formulation A (empty stomach).*

Although the scintiphotos gave a qualitative picture of the release of the capsule contents, quantitative determination of the absolute capsule disintegration rate was performed with the aid of a computer. We chose an area of interest directly over the capsule and an area of

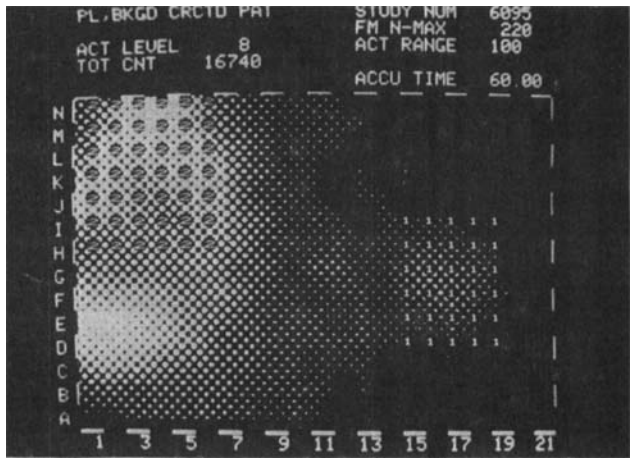

Figure 2—*Scintiphotos showing the two computer areas of interest within the stomach. Key: 1, area of interest over the capsule; and 2, area of interest over the pyloric region of the stomach.*

[1] Gelatin capsules No. 0, Eli Lilly and Co., Indianapolis, IN 46206
[2] Osteoscan, Procter and Gamble Co., Cincinnati, Ohio.
[3] Gamma-camera (Baird Atomic-System 77) equipped with a computer and magnetic tape and possessing storage and replay capability.

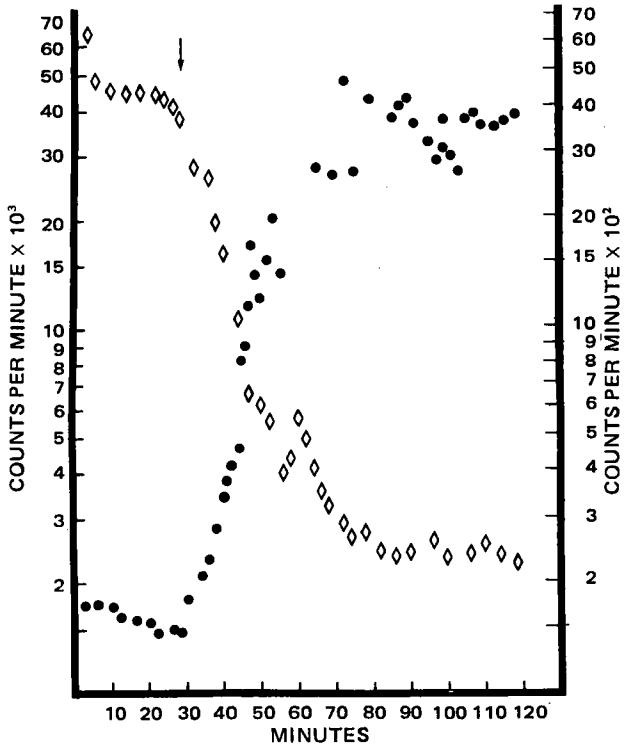

Figure 3—*Graphic display illustrating release of radioactivity from a gelatin capsule in the human stomach using Formulation A (empty stomach). Key: ◊, disappearance of radioactivity from the capsule region (Area 1, Fig. 2); and ●, concomitant appearance of radioactivity in the pyloric region of the stomach.*

interest in the lower pyloric region of the stomach (Fig. 2). Continuous monitoring of the radioactivity in the two regions, as a function of time, showed a sharp decrease in radioactivity in the capsule region, marking the time of its collapse, with a concomitant increase at the pyloric region. A typical plot is shown in Fig. 3. Further follow-up (Fig. 3) on the rate of passage of radioactivity through the lower stomach provided data for the estimation of gastric emptying times (1).

When the Formulation A capsule was administered to two subjects on an empty stomach, the scintiphotos and the integrated computer plots showed that the release of the capsule contents began 30 (Subject 1, Fig. 3) and 40 (Subject 2) min after ingestion. On a full stomach, the same two subjects exhibited much longer times for initial release of the contents, 93 and 120 min, respectively. In all cases, the capsule remained stationary and the capsule contents dispersed immediately to the other regions of the stomach after the initial release.

Upon administration of the Formulation B capsule to Subject 1 on an empty stomach, the initial release of radioactivity occurred after only 6 min. Considerable swelling of the capsule was also observed before the release. The decrease of activity from the capsule region was gradual up until 56 min after administration. At this point, there was a sharp break in the curve, indicating virtually complete disappearance of radioactivity from the capsule region.

The observed differences in the times of release of Formulations A and B from identical capsules can be explained on the basis of the differences in these formulations. The relatively large (40–100 mesh) insoluble resin particles of Formulation A can be dispersed into the stomach only after major collapse of the capsule walls, a rather lengthy process. But the water-soluble Formulation B can be released in a shorter time because the gastric juices gain access to the interior of the capsule *via* a small orifice or diffusion through the walls. These findings are consistent with the previously reported observation that increasing the water-soluble nature of a formulation will increase its rate of release from a gelatin capsule (2–4). It is also known that particle size and type of diluents or fillers used in various formulations can drastically affect the rate of their release from gelatin capsules (5).

In conclusion, this technique can provide valuable information regarding the *in vivo* behavior of capsules. The present method is noninvasive and exposes the subjects to an extremely low radiation dose. If the experiment is conducted with 20 μCi of technetium Tc 99m, the radiation dose to the whole body is 1 mrad and that to the stomach is 10 mrads (1). The present study illustrates the great potential of external scintigraphy in the assessment of drug formulations.

(1) M. C. Theodorakis, Ph.D. thesis, University of Kentucky, Lexington, Ky., 1975.

(2) L. L. Augsburger, in "Sprowls' American Pharmacy," 7th ed., L. W. Dittert, Ed., Lippincott, Philadelphia, Pa., 1974, chap. 10.

(3) J. M. Newton, G. Rowley, and J. F. V. Thornblom, *J. Pharm. Pharmacol.*, **23**, 452(1971).

(4) *Ibid.*, **23**, 156S(1971).

(5) J. G. Wagner, "Biopharmaceutics and Relevant Pharmacokinetics," 1st ed., Hamilton Press, Hamilton, Ill., 1971, p. 116.

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High-Pressure Liquid Chromatographic Determination of Polythiazide in Pharmaceutical Dosage Forms

Keyphrases □ Polythiazide—high-pressure liquid chromatographic analysis, pharmaceutical dosage forms □ High-pressure liquid chromatography—analysis, polythiazide in pharmaceutical dosage forms □ Diuretics—polythiazide, high-pressure liquid chromatographic analysis in pharmaceutical dosage forms

To the Editor:

A recent report by Moskalyk *et al.* (1) utilized a high-pressure liquid chromatographic (HPLC) method