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THE HYDRODYNAMICALLY BALANCED SYSTEM (HBS™): A NOVEL DRUG DELIVERY SYSTEM FOR ORAL USE

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ABSTRACT

Data on the gastric retentive characteristics of the HBS™ with diazepam are presented. Data to support the mechanism of drug release for chlordiazepoxide from an HBS™ system are also presented, as well as the blood level-time profiles for both drugs. The majority of data has been previously used to support the advertising of Valrelease™ to the medical profession.

The Hydrodynamically Balanced System (HBS™) is an oral dosage form (capsule or tablet) that is designed to prolong the residence time of the dosage form within the gastrointestinal G.I. tract. It is a formulation of a drug with gel-forming hydrocolloids meant to remain buoyant on stomach contents. This not only prolongs G.I. residence time, but does so in an area of the G.I. tract that would maximize drug reaching its absorption site in solution, and hence ready for absorption. Drug dissolution and release from the capsule retained in stomach fluids occur at the pH of the stomach, under fairly controlled conditions. The microenvironmental pH can be further controlled via drug product formulation. The retentive characteristics of the dosage form are most significant for drugs:

(a) insoluble in intestinal fluid;
(b) that act locally;
(c) that exhibit site-specific absorption.

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However, the system can be used for most drugs where controlled (sustained) release of drug from the dosage form is desired by the oral route.

The formulation of the dosage form must comply with three major ceiteria for Hydrodynamically Balanced System™:

(1) it must have sufficient structure to form a cohesive gel barrier;
(2) must maintain an overall specific gravity lower than that of gastric contents (reported as 1.004 - 1.01) (2); and
(3) should dissolve slowly enough to serve as a "reservior" for the delivery system.

Figure 1 shows the in vitro "floating" characteristics of the HBS™ dosage form, compared to a conventional capsule. Figures 2-5 show a time sequence of the in vitro behavior of the HBS™ capsule immersed in simulated gastric fluid over many hours. After immersion for 1 hour, the gel barrier is thin, with undissolved powder (drug, hydrocolloid and excipients) still within the core of the gel. The size is not much greater than the size of the original capsule. After 4 hours, loose unwetted powder is still visible in the gel core. At 6 hours, there is still little change in size or shape. Only at 8 hours does the size reduction become obvious. Their relative consistency of size and shape maintains a fairly constant surface area for drug/solvent diffusion. It is postulated that when the HBS™ dosage form comes in contact with an aqueous media, the hydrocolloid starts to hydrate by first forming a gel. This gel, at the surface of the HBS™ then controls the rate of diffusion of solvent-in and drug-out of the dosage form. As the exterior surface of the dosage form goes into solution, the gel layer is maintained by the hydrocolloid from the immediate adjacent layer going into hydration. The drug dissolves in and diffuses out with the diffusing solvent, creating a "receding boundary" within the gel structure.

In vitro visualization is helpful, but in vivo visualization is the crucial parameter for evaluating the G.I. tract retentive characteristics of the dosage form. Figure 6 is an x-ray showing the in vitro behavior of two capsules; one the HBS™ (containing two small barium sulfate tablets) floating at the surface, and the other a conventional capsule containing a single barium sulfate tablet, sunk at the bottom of the vessel. When these two capsules are ingested simultansously by a human volunteer, the positional analysis indicates the gastric retention of the HBS™, while the conventional capsule can be seen much lower in the tract (Figure 7).

An additional technique was employed to further study the in vivo behavior of the HBS™. External scintigraphy is a technique whereby the in vivo behavior of a dosage form can be monitored noninvasively, minute by minute(3). A dosage form is prepared to contain a gamma-emitting radionuclide, swallowed by human volunteers, and monitored by external scintigraphy. A collimating plate is placed between the subject and the camera. Only those gamma emissions perpendicular to the collimator penetrate to the gamma camera, thereby giving positional analysis. The computer accumulates the counts impacting on each separate crystal, the summation of which gives a quantitiative analysis of the radioactivity in any zone covered by the total crystal array. Figure 8 is a photograph of the T.V. screen used to visually monitor the dosage form. If the dosage form depicted was a disintegrating one, at the end of the disintegration process the entire screen would portray radioactivity. If it was a non-disintegrating dosage form, it would move towards the bottom center of the screen, and then exit the screen near the top left-hand corner. This movement would indicate dosage form travel through the pyloric valve. The visualized size, for a non-disintegrating dosage form, would be essentially constant. Figure 9 shows two dosage forms labelled with Technetium^{99m} (Tc^{99m}) chelated with etidronate disodium[a], in vivo in a human subject, two minutes post ingestion. The dosage form labelled A is an HBS™ capsule, while B is a conventional tablet. The stomach outline is visualized because the dosage forms were ingested with 200 ml of water, radiolabelled with Indium^{111}. The disproportionate size of the dosage forms to the size of the stomach is due to the intensity of the Tc^{99m} label, creating greater scatter. Note the height differential of the HBS™ and the tablet. Figure 10 is one hour later, and indicates not only a difference in position, but also loss of Tc^{99m} from the tablet. The stomach outline is further illustrated by the ingestion of an additional 100 ml of Indium^{111}-labelled water. Figure 11 shows not only the complete loss of the tablet from the stomach, but the position and intactness of the HBS™. Figure 12 shows the intact retained HBS™, and sufficient release of Tc^{99m} to be visible throughout the fluid of the stomach. As previously stated, the number of counts can be quantitated, and are shown for two subjects (Figures 13, 14). As can be seen, the HBS™ was retained in the stomach for a much longer period of time than conventional tablets swallowed concurrently, and showed gastric retention times up to 6 hours. The other two subjects showed similar results.

Another critical in vivo performance characteristic is the blood level-time profile from the HBS™ compared to conventional dosage forms. Figure 15 compares the blood level-time profiles obtained from VALIUM(R)

[a] Osteoscan, Proctor & Gamble Co., Cincinnati, OH

15-mg (HBS) capsules[b] both in fasted and fed states, to three 5-mg VALIUM(R) tablets, dosed at 0, 5 and 10 hours. Food displaces the curve slightly to the right, but indicates the same peak height and area under the curve in both fasted and fed subjects. In multiple dosing, shown in Figure 16, 5-mg VALIUM® tablets dosed t.i.d. were administered on days 1 through 13. On day 14, the subjects were crossed over to 15-mg VALIUM HBS[b] for an additional 11 days. The data clearly shows the blood level equivalence of once/day dosing with the HBS to three times daily dosing from conventional tablets.

The mechanism whereby drug is better absorbed from the HBS™ is best illustrated with solubility data of chlordiazepoxide HCl. This drug is very insoluble at higher pH values, data indicating a 4000-fold difference in solubility going from pH 3 to pH 6 (Figure 17). Conventional controlled release preparations always led to poor bioavailability. This drug, when formulated into the HBS™ (30 mg) shows a blood level-time profile comparable to three 10-mg LIBRIUM® capsules[c] administered at 0, 4 and 8 hours (Figure 18).

The in vitro release characteristics (USP, Apparatus 1, artificial gastric fluid) shows 100% release at about 12 hours (Figure 19). When the data is treated for diffusional release from a receding barrier, and the "Percent Released" graphed versus "Time$^{1/2}$," linear release is observed for about 4 hours, corresponding to about 70% drug release (Figure 20). This 4 hours coincidentally corresponds to the 4-6 hours for which we observed dry material in the gel core (Figures 4, 5). The slope of the linear portion of this in vitro release curve is 35.02 (γ = 1.000). To verify the mechanism of release, three parameters were examined (4) for the first 4 hours of release. When the log of the "Amount Released" is graphed versus the log of "time," the resultant line has a slope of 0.53, compared to a theoretical 0.50 (Figure 21). When the second derivative of release is examined, it is clear that a graph of the "Rate of Release" versus the reciprocal of the "Amount Released" indicates excellent linearity, and has a correlation coefficient of 0.998 (Figure 22), corresponding to the linearity expected from receding barrier-type release. On the other hand, when the "Rate of Release" versus the "Amount Released" is plotted (Figure 23), the data is clearly non-linear, indicating non-conformance to first-order kinetics. These last three graphs support the contention of release of drug from the HBS™ as being matrix (or receding barrier) controlled release.

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[b] Valrelease™, 15 mg, Hoffmann-La Roche Inc., Nutley, NJ

[c] LIBRIUM(R), Hoffmann-La Roche Inc., Nutley, NJ

When a graph is constructed of the "Percent of Maximum Blood Level" versus the "Square Root of Time," it is linear, and has a slope of 33.63, within 4% of the *in vitro* release rate curve (Figure 24). If the blood concentration at early times is dependent primarily upon drug release characteristics, then this data is indicative of the *in vivo* release characteristics, and the *in vitro* and *in vivo* rates of drug release are equal. If this is correct, then a plot of "Percent of Maximum Blood Level" versus "Percent of Drug Released" should be linear, with a slope of 1.000; the data does indicate linearity, with a slope of 1.007 (Figure 25).

The mechanism of drug release has also been confirmed by others using similar dosage forms (5, 6). Drs. Touitou and Donbrow at the Hebrew University confirm that release of drugs from hydrophilic polymers follows a square root of time dependency, and that the rate of release is proportional to drug content, and semi-logarithmically to polymer content.

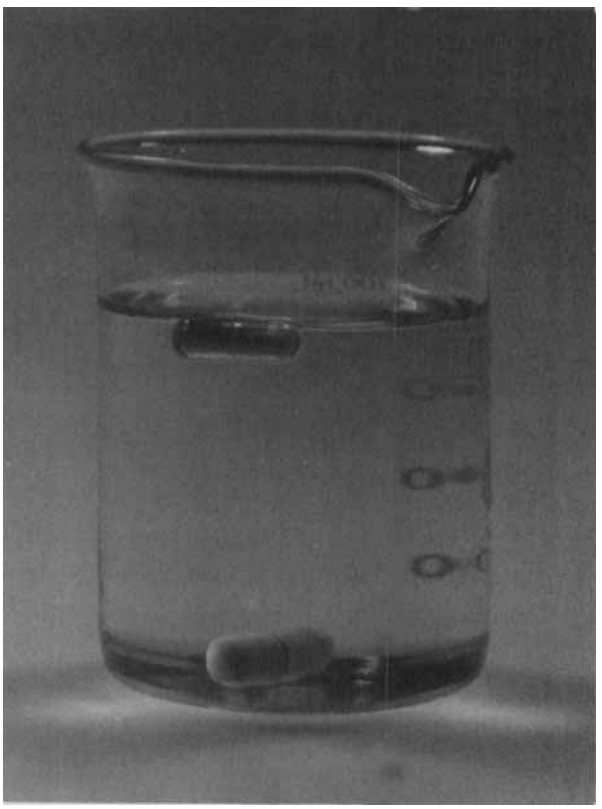


FIGURE 1. Floating characteristic of the HBS capsule, compared to a conventional capsule in artificial gastric fluid (without enzymes).

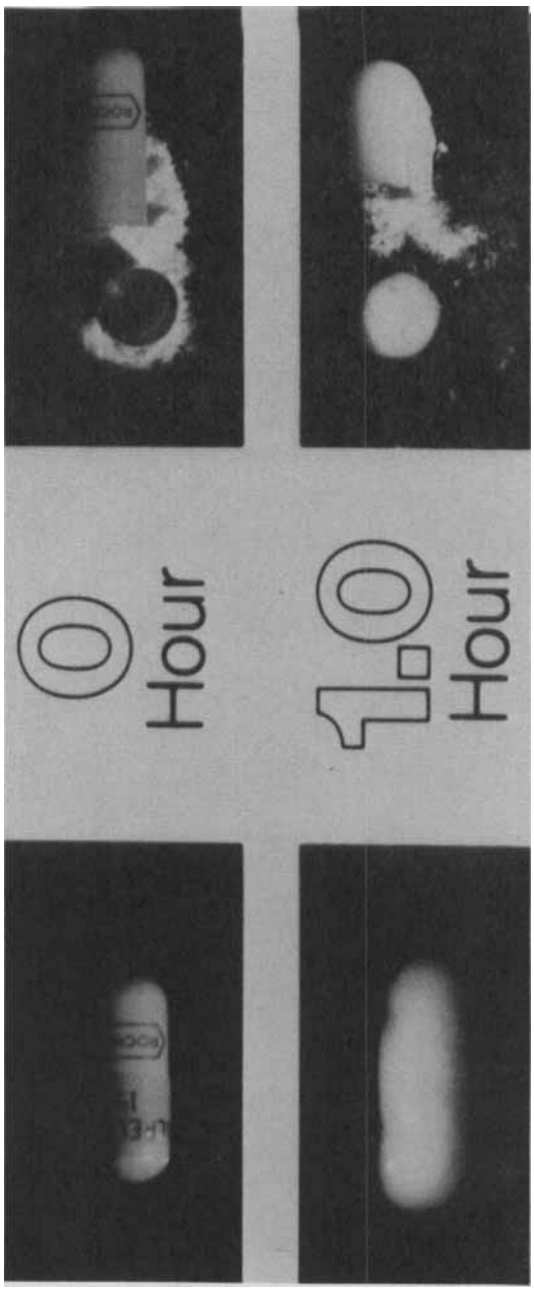


FIGURE 2. Effect of time on HBS capsule appearance after immersion in artificial gastric fluid (without enzymes) for times specified.

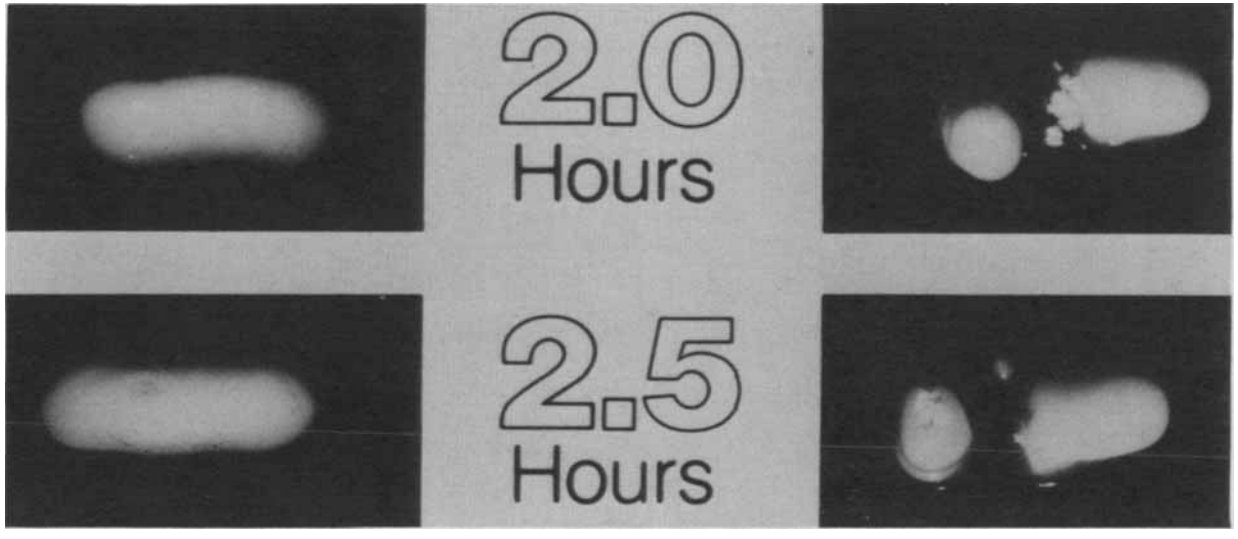


FIGURE 3. Effect of time on HBS capsule appearance after immersion in artificial gastric fluid (without enzymes) for times specified.

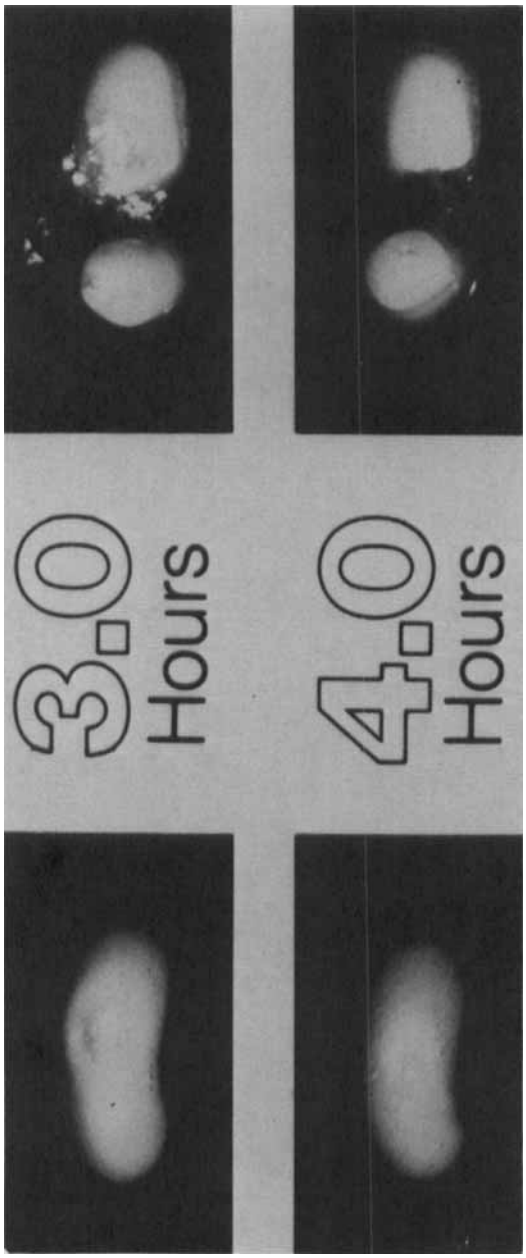


FIGURE 4. Effect of time on HBS capsule appearance after immersion in artificial gastric fluid (without enzymes) for times specified.

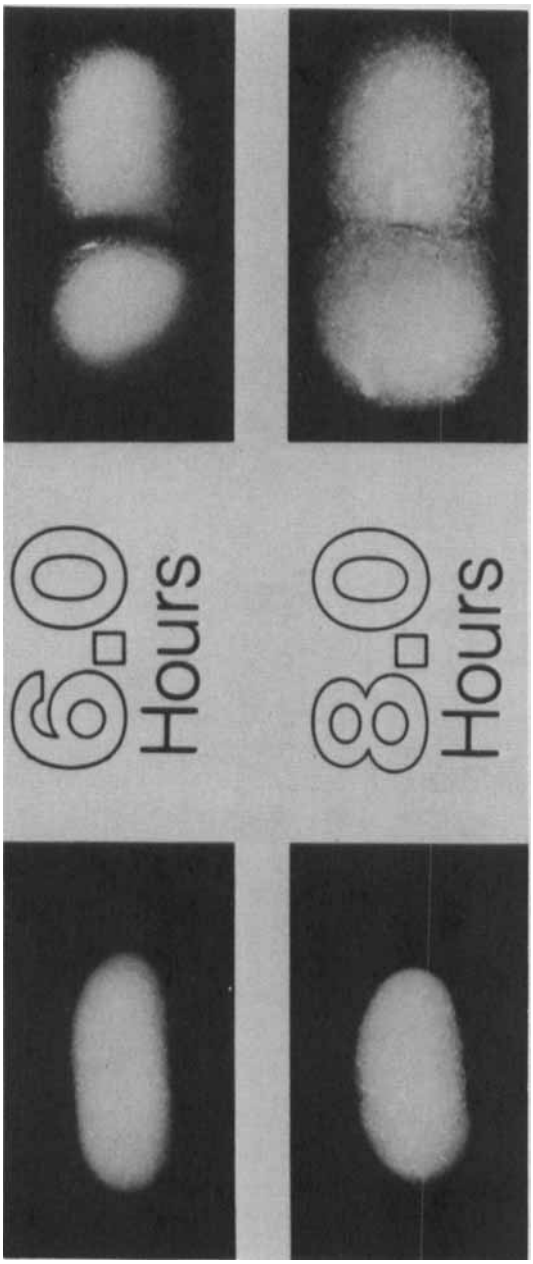


FIGURE 5. Effect of time on HBS capsule appearance after immersion in artificial gastric fluid (without enzymes) for times specified.

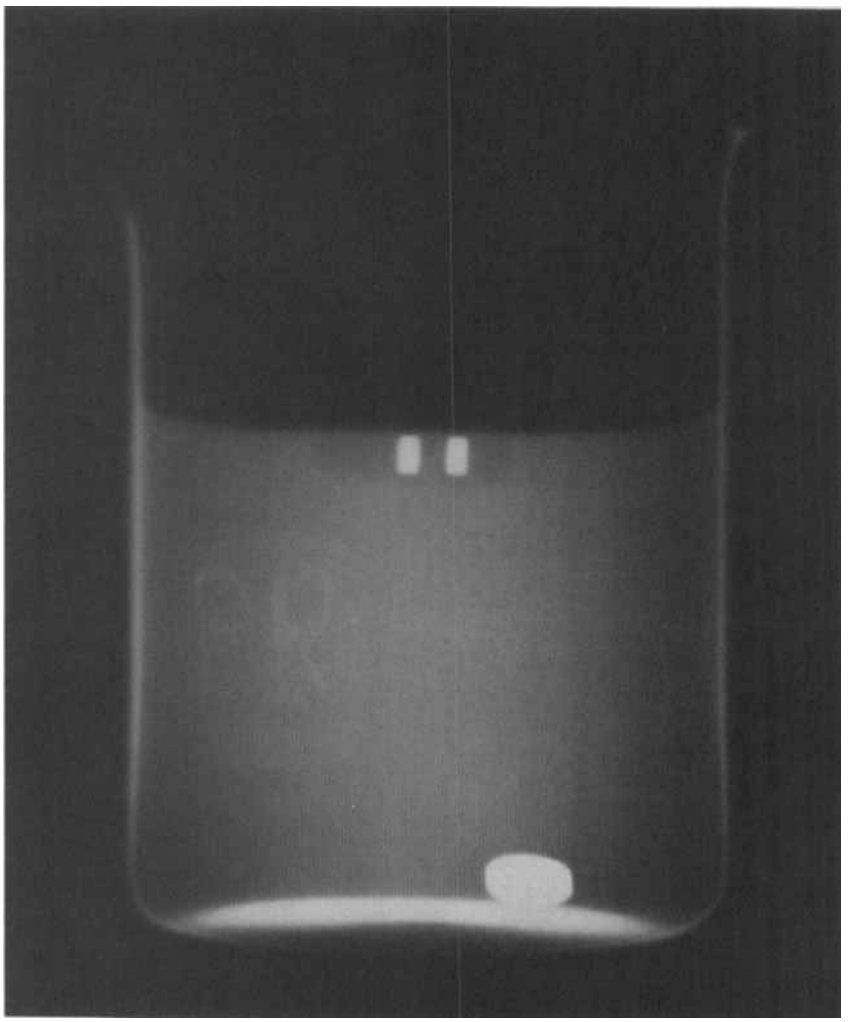


FIGURE 6. X-ray of HBS and conventional capsules with radiopaque $BaSO_4$ tablets. The HBS has two $BaSO_4$ tablets within it to facilitate identification.

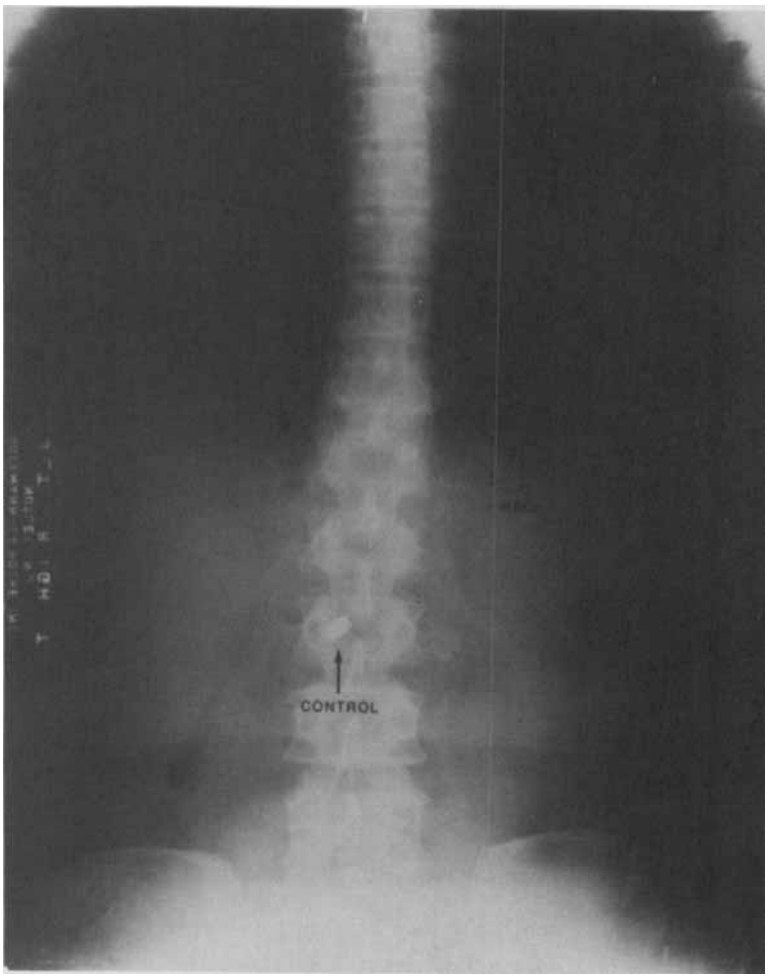


FIGURE 7. X-ray of HBS capsule and conventional capsule (control) in human subject after simultaneous ingestion.

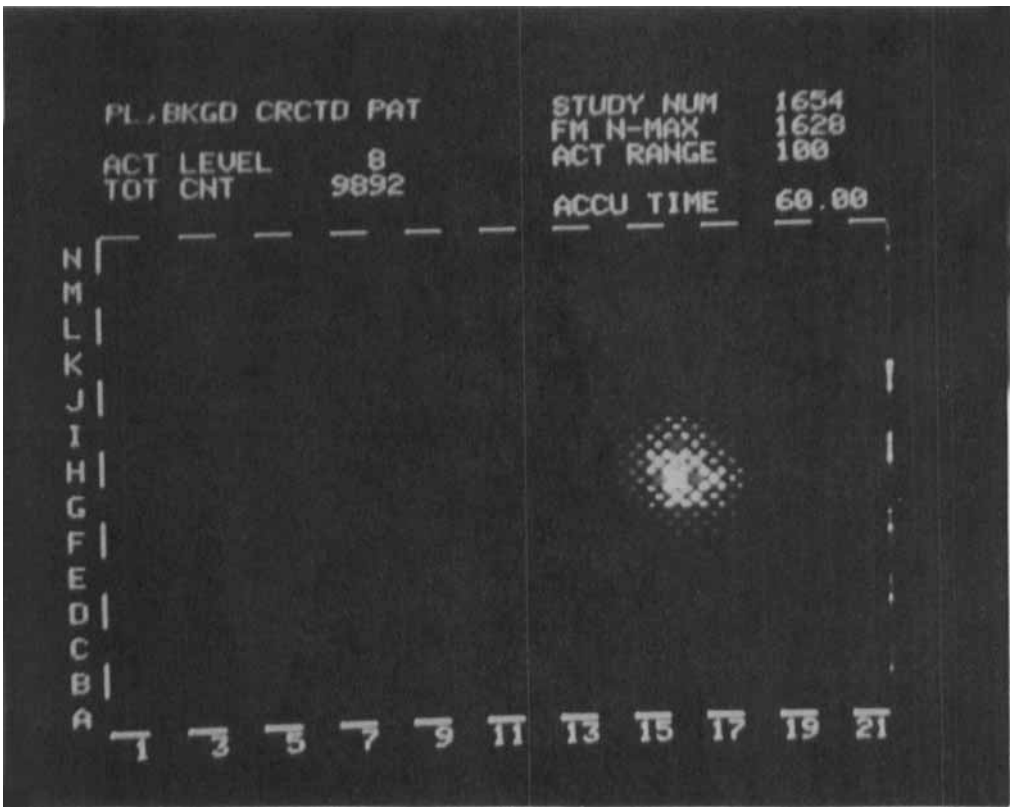


FIGURE 8. Monitor screen of scintigraphy apparatus showing one dosage form (non-disintegrated).

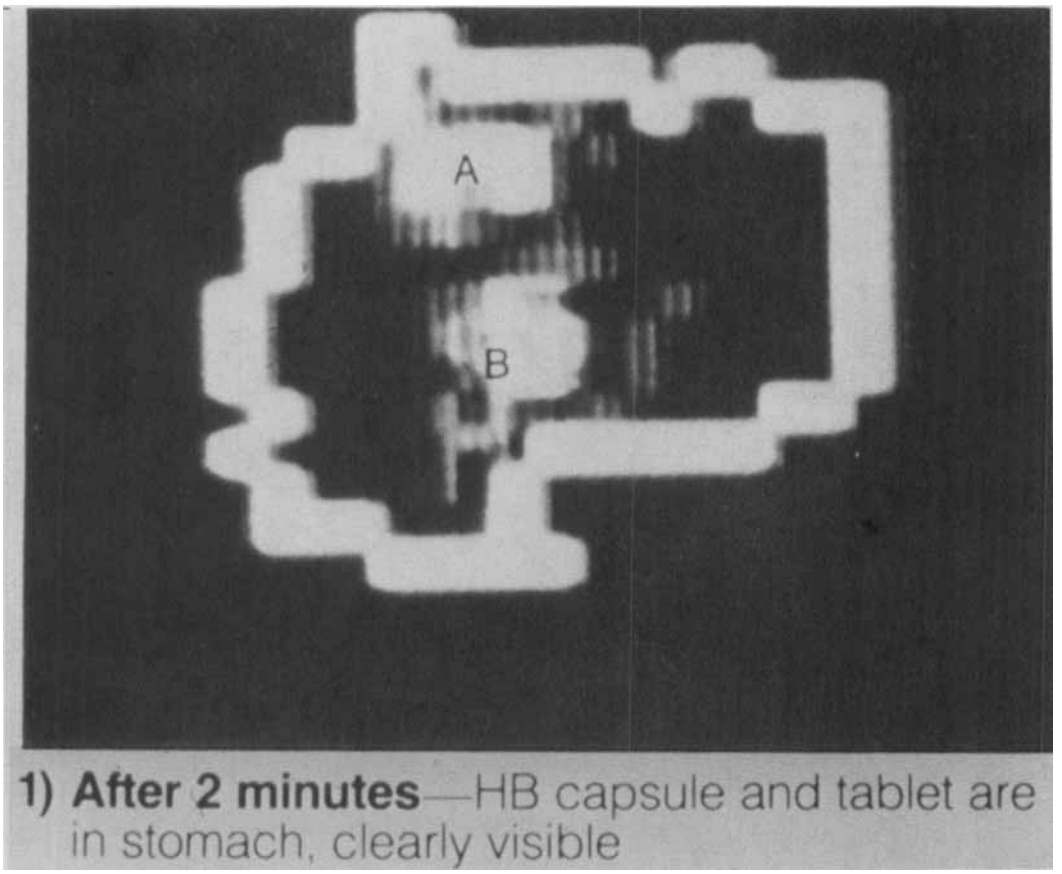


FIGURE 9. Computerized output of radioactivity from Tc^{99m} labelled HBS Capsule and conventional tablet, swallowed simultaneously with In^{111} labelled water. Time as noted.

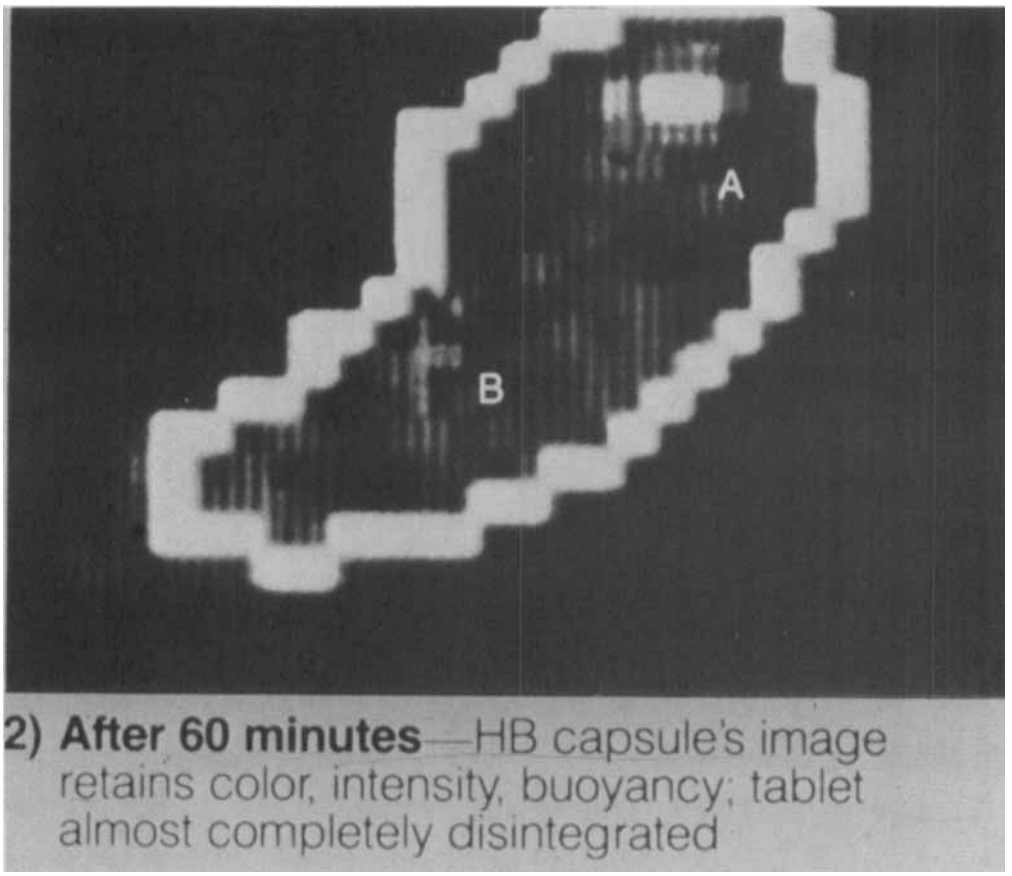


FIGURE 10. Computerized output of radioactivity from Tc^{99m} Labelled HBS capsule and conventional tablet, swallowed simultaneously with In^{111} labelled water. Time as noted.

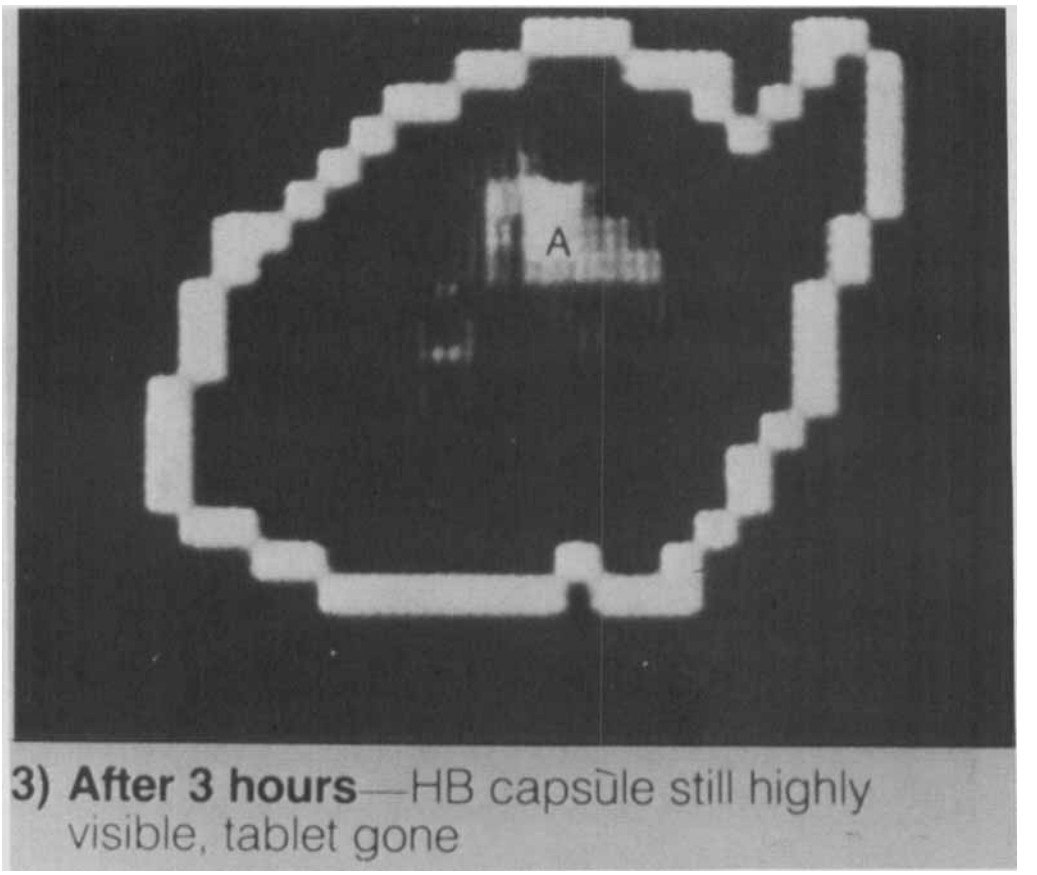


FIGURE 11. Computerized output of radioacticity from Tc^{99m} labelled HBS capsule and conventional tablet, swallowed simultaneously with In^{111} labelled water. Time as noted.

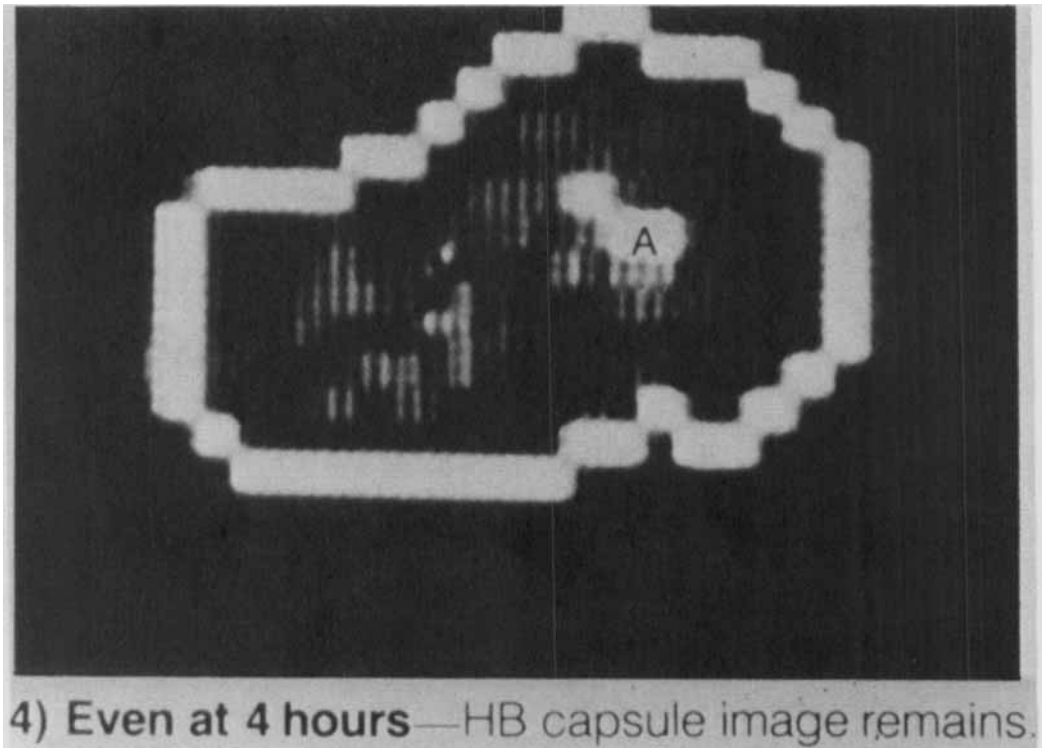


FIGURE 12: Computerized output of radioactivity from Tc^{99m} labelled HBS capsule and conventional tablet, swallowed simultaneously with In^{111} labelled water. Time as noted.

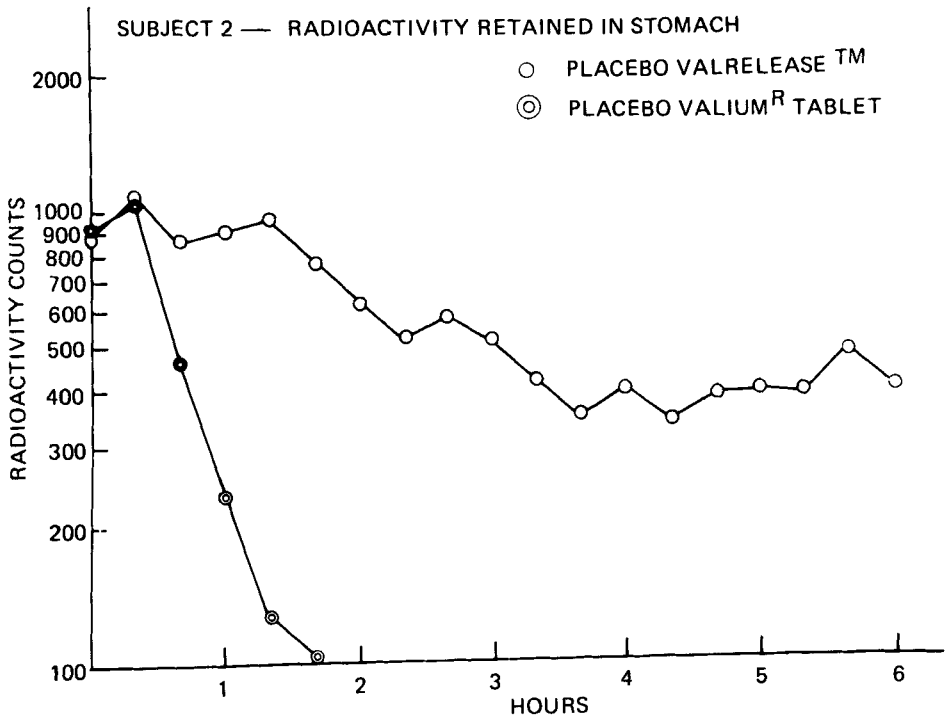


FIGURE 13. Quantitated data from scintigraphy study, showing gastric retention as a function of time for the HBS capsule and a conventional tablet (Subject 2).

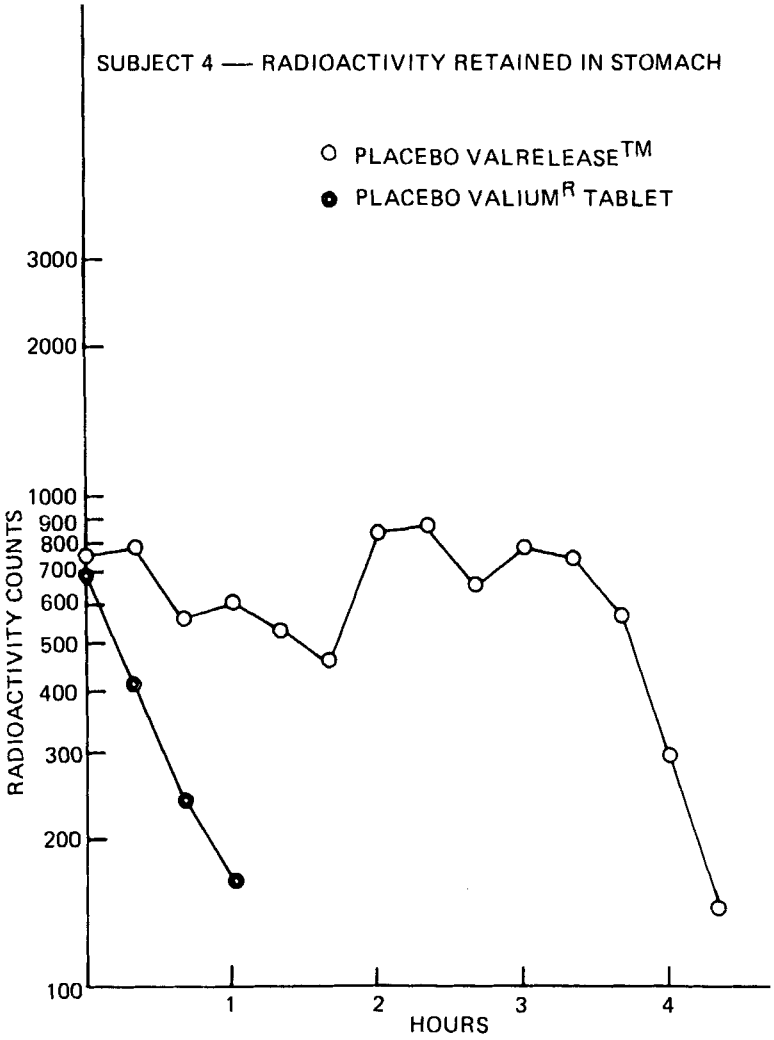


FIGURE 14. Quantitated data from scintigraphy study, showing gastric retention as a function of time for the HBS capsule and a conventional tablet (Subject 4).

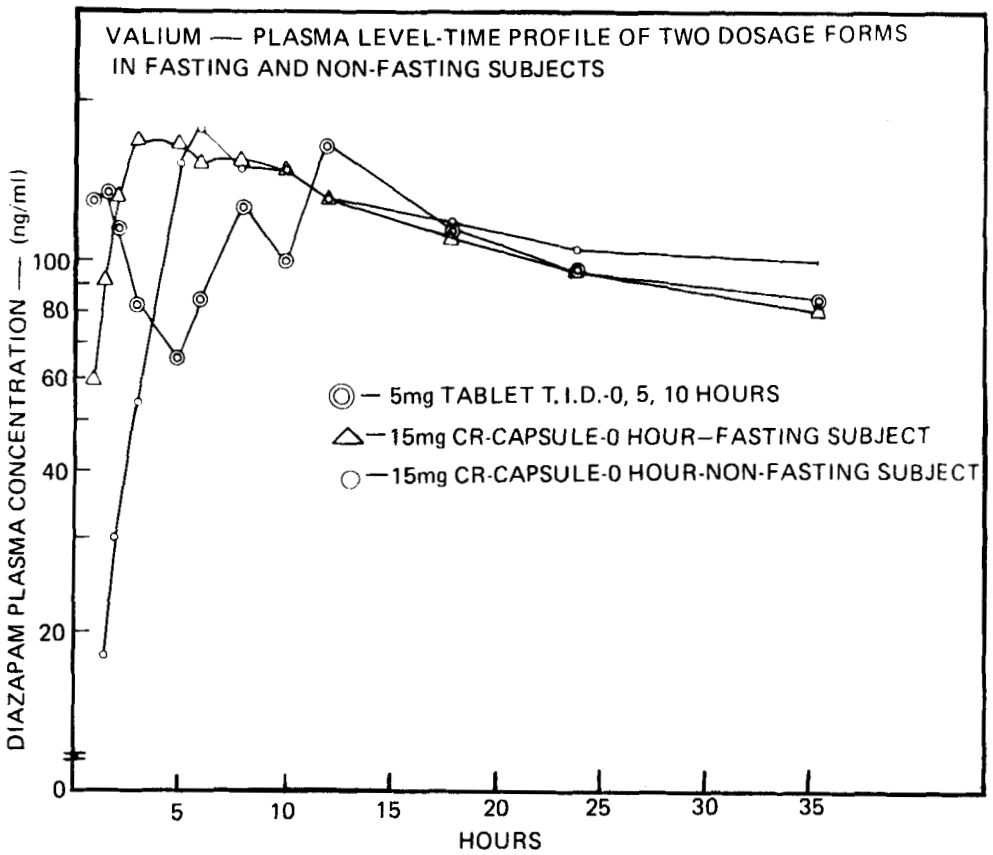
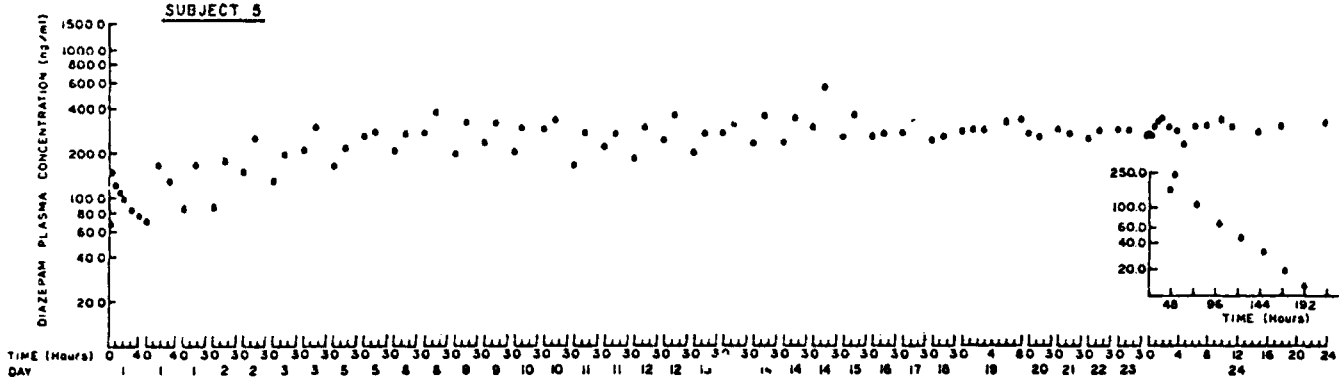


FIGURE 15: Diazepam blood levels following single dose administration of the HBS capsule (in fasted and fed subjects) compared to three tablets administered at 0, 5 and 10 hours.



Diazepam plasma concentration-time profile during chronic oral administration.

Day 1-13 VALIUM(R) 5-mg tablet at 0, 5, and 10 hours (t.i.d.)

Day 14-24 VALIUM(R) CR 15-mg HBC at 0 hour

Insert: plasma time profile after the last dose

FIGURE 16. Blood levels obtained from 5-mg VALIUM(R) tablets administered three times daily for 13 days, followed by 15-mg VALRELEASE(TM) capsules administered once daily.

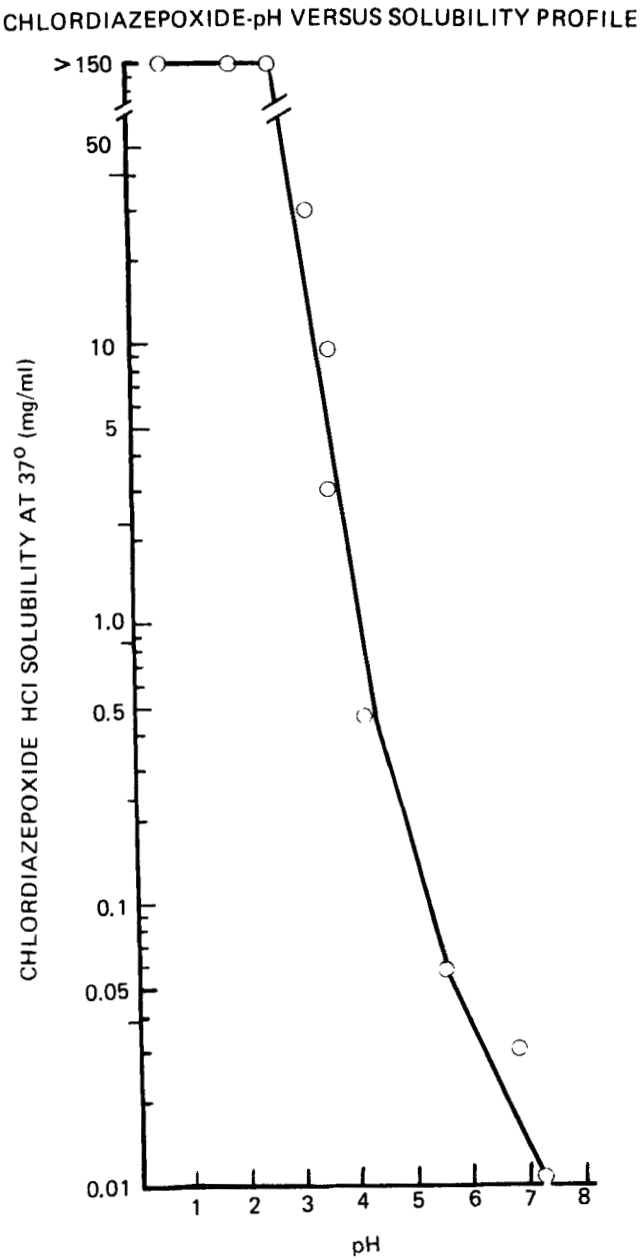


FIGURE 17. Solubility -- pH profile for chlordiazepoxide HCl.

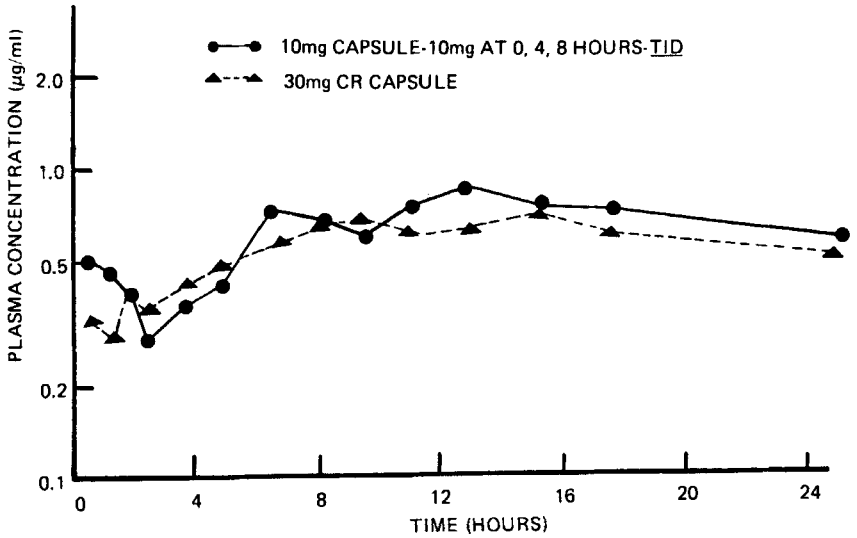


FIGURE 18. Blood level profile of 10-mg Librium(R) capsules administered at 0, 4 and 8 hours compared to a single administration of a 30-mg chlordiazepoxide HBS capsule.

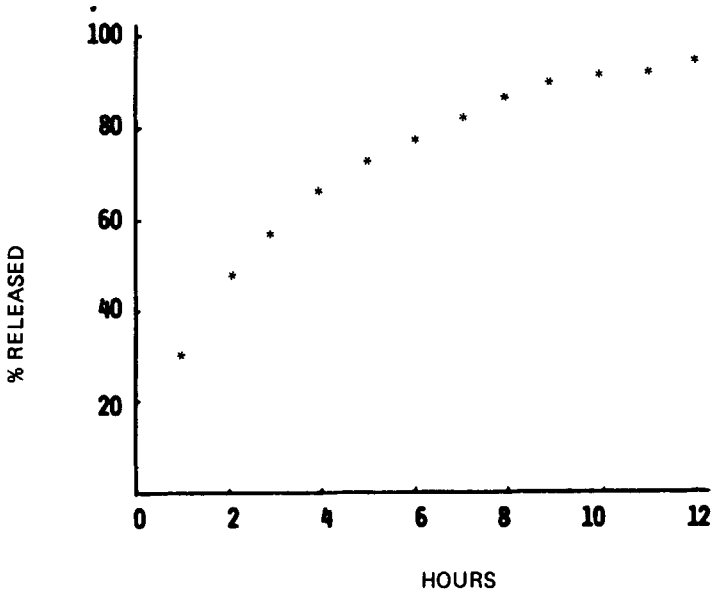


FIGURE 19. Percent of chlordiazepoxide released from HBS capsule as a function of time.

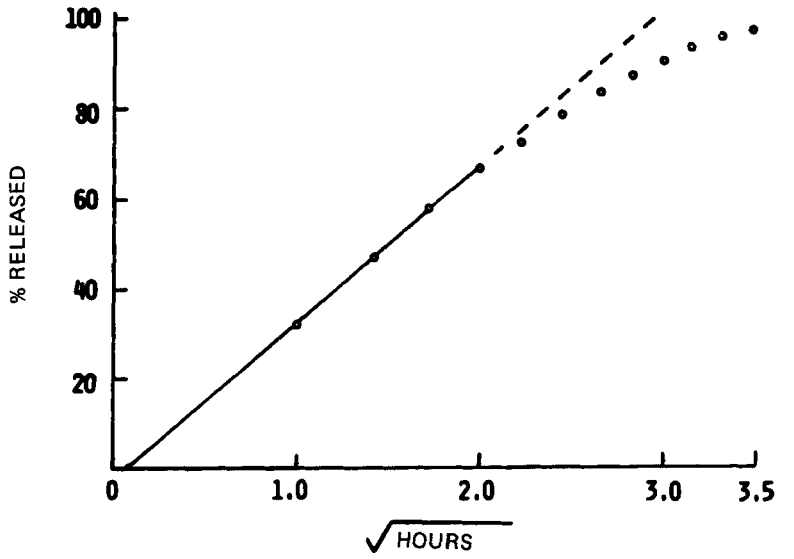


FIGURE 20. Percent of chlordiazepoxide released from HBS capsule as a function of $(\text{Time})^{1/2}$.

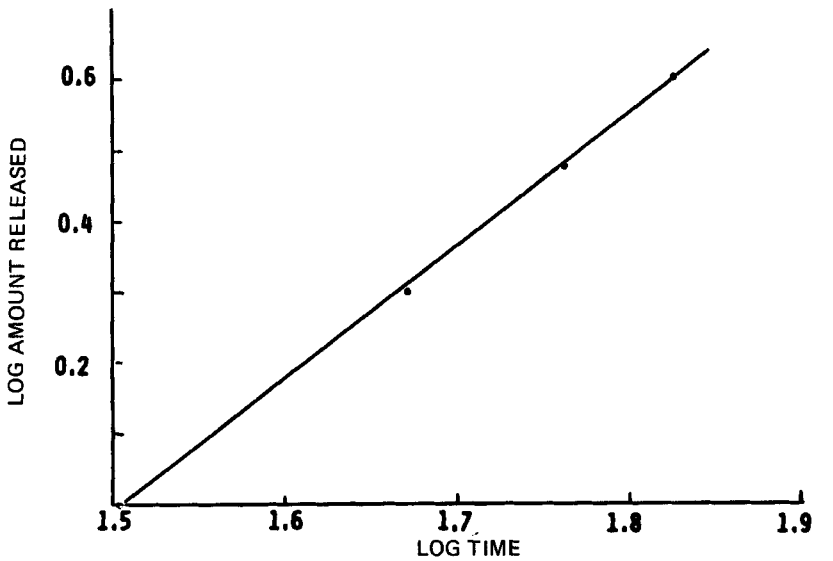


FIGURE 21. Log-log graph of amount of chlordiazepoxide released vs. time from HBS capsule.

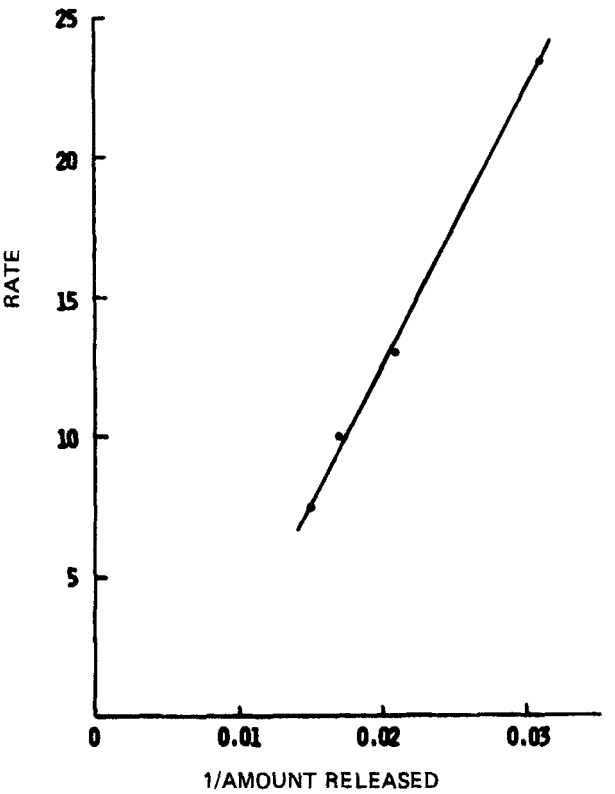


FIGURE 22. Second derivative plot of chlordiazepoxide release data: Rate vs. reciprocal of amount released from HBS capsule.

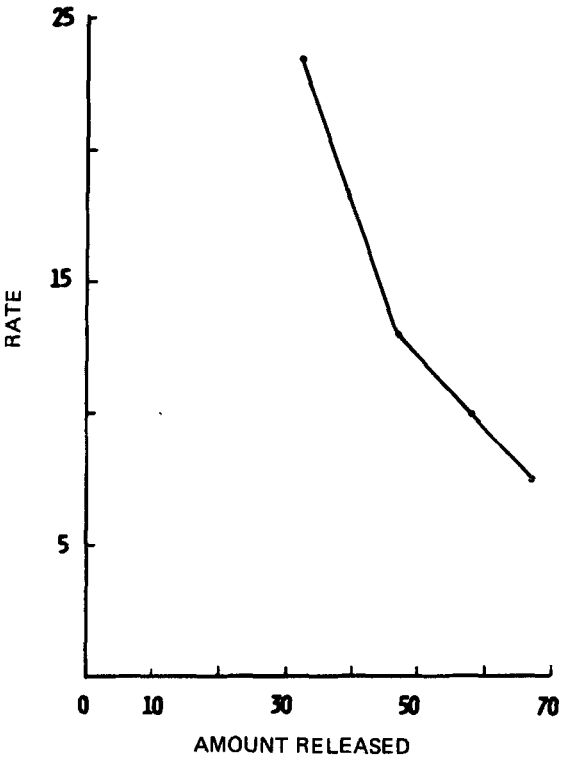


FIGURE 23. Second derivative plot of chlordiazepoxide release data: Rate vs. amount released from HBS capsule.

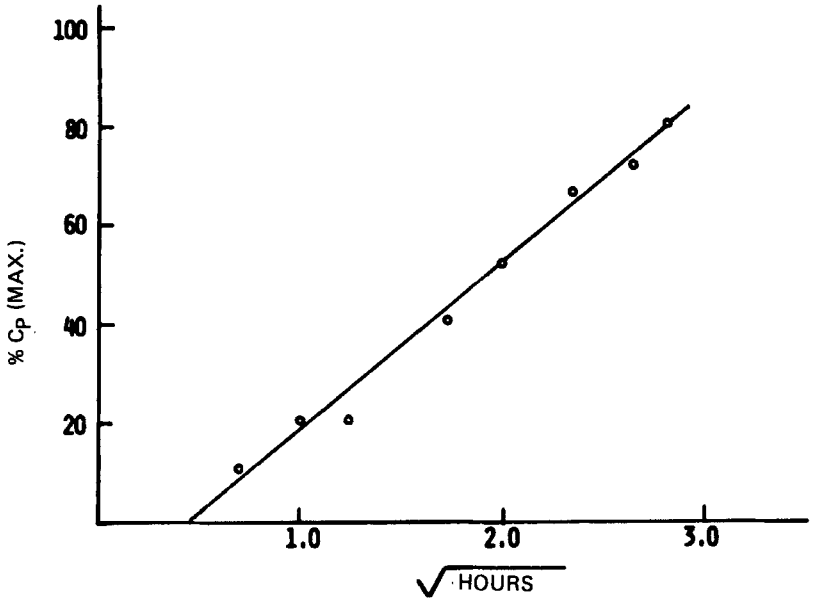


FIGURE 24. Percent of maximum plasma concentration of chlordiazepoxide vs. $(\text{Time})^{1/2}$ from HBS capsule.

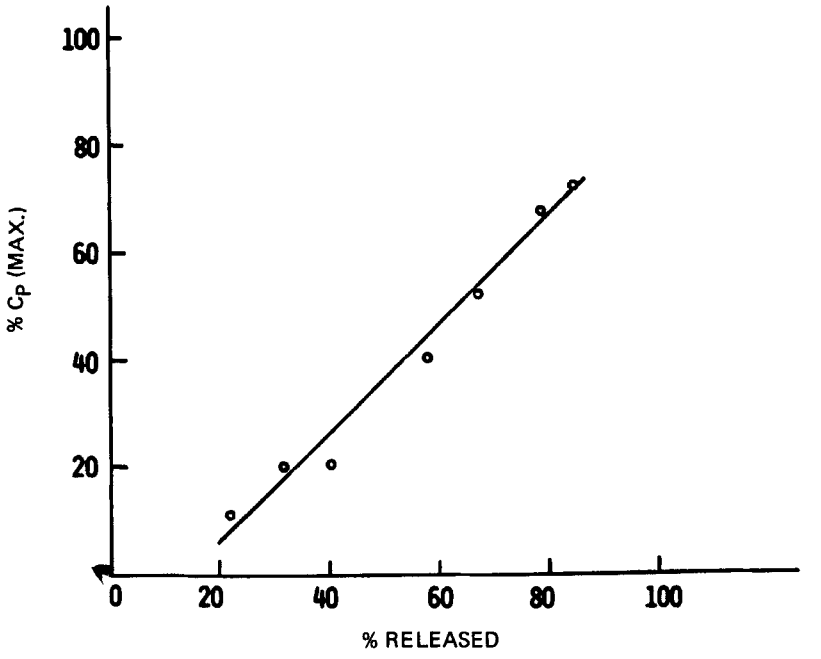


FIGURE 25. Percent of maximum plasma concentration vs. percent released for chlordiazepoxide from HBS capsule.

ACKNOWLEDGEMENTS

Dr. A. H. Goldberg, Director of Pharmacy R&D made the above presentation at at the "Oral Controlled Drug Administration" conference, held at Rutgers University, Jan. 19-20, 1983.

(All pharmacokinetic data are from the Department of Biopharmaceutics and Pharmacokinetics, Hoffmann-La Roche Inc., Nutley, New Jersey.)

FOOTNOTE

This paper was presented at the Rutgers 1983 Industrial Pharmaceutical R & D Symposium: Oral Controlled Release Administration. This conference was organized by Dr. Yie W. Chien. Because of technical problems in manuscript preparation the publishers were unable to include it in the special Rutgers Conference Issue, volume 9 number 7. The editor believes that this paper will be received with interest by our readers.

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4) Schwartz, J. B., Simonelli, A. P., and Higuchi, W. I., J. Pharm. Sci., 57, 274 (1968).

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6) Ibid, 11, 355 (1982).