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BIOEFFICIENT PRODUCTS
A Novel Delivery System

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ABSTRACT

Studies have shown that a bioefficient/HBS™ dosage form is more bioavailable than the conventional product. This is true with compounds which are absorbed from the upper portion of the small intestine or intended to act in the stomach contents. The increase in bioavailability is due to the design of this delivery system which is based on the HBS™ having a prolonged retention in the stomach, as shown by scintillation studies. Vitamins evaluated in these experiments include riboflavin, thiamine and a vitamin C plus E combination product.

INTRODUCTION

Pharmacokinetically, it is often desirable to administer a single dose of medication which releases the active ingredient over an extended period of time rather than to administer a number of single doses at regular intervals.[1-3] Patient compliance is more assured with a single dose rather than with a multiple

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dose regimen[4], while maintaining a consistent and uniform blood level. In most conventional sustained release preparations, the medicinal agents are either coated with varying thicknesses of a relatively insoluble polymer or else are embedded into the matrix of water-insoluble ingredients. The objective in such preparations is to provide a continuous amount of drug for absorption into the blood stream to replace the amount eliminated, while the dosage form is passing through the gastrointestinal tract.

In Figure 1, the plasma level profiles of a hypothetical compound are shown when administered in a conventional rapid-releasing form and in controlled release dosage forms. When administered in a multiple dosage regimen, the rapid-releasing product establishes a seesaw pattern which is dependent on its biological half-life. The ideal controlled release dosage form establishes an appropriate plasma level which lasts for a long period of time and is bioequivalent to the drug given by a multiple dose regimen.

In many sustained release products, a relatively fast-releasing formulation produces undesirably high plasma concentrations, while slow releasing formulations fail to reproduce the bioavailability of the multiple dosing regimen. This is because the conventional approach to sustained release formulations is generally unsuitable for certain classes of drugs or active ingredients which are not adequately absorbed during their

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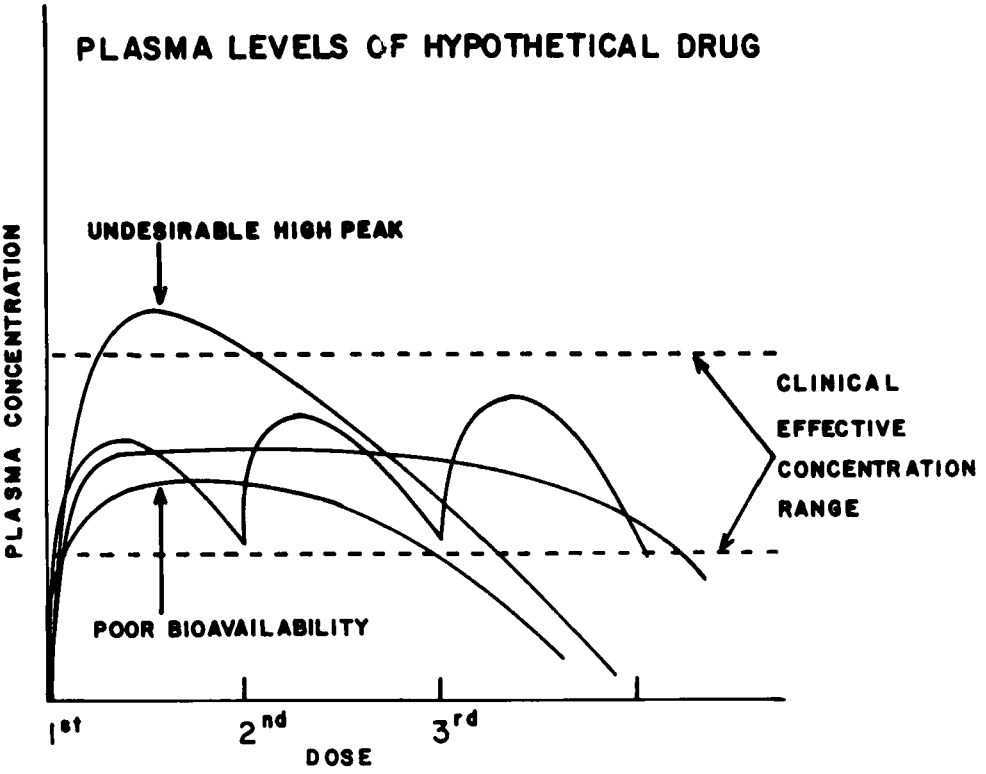

Figure 1 - Plasma Levels of Hypothetical Drug

passage through the gastrointestinal tract. This can be due to either their physicochemical properties or their requirement of a particular site of absorption. This is true for several medicaments and particularly for vitamins and minerals.

For example:

1. Certain medicinals are better solubilized in the acidic medium of the stomach rather than in the neutral or alkaline environment of the intestine. Obviously, the passage of the controlled release dosage form into the neutral or alkaline

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regions of the G.I. tract could result in a potential decrease in the dissolution and absorption rates of the sustained release agent. This fact was shown with chlordiazepoxide HCl, reported previously.[5]

2. Many active ingredients and vitamins are principally absorbed from the upper portion of the small intestine and it is not possible to establish a uniform plasma level by the administration of a conventional controlled release system which may deliver the active ingredient beyond the site of absorption.

3. Compounds such as antacids or nitroso-compound blocking agents are intended to act in the stomach contents and will lose their beneficial effects if they pass into the intestine.

In view of the above considerations, it is obvious that a large number of medicinals, vitamins and minerals would not be ideally bioavailable from conventional sustained release formulations because these dosage forms are not retained in the stomach and/or may release the medication beyond the optimum site of absorption or activity. It is equally apparent that a sustained release formulation that is retained in the stomach, where it acts as a reservoir and slowly releases the active ingredient in the stomach over an extended period of time, would be best suited for these compounds. The Hydrodynamically Balanced controlled release delivery System (HBS™) was found to

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fulfill these requirements. Vitamin and minerals by the nature of their absorption mechanism are excellent candidates for this new delivery system.

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The Principle of Bioefficient Dosage Forms

Bioefficient dosage forms are based on the Hydrodynamically Balanced Drug Delivery System (HBS™). The product (capsule, tablet or beadlets) acquires, upon contact with gastric fluid, a bulk density of less than one*, it then remains buoyant in the gastric fluid (Figure 2) with a resultant prolonged residence time in the stomach.

The buoyancy and the release characteristics of the dosage form are achieved by the use of specific excipients which play a significant role in the design of the product. The drug is gradually and uniformly released from the dosage form as the stomach fluid slowly permeates the matrix. The new delivery system not only prolongs the stomach residence time, but does so in an area of the gastrointestinal tract such that the active ingredients reach their optimum absorption site in solution and are ready for absorption.

The controlled release properties of bioefficient products can maximize the desired pharmacological response or blood level

*The specific gravity of gastric fluid is approximately 1.004-1.010 according to the "Documenta Geigy."

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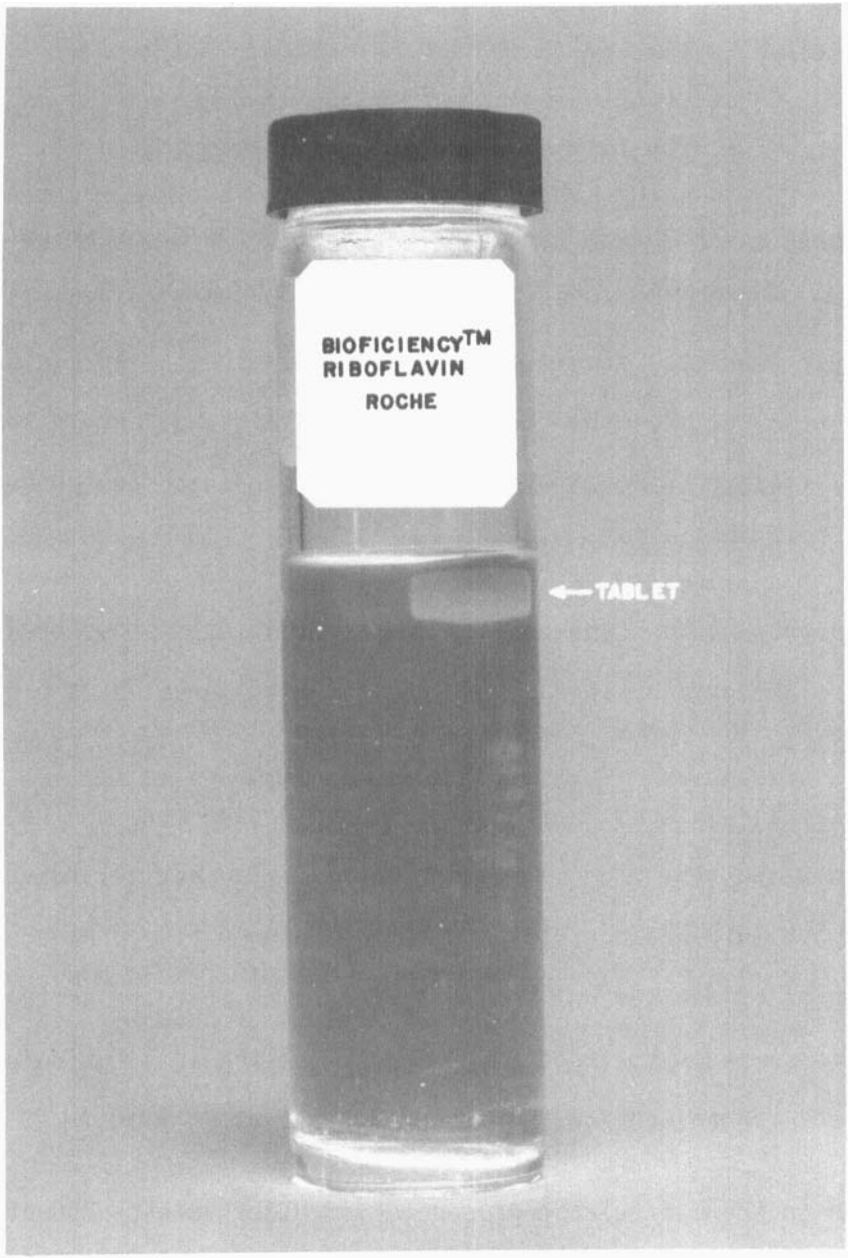

Figure 2 - Bioefficient/HBS Riboflavin Tablet

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profile of certain compounds in a unique fashion which is not possible using conventional sustained release technology. This has been shown with a number of pharmaceutical agents and now has been used successfully to increase the bioefficiency* of vitamins and minerals such as riboflavin, ascorbic acid and thiamine.

Accordingly, the HBS™ drug delivery system is valuable for administering a single daily dose of these compounds and can eliminate the need for frequent daily administration, to establish appropriate physiological activity. In addition, it can be of great value for those compounds which act primarily in the stomach, as shown with vitamin C plus E HBS™ product in blocking nitroso compound formation, a condition which would require a multiple dose with conventional dosage forms.

Experiments to Ascertain the Gastric Retention of the HBS™ Capsule

Several experiments were performed to ascertain the residence time and the floating properties of the HBS™ capsule in the stomach.[5] The present experiment is based on scintillation studies[6] where the behavior and the stomach residence of a fast disintegrating capsule and an HBS™ capsule were compared. The two dosage forms were radiolabelled with technetium 99m, a gamma ray emitting radionuclide, and were administered to subjects after a

*Bioficiency® is a Roche registered name.

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light breakfast which consisted of cornflakes with milk, 4 ounces of orange juice, two slices of toasted bread with jelly.

The technetium 99m radiolabelled compound is a solution of ^{99m}Tc-pertechnetate.* The technetium was incorporated into the excipients of the formulations immediately prior to administration because of its short half-life (6 hours). Each dosage form contained about 30 microcuries of technetium 99m.

Following oral administration of the dosage form with 240 ml of water, the subject was placed in a sitting position in front of the collimating detector of a multicrystal scintillation camera. The stomach was positioned opposite the detector by means of an external radioactive source (radiolabelled cobalt) placed on the xyphoid tip and left costal margin of the subject. The limits of the stomach were expected to occupy the area between these two locations. This technique insured that the initial position of the dosage form would be within the area of the collimating detector (6 x 9 inches) and was also used to relocate the subject in case of a recess during the test.

The total amount of radioactivity emitted over a one-minute time period by the dosage form was transmitted to the TV screen, which displays the computer picture of the signals as a "hot" spot in the stomach. In addition, sequential scintiphotos were

*Osteoscan, Proctor & Gamble Co., Cincinnati, OH.

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taken every minute to monitor the behavior and the position of the dosage form.

In order to evaluate both the release of radioactivity and movement of the dosage form, an arbitrary area was designated as the "flagged region." In this study, the stomach area was divided into three different zones (Figure 3), with the capsule position designated zone 1, the pyloric region designated as zone 3 and the intermediate area designated as zone 2.

Continuous monitoring of the radiation in these flagged regions as a function of time can indicate either the disintegration of the control capsule or the displacement of the controlled release capsule when the high intensity readings shift. Further followup on the rate of passage of radioactivity through the lower stomach provides data for the estimation of gastric emptying time.

Figure 4 shows the behavior of the disintegrating control capsule; once the shell was ruptured (approximately 20 minutes after swallowing) the contents settled and dispersed. Figure 5 displays on semilogarithmic plot the intensity of radioactivity decrease in zone 1 (capsule region) with a concomitant increase of radioactivity in zone 3. The half-life of the stomach emptying time was calculated to be about 37 minutes.

The controlled release capsule remained in the stomach without disintegrating; the sequential scintiphotos show the

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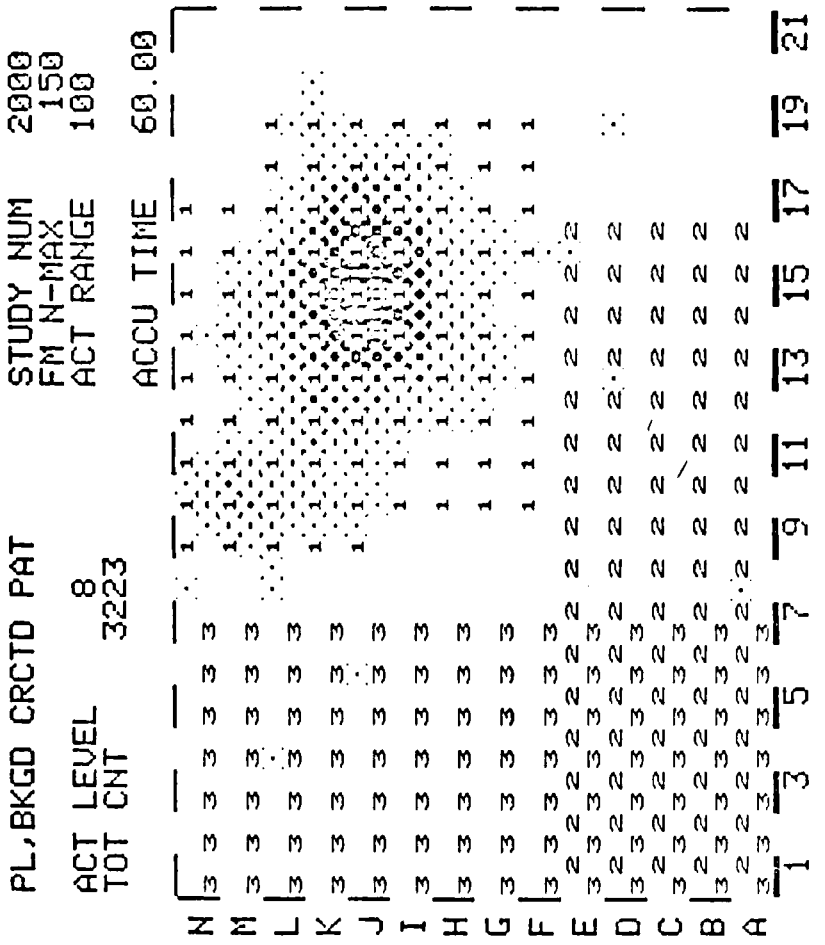

Scintiphoto showing the computer zones of interest within the stomach.

ZONE 1 - over capsule
ZONE 2 - intermediate region
ZONE 3 - phyloric region

Figure 3 - Scintiphoto Showing the Computer Zones of Interest Within the Stomach

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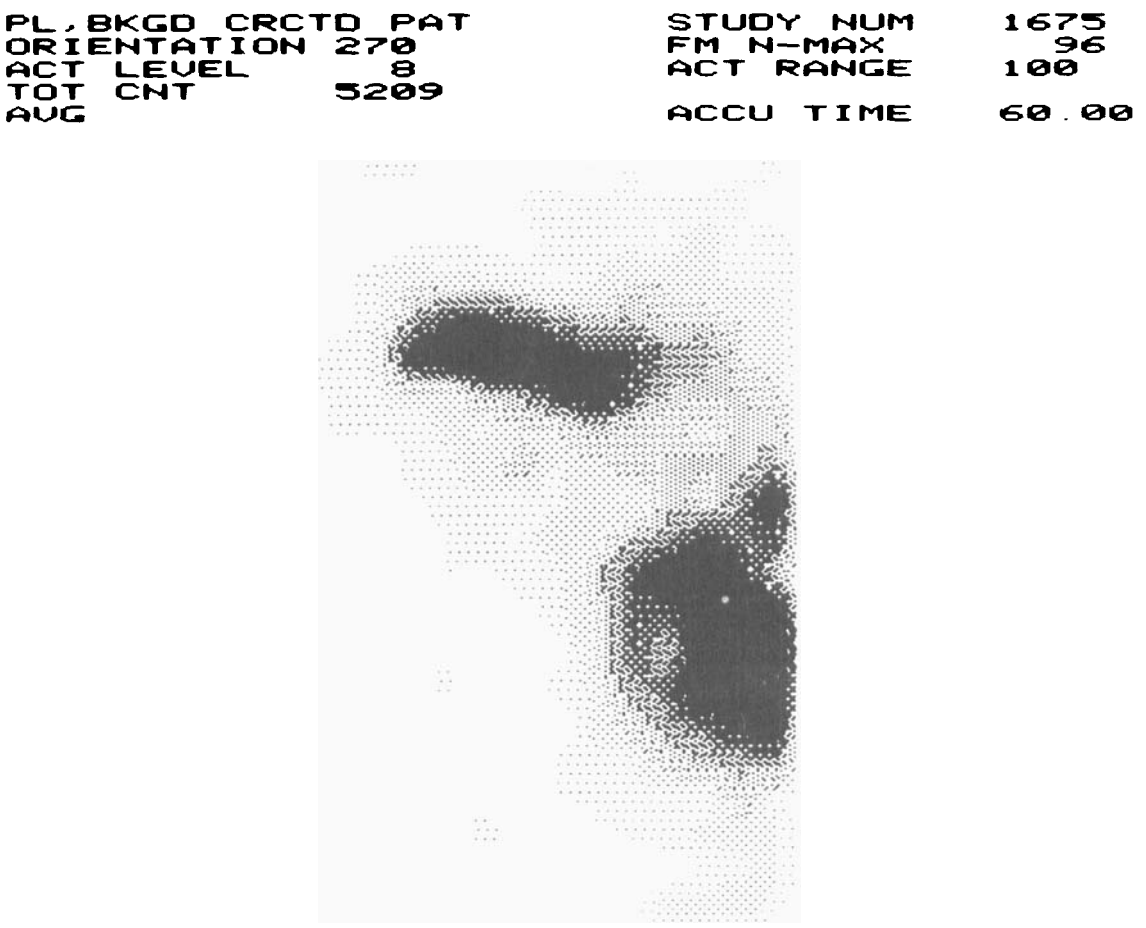

Figure 4 - Scintiphoto of the Disintegrating Control Capsule

capsule in the stomach for more than 2½ hours (total period of investigation).

The results are shown on the computer integrated plot or the radioactivity-time profile on the semilog scale (Figure 6) where the intensities of radioactivity in zones 1, 2 and 3 are plotted. The intensity of the radioactivity in each zone seems to increase

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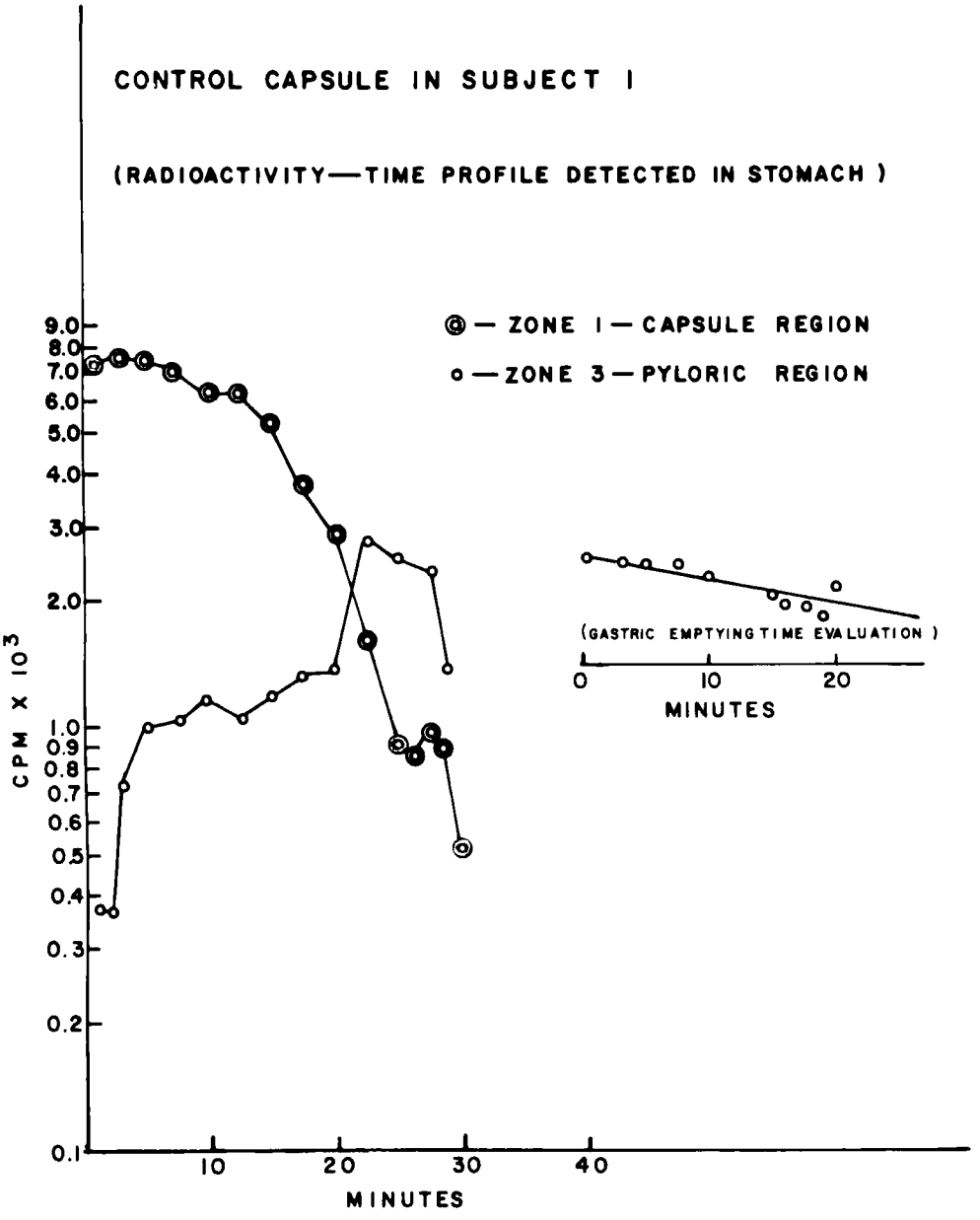

Figure 5 - Radioactivity-Time Profile of Control Capsule

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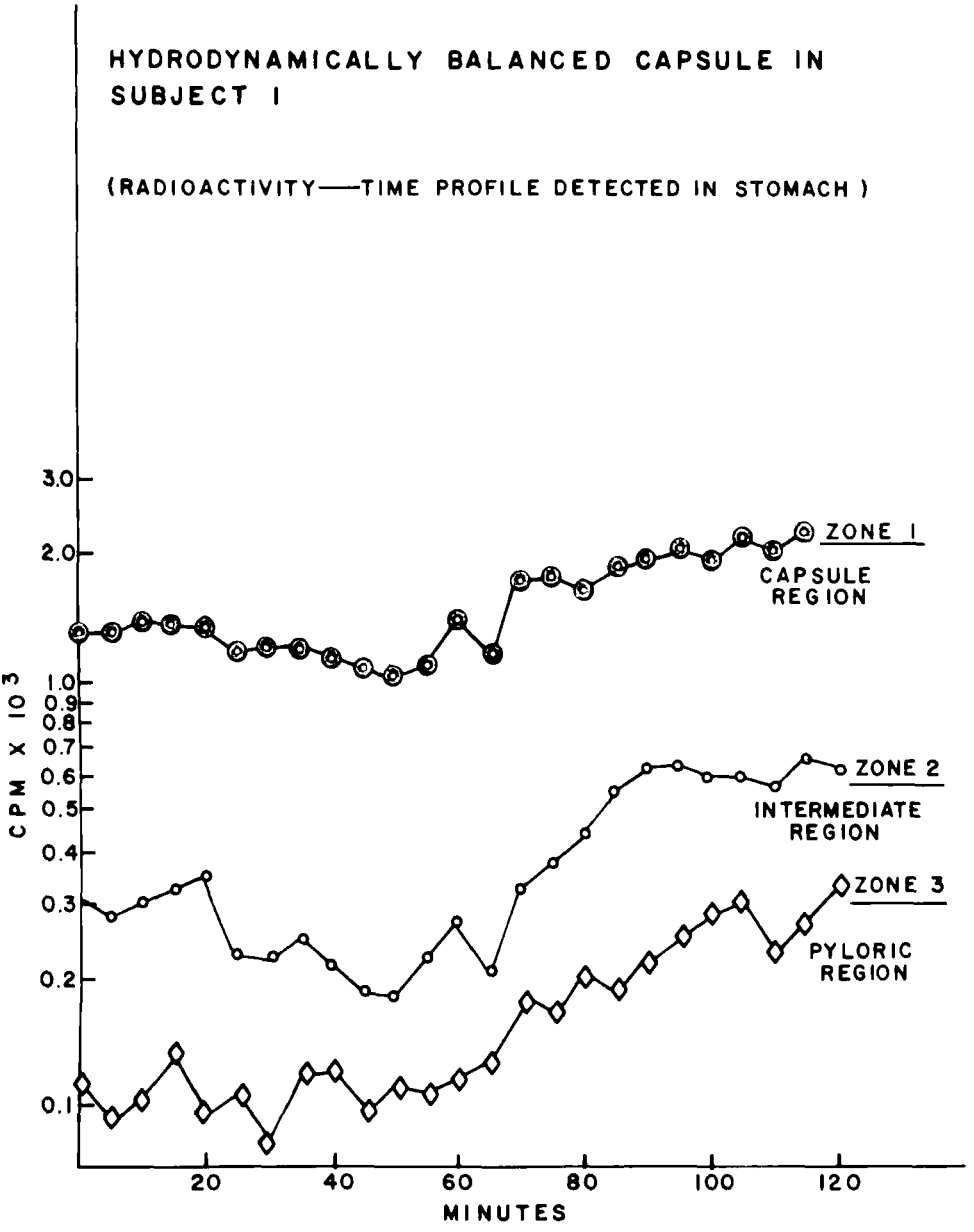

Figure 6 - Radioactivity-Time Profile of HBS Capsule

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unexpectedly with time, probably due to approach of the dosage form towards the camera.

These results demonstrate the prolonged retention of the HBS™ dosage form in the stomach and show that the capsule does not enter rapidly into the intestine.

Bioefficient Riboflavin

Riboflavin is known to be absorbed from the proximal end of the small intestine by a specialized transport process which is saturable.[7,8] The compound is often used by G. Levy and his co-workers to determine the factors which affect the gastric emptying time and proximal intestinal transit rate. Morrison, et al.[9], have examined the validity of the claims made for several conventional sustained release vitamin products by testing the physiological availability and measuring the in vitro release rates of riboflavin. They concluded that, in humans, it is not possible to maintain a sustained release effect of riboflavin using conventional controlled release products.

The Canadian Ministry of Health in the early 1960's showed incomplete absorption of riboflavin in humans from sustained release multivitamin products. Based on these studies, multivitamin sustained release preparations were withdrawn from the market in Canada and in the USA.

If the dosage form remains in the stomach, where it acts as a reservoir and releases riboflavin, one can expect a significant

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increase in absorption from this type of product. The improved absorption was found to occur with bioefficient/HBS™ products containing riboflavin.

The following investigations were carried out to compare in humans, the bioavailability of riboflavin from HBS™ capsule and tablet formulations, and the fast releasing control capsule formulation. Each formulation contained sodium riboflavin 5'-phosphate, equivalent to 15 mg riboflavin.

The in vitro tests were carried out by the modified NF method in simulated gastric fluid at 40 rpm and riboflavin was analyzed by the USP method. The control capsule released the content rapidly within 1/2 hour, while the release of riboflavin was slow with HBS™ products. The data are plotted in Figure 7 in which the HBS™ capsule and tablet have slightly different release rates.

In the in vivo studies, the dosage forms were administered to six volunteers about 1.5 hours after breakfast (about 9 a.m.). The subjects were saturated with riboflavin prior to the study and the basal excretion was established the day before the dosage form was administered. Urine was collected and the amount of extra riboflavin excreted was determined. Figure 8 summarizes the mean extra urinary excretion rate of riboflavin in milligrams from the three dosage forms at specified times on a semilogarithmic plot. The results of the urinary excretion rate show that the control capsule establishes an average peak height which does

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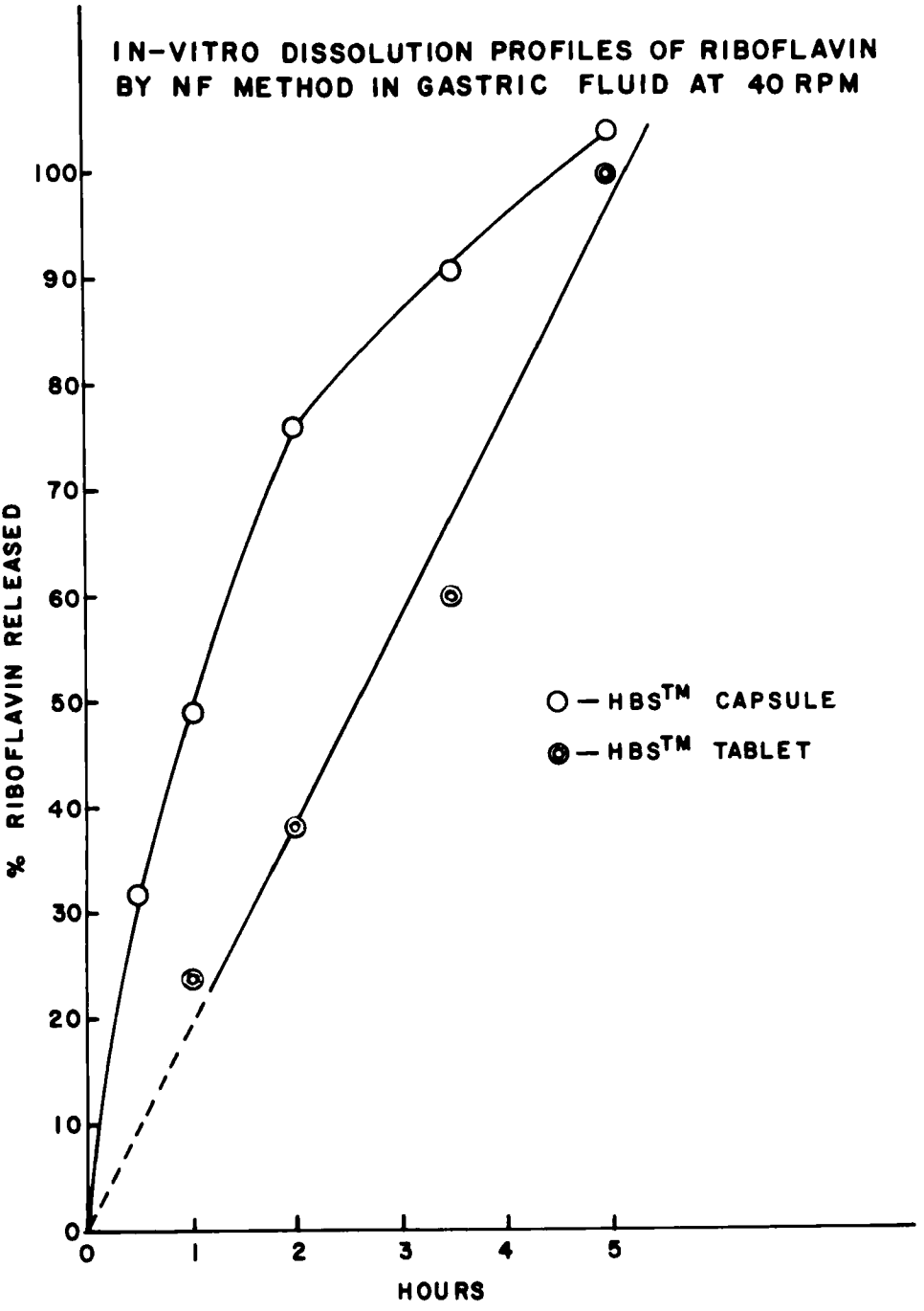

Figure 7 - In-Vitro Release Rates for HBS Tablet and Capsule

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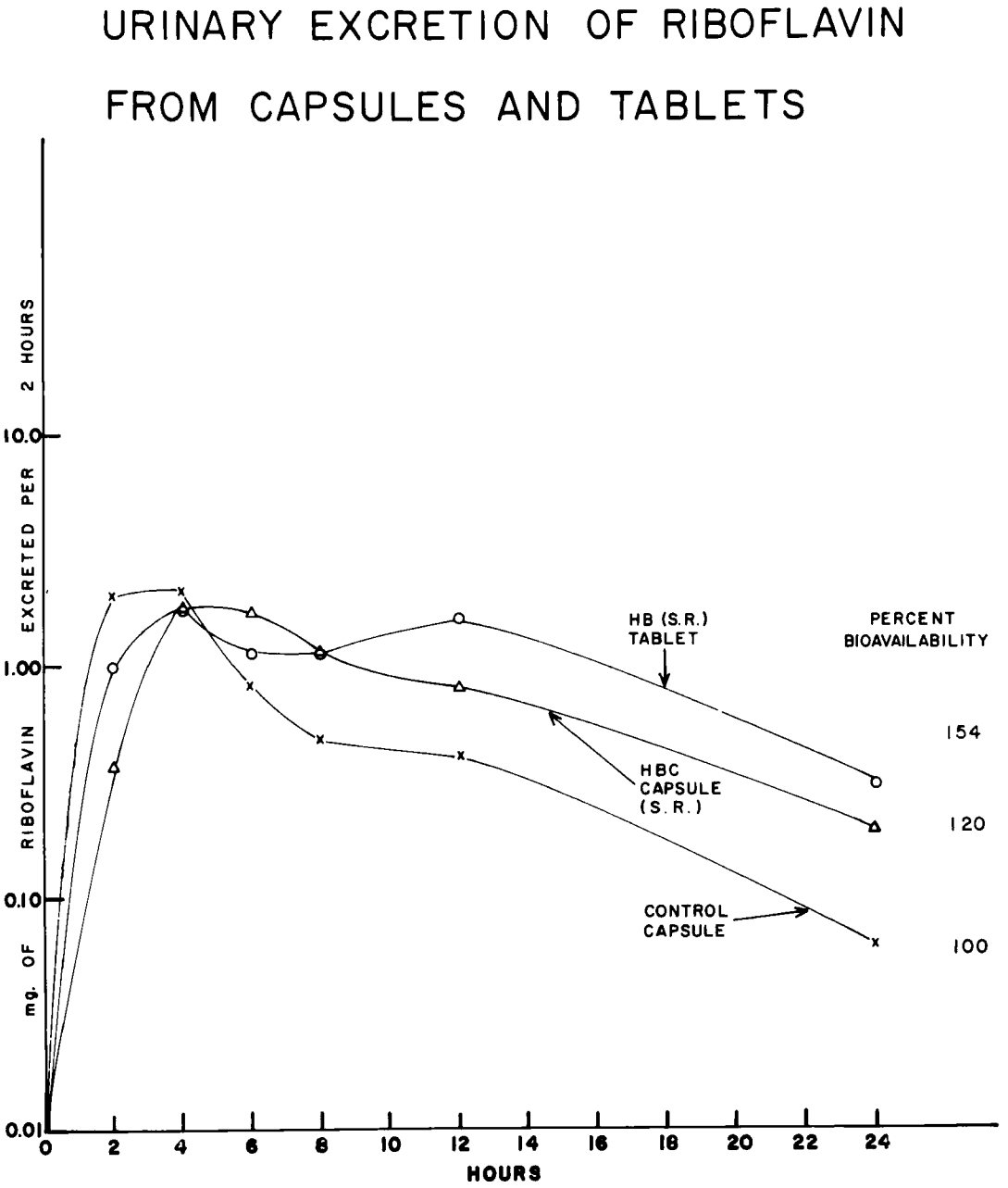

Figure 8 - Urinary Excretion Rates of Riboflavin From Capsules and Tablets

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not exceed 2 mg in 2 hours after dosing and drops rapidly after two to four hours. In the hydrodynamically balanced drug delivery system, an acceptable peak height was attained but the time was somewhat delayed due to the controlled release effects. However, there was a prolonged and uniform excretion of riboflavin indicating continuous absorption with the HBS™ products. In Table 1, the average amount of riboflavin excreted in 24 hours from the 3 dosage forms tested are presented. The relative bioavailabilities from the HBS™ capsule and tablet were 120% and 154%, respectively, using the control as a standard.

The data show that the use of the HBS™ products resulted in a significant increase in bioavailability, a clear indication of the controlled release and prolonged absorption of riboflavin from this new delivery system. The improvement is mainly due to the effects of the hydrodynamically balanced system, which has buoyant properties and slowly releases the riboflavin to the site of optimum absorption in the duodenum.

Vitamin C plus E Dosage Form

Concern over the nitrosation of susceptible amines or amides in the gastric environment, leading to the formation of carcinogenic nitrosamines and/or nitrosamides, initiated these investigations. Although vitamins C and E are normally needed for well-being, they were used in this study to prevent nitroso compound formation in the stomach.[10] The experiment was carried

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Table 1 - Extra Urinary Excretion of Riboflavin

Time Interval	Riboflavin Excreted mg Control Capsule	Hydrodynamically Balanced Capsule	Hydrodynamically Balanced Tablet
0-2	2.03	0.38	0.98
2-4	2.11	1.83	1.79
4-6	0.84	1.68	1.14
6-8	0.47	1.18	1.14
8-12	0.84	1.60	3.23
12-24	0.38	1.25	1.86
	6.67 mg	7.92 mg	10.14 mg
Percent of dose excreted in 24 hours:	44%	53%	67.5%
Percent Bioavailability:	100%	120%	153.4%

out in vitro in a simulated stomach environment designed to mimic one of the key features of a human stomach, that is, a flow-through environment (Figure 9). The flow rate used in this study was ca. 200ml/hour, which approximates the amount of fluids passing through the stomach from exogenous sources including food, water, saliva and normal gastric secretions.

The nitrosation reaction is based on the aminopyrine-nitrite interaction at pH 1.3 in equimolar concentration of 0.0296mM/hour (6.83 and 2.04 mg/hour, respectively). The reaction product,

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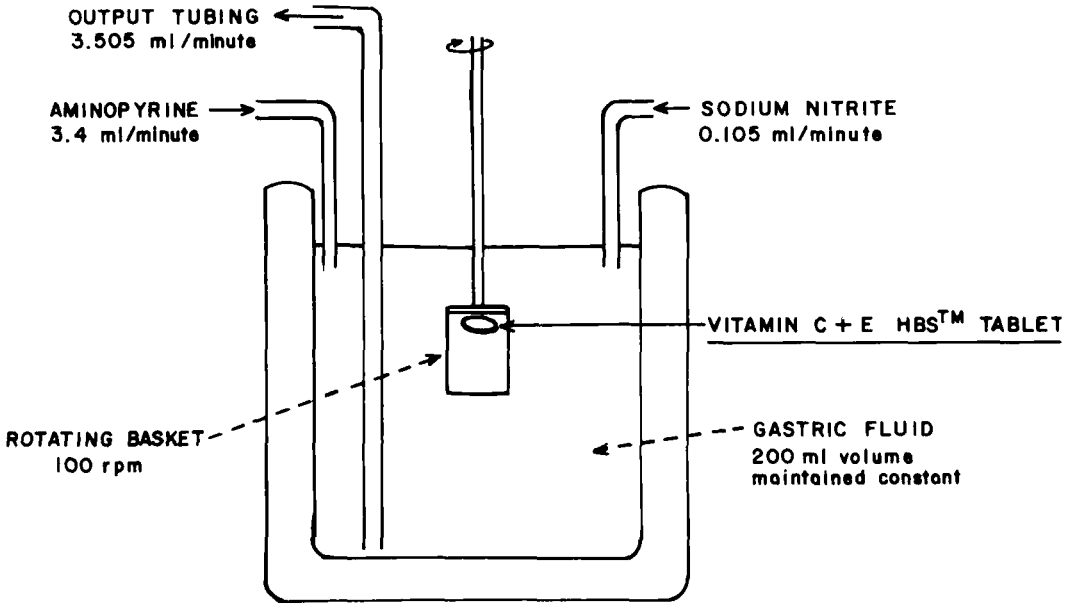

IN-VITRO MODEL FOR NITROSAMINE INVESTIGATION IN A FLOW THROUGH ENVIRONMENT

Figure 9 - Flow Through Environment for Nitrosamine Investigation

dimethylnitrosamine (NDMA), is formed sufficiently fast to be used as a sensitive system to evaluate the potential for nitrosamine formation and as such is also a good model for studying inhibition.

An HBS™ tablet containing 100 mg each of vitamin C (ascorbic acid) and vitamin E (d,l-alpha tocopherol) was tested in this apparatus and compared with vitamin C (ascorbic acid powder). The amount of ascorbic acid in the flow through environment from vitamin C powder and HBS™ tablet using the USP dissolution apparatus are shown in Figure 10.

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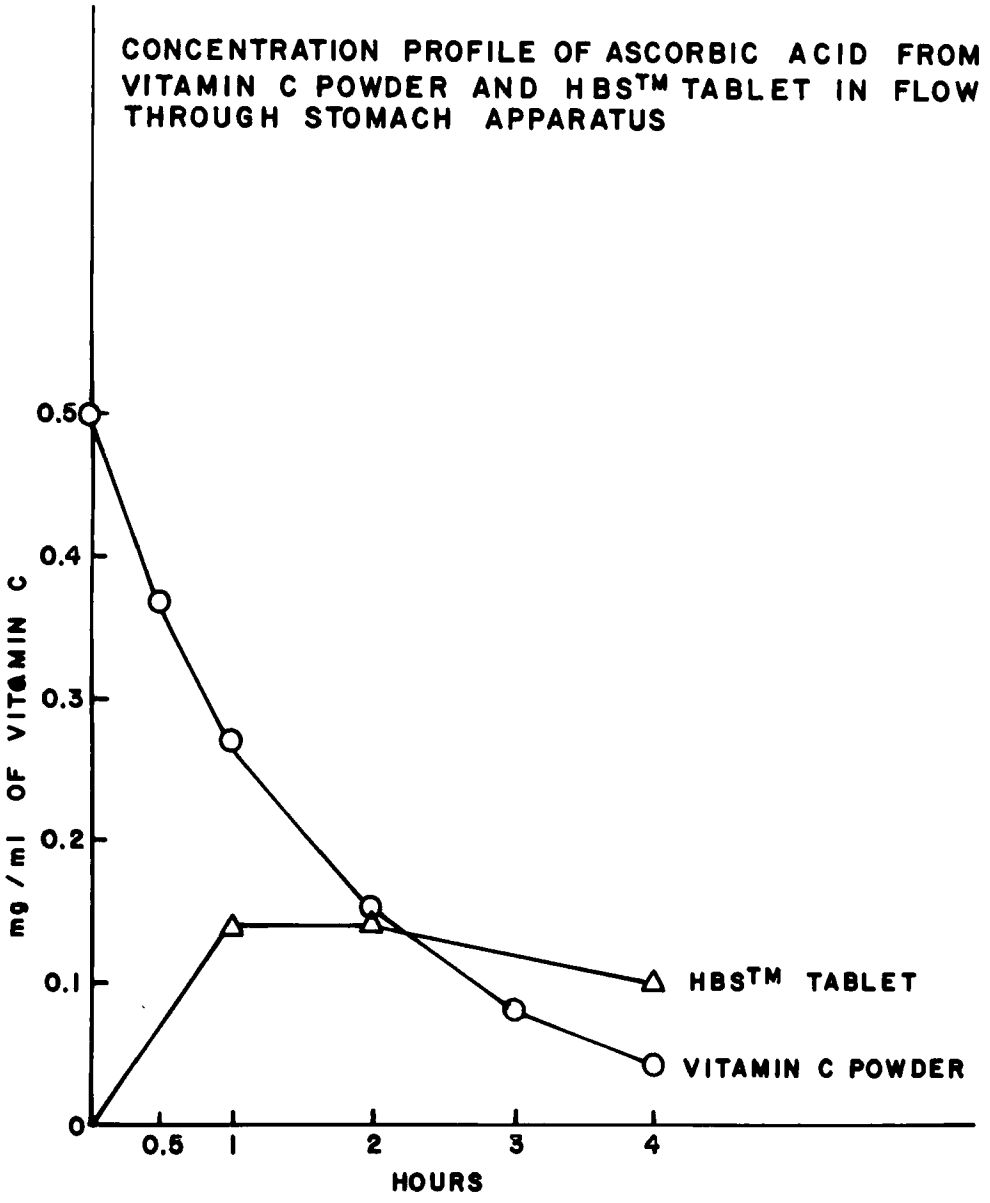

Figure 10 - Concentration Profile of Ascorbic Acid from Vitamin C Powder and HBS™ Tablet

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The results indicate that in the model environment, the concentration of vitamin C declines steadily with time from vitamin C powder while the HBS™ tablet initially builds in concentration and maintains a constant level in the reaction pool. Four hours after the experiment began, 25% of the vitamin C in the HBS™ tablet remained to be released.

Figure 11 contains the results of the first nitroso-compound inhibition experiment. Vitamin C powder was compared to the HBS™ tablet containing 100 mg of both ascorbic acid and d,l-alpha tocopherol and a substantial difference in blocking ability was observed between the two preparations. After 3.5 hours, the last data point for the pure vitamin C powder, 54% of the nitrosamine formation was inhibited by the ascorbic acid alone, while the blocking by the HBS™ tablet was greater than 98%.

In order to compare the blocking capacity of dosage forms on an equimolar basis, a second evaluation was performed using a chewable 100 mg vitamin C plus 100 mg vitamin E tablet in place of ascorbic acid (Figure 12). Once again, the HBS™ tablet was shown to be far superior to the chewable tablet, indicating that the HBS™ offers a distinct advantage over more conventional dosage forms in preventing nitrosamine formation in a simulated gastric environment.

The bioavailability of ascorbic acid from an HBS™ tablet containing vitamin C plus E 100 mg each was examined in six subjects

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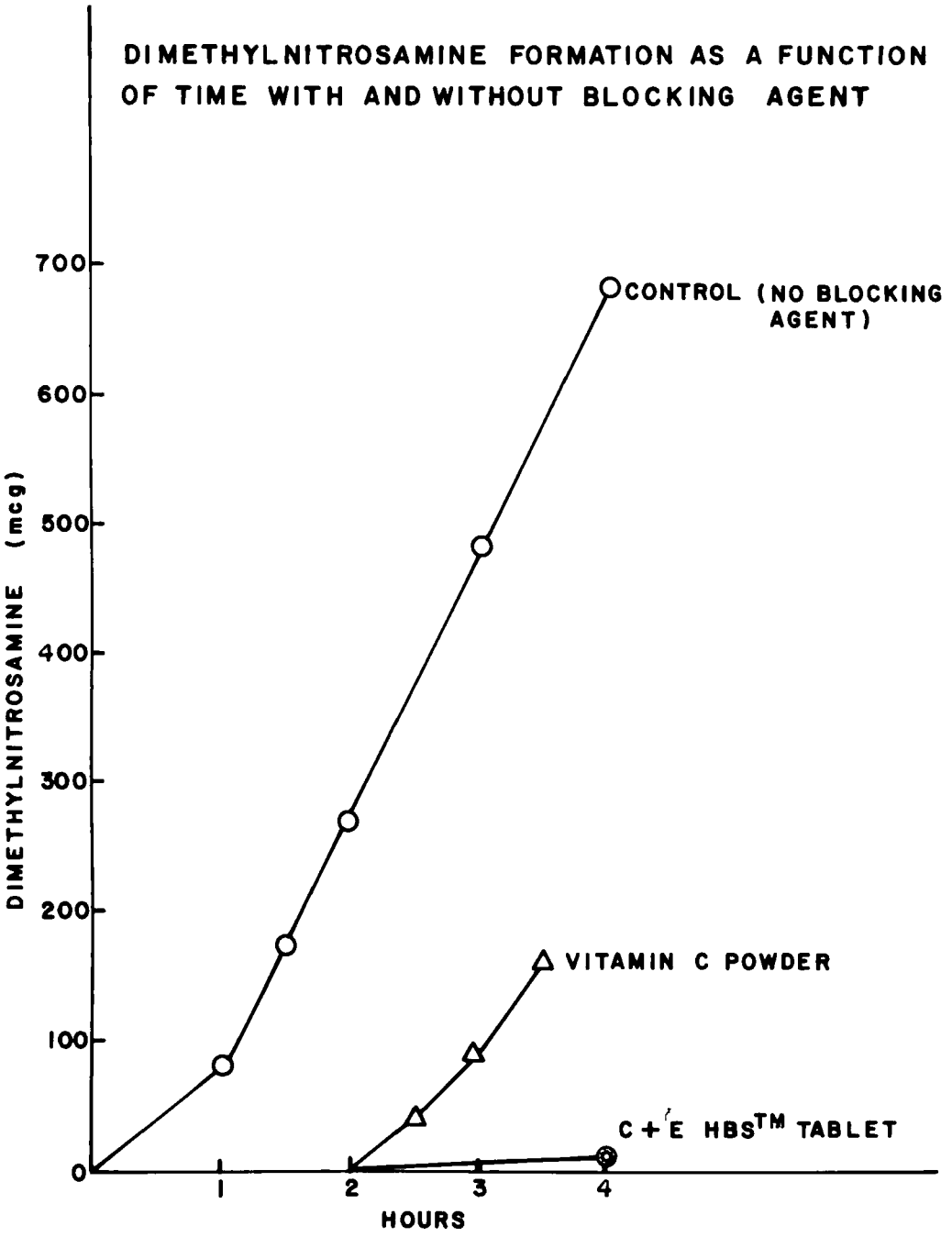

Figure 11 - NDMA Formation With and Without Blocking Agent (Vitamin C Powder vs. HBS Tablet)

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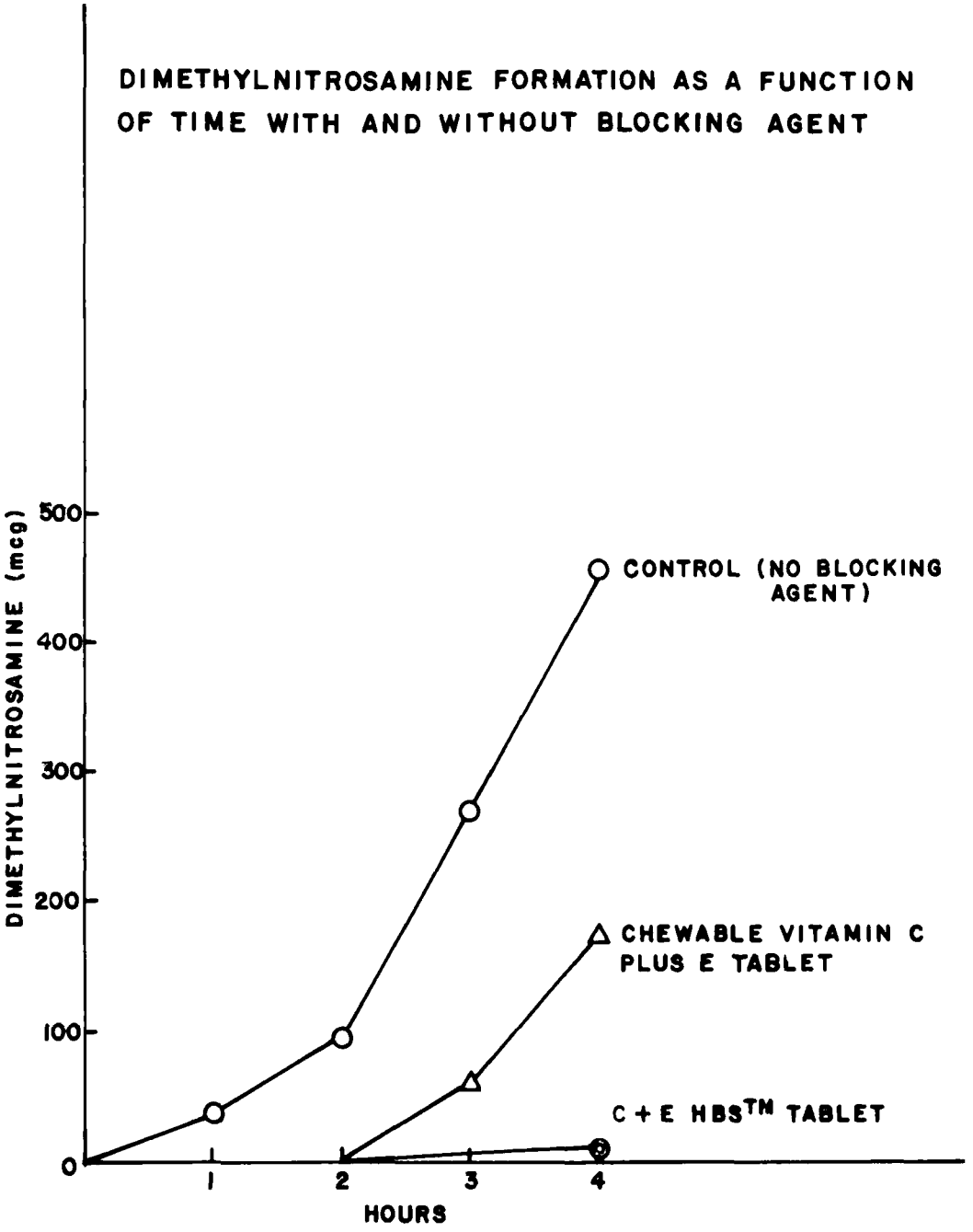

Figure 12 - NDMA Formation With and Without Blocking Agent (Chewable Tablet vs. HBS Tablet)

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Table 2 - Average Extra-Urinary Excretions of Ascorbic Acid in 24 hours:

Time (hours)	Milligrams of Ascorbic Acid Excreted Due to Dose	
	Standard	HBS™ Tablet
0-2	16.1	13.7
2-4	40.7	24.7
4-6	29.8	30.3
6-8	13.8	20.0
8-12	26.6	47.4
12-24	13.9	27.7
Total in mg	140.9	163.8
Percent bioavailability as compared with standard	100%	116%

who had been saturated with vitamin C prior to investigation. The extra-urinary excretion of ascorbic acid was determined by administering the HBS™ tablet at the 300 mg dose level. The results of this trial were compared to the results obtained when the 300 mg dose of ascorbic acid in solution was administered to the same subject in crossover fashion. Table 2 shows the average extra-urinary excretion from these doses, while Figure 13 represents the rate of excretion on a semilogarithmic plot.

Based on the average total human urinary excretion (24 hours), the bioavailability of ascorbic acid from the HBS™ controlled release formulation was about 116% of the standard solution. The lower urinary excretion in the early hours after

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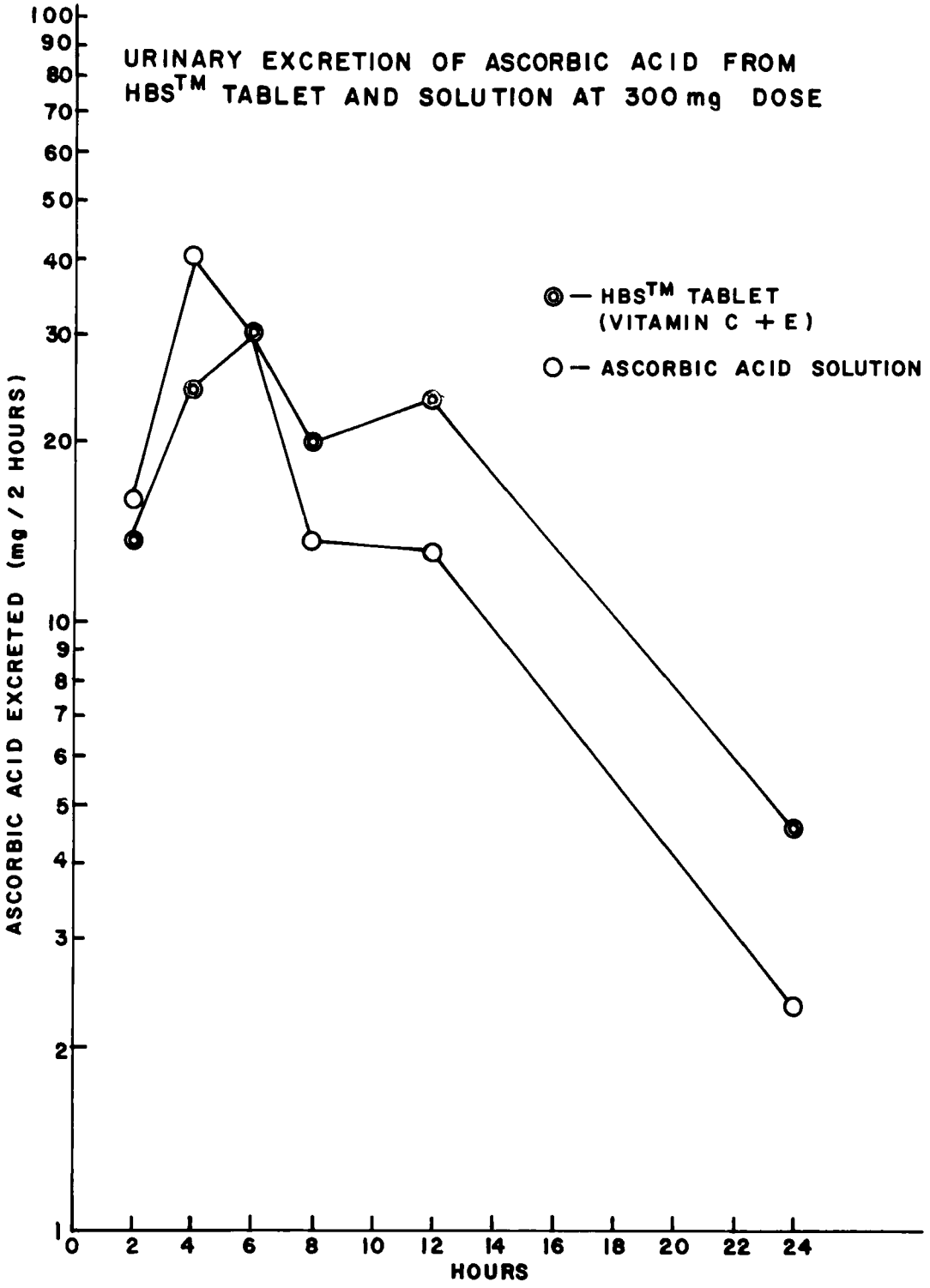

Figure 13 - Urinary Excretion Rate of Ascorbic Acid From HBS™ Tablet and Solution

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administration of the HBS™ tablet demonstrated the delayed release of ascorbic acid as compared to the standard dose of ascorbic acid solution. The controlled release product, however, showed higher excretion after 6 hours with 32% of the dose for HBS™ tablet and 18% for the standard solution.

Bioefficient Thiamine

Thiamine is another compound that is better absorbed from the upper portion of the small intestine and the "window" is claimed to be very narrow in alcoholic patients. It is difficult to achieve a continuous absorption of thiamine from a conventional sustained release product due to its rapid passage through the gastrointestinal tract.

Two HBS™ formulations, a tablet and a capsule, each containing 15 mg thiamine as the mononitrate were developed. Figure 14 represents the in vitro release time profile by the USP basket method in gastric fluid at 100 rpm. Both products were administered to 6 subjects after breakfast and the extra excretion of thiamine from these formulations were compared to those of a fast disintegrating capsule used as a standard. The subjects were saturated with thiamine prior to investigation and the basal excretion was determined. Since the diet was not controlled, the average basal value was calculated for each subject, and subtracted from the total excretion value to obtain the extra excretion of thiamine.

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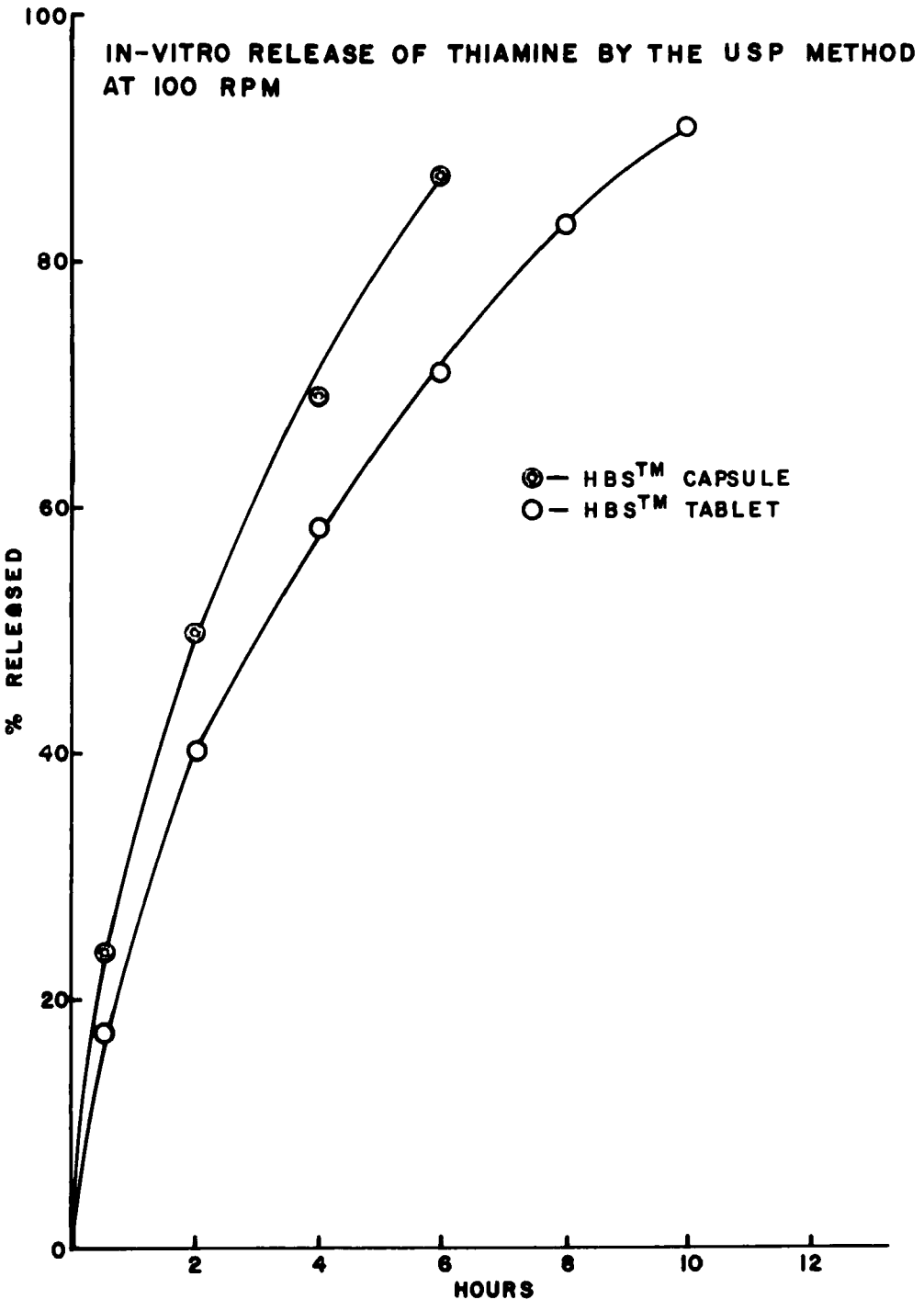

Figure 14 - In-Vitro Release of Thiamine by the USP Basket Method in Gastric Fluid at 100 RPM

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Table 3 - Average Extra-Urinary Excretion of Thiamine in 6 Subjects

Collection Period	Control	HBC Capsule	HBC Tablet
0-4 hour	0.44	0.33	0.20
4-8 hour	0.15	0.43	0.38
8-23 hour	0.23	0.39	0.48
	0.82 mg	1.15 mg	1.06 mg
% Bioavailability	100%	140%	129%

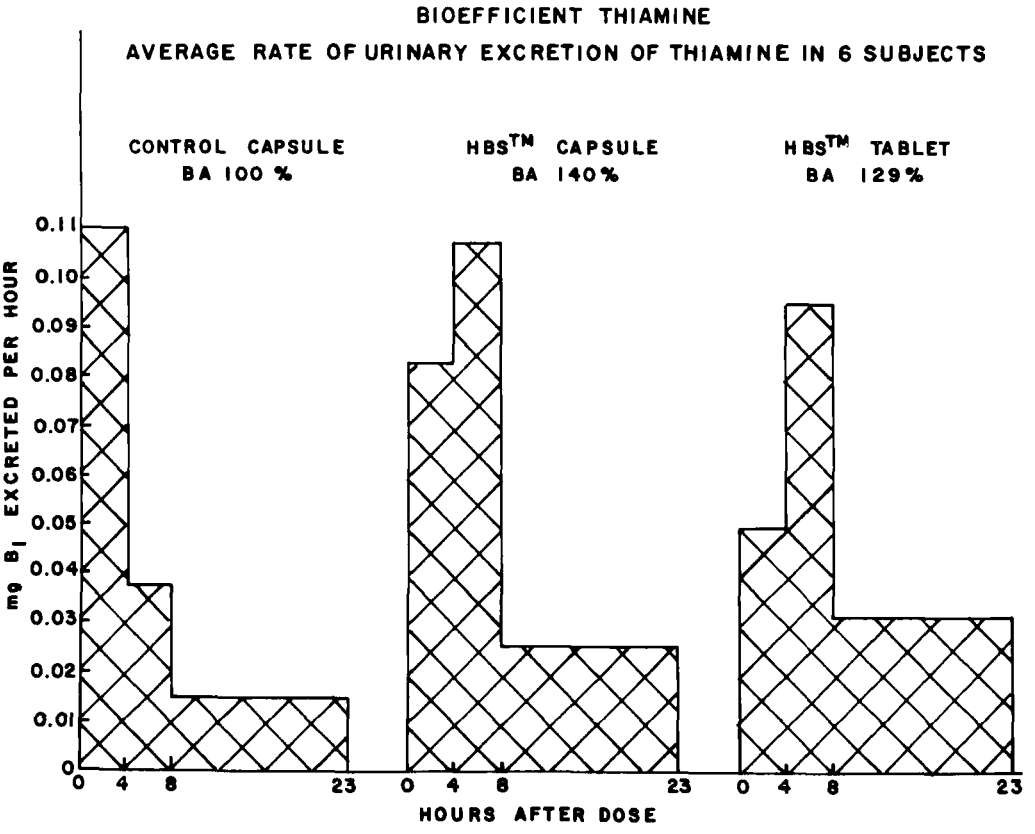

Figure 15 - Urinary Excretion Rate of Thiamine (Control vs. HBS Capsule vs. HBS Tablet)

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Table 3 presents the urinary excretion of thiamine determined in this experiment; the rate of excretion is shown in Figure 15.

As expected, the fast releasing capsule yielded the highest excretion rate in the first 4-hour collection period. The HBS™ capsule appears to release the thiamine more rapidly than the HBS™ tablet as judged by the larger amount excreted in the first 8 hours after administration. In an 8 to 23 hour period, both HBS™ products show higher levels of excretion than did the control capsule. The total extra excretion was 140% for the HBS™ capsule and 129% for the HBS™ tablet, taking the control as standard. Accordingly, these results indicate that the HBS™ thiamine products are bioefficient and can achieve an improved bioavailability, through continuous absorption.

SUMMARY

The bioefficient products utilize the HBS™ delivery system to administer medicinals in a controlled release fashion. In a refinement of traditional pharmaceutical art, however, this system has been shown to increase the efficiency and the bioavailability of the compounds especially those which are absorbed from the upper portion of the small intestine. Furthermore, the system can be used to maintain substances in the stomach for specific purposes. Using this delivery system, a combination vitamin C plus E HBS™ product was able to inhibit

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nitrosamine formation in the stomach model for a long period of time, as shown in in vitro tests.

The bioavailability of certain vitamins poorly absorbed from the intestines has been significantly improved using the HBS™-bioefficient system. A single dose of bioefficient HBS™ product can achieve absorption characteristics not attainable with conventional sustained release preparations.

Finally, the use of the controlled-release bioefficient/HBS™ delivery system provides absorption characteristics normally only achieved with multiple dosing regimens when using conventional tablets or capsules.

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