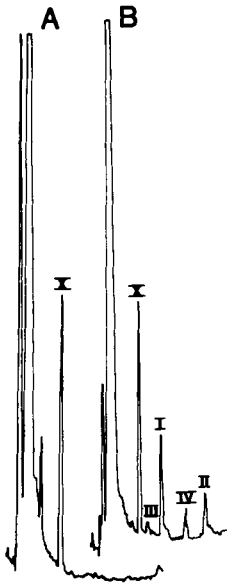

Figure 5—*Typical chromatograms of extracts of 1 ml of plasma, injection volume 30 μl, absorbance at 245 nm. Key: (A) drug free; (B) patient receiving I orally. Concentrations of compounds expressed as ng/ml of plasma are I = 87, II = 50, III = 7, and IV = 38.*

The ratios of the peak heights of the drugs and metabolites to the peak height of the internal standard were calculated. Statistical analysis of the data (Table I) by linear regression indicated linearity and reproducibility in the 20–400-ng/ml range of plasma. This range includes the therapeutic range of the drugs. Absolute recovery of the drugs and metabolites ranged from 55 to 80% of the theoretical amounts. This low recovery may be responsible for the variation in the amount found at low concentrations (Table I). The minimum detectable limit for the compounds is <5 ng/ml of plasma.

No interference from normal plasma constituents was observed (Fig. 5A). Also, several drugs which might be prescribed simultaneously with tricyclics were chromatographed. The retention times are listed in Table II.

The method has been applied to many patient samples and is being used routinely in the laboratory for monitoring therapeutic levels (Fig. 5B). Major advantages of the method are its simplicity, rapidity, and high sensitivity. All of the drugs and metabolites, including the 10-hydroxy metabolites of amitriptyline and nortriptyline, are determined using a single procedure. Adsorbance of the drugs onto glass has been minimized.

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Chelation of Mercury by Polymercaptal Microspheres: New Potential Antidote for Mercury Poisoning

S. MARGEL ˣ **and J. HIRSH**

Received February 18, 1981, from the *Department of Plastics Research, The Weizmann Institute of Science, Rehovot, Israel.* Accepted for publication November 17, 1981.

Abstract □ Newly synthesized polymercaptal microspheres of 0.8 ± 0.02 μm were shown to have a specific and fast intake of mercury compounds over a whole range of pH while maintaining low toxicity. The microspheres bind easily with mercury compounds which are already bound to the biological mercury binders, albumin or cysteine. Mercury was recovered completely from the microspheres by using a solution of thiourea in hydrochloric acid. Due to their high surface area, low toxicity, and strong affinity toward mercury compounds, the microspheres have a potential use as a new oral drug for treatment in cases of mercury poisoning.

Keyphrases □ Microspheres—chelation of mercury, polymercaptal, new potential antidote for mercury poisoning □ Mercury—chelation by polymercaptal microspheres, new potential antidote for poisoning □ Chelation—mercury, polymercaptal microspheres, new potential antidote for mercury poisoning

Mercury compounds, both organic and inorganic, constitute an environmental and agricultural hazard (1, 2). Severe poisoning is known to cause brain damage, fetal disabilities, and death (2, 3). The therapy for mercury poisoning includes intravenous administration of the chelating drugs dimercaprol and/or penicillamine (4).

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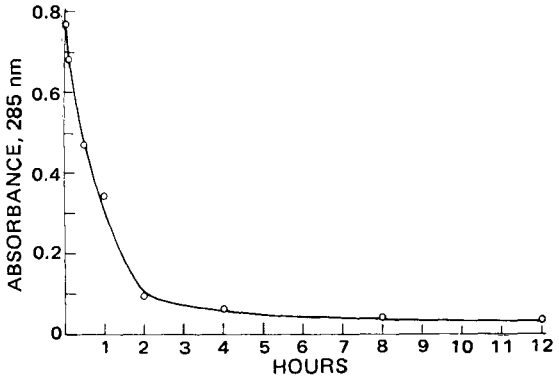


Figure 1—*Change of the absorbance at 285 nm during the reaction between glutaraldehyde and pentaerythritol tetrathioglycolate. The reaction was carried out by stirring 4.5 mmoles of glutaraldehyde with 4.5 mmole of pentaerythritol tetrathioglycolate in 30 ml of H_2O at pH 4.0, at room temperature.*

Recently, new types of water soluble drugs, 2,3-dimercapto-succinic acid (5) and dithiocarbamate compounds (6) were synthesized and suggested as intravenously administered antidotes for mercury poisoning. Another approach which has been tried successfully in cases of mercury poisoning, in particular methyl mercury, is based on the oral administration of insoluble polythiol resins which bind mercury compounds and thereby increase their fecal excretion (7–9).

In the present study the use of insoluble chelating microspheres specific for mercury compounds as a potential oral antidote for mercury poisoning is suggested. For this purpose polymercaptal microspheres of 0.8 ± 0.02 μm were synthesized. The large surface area of these microspheres, as well as their low toxicity and strong affinity toward mercury compounds renders them as good candidates to be used in cases of mercury poisoning.

EXPERIMENTAL

Reagents—All reagents were of analytical grade and used as received. A phosphate-buffered solution was prepared by adding sodium hydrogen phosphate solution (0.1 *M*) to an aqueous solution of sodium dihydrogen phosphate (0.1 *M*) until a pH of 7.2 was reached. The solution was then diluted 10 times with distilled water. Phosphate-buffered saline solution was prepared by adding sodium chloride to the phosphate-buffered solution to obtain a final concentration of 0.15 *M*. The following reagents gave a very small mercury blank value and could be used without further purification: sulfuric acid, hydrochloric acid, stannous chloride, hydroxylamine hydrochloride, potassium permanganate, and deionized water. The stock solution of mercuric chloride and of methyl mercury chloride was prepared in 10% HCl. Standards were prepared from the stock solution by diluting with 10% HCl. Glassware was soaked in concentrated nitric acid for several hours before use.

Mercury Analysis—Mercury was determined by cold vapor atomic absorption with a cold vapor analyser kit[1] (10). The limit of detection for this procedure is 0.15 ng in 1.0 ml of solution.

Binding of Mercury Compounds to Albumin—A phosphate-buffered saline solution containing 4.0% normal human albumin was shaken for 2 hr with methyl mercury chloride or with mercuric chloride (20 ppm Hg). The binding with mercuric chloride was determined by placing the solution into ultrafiltration membranes[2] and centrifuging it for 5 min at 1000 rpm. The binding with methyl mercury chloride was determined by ultrafiltration of the solution through a dialyzing membrane with a permeability corresponding to a molecular weight of 10,000. In both cases mercury was not detected in the ultrafiltrate, indicating that the mercury compounds were completely bound to albumin.

Chelating Microspheres—An aqueous solution containing 0.2% (v/v) polyoxyethylene sorbitan monolaurate[3] as surfactant and 5% (v/v) pentaerythritol tetrathioglycolate was vigorously stirred for several hours until a stable aqueous emulsion of pentaerythritol tetrathioglycolate was produced. Thereafter, 5.5 ml of 25% glutaraldehyde was added to the emulsion solution which was then shaken for 12 hr. The reaction product was composed of a solid sticky compound that resulted from the agglutination of chelating microspheres and 60% disperse solid chelating microspheres. The microspheres were separated by decantation from the sticky part and cleaned from impurities either by dialysis or by slow spinning. The appearance and size of the microspheres was determined by scanning electron and light microscopy.

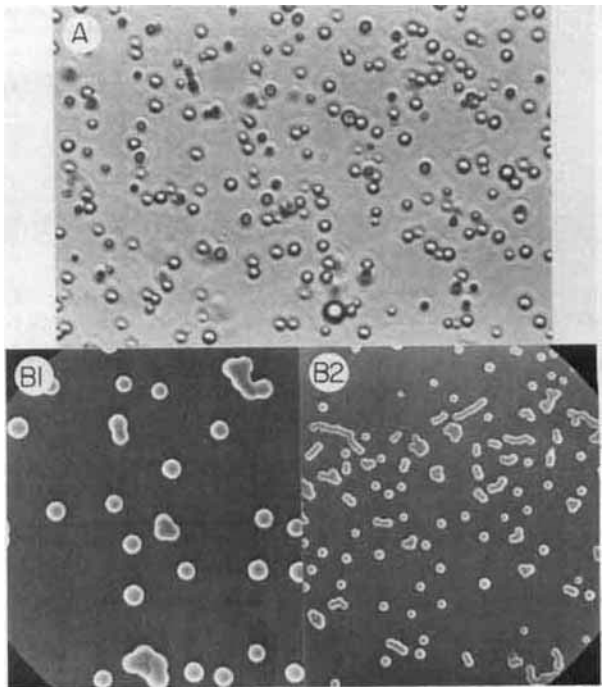


Figure 2—*(A) Light microscopy photomicrograph of chelating microspheres (×3000). (B) Scanning electron microscopic photomicrographs of chelating microspheres (1, 3100×; 2, 6300×).*

Toxicity—The acute median lethal dose (LD_{50} orally) to 40 mice[4] of the chelating microspheres was found to be 1.0 g/kg of body weight.

Intake of Mercury Compounds by Chelating Microspheres—The chelating microspheres were added to a stirred phosphate-buffered saline solution containing mercury compounds. Samples to be tested for mercury concentration were spun at 10,000 rpm for 10 min, thereby separating the solution from the precipitating microspheres. Control experiments were carried out in the same way but without chelating microspheres. (Spinning of the control samples did not show any precipitation of mercury compounds.)

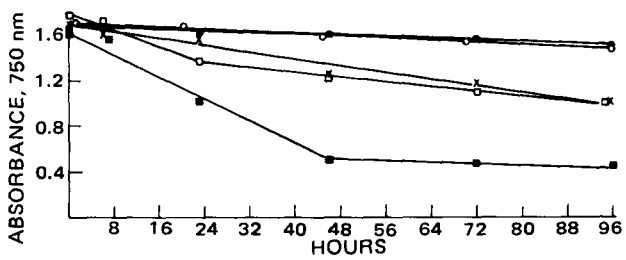


Figure 3—*Aggregation properties of the chelating microspheres. The absorbances at 750 nm were obtained by diluting 0.05 ml of the chelating microsphere suspension (containing 20 mg/ml) with 2.5 ml of H_2O. Key: (○) microspheres in H_2O; (×) microspheres in phosphate-buffered solution; (□) microspheres in phosphate-buffered saline solution; (■) microspheres in aqueous solution at pH 1.1; and (●) microspheres in phosphate-buffered saline solution under shaking.*

[1] Varian model 1200, Mulgrave, Victoria, Australia.
[2] Amicon 2100, CF-50, Lexington, Mass.
[3] Tween 20, Sigma Chemical Co., St. Louis, Mo.
[4] ICR mice.

Table I—Yield of Chelating Microspheres as a Function of pH [a]

pH [b]	Yield, %
7.0	70
4.0	60
2.0	6
0.5	1

[a] Glutaraldehyde (25%, 5.5 ml) was added to a shaken aqueous suspension (100 ml) of pentaerythritol tetrathioglycolate (5 ml), at various pHs. [b] pH 7.0 was obtained by adding sodium hydroxide to the aqueous suspension; pH 2.0 and pH 0.5 were obtained by adding hydrochloric acid to the aqueous suspension.

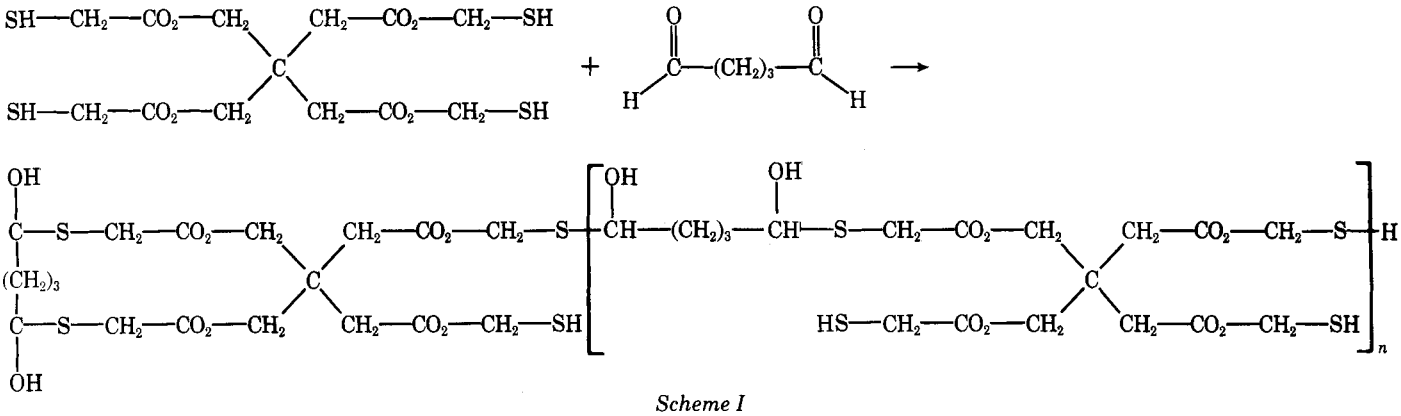
Recovery of Mercury Compounds from Chelating Microspheres—Fast and quantitative recovery of mercury compounds bound to microspheres was carried out by adding thiourea and hydrochloric acid to a stirred solution up to a final concentration of 1.0% CH_4N_2S and 0.5% HCl. In <10 min 100% of the mercuric chloride or of the methyl mercury chloride were recovered from the microspheres.

Photomicrographs—A photomicrograph of the microspheres was prepared by using a photographic flash light attached to a light microscope, thereby obtaining a focused picture of most of the moving microspheres.

A sample for scanning electron microscopy was prepared by drying a drop of a diluted solution of the microspheres on a cover slide which was then coated with gold.

RESULTS

The chelating microspheres were prepared by carrying out the reaction of glutaraldehyde and pentaerythritol tetrathioglycolate in the presence of the mentioned surfactant. The assumed reaction is shown in Scheme I:



Scheme I

The rate of the reaction was measured by following the disappearance of the absorbance at 285 nm, related to the aldehyde groups of glutaraldehyde (Fig. 1). The surfactant stabilized micelles of pentaerythritol tetrathioglycolate which were interacted with glutaraldehyde to form the insoluble microspheres (Fig. 2).

The chelating microspheres were found to be monodispersed with a diameter of 0.8 ± 0.02 μm. They were spherical with a calculated surface area with an average microsphere size of 8.04×10^{-8} cm^2. The yield of the microspheres is dependent on the pH of the reaction. At a lower pH the microspheres tend to agglutinate more and therefore their yield is lower (Table I). The stability of the chelating microsphere suspension was checked by following the change in the turbidity of the suspension (Fig. 3). Aggregation of microspheres was indicated by the decrease in the turbidity. The chelating microsphere suspension is stable in water and there was no indication of aggregation even after a year. The microspheres tend to sink slowly to the bottom of the container and can be resuspended by shaking them again. The tendency of the microspheres to aggregate at acidic pH or at a high salt concentration was prevented by continuous shaking. Supporting evidence for the stability results was obtained by looking at the monodispersity of the microspheres under a light microscope (Fig. 2A). In water, the monodispersed microspheres moved in a Brownian motion, and there was no indication of agglutinated microspheres even after a year. Under strong acidic conditions (pH 1.0) large aggregates slowly formed. Attempts were made to obtain a scanning electron microscopic photomicrograph of the microspheres (Fig. 2B-1 and B-2). However, some small aggregates of microspheres were obtained

Table II—Intake of Mercury Compounds by Chelating Microspheres in Presence of Alkali and Alkaline Earth Metallic Compounds [a]

[Hg], ppm	Metallic Compounds, *M*	Microspheres, mg	Hg Intake, %	Ca, Na, and Mg Intake, %
20 (Mercuric Chloride)	0.001 $CaCl_2$	15	100	0
20 (Mercuric Chloride)	0.15 NaCl	15	100	0
1 (Mercuric Chloride)	0.1 NaCl + $CaCl_2$ + $MgCl_2$	10	~95	0
20 (Methyl Mercury Chloride)	0.15 NaCl	15	100	0
1 (Methyl Mercury Chloride)	0.1 NaCl + $CaCl_2$ + $MgCl_2$	10	~95	0

[a] The mercury compounds were stirred with chelating microspheres for 15 min in 20 ml of aqueous solution.

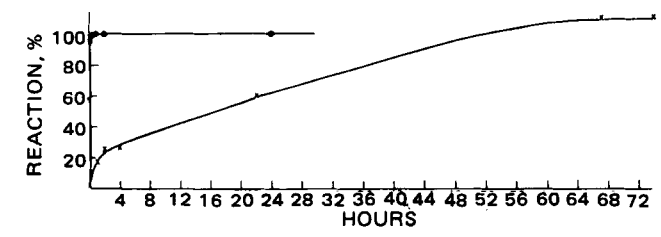


Figure 4—*Comparison of the rate of intake of mercuric chloride by chelating microspheres and agglutinated chelating microspheres. The reaction was carried out by stirring 10^{-4} M mercuric chloride (20 ppm Hg) and 20 mg of the chelating polymer in 50 ml of phosphate-buffered saline solution. Key: (●) chelating microspheres; (X) agglutinated chelating microspheres.*

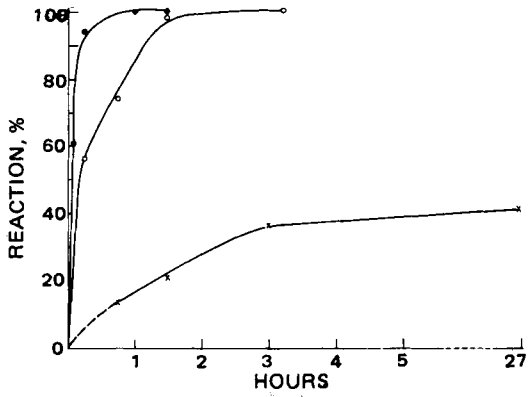


Figure 5—*Rate of intake of mercuric chloride by chelating microspheres. The reaction was carried out by stirring 10^{-4} M mercuric chloride in 80 ml of phosphate-buffered saline solution in presence of: (X) 3.5-mg microspheres; (○) 20-mg microspheres; (●) 60-mg microspheres.*

Table III—Percent Reaction of Mercuric Chloride with Chelating Microspheres at Various pH [a]

Time, min	pH [b]			
	2.0	4.0	7.1	8.5
10	98	98	97	98
120	100	100	100	97
240	100	100	100	95

[a] Mercuric chloride (10^{-4} *M*) was stirred with chelating microspheres (25 mg) in 50 ml of aqueous solution. [b] pH 2.0 and pH 4.0 were obtained by adding hydrochloric acid to 0.1 *M* sodium hydrogen phosphate aqueous solution. pH 8.5 was received by adding sodium hydroxide to 0.1 *M* H_2NaO_4P aqueous solution.

due to the drying of the sample. A photograph of higher concentration of microspheres could not be obtained since large aggregates of the microspheres were formed and single microspheres could not be found.

The chelating microspheres had a high surface area, and therefore, their rate of mercury intake was much higher than that of the same chelating compound in bulk (Fig. 4). Organic and inorganic mercury compounds are taken in by the microspheres very rapidly (Figs. 5 and 6), but do not interact with alkaline or alkaline earth metallic compounds (Table II). They bind the mercury compounds over a broad range of pH (Table III) and compete and bind mercury compounds which are already bound to albumin or to cysteine (Tables IV and V). Comparison with commercial resins reported to have a high affinity for mercury, *e.g.*, styrene–divinylbenzene derivatized either with iminodiacetates[5] or with Srafion NMRR[6] (11) showed that the iminodiacetate derivative did not bind methyl mercury chloride, although it bound quantitatively Hg^{2+}, while the Srafion NMRR bound mercury compounds under physiological conditions much slower than the chelating microspheres (Fig. 7). A quantitative elution of the bound mercury is obtained by adding thiourea and hydrochloric acid to the suspended microspheres.

DISCUSSION

The structure of the chelating compound produced by the reaction of the aldehyde groups of glutaraldehyde and the thiol groups of pentaerythritol tetrathioglycolate seems to be complicated, and does not agree with the ideal structure of a polymer as suggested previously (12). The mercury compounds are probably bound to the chelating compound through its free thiol groups, and the S—C(OH) groups (hemi thio acetal). The structure of the chelating compound and of its binding to mercury compounds is currently being investigated. The chelating microspheres bind the mercury compound very strongly and reverse the binding from the biological receptors to the microspheres:

$$\text{Metallic compounds (R—M)} \xrightarrow{\text{Biological receptor}} \text{R—M} \cdots \text{Biological receptor} \xrightarrow{\text{Microspheres}} \text{R—M} \cdots \text{Microspheres} + \text{Biological receptors}$$

Scheme II

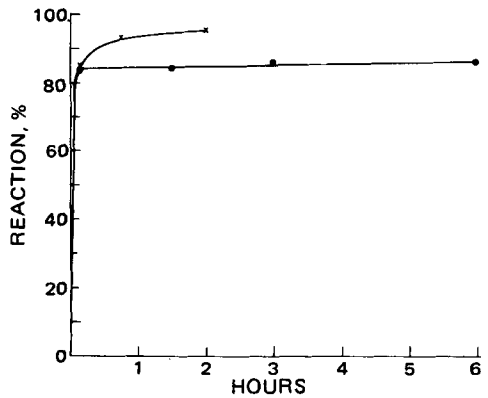


Figure 6—*Rate of intake of methyl mercury chloride by chelating microspheres. The reaction was carried out by stirring 10^{-4} M methyl mercury chloride in 80 ml of phosphate-buffered saline solution in the presence of: (●) 4.6-mg microspheres; (X) 60-mg microspheres.*

[5] Chelex 100 prepared by Bio-Rad Lab., Richmond, Calif.
[6] NMRR prepared by Ayalon Water Conditioning Co., Haifa, Israel.

Table IV—Rate of Intake of Mercury Compounds from Albumin [a]

Mercury Compound	Time, min	Reaction, %
Mercuric chloride	10	81
Mercuric chloride	60	81
Mercuric chloride	120	83
Mercuric chloride	1320	88
Methyl mercury chloride	10	78
Methyl mercury chloride	120	68
Methyl mercury chloride	1320	72

[a] Mercury compounds (5 ppm Hg) were stirred for 2 hr with 60 ml of 4% human albumin in phosphate-buffered saline solution, and then chelating microspheres were added (48 mg in the reaction with mercuric chloride and 60 mg in the reaction with methyl mercury chloride). In control experiments the loss of mercury compounds was negligible (<3%).

Many of the heavy metallic compounds are excreted by the liver *via* the bileduct and intestinal tract, but a great part of the metallic compound (~90% of methyl mercury chloride) is reabsorbed by the intestine. Therefore, it seems feasible that a nonabsorptive binding material, administered orally might bind the metallic compound secreted *via* the bile, prevent reabsorption of the metal, and greatly increase its fecal excretion. Several investigators (7–9) showed that oral administration of indigestible and nonabsorbable resin that binds methyl mercury enhances the fecal excretion of methyl mercury from animals. It was also observed (7) that nonabsorbable polythiol resin given orally can substantially reduce the level of methyl mercury in the blood, brain, kidney, and liver. In an epidemic of methyl mercury poisoning in Iraq (13) a group of scientists reported that oral administration of the same polythiol resin to humans significantly decreased their whole body levels of mercury. In most cases (diffusion control) the rate of mercury intake is directly proportional to the surface area of the mercury binder resin. For a resin with a spherical shape, the rate is directly proportional to the ratio $1/r$:

$$v \alpha n \pi r^2 = \frac{3V}{4\pi r^3} \pi r^2 = 0.75\, V \frac{1}{r} = k \frac{1}{r} \qquad \text{(Eq. 1)}$$

where v is the rate of mercury intake, V is the spherical volume, and n is the number of spheres having a radius r.

For example, spheres with a radius of 1 μm will intake mercury 100 times faster than those with a radius of 100 μm. The dramatic effect of the high surface area of the chelating microspheres (radius of 0.4 μm as compared with hundreds of micrometers of the polythiol resin) are clearly shown in Fig. 4. In 30 min 100% of mercuric chloride was taken in by the microspheres while during the same period of time the agglutinated microspheres bound only 5% of the mercuric chloride.

In conclusion, polymeric microspheres were shown to have a potential use for various applications such as cell labeling and cell separation (14, 15), drug delivery (16), and diagnostic purposes (17). A new application for microspheres is suggested. Chelating microspheres may be very useful

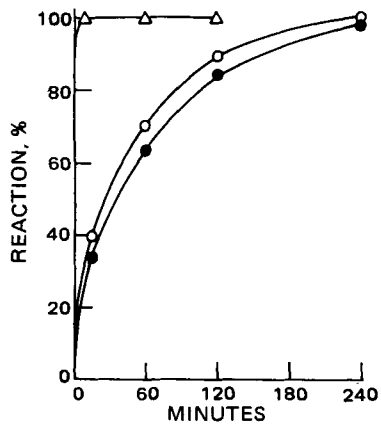


Figure 7—*Rate of intake of mercuric chloride and methyl mercury chloride by the Srafion NMRR–styrene divinylbenzene copolymer resin and the chelating microspheres. The reaction was carried out by stirring 50 ml of phosphate-buffered saline solution containing 10^{-4} M mercuric chloride or methyl mercury chloride with 100 mg of the chelating polymers. Key: (●) Srafion NMRR–styrene divinylbenzene copolymer resin with mercuric chloride; (○) Srafion NMRR–styrene divinylbenzene copolymer resin with methyl mercury chloride; (△) chelating microspheres with either mercuric chloride or methyl mercury chloride.*

Table V—Rate of Intake of Mercury Compounds from Cysteine [a]

Mercury Compounds	Time, min	Reaction, %
Mercuric chloride	10	95
Mercuric chloride	60	97
Mercuric chloride	240	99
Mercuric chloride	1320	100
Methyl mercury chloride	10	91
Methyl mercury chloride	60	91
Methyl mercury chloride	240	91

[a] Mercury compounds (20 ppm Hg) were stirred for 2 hr with 20 ml of 10^{-2} *M* cysteine in phosphate-buffered saline solution. Chelating microspheres were then added (20 mg in the reaction with methyl mercury chloride and 50 mg in the reaction with mercuric chloride). In control experiments the loss of mercury compounds was negligible.

as an oral antidote for treatment in cases of heavy metal poisoning, due to their high surface area. As a model, the potential of polymercaptal microspheres for mercury poisoning was demonstrated *in vitro* and future experiments will have to be carried out *in vivo* as well. Moreover, the affinity of chelating microspheres toward other heavy metallic compounds such as arsenic, cadmium, lead, and copper, *etc.*, will be investigated to evaluate their potential use for treatment of poisoning with these heavy metals.

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Relative Bioavailability of Commercially Available Ibuprofen Oral Dosage Forms in Humans

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Received August 20, 1981, from the *Clinical Biopharmaceutics Research Unit, The Upjohn Company, Kalamazoo, MI 49001.* Accepted for publication December 1, 1981.

Abstract □ Two human bioavailability studies were conducted to assess the *in vivo* performances of recently marketed 200-, 300-, and 400-mg ibuprofen capsules relative to the innovator's 300- and 400-mg tablets when administered as single oral 300- or 400-mg doses. An ibuprofen oral solution was also administered in each trial. Within each study, the products were equivalent to each other and to the oral solution with respect to the extent of ibuprofen absorption. Absorption rates, however, differed markedly among the products studied. Ibuprofen was more slowly absorbed from the 300- and 400-mg capsules than from the respective strength tablets. The 200-mg capsule exhibited an absorption rate comparable to the 400-mg tablet but more rapid than the 400-mg capsule. It was concluded that two of the duplicator's 200-mg capsules were bioequivalent to one of the innovator's 400-mg tablet. The duplicator's 300- and 400-mg capsules were bioinequivalent to the innovator's 300- and 400-mg tablets, respectively, due to their slower rates of absorption.

Keyphrases □ Bioavailability—commercially available ibuprofen oral dosage forms in humans □ Ibuprofen—bioavailability of commercially available oral dosage forms in humans □ Dosage forms, oral—bioavailability of commercially available ibuprofen in humans

Ibuprofen is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic activities and is widely utilized in the treatment of osteoarthritis, rheumatoid arthritis, and mild to moderate pain (1, 2). Recently, it has become a multiple-source drug product in Canada; thus, the question arises whether the new products are equivalent relative to the quality and performance of the innovator's products. Of particular importance is their *in vivo* performance in terms of the extent and rate of ibuprofen GI absorption from the solid oral dosage forms.

A previous study demonstrated the bioequivalence of a pilot plant lot of the 300-mg capsule product to the innovator's 300-mg tablet (3). The present studies were conducted to assess the bioavailability of full-scale production lots of the recently introduced 200-, 300-, and 400-mg capsules relative to the innovator's 300- and 400-mg tablets.

EXPERIMENTAL

Products Studied—Two comparative bioavailability studies were conducted to evaluate the five commercially available ibuprofen products (A, B, C, D, and E) listed in Table I.

An aqueous solution of sodium ibuprofen (F, Table I) was utilized as a reference standard to which the other formulations could be compared. With the exception of the solution, the products were obtained from usual commercial sources without any attempt to procure or select specific lots.

The ibuprofen dosage forms were administered as single, oral 300-mg doses in Study I and as single, oral 400-mg doses in Study II.

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