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Use of Microcapsules as Timed-Release Parenteral Dosage Form: Application as Radiopharmaceutical Imaging Agent

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Abstract □ The development of a new type of parenteral dosage form is described. A system of microencapsulation was formulated which produced microcapsules containing a water-soluble core material. The basic microencapsulation system could be altered to produce microcapsules with varied timed-release characteristics. Tracer methodology was employed as a sensitive and versatile analytical tool for the development and evaluation of the microencapsulation system. The core material was labeled by neutron activation after microcapsule formulation, which eliminated the radiation hazard and contamination problems that could occur during formulation with a labeled core material. Both *in vitro* and *in vivo* testing showed that the release patterns of labeled core material could be altered and detected. The microcapsules developed have potential as a timed-release parenteral dosage form and as an organ-imaging radiopharmaceutical.

Keyphrases □ Microcapsules—formulated, potential as timed-release parenteral dosage form and organ-imaging radiopharmaceutical evaluated *in vitro* and *in vivo*, mice □ Dosage forms, parenteral—timed-release microcapsules formulated, evaluated *in vitro* and *in vivo*, mice □ Radiopharmaceuticals—timed-release microcapsules formulated, potential use in organ imaging evaluated, mice

A dependable parenteral timed-release dosage form would eliminate many problems associated with oral administration. The process of microencapsulation may hold the key to the ideal timed-release dosage form because of the smallness of the produced microcapsules and the various properties instilled into the microcapsules. However, such a dosage form must contain microcapsules with very precise properties.

The main objective of this investigation was to develop a microencapsulating system that utilized a water-soluble polymer as the chief capsule wall component and allowed for the encapsulation of a water-soluble material. Other desired characteristics included microcapsules from 1 to 20 μm in diameter and formulation flexibility allowing alterations in core release rates. Tracer methodology was selected as the analytical tool for evaluation of the microcapsules. A second objective was to produce radioactivity in the core material by neutron activation after formulation. *In vitro* and *in vivo* test procedures were derived to evaluate the microcapsules as a timed-release parenteral dosage form and as a radiopharmaceutical imaging agent.

EXPERIMENTAL

Basic Procedure—Coacervation was selected as the microencapsulation method after a review of other methods (1–16). The following general procedure (Table I) was used in preparing all microcapsules.

Forty milliliters of dioxane[1], analytical grade, was added to a 50-ml beaker. A 1.25-cm magnetic stirrer bar was placed in the beaker, which

[1] Mallinckrodt Chemical Works, St. Louis, Mo.

Table I—Formulations Used to Prepare Microcapsules for *In Vivo* Testing

Step	Formulation 1	2	3	4	5
Manufacturing media (dioxane), ml	40	40	40	40	40
Sphere former[a] (glycerin), ml	0.23	0.23	0.23	0.23	0.23
Mechanical step	—	—	—	—	—
Core material (gold sodium thiosulfate), mg	40	40	40	40	40
Polymer[a] (polyethyleneimine-18), ml	3	3	3	3	3
pH controlling agent[a], ml	0.06, sulfuric acid	0.14, hydrochloric acid	0.03, ammonium hydroxide	0.057, hydrochloric acid	0.07, hydrochloric acid
Anticlumping agent (ethylcellulose), ml	0.08	0.08	0.08	0.08	0.08
Hardening agent[a], ml	0.365, glutaraldehyde	0.22, glutaraldehyde	0.22, glutaraldehyde	0.22, glutaraldehyde	0.08, formaldehyde
Hardening process[a]	45 min, 65°	15 hr, 23°	20 min, 75°	20 min, 75°	20 min, 75°
Washing step	Dioxane	Dioxane	Dioxane	Dioxane	Dioxane
Washing step	Dioxane	Dioxane	Dioxane	Dioxane	Dioxane
Capsule drying	Steam bath	Steam bath	Steam bath	Steam bath	Steam bath

[a] Variable.

was then positioned on a stirrer hot plate and warmed to 35° (the time can vary). Glycerin USP was added and allowed to go into solution. Heating was terminated, and the magnetic stirrer was removed.

The beaker was then placed in an ultrasonic bath[2]. Micronized core material was added and dispersed by holding the beaker in the bath for 30 sec. When the core material was well dispersed, polyethyleneimine-18[3] solution was added, and the beaker was held in the ultrasonic bath for 15 more sec. The beaker was then removed from the ultrasonic bath, and a pH-controlling agent was added with light stirring.

After the mixture was allowed to stand for a desired length of time, ethylcellulose[4] solution was added with stirring. The ultrasonic bath was again used to disperse the microspheres. Glutaraldehyde[5] solution was added, and the beaker was left standing for 5 min. Then it was placed in a water bath at the desired temperature with moderate agitation for a desired time period. After the beaker was removed from the water bath, the contents were poured into a test tube and centrifuged. The top liquid was decanted off and replaced with fresh dioxane.

The microcapsules were redispersed in dioxane and left standing for 5 min. They were then centrifuged and washed with dioxane. After washing, the microcapsules were poured on a watch glass over a steam bath and allowed to dry. Microcapsules were recovered as a dry fine powder.

Core Material and Neutron Activation—Amaranth was used as the core material in the preliminary development of the microencapsulation system because it is a water-soluble colored material of a complex organic nature. These qualities simplified the microscopic examination of the effects of water on microcapsules. In the later stages of experimentation, gold sodium thiosulfate and sodium chloride were used as core materials. These three materials are water soluble, relatively nontoxic, and compatible with the microencapsulation system, and they can be micronized[6] to a particle size of 1–15 μm and labeled by exposure to a thermal neutron flux. The elemental gold-197 and sodium-23 contained in gold sodium thiosulfate and the sodium-23 in sodium chloride and amaranth were easily activated upon exposure to the thermal neutron flux of a reactor[7].

All samples to be activated in both the encapsulated and unencapsulated form were placed in polyethylene irradiation vials. The samples were then placed in a styrofoam container and lowered down a 10-cm diameter tube located at the face of the reactor core. The reactor was operated at a power level of 900 w, and the sample was irradiated for 60 min. The estimated fluence rate was 10^9 neutrons/cm^2/sec. After neutron exposure, the specific activity of samples was calculated.

Sample Counting—A sodium iodide scintillation crystal (25 × 27.5 cm) with a well[8] (10 × 20 cm) attached to a single-channel analyzer[9] was used in the detection of the γ-rays emitted by gold-198 and sodium-24, which were the respective radionuclides obtained from the activation of gold-197 and sodium-23. Differential counting was used for both nuclides to allow counting of one radionuclide in the presence of the other. Counting correction factors, applied as necessary, included coincidence loss, background, geometry, instrumentation efficiency, and radioactive decay.

Microcapsule Timed-Release Dosage Form *In Vitro* Testing Procedure—An *in vitro* test was designed to evaluate quantitatively the release rate of core material from microcapsules. The procedure allowed test fluid to contact the microcapsules and to leach out the core material contained inside. The core material, being radioactive and in solution, could be sampled and counted and the rate of release could be determined.

The *in vitro* test apparatus (Fig. 1) consisted of a constant-temperature water bath fabricated from a 10-cm deep plastic rectangular container supported by a wood platform. The platform was of sufficient height to allow a magnetic stirrer to be placed underneath. The plastic container was filled with water, which was circulated and kept at 3°. A 12.5-cm, 100-ml graduated cylinder containing a 1.88-cm magnetic stirring rod was placed in the center of the bath directly above the magnetic stirrer. The cylinder was filled with 100 ml of test fluid, which was isotonic sodium chloride solution at pH 7.4.

The *in vitro* test chamber consisted of a glass tube with a syringe on top and a filtering system on the lower portion. Microcapsules were placed within the chamber; the test fluid was drawn in and expelled through the filter, which retained all of the microcapsules. The chamber was supported by a ring stand with the lower portion of the chamber immersed in the test fluid in the graduated cylinder.

The test fluid was drawn into the chamber and expelled at set time intervals. One-milliliter samples of the test fluid in the cylinder were drawn for counting at the end of each expulsion from the test chamber. Then 1 ml of fresh test solution was added to the cylinder to maintain the volume. The procedure was repeated until the desired number of samples was obtained.

The samples were counted, and all necessary counting corrections were made. Based on the count rate of the samples, standards, and microcapsules prior to placement in the test chamber, the amount of core material removed from the microcapsules was determined.

Effect of Hardening Process on Microsphere Droplets—The basic formulation procedure was used to microencapsulate amaranth. During the hardening process, the microsphere droplets were exposed to 0.18 ml of glutaraldehyde at 60°. Samples of the microcapsules were removed after 1.5, 5, and 15 min of exposure and placed on separate glass slides, and a drop of isotonic sodium chloride solution at pH 7.4 was added.

Influence of pH on Dissolution Patterns—To investigate the effect

[2] Branson ultrasonic bath, Branson Instrument Co., Stamford, Conn.
[3] PEI, Dow Chemical Co., Midland, Mich.
[4] Ethocel, Hercules Inc., Wilmington, Del.
[5] Eastman Chemicals, Rochester, N.Y.
[6] Gem-T Risen Micronizer, Trost Co., Newton, Pa.
[7] RUR-I is a light water, graphite-moderated, swimming pool-type reactor fueled with enriched uranium-235 (Department of Nuclear Engineering, Purdue University, Lafayette, Ind.).
[8] Harshaw NaI(Tl) scintillation crystal detector, Harshaw Chemical Co., Cleveland, Ohio.
[9] Ortec Inc., Oak Ridge, Tenn.

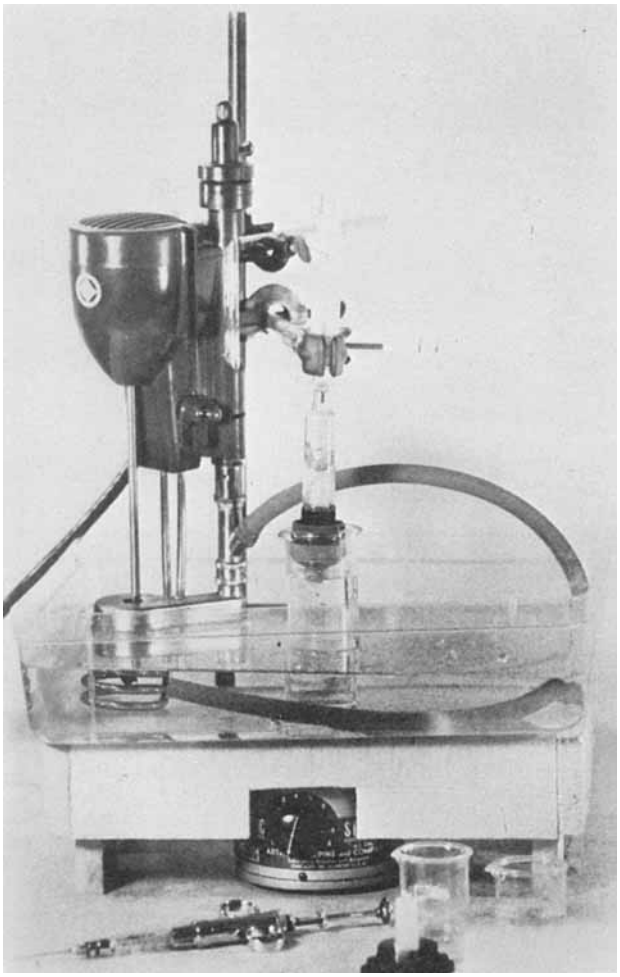

Figure 1—In vitro *test apparatus.*

of pH on the microcapsule properties, gold sodium thiosulfate was encapsulated using the basic formulation procedure except that the pH of the microencapsulating system was varied during the process. The pH was varied by the careful addition of 0.14 ml of hydrochloric acid stock solution[10] to one batch, 0.06 ml of sodium hydroxide stock solution[11] to a second batch, and no pH-controlling agent to the third batch. After the microcapsules were dried and collected, they were exposed to thermal neutrons, counted, and tested *in vitro* as described previously.

Influence of Test Fluid pH—To investigate the influence of test fluid pH on the release of gold-198, procedures similar to those in NF XIV (17) were followed. Two batches of microcapsules were prepared using the basic procedure, and neutron exposure and counting procedures were used as before. One batch was studied *in vitro* with a pH 5 test fluid while the other was placed in a test fluid of pH 7. When a dissolution plateau was reached, sodium hydroxide solution was added to change the pH of the test fluid to 8.

Screening of Microencapsulation Formulations—By using the basic formulation procedure and different combinations of materials, microcapsules were produced containing gold sodium thiosulfate. These microcapsules were exposed to thermal neutrons, counted, and subjected to *in vitro* testing as described previously. In evaluating the formulations, certain values were considered. The ratio between core material weight and encapsulation weight of the microcapsules and the percent of core material placed in the microencapsulated system were used to indicate microencapsulating system efficiency. The amount of core material released during *in vitro* testing within the first 15 min and the amount released at 120 min were important. Also, the difference between the two values was used as a basis for projecting *in vivo* release patterns from *in vitro* data.

[10] Hydrochloric acid stock solution was prepared by adding 0.8 ml of hydrochloric acid, reagent grade, to 29.2 ml of dioxane.

[11] Sodium hydroxide stock solution was prepared by adding 1 ml of 1 *M* NaOH solution, reagent grade, to 29 ml of dioxane.

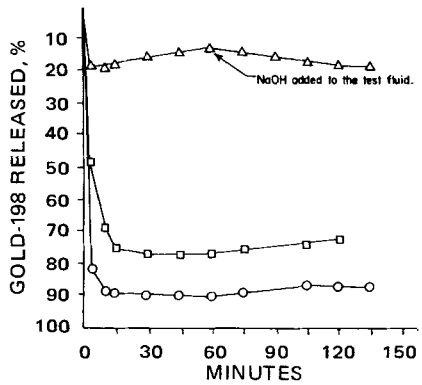

Figure 2—*Effect of the microencapsulation system pH on the release of gold-198. Key:* △, *hydrochloric acid added during microcapsule formation;* □, *no acid or base added during microcapsule formation; and* ○, *sodium hydroxide added during microcapsule formation.*

Five formulations (Table I) produced dissolution curves showing promise for use for either *in vivo* timed-release or radiopharmaceutical imaging studies.

Timed-Release Dosage Form *In Vivo* Testing Procedure—The *in vivo* testing was conducted to determine the levels of gold-198 in the blood and organs of a mouse after the injection of either unencapsulated or microencapsulated labeled gold sodium thiosulfate. The investigation consisted of injecting three groups of 21 mice[12] as follows. The first group was subcutaneously injected with unencapsulated labeled gold sodium thiosulfate. The second group was injected with microcapsules containing labeled gold sodium thiosulfate that had shown a relatively small release of gold-198 *in vitro* (Formulation 1, Table I). The third group was injected with microcapsules containing labeled gold sodium thiosulfate that had shown a timed-release pattern *in vitro* (Formulation 2, Table I).

The microcapsules and unencapsulated gold sodium thiosulfate were exposed to thermal neutrons, and the specific activity of each sample was calculated. The radioactive samples were suspended in a 50% glycerin–water for injection vehicle just prior to administration. To aid in microcapsule dispersion, 0.05 ml of polysorbate 80[13] was added to the injection vehicle. The mixtures were placed in an ultrasonic bath until good dispersion was observed.

Volumes of 0.25 ml of each material containing the same amount of either encapsulated or unencapsulated ^{198}Au-labeled gold sodium thiosulfate were injected subcutaneously behind the heads of 25–30-g mice, using a 1-ml tuberculin syringe fitted with a 26-gauge needle. At 2, 5, 8, 11, 16, 20, and 23 hr, three mice from each group were removed, and blood samples were obtained by means of ocular puncture. Blood was weighed according to the method of tares. The mice were sacrificed; their kidneys, lungs, livers, and spleens were removed, washed with saline, weighed, and stored individually. The remainder of the mouse, which was referred to as the carcass, was weighed and stored.

Each complete mouse was counted in the well detector after dissection by pooling the dissected parts of the mouse and the carcass. The count

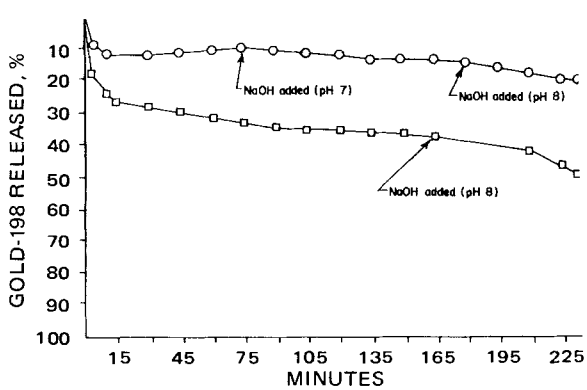

Figure 3—*Effect of test fluid pH on the release of gold-198. Key:* ○, *initial pH 5; and* □, *initial pH 7.*

[12] Cox Swiss male mice, Laboratory Supply, Indianapolis, Ind.

[13] Tween 80, ICI America, Inc., Wilmington, Del.

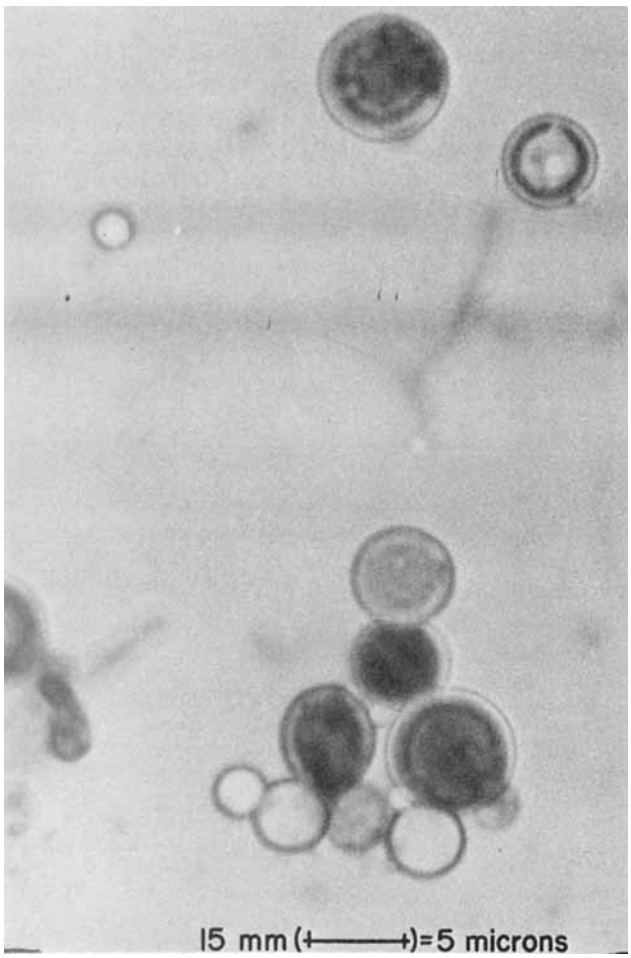

Figure 4—*Microcapsules with amaranth.*

rate of the pooled tissues was considered to represent 100% of the gold-198 activity. Organs were counted individually, and the percent of radioactivity in each organ was determined relative to the total mouse. The percent of activity per organ was divided by the milligram weight of the organ, with the resultant data referred to as the percent of total activity per milligram (% *Ta*/mg).

Radiopharmaceutical Imaging Agent *In Vivo* Testing Procedure—This test procedure was conducted to determine if Formulation 1 microcapsules (Table I), which exhibited low release of gold-198, had potential as imaging agents. The influence of microcapsule size on organ distribution was investigated.

Formulation 1 microcapsules were separated by scalping with nylon screens[14] into four size ranges: ≤5, 6–10, 11–15, and ≥16 μm. With a standard light microscope, the sizes were compared to reference pollen samples for verification of the scalping technique. No microcapsules exceeded 20 μm in diameter. Once the microcapsules were separated and dried, they were placed in separate 1-ml polyethylene vials and exposed to thermal neutrons. Unencapsulated gold sodium thiosulfate was also exposed. After exposure, the specific activity of each material was determined. The injection vehicle consisted of water for injection USP with 0.05 ml of polysorbate 80 added.

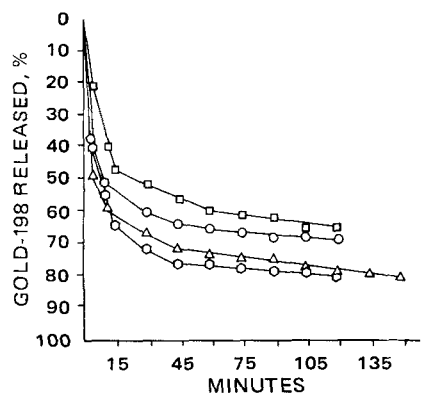

Figure 5—In vitro *release patterns of gold-198 from microcapsules. Key:* □, *Formulation 2;* ○, *Formulation 4;* △, *Formulation 5; and* ○, *Formulation 3.*

[14] Nitex nylon screen cloth, Kressilk Products, Inc., Des Plaines, Ill.

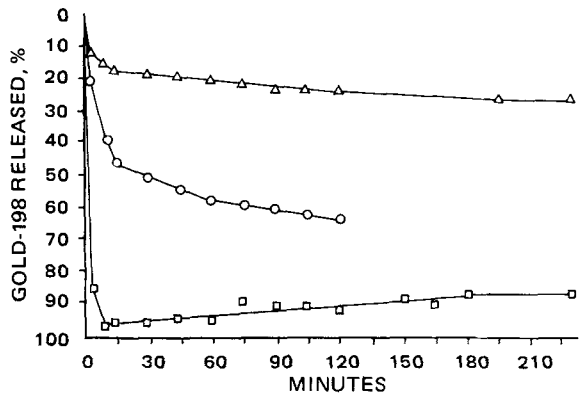

Figure 6—In vitro *release patterns in isotonic test fluid for timed-release dosage form samples later studied* in vivo. *Key:* △, *Formulation 1;* ○, *Formulation 2; and* □, *unencapsulated labeled gold sodium thiosulfate.*

With a 1-ml tuberculin syringe and a 27-gauge needle, 0.2 ml of suspension was injected intravenously into the tail vein of each mouse. Each group of animals consisted of seven mice. One group was injected with unencapsulated labeled gold sodium thiosulfate. A separate group was used for each size range of microcapsules. Two hours after injection, all mice were sacrificed. The liver, spleen, heart, lungs, and kidneys of each mouse were removed. The procedures of counting and calculation were identical to those utilized for testing the microcapsule timed-release dosage form.

RESULTS AND DISCUSSION

Changes in the basic formulation procedure influenced the microcapsules and their properties. Variables noted were: order of mixing of ingredients, temperature of the system during microcapsule formation, strength and type of acid used, the plasticizer, the hardening agent, the concentration, and the length of time microcapsules were hardened. These findings are consistent with those of earlier investigators (10).

The influence of pH during the encapsulation process is illustrated in Fig. 2. The dissolution curves show an alteration in the release of gold-198 activity resulting from variation in pH during this process. The labeled core material discussed throughout this section is based upon the gold-198 activity except where otherwise noted.

During the *in vitro* testing of the microcapsules prepared with hydrochloric acid, sodium hydroxide solution was added after a plateau in gold-198 release occurred (Fig. 2). An immediate increase in activity was noticed in the test fluid, indicating that the test fluid pH influenced the

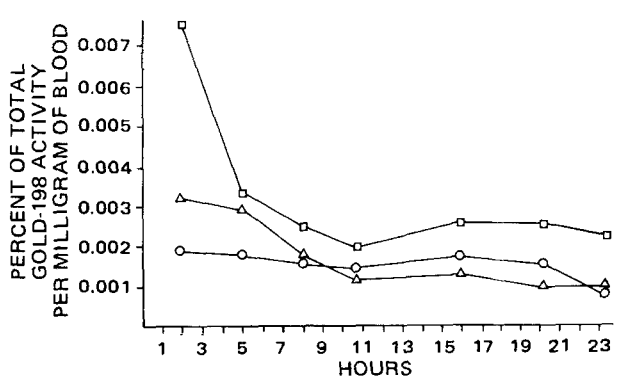

Figure 7—*Gold-198 blood concentration from timed-release study. Key:* □, *unencapsulated labeled gold sodium thiosulfate;* ○, *Formulation 2; and* △, *Formulation 1.*

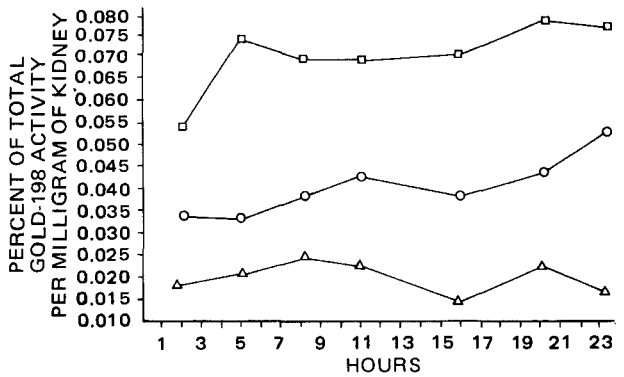

Figure 8—*Gold-198 kidney concentration from timed-release study. Key: □, unencapsulated labeled gold sodium thiosulfate; ○, Formulation 2; and △, Formulation 1.*

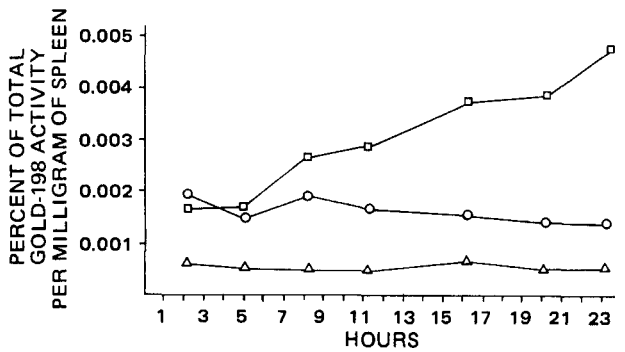

Figure 10—*Gold-198 spleen concentration from timed-release study. Key: □, unencapsulated labeled gold sodium thiosulfate; ○, Formulation 2; and △, Formulation 1.*

release of gold-198. The observation was confirmed with additional experimentation. More gold-198 was released from microcapsules in a test fluid of pH 7 than of pH 5 (Fig. 3). The addition of sodium hydroxide solution increased the release of gold-198 after a plateau was reached.

Microscopic examination of microcapsules containing amaranth was used to study the influence of the hardening process on core release. As the time of exposure to the hardening agent was increased, diffusion of the amaranth through the microcapsules decreased. Amaranth was used to aid in defining the hardening process. Figure 4 is representative of microcapsules produced throughout the investigation.

After extensive investigation, five formulations produced dissolution curves showing promise for use as either *in vivo* timed-release agents or radiopharmaceutical imaging agents. The formulations are listed in Table I, and dissolution curves are illustrated in Figs. 5 and 6. The apparent loss in activity by the unencapsulated sample with time (Fig. 6) could be eliminated by the addition of unlabeled gold sodium thiosulfate. This phenomenon was probably due to the adsorption of the labeled material of high specific activity by the test chamber.

The dissolution curves showed that the basic microencapsulation formulation could be altered to produce microcapsules with differing timed-release characteristics. A rather extensive release of gold-198 was attained with Formulations 2–5 in contrast to a limited gold-198 release from Formulation 1. The maximum release of gold-198 was variable among Formulations 2–5. Representative aliquots of formulations prepared for *in vivo* experimentation were subjected to *in vitro* testing. Dissolution curves for the samples are presented in Fig. 6. The release patterns showed that Formulation 1 microcapsules inhibited the release of the labeled core material more than Formulation 2 microcapsules. The dissolution rate for unencapsulated labeled core material was much greater than exhibited by the microcapsules.

***In Vivo* Timed-Release Dosage Form Study**—The percent of total activity per milligram (% *Ta*/mg) of organ, carcass, and blood was calculated for samples obtained during the *in vivo* study. The data, presented as mean values for each group of three mice sacrificed at a particular time period (Figs. 7–12), were subjected to statistical examination. A Burr–Foster test was employed to determine homogeneity of variance of the means; a two-way analysis of variance also was applied, followed by a Newman–Keuls test for comparison of the means.

The results of the statistical analysis showed that the three lines in each figure (Figs. 7–12) were statistically different and distinct from each other at the 95% confidence level. The unencapsulated labeled gold sodium thiosulfate produced the highest activity levels in the blood, kidneys, lungs, spleen, and liver; the least amount of activity remained in the carcass, indicating an extensive removal of the unencapsulated labeled compound from the site of injection. Formulation 1 microcapsules provided the lowest tissue activity levels and resulted in the highest amount of labeled gold sodium thiosulfate remaining at the site of injection. Gold-198 release exhibited by Formulation 2 microcapsules fell between the two extremes shown by unencapsulated gold sodium thiosulfate and Formulation 1 microcapsules. The timed-release data from the *in vivo* study correlated with the data generated by the dissolution curves.

Statistically, there was no evidence at the 95% confidence level that the three lines within each figure (Figs. 7–12) were anything but parallel to each other. If present, differences in slopes were not observed statistically because of the variance error in the data resulting from the small number of animals per time interval and the short duration of the *in vivo* study.

***In Vivo* Radiopharmaceutical Imaging Agent Study**—The data for this phase of the investigation were subjected to statistical examination as in the timed-release phase. The data are presented as a mean value per organ per micrometer particle-size range in Fig. 13.

The gold-198 level in the lungs of animals receiving microcapsules of ≤5, 6–10, and 11–15 μm was statistically greater at the 95% confidence level than the activity present in the lungs of mice receiving unencapsulated labeled gold sodium thiosulfate. The largest lung uptake was observed with 11–15-μm microcapsules. The microcapsules exhibited localization properties favorable for a radiopharmaceutical lung-imaging agent.

No consistent statistical differences were found between the microcapsules of differing micrometer ranges and the unencapsulated labeled gold sodium thiosulfate for the carcass, spleen, kidneys, liver, and heart. The data may reflect the high level of free gold-198 produced in the process of separating the microcapsules into size ranges.

The *in vivo* data only illustrate the applicability of the basic microcapsule formulation for the production of a radiopharmaceutical imaging agent. Extensive experimentation must be conducted to ascertain the true potential of the microcapsules.

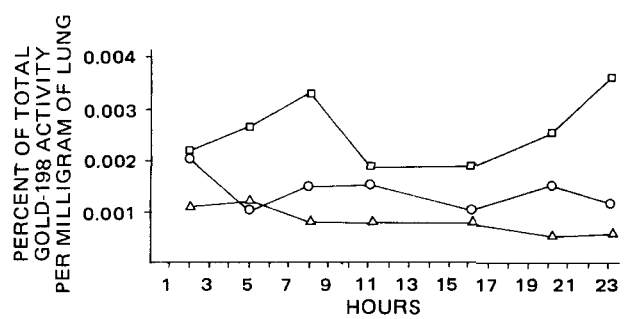

Figure 9—*Gold-198 lung concentration from timed-release study. Key: □, unencapsulated labeled gold sodium thiosulfate; ○, Formulation 2; and △, Formulation 1.*

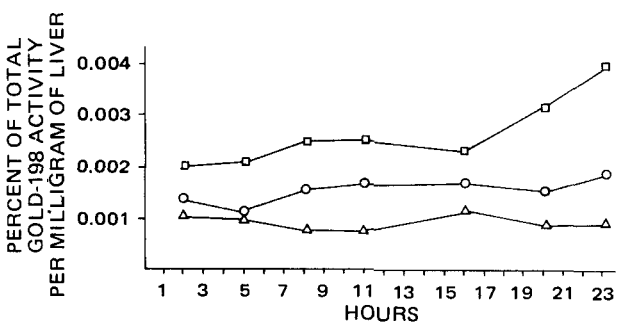

Figure 11—*Gold-198 liver concentration from timed-release study. Key: □, unencapsulated labeled gold sodium thiosulfate; ○, Formulation 2; and △, Formulation 1.*

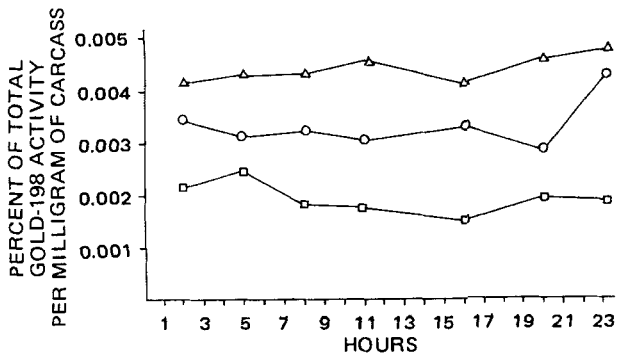

Figure 12—*Gold-198 carcass concentration from timed-release study. Key:* □, *unencapsulated labeled gold sodium thiosulfate;* ○, *Formulation 2; and* △, *Formulation 1.*

SUMMARY AND CONCLUSIONS

A new method of preparing parenteral dosage forms was developed. A system of microencapsulation was formulated that produced microcapsules containing a water-soluble core material. The microcapsules ranged in size from 1 to 20 μm and could be collected as a fine powder. The basic microencapsulation system allowed for many variable changes which affected the properties of the microcapsules. Only a few of these variables and their effects on the microcapsules were studied. Although a great deal of research on this microencapsulation system still must be accomplished, a basic workable process was developed which can serve as a model for further study for parenteral application.

Neutron activation of the microencapsulated core material proved to be an efficient and convenient procedure for producing a radioactive core material. Contamination problems that would occur if the core material was labeled during formulation were avoided. The radioactivity was used as a sensitive and versatile analytical tool in evaluating the microencapsulation system and the properties of the microcapsules.

An *in vitro* test for ascertaining the properties of the microcapsules was developed and proved to be sensitive and reproducible. The test was designed to evaluate the applicability of the labeled microcapsules produced in the study as a timed-release dosage form and as a radiopharmaceutical.

In vitro and *in vivo* experimentation showed that release patterns of labeled core material could be altered by the formulation process. A direct correlation in release patterns was found for microcapsules studied *in vitro* and *in vivo*. The data showed that the basic microencapsulation system developed in this investigation has potential as a timed-release parenteral dosage form.

Microcapsules containing labeled gold sodium thiosulfate concentrated in the lungs after intravenous injection. The potential of the basic microencapsulation system as an *in vivo* diagnostic radiopharmaceutical was illustrated. Further testing is needed to demonstrate the total potential of this microcapsule in the parenteral field.

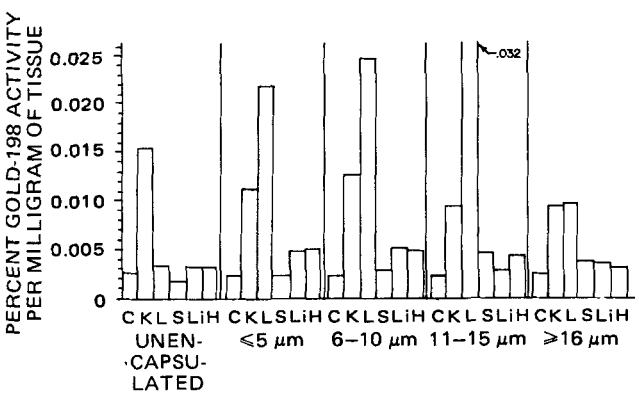

Figure 13—*Gold-198 organ distribution from radiopharmaceutical study. Key: C, carcass; K, kidneys; L, lungs; S, spleen; Li, liver; and H, heart.*

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