TABLE III—ANALYSIS OF TESTOSTERONE PROPIONATE IN OIL BY U.S.P. XVII ASSAY PROCEDURE

Concn., mg./ml. of Oil	Vehicle Compn.[a]	Testosterone Propionate mg. Taken	mg. Found	% Recovered
10	*A*	51.0	67.1	131.5
25	*A*	50.2	59.6	118.7
25	*A*	50.4	54.2	107.7
25	*B*	50.1	55.4	110.6
25	*B*	51.8	54.9	106.0
50	*A*	51.0	51.0	100.0
50	*A*	51.1	52.4	102.5
50	*B*	50.0	50.1	100.2
50	*B*	50.8	51.3	101.0
50	*C*	55.2	57.1	103.4
50	*C*	51.9	53.4	103.0
50	*D*	48.2	54.1	112.2
50	*D*	48.0	54.1	112.7
50	*E*	48.2	53.0	110.0

[a] *A*, Three per cent benzyl alcohol in sesame oil; *B*, 3% benzyl alcohol, 0.5% chlorobutanol in sesame oil; *C*, sesame oil; *D*, sesame oil: sample heated on water bath for 5 min. to dissolve testosterone propionate; *E*, sesame oil: sealed in ampul, heated at 160° for 2 hr.

tained from the standards and from the commercial samples. Several of the latter gave in addition a spot corresponding to free testosterone semicarbazone.

In contrast, the testosterone propionate isolated by the proposed procedure gives a single spot by thin-layer chromatography.

SUMMARY

Spectrophotometrically and chromatographically pure testosterone propionate is recovered quantitatively from its oil dosage forms by a combination of reverse phase and direct phase partition chromatography. The testosterone propionate, together with sterols and triterpenoids as well as any free testosterone, is separated from the bulk of the oil in the reverse phase process; it is then isolated free of these substances by direct phase partition. The procedure is applicable to samples containing such adjuvants as benzyl alcohol, benzyl benzoate, chlorobutanol, phenol, and the parabens.

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Technical Articles

Effects of Selected Variables on the Microencapsulation of Solids

By L. A. LUZZI* and R. J. GERRAUGHTY

The hypothesis that solid particles may be protectively encapsulated by coacervation led to the investigation of the extractability of microcapsules, which contained solids, by gastrointestinal fluids. Starting pH, starting temperature, ratio of solid to encapsulating materials, quantity of denaturant, and final pH were varied. The effects of the variables studied on microcapsules were determined by submitting samples to simulated gastrointestinal fluids for periods of up to 2.5 hr. and then comparing the extracts spectrophotometrically to known absorption spectra. Results showed that all variables effected some degree of change in microcapsules.

THE TERM "coacervation" has recently been used to describe the salting out of a lyophilic solid into liquid droplets rather than solid aggregates (1). The term was introduced into colloidal chemistry by Kruyt and Bungenberg de Jong (2) to describe the flocculation or separation of liquids from solution, where at least one of the liquids contained a colloidal solute.

Coacervation has been subdivided into simple coacervation and complex coacervation. Briefly,

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simple coacervation usually deals with systems containing only one colloidal solute, while complex coacervation usually deals with systems containing more than one colloid (3, 4).

Complex coacervation has been found to be primarily dependent on pH. It has been reported that in a gum arabic–gelatin system, complex coacervation into microcapsules occurred at pH values below the isoelectric point of the gelatin and would not occur above this pH regardless of how other factors were changed (5). The same was true of other systems containing two dispersed colloids of opposite electrical charge.

The optimum conditions for complex coacervation were achieved by adjusting the pH to a point at which equivalents of oppositely charged molecules of the two colloids were present, since, at this pH, the greatest number of salt bonds were formed (5). In such a system, the pH must be adjusted so that the gelatin particles are positively charged (below the isoelectric point), since gum arabic particles are always negative in colloidal dispersions (6). Therefore, the principal condition necessary for successful complex coacervation is pH. This factor is easily and precisely controlled and since the author had previous experience with this system, it was decided that encapsulation by way of complex coacervation would be suited to the purposes of this study.

Green and Schleiker made practical use of the process of coacervation in various patents (7–11). Two of the patents (7, 10) indicated that oils, some of which contained dissolved dyes, had been entrapped in gelatin–acacia microcapsules. No quantitative method to evaluate the strength of the capsules or the degree of encapsulation was given.

It appears that encapsulation through coacervation has great potential application in pharmacy. Some properties that might be especially useful include (*a*) prevention of vaporization of volatile substances (*e.g.*, volatile oils), (*b*) protection of moisture-sensitive or light-sensitive substances (*e.g.*, vitamins A and K), (*c*) separation of incompatible substances within a single system, (*d*) aid in the dispersion of water-insoluble substances in aqueous media and, (*e*) controlled release of encapsulated substances to the environment (*e.g.*, long acting medication).

Before such application could be explored, it was apparent that some methods should be available to predict necessary conditions to achieve good encapsulation. Luzzi and Gerraughty (12) examined some properties of oils used in pharmacy and found that the acid value and the surfactant properties of the oil affected the extraction of oils from microcapsules, whereas saponification values had little or no effect on extractability when subjected to ethyl ether.

With these considerations in mind, the system of Luzzi and Gerraughty (12) was examined. It was the intent of this study to develop a means to encapsulate solids through complex coacervation and to determine: (*a*) the effects of varying the starting pH, the starting temperature, the quantity of denaturant, the ratio of material to be encapsulated to encapsulating agents, and the final pH on the permeability of capsule shell when in contact with gastrointestinal fluids; and (*b*) to evaluate the effect of such variations on the system.

EXPERIMENTAL

Preparation of Microcapsules—The basic procedure employed by Luzzi and Gerraughty (12) for the preparation of microcapsules was used. The primary encapsulating solutions were made by dissolving 3.0 Gm. of acacia and 3.0 Gm. of gelatin separately in 100 ml. of purified water at 55°. The acacia used was powdered acacia U.S.P.; the gelatin used was 300 bloom pigskin gelatin[1] with an isoelectric point at pH 8.0.

A 20% sodium hydroxide solution was used to adjust the starting pH of the solution to 6.5. Acacia particles in solution are negatively charged and at this pH the gelatin particles are sufficiently negative so that they will not interact with the acacia.

A suspension was formed by adding the solid to be encapsulated to the solution of gelatin and acacia with gentle agitation. The pH of the mixture was then adjusted to 4.5 by the dropwise addition of diluted hydrochloric acid U.S.P., while stirring. At the pH, the gelatin particles were positively charged and were attracted to the negatively charged acacia particles. The combined particles coalesced about the suspended solid and isolated it from the rest of the system. At this point, 10 ml. of formaldehyde solution U.S.P. was added to the mixture and it was cooled to 10° by immersion in an ice bath.

The pH was then adjusted to a final pH of 9.0 by the dropwise addition of 20% sodium hydroxide solution. In order to remove solubilized drug and excess formaldehyde, the mixture was then diluted to approximately 400 ml. with distilled water and filtered. The wet mass was firmly wrapped in blotting paper to remove most of the remaining liquid. A coarsely granular material was obtained from the resulting soft rubbery mass by passing it through a 20-mesh screen and drying it at 50° for 24 hr.

To determine the effect of each variable all other variables were held at the values given in the above procedure. Each variable was studied within the following limits: (*a*) the starting pH was varied between 5.0 and 7.0; (*b*) the ratio of materials to be encapsulated to encapsulating materials (dry weight) was varied from 2/6 through 20/6; (*c*) the quantity of formaldehyde solution was varied from

[1] American Agricultural Chemical Co., Detroit, Mich.

1 ml. to 20 ml. for each 100 ml. of 3% gelatin dispersion; (*d*) the starting temperature was varied from 34° to 42°; and (*e*) the final pH was varied from 6.5 to 8.8.

Choice of Materials—The primary objective of the research was to determine whether a solid particle could be encapsulated by this particular process. Preliminary investigation showed that: (*a*) the solid to be encapsulated should be insoluble, or nearly so, in the system; (*b*) the solid particles should be readily dispersable in either gelatin or acacia solution; (*c*) the solid should contribute no surfactant properties; (*d*) the solid should be quickly soluble when exposed to the proper solvent; and (*e*) the solid should not degrade appreciably when exposed to aqueous systems for several hours.

The materials encapsulated for possible elucidation of one or more of the previously mentioned aims were: colloidal sulfur, special flowers of sulfur, aspirin anhydride (recrystallized from ethyl acetate solutions to a m.p. of 81°–83°), acetophenetidin U.S.P., barbituric acid, lycopodium spores, DDT, pentobarbituric acid (m.p. 127°–128°), and carbon black.

With one exception, difficulties in assay and stability precluded the use of all of these materials for use in these studies. The exception was pentobarbituric acid. The advantages in this case were those of relative insolubility in acid aqueous media and solubility, as a salt, in alkaline aqueous media. In addition, quantitative spectrophotometric determinations for sodium pentobarbital are easily accomplished.

METHOD OF EVALUATION OF MICROCAPSULES

The method used to evaluate the susceptibility of the coacervate shell to the action of U.S.P. simulated gastrointestinal fluids was based principally on the ability of the fluids to expose and/or extract the encapsulated material. In order to determine the degree of destruction or permeability, or both, caused by the gastrointestinal fluids, a spectrophotometric method of assay was used.

The microcapsules were prepared in the manner previously described and 0.25-Gm. samples of the dried capsules were exposed consecutively, then separately to 100 ml. of gastric fluid and 100 ml. of intestinal fluid, employing a Burrell wrist action shaker.[2]

In the first instance, the samples remained in contact with 100 ml. of gastric fluid for 0.5 hr., were filtered, and the filter paper and remaining sample were then transferred to 100 ml. of intestinal fluid; the filter paper was broken up prior to immersion in intestinal fluid. A 1.0-ml. sample of the intestinal fluid was withdrawn through a cotton pledget after 1 hr., and after 2 hr. the intestinal fluid was removed from the microcapsules by filtration.

The removal of the sample from gastrointestinal fluids was preceded in each instance by the adjustment of pH to 9.25. If the samples were to remain in a fluid for further extraction, the pH was again adjusted to official (U.S.P.) suggested values for that fluid using diluted hydrochloric acid U.S.P. or 20% sodium hydroxide solution.

[2] Burrell Corp., Pittsburgh, Pa.

Pentobarbituric acid has a pKa of 8.11 (13) and, therefore, at pH 9.1 the ratio of sodium pentobarbital to pentobarbituric acid becomes 10 to 1. Spectrophotometric studies of solutions of sodium pentobarbital indicated that absorption increased with increased pH values and that at pH 9.0, as may be predicted from theory, a gradual decrease in the slope of the curve occurred. Since pH values of 9.25 could be achieved with relative accuracy (±0.05 pH units) and ease, and since a great majority of the solute is in the salt form at this pH, this was the pH at which all liquid filtrates were compared.

The samples of filtered gastric fluid were assayed for content of active constituents, as were the filtered samples of intestinal fluids. The solutions were scanned for wavelength of maximum absorption using a recording spectrophotometer.[3] A broad peak was found with a maximum at 241 to 242 mμ. Beer's law plots were prepared using a Beckman spectrophotometer.[4] The concentration of the liquid filtrates, obtained by the extraction methods already described, were determined by comparing their respective Beer's law plots to the absorbance observed.

The total quantity of pentobarbituric acid in each sample was found by disintegrating a known weight of capsules in a Virtis blender[5] with a known volume of distilled water at pH 9.25, the sample was filtered and the resulting liquid adjusted, if necessary, to pH 9.25. Additional blending and maceration indicated that substantially all pentobarbituric acid had been released by the capsules. Aliquots were prepared and spectrophotometric data were collected which, when compared to the Beer's law plot yielded the information from which the calculations for total pentobarbituric acid content were carried out.

Microphotography of Microcapsules—It is the intent of this section to illustrate the typical formation and general appearance of microcapsules under various conditions.

Figure 1 shows a dispersion of pentobarbituric acid particles in a 3% gelatin solution. It can be seen that the particles are quite well dispersed.

Figure 2 is typical of groups of microcapsules found when there is nearly an optimum relationship between solid particles and encapsulating agents. The ratio of material to be encapsulated to encapsulating material was 8/6.

Figure 3 depicts both filled and unfilled microcapsules. The ratio of material to be encapsulated to encapsulating material was 4/6.

RESULTS

Effect of Starting pH on Microcapsules—A series of samples ranging from pH 5.0 to pH 7.0 was prepared and 0.25 Gm. of each was assayed in the manner previously described. Table I shows that, throughout the entire series, the maximum difference in per cent of total pentobarbituric acid released after 2.5 hr. of exposure to gastrointestinal fluids was only 4.8. The difference in per cent released was somewhat greater (9.9) after 0.5 hr. exposure to gastric fluid alone.

[3] Bausch & Lomb Spectronic 505, Bausch & Lomb Optical Co., Rochester, N. Y.

[4] Beckman DU spectrophotometer, Beckman Instruments, Inc., Fullerton, Calif.

[5] Virtis "45," Precise Products Corp., Racine, Wis.

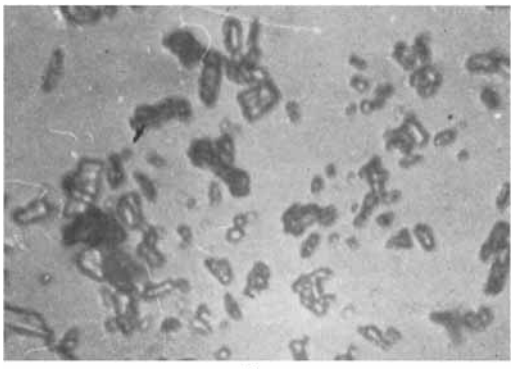

Fig. 1—Dispersion of pentobarbituric acid particles in a 3% gelatin solution.

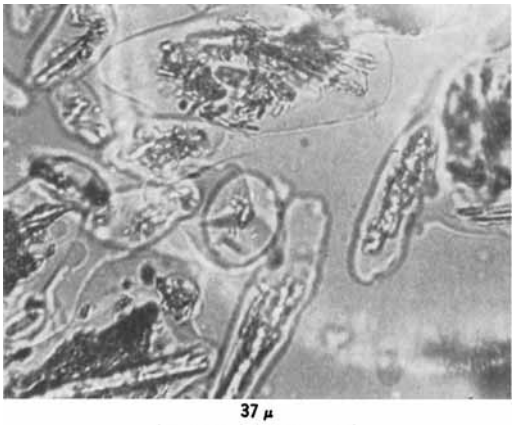

Fig. 2—Typical group of microcapsules found when there is nearly an optimum relationship between solid particles and encapsulating agents.

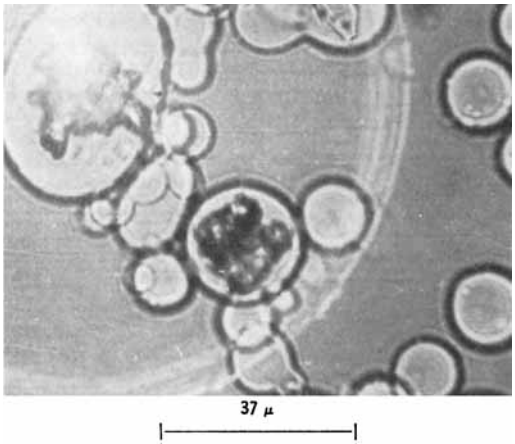

Fig. 3—Filled and unfilled microcapsules.

Effect of Starting Temperature on Microcapsules—Table II shows that the range of starting temperatures employed was between 34° and 42°. In all cases observed, except after 0.5 hr. in gastric fluid, the per cent of pentobarbituric acid that was released was found to be at a maximum at 34° starting temperature and reached a minimum at 37°.

Effect of Ratio of Solid to Encapsulating Materials—This series consisted of ratios ranging from 4.0 Gm. of pentobarbituric acid to 6 Gm. total dry weight of encapsulating materials (4/6), through 20.0 Gm. of acid to 6 Gm. total dry weight of encapsulating materials (20/6). Table III shows that the per cent of total acid which was released from the samples increased as the ratio of solid to encapsulating materials increased. Table III, it should be noted, also shows that the increase in per cent released, from 1 to 2 hr. exposures to intestinal fluid, decreased or the ratio increased.

Effect of Different Quantities of Denaturant on Microcapsules—Formaldehyde acts as a denaturant to harden and fix the wet gelatinous shell. In

TABLE I—EFFECT OF STARTING pH ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Starting pH	After 0.5 hr. in Gastric Fluid[b]	After 1 hr. in Intestinal Fluid	After 2 hr. in Intestinal Fluid	Total in Gastric and Intestinal Fluids
5.0	33.8	15.9	24.0	57.8
5.3	27.0	14.8	26.9	53.9
6.0	30.1	13.3	23.6	53.7
6.5	23.7	10.9	29.3	53.0
7.0	30.5	13.3	24.0	54.5

[a] All values expressed as per cent of total pentobarbituric acid found in microcapsules. [b] After removal of gastric fluid, the samples were transferred to intestinal fluid.

TABLE II—EFFECT OF STARTING TEMPERATURE ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Starting Temp.	After 0.5 hr. in Gastric Fluid[b]	After 1 hr. in Intestinal Fluid	After 2 hr. in Intestinal Fluid	Total in Gastric and Intestinal Fluids
34	44.3	24.4	27.6	71.9
36	37.8	16.4	25.3	63.1
37	36.8	13.2	22.0	58.8
40	34.8	19.2	26.3	61.1
42	38.8	18.9	26.8	65.6

[a] All values expressed as per cent of total pentobarbituric acid found in microcapsules. [b] After removal of gastric fluid, the samples were transferred to intestinal fluids.

TABLE III—EFFECT OF RATIO ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Ratio	After 0.5 hr. in Gastric Fluid[b]	After 1 hr. in Intestinal Fluid	After 2 hr. in Intestinal Fluid	Total in Gastric and Intestinal Fluids
4/6	28.7	13.3	24.0	42.7
8/6	36.8	13.2	22.0	58.8
12/6	39.1	18.4	26.6	65.7
16/6	40.2	26.1	30.7	70.9
20/6	45.2	26.2	29.1	74.3

[a] All values expressed as per cent of total pentobarbituric acid found in microcapsules. [b] After removal of gastric fluid, the samples were transferred to intestinal fluid.

TABLE IV—EFFECT OF FORMALDEHYDE ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Formaldehyde Soln., ml./100 ml.	After 0.5 hr. in Gastric Fluid[b]	After 1 hr. in Intestinal Fluid	After 2 hr. in Intestinal Fluid	Total in Gastric and Intestinal Fluids
1	Sample not collectable			
2	Sample not collectable			
4	40.2	22.6	30.0	70.2
6	38.0	16.6	26.8	64.8
8	32.9	17.3	26.4	59.3
10	37.8	16.4	25.3	63.1
20	47.8	18.2	23.8	71.6

[a] All values expressed as per cent of total pentobarbituric acid found in microcapsules. [b] After removal of gastric fluid, the samples were transferred to intestinal fluid.

TABLE V—EFFECT OF FINAL pH ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES EXPOSED TO GASTROINTESTINAL FLUID[a]

Final pH	After 0.5 hr. in Gastric Fluid[b]	After 1 hr. in Intestinal Fluid	After 2 hr. in Intestinal Fluid	Total in Gastric and Intestinal Fluids
6.5	27.0	14.7	23.5	50.5
7.0	23.7	28.4	29.3	53.0
7.5	29.4	13.1	22.4	51.8
8.0	28.6	17.7	27.2	55.8
8.8	36.7	33.7	36.0	72.7

[a] All values expressed as per cent of total pentobarbituric acid found in microcapsules. [b] After removal of gastric fluid, the samples were transferred to intestinal fluid.

order to test this effect, concentrations of from 1 to 20 ml. of 37% formaldehyde solution were added to the microencapsulation process for each 100 ml. of 3% gelatin solution. Table IV shows that 1- and 2-ml. quantities of formaldehyde solution were insufficient to allow collection of samples. When 4 ml. of formaldehyde solution was used, the samples became collectable and continued so throughout the remainder of the series. An interesting observation was that during initial exposure to either gastric or intestinal fluids, the per cent of pentobarbituric acid released was greater in those samples to which the largest quantity of formaldehyde had been added.

Effect of Final pH on Microcapsules—A series of samples was prepared with final pH values ranging between 6.5 and 8.8. Table V shows that after initial exposure to gastric fluids, the per cent of acid released from samples prepared at pH 7.0 was less than the acid released from samples prepared at pH 6.5. In intestinal fluid, the per cent of acid released after initial exposure was less for samples prepared at pH 7.5 than for those prepared at pH 6.5. Thereafter, a gradual increase was noted throughout the remainder of the series.

Table V indicates that in assays carried out after 1- and 2-hr. periods, on samples transferred from gastric fluid to intestinal fluid, the per cent of pentobarbituric acid extracted was erratic, with a slight tendency to increase as the final pH was increased. Table V also shows, however, that the over-all per cent extracted increased with increasing final pH.

DISCUSSION AND CONCLUSIONS

Encapsulation of solids occurred when oppositely charged colloidal particles agglomerated about the solid particles to form a shell which may contain one or several solid particles.

There seemed to be little difference in the quantity of solid extracted over a 2.5-hr. period when the starting pH was the variable. It was expected that maximum amounts of solid would be extracted at the extremes and lesser quantities in the median ranges. Although this was the trend, a wider range of pH values would be necessary to establish this clearly.

The minimum in amount extracted at starting temperature 37° (Table II) may have been due to a combination of adequate fluidity on the part of the colloidal particles and the relative insolubility of the solid.

The study of ratio of solid to encapsulating material (Table III) seems to indicate that the smaller the ratio the greater the retaining power of the capsule. This could be due to multiple droplet thickness of the wall or to the attraction of empty capsules to filled capsules.

Although microscopic examination of samples prepared with little or no formaldehyde indicated that capsule formation did take place, the capsules seemed to disappear when the temperature of the mixture was raised from 10° through 25° to 40°. When the capsules did remain intact the increase in the per cent of solid released at lower formaldehyde concentrations (Table IV) was probably due to two factors, both of which could result from inadequate denaturization. First, the gelatin–acacia shell might not have been sufficiently denatured, thus promoting a partial solubilization of the capsule during washing. This may have made the shell less impervious to the action of gastrointestinal fluids through lack of adequate denaturization. The increased per cent of acid that was extracted when greater amounts of formaldehyde were added was probably due to a cracking, resulting from excessive denaturization, of the capsule shell on drying.

As the final pH of the encapsulating process was increased the quantity of pentobarbituric acid extracted increased (Table V). This was probably due to a solubilization of the acid at the higher pH values and the subsequent weakening of the capsule wall by the resulting increased salt content of the mixture.

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