Effect of Additives and Formulation Techniques on Controlled Release of Drugs from Microcapsules

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The objectives of this study were to evaluate the effects of polysorbate 20 and a polyelectrolyte dispersing agent on the release of solids from microcapsules and to formulate microcapsules which, when subjected to gastrointestinal fluids, would release the encapsulated material at a predictable rate. Samples of microcapsules were subjected to simulated gastric fluid for 0.5 hr. and transferred to simulated intestinal fluid for an additional 2-hr. period. The filtered gastrointestinal fluids were compared spectrophotometrically to known absorption spectra in order to determine the quantity of solid released after each time interval. Results showed that the additives generally increased the release rate and that a large differential in release rate could be obtained without additives.

PREVIOUS WORK carried out by these authors and reported in *J. Pharm. Sci.* (1, 2) has indicated that the release of materials encapsulated by the process of complex coacervation could be controlled to make the encapsulated material available at a relatively predictable rate.

It was reported (1) that certain surfactants, when added to the system, would decrease the protection offered to the encapsulated substance. In this case, the encapsulated substance was mineral oil and the extracting substance was ethyl ether.

In another work (2) it was reported that solid particles (pentobarbituric acid) had been encapsulated in the same system and that a certain amount of control of the release rate of the solid to gastrointestinal fluids could be attained when conditions used in the encapsulation process were varied. The variables included: starting pH, starting temperature, ratio (dry weight) of solid to encapsulating material, quantity of formaldehyde added, and final pH.

With the above in mind, it became desirable to determine the effect of surfactants on microencapsulation as well as to attempt the formulation of fast and slow release microcapsules.

EXPERIMENTAL

Preparation of Microcapsules—The method of preparation of microcapsules followed that of Green and Schleicher (3, 4), as modified by Luzzi and Gerraughty (1). A previously described method of including solids (2) was incorporated into the process. Changes in pH were brought about by the addition of either 20% sodium hydroxide or diluted hydrochloric acid U.S.P.

Polysorbate 20[1] and a polyelectrolyte dispersing agent[2] were added in various quantities to the aqueous phase prior to the addition of the solid. In order to minimize the degradation of pentobarbituric acid, the temperature at which the capsules were dried was reduced from 50° to 40°.

The conditions incorporated into the formulation of fast release microcapsules are as follows: the starting pH was 5.0, the starting temperature was 34°, the ratio (dry weight) of pentobarbituric acid to encapsulating agents was 20/6; 4 ml. of formaldehyde solution U.S.P. was added for each 100 ml. of 3% gelatin solution, and the final pH was 8.8.

Samples for slow release microcapsules were prepared using the following conditions: the starting pH was 6.0, the starting temperature was 37°, the ratio of pentobarbituric acid to encapsulating agents was 4/6; 8 ml. of formaldehyde solution was added for each 100 ml. of 3% gelatin solution, and the final pH was 6.5.

The conditions accompanying the addition of both polysorbate 20 and the dispersing agent were as follows. The starting pH was 6.0, the starting temperature was 40°, the ratio of pentobarbituric acid to encapsulating agents was 8/6; 10 ml. of formaldehyde solution for each 100 ml. of 3% gelatin solution was added, and the final pH was 7.5. In addition samples of microcapsules containing the dispersing agent were prepeard where the lowest encapsulating pH values were 4.8 and 3.5 rather than the usual 4.0.

Method of Evaluation of Microcapsules—The method used to evaluate the microcapsules formed with the additives and for fast and slow release follows the method outlined by Luzzi and Gerraughty (2). The dried capsules were immersed in simulated gastric fluid and shaken for 0.5 hr. after which they were transferred to intestinal fluid and assayed after 1 and 2-hr. periods.

The assay method consisted of spectrophotometrically comparing the properly diluted, filtered extracts to known absorption spectra.

Photography—Photomicrographs of the wet microcapsules, taken prior to drying, were made to determine any visual peculiarities of the various formulations. The microscope slides were prepared for photography by placing 1 drop of slurry on a slide and covering it with a cover slip. The slurry was taken from the preparation while it was being filtered.

Polysorbate 20 (0.0071%) was added to the system shown in Fig. 1. In this photograph both

Received February 9, 1967, from the College of Pharmacy, University of Rhode Island, Kingston, RI 02881

Accepted for publication June 5, 1967.

Presented to the Basic Pharmaceutics Section, A.PH.A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

Abstracted in part from a thesis submitted by L. A. Luzzi to the Graduate School, University of Rhode Island, in partial fulfillment of Doctor of Philosophy degree requirements.

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[1] Polyoxyethylene sorbitan monolaurate. Marketed as Tween 20 by Atlas Powder Co., Wilmington, Del.

[2] Obtained as Darvan 7 from the R. T. Vanderbilt Co., New York, N.Y.

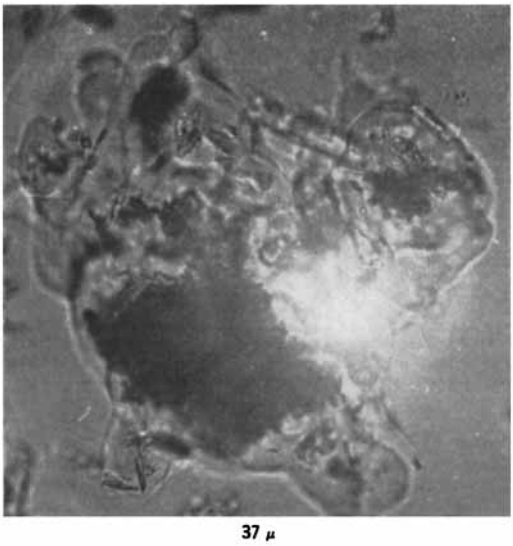

Fig. 1—Photograph of incomplete microencapsulation due to the addition of polysorbate 20.

Fig. 2—Photograph of large groups of microcapsules to which 0.019% of dispersant had been added to the system.

encapsulated and unencapsulated particles are visible. Photographs of a system containing less surfactant were prepared and, although not shown, suggested a progressive interference with encapsulation as the per cent of surfactant was increased.

Figure 2 is a photograph made of capsules containing 0.019% of the dispersing agent. It can be seen that the particles were not well dispersed and that large groups of particles seem to have gathered together to form a large group or groups of capsules. Figure 3 is a photograph prepared from microcapsules to which 0.029% of the dispersing agent had been added and shows elongated capsules filled with solid particles. The elongation of capsules seemed to be typical when moderate quantities of this dispersant were used. A comparison of the shell thickness of the over-all capsules to the shell thickness of capsules with no additive seemed to

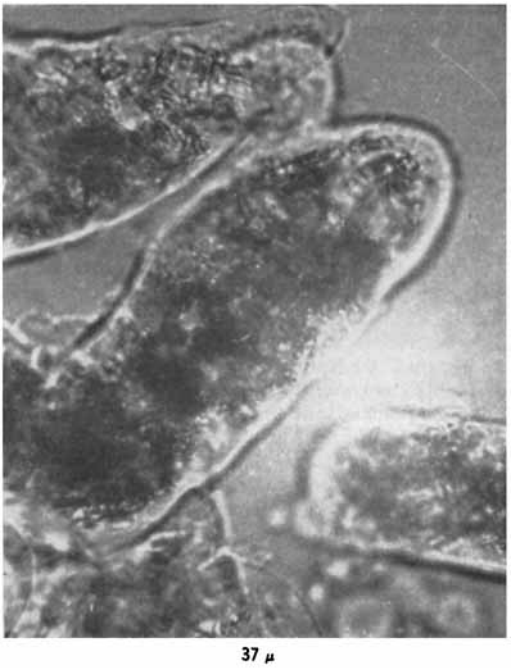

Fig. 3—Photograph of typical elongated groups of microcapsules which were present when 0.029% dispersant was added to the system.

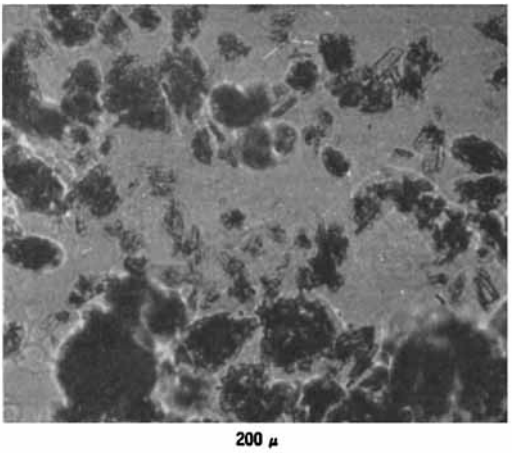

Fig. 4—Photograph of well dispersed microcapsules to which 0.116% of dispersant had been added.

indicate that high concentrations of the dispersant tend to decrease the wall thickness.

Figure 4 is a photograph of microcapsules to which 0.0071% polysorbate 20 had been added and was made at a slightly reduced enlargement. With this as a consideration, it can still be seen that the solids are in smaller groups, that the walls are quite thin, and that some capsules are not filled.

RESULTS

Effect of Polysorbate 20 on Microcapsules—Luzzi and Gerraughty (1) showed that polysorbate 20 in concentrations of 2% completely inhibited the encapsulation of mineral oil; it was thought that the orientation of polysorbate 20 molecules at the oil–water interface acted to prevent shell forming coacervate droplets from becoming oriented at the interface of the oil. The preparation of a series of microcapsules was undertaken in an attempt to establish the effect on microencapsulation of polysorbate 20 in systems employing solid rather than liquid particles.

In this series the per cent of polysorbate 20 included in the aqueous phase was varied from zero to 0.0142%. Table I shows that, under the conditions described, there was no significant change in the per cent of pentobarbituric acid released except at the highest concentration of polysorbate 20.

Effect of Dispersant on Microcapsules—Since the solid particles of pentobarbituric acid tended to settle out of suspension and were at times difficult to disperse, the dispersing agent was added to three separate series. Also, since preliminary work indicated that the dispersant was basic (pH 8.5–9.0) in the concentrations used, it was desirable to determine what effect changing the lowest pH would have on microcapsules as well as on the activity of the dispersant. The three series differed in that the lowest pH's attained during the encapsulating process were 4.0, 4.8, and 3.5, respectively.

The samples of Table II were prepared in an identical manner to those in the polysorbate 20 series (Table I), the only difference being that the dispersing agent rather than polysorbate 20 was added. At the lowest concentrations of the dispersant there seemed to be less acid extracted by the gastrointestinal fluids than in those samples prepared with no dispersant: thereafter, the per cent of acid released became greater with increasing additions of the dispersant.

Where the samples of Table III correspond to the dispersant concentrations of those in Table II, they are identical, with the exception that the lowest pH in the former was 4.8 rather than 4.0. Table III shows that there was a greater release of pentobarbituric acid as the concentration of the dispersant was increased and also that all of the samples of Table III released a greater percentage of acid than the corresponding members of Table II.

All of the samples within the series found in Table IV were also prepared in a manner similar to those of the polysorbate 20 group with the exception that the lowest pH was at 3.5 rather than at 4.0. Table IV shows that samples were not collectable until the second increment of the dispersant had been added; with the addition of the second increment of the dispersant, they become collectable.

TABLE I—EFFECT OF POLYSORBATE 20 ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Polysorbate 20, %	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
...	34.8	19.2	26.3	61.1
0.0001	35.0	17.5	26.8	61.8
0.0002	33.9	18.5	27.0	60.9
0.0006	32.7	20.1	28.3	61.0
0.0071	34.4	19.7	28.2	62.6
0.0142	40.7	20.0	26.1	66.8

[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 DISPERSANT ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES (FORMATION pH 4.0) EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Dispersant, %	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
...	34.8	19.2	26.3	61.1
0.0195	30.2	18.4	24.6	54.8
0.0290	35.0	20.1	25.6	60.6
0.0580	39.1	22.1	27.1	66.2
0.1160	34.7	19.7	28.1	62.8
0.1450	43.0	21.5	26.2	67.2
0.1740	38.0	23.1	30.7	68.7

[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.

TABLE III—EFFECT OF DISPERSANT ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES (FORMATION pH 4.8) EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Dispersant, %	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
...	42.2	21.7	25.9	68.8
0.029	43.5	21.2	25.7	69.2
0.116	45.3	16.3	24.7	70.0
0.174	48.5	28.4	30.7	79.2

[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 DISPERSANT ON THE PER CENT OF PENTOBARBITURIC ACID EXTRACTED FROM MICROCAPSULES (FORMATION pH 3.5) EXPOSED TO GASTROINTESTINAL FLUIDS[a]

Dispersant, %	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
.....	Sample not collectable			
0.029	... Sample not collectable ...			
0.058	39.8	24.6	32.5	72.3
0.116	40.4	23.4	30.3	70.7
0.174	41.3	32.1	36.7	78.0
0.232	41.0	22.2	29.9	70.9

[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.

Formulation of Fast and Slow Release Microcapsules—Using the information gathered from a previous work by the authors of this paper (2), an attempt was made to formulate microcapsules which would release all or nearly all of the pentobarbituric acid which they contained. An attempt was also made to formulate microcapsules which would retain more than 50% of this original content of acid after 2.5-hr. exposure to gastrointestinal fluids. Samples of both formulations were prepared, and they were subjected to the gastrointestinal fluids as previously described (2).

The results of assays for fast release microcapsules revealed that 47.3% of the drug was extracted after 0.5-hr. exposure to gastric fluid. After being transferred to intestinal fluid and remaining immersed for 1 hr., an additional 30.1% was extracted and during the second hour in intestinal fluid 1.1% of the original quantity of acid was released; for a total of 78.5% released after 2.5-hr. exposure to gastrointestinal fluids.

The results of assays for slow release microcapsules revealed that 37.7% of the drug was released during 0.5-hr. exposure to gastric fluid. After being transferred to intestinal fluid and remaining immersed for 1 hr., an additional 13.0% was extracted, and during the second hour in intestinal fluid 5.5% of the original quantity of acid was released for a total of 56.2% released after 2.5-hr. exposure to gastrointestinal fluids.

In the fast release samples there was a difference of 1.1% in total per cent acid extracted between 1- and 2-hr. exposure periods to intestinal fluid, whereas there was a difference of 5.5% acid extracted under the same conditions for slow release samples.

Although the per cent of pentobarbituric acid released after the 2.5-hr. assay period fell somewhat short of the goal of this experiment, there seemed to be a significant difference in the per cent of acid released between the two types of samples.

DISCUSSION

Reasoning concerning the effect of starting pH, starting temperature, ratio, and quantity of formaldehyde on the strength or stability of capsule walls when in contact with gastrointestinal fluids has been given elsewhere (1, 2). That is, the starting pH will affect the coacervation already present at low pH values (*i.e.*, 5) or to the salt present (in the case of pentobarbituric acid) at high pH values; the starting temperature will affect the mobility of the micromolecules or the formed coacervate droplets thus limiting encapsulation; the ratio of solid encapsulating agents may affect the shell thickness; the quantity of formaldehyde may be insufficient to cause stable droplets to form or may possibly cause cracking of the shell when present in excess.

Combination of those conditions contributing to optimum shell strength were incorporated into the slow release microcapsules and selected conditions (those where collection of samples could be made) away from the optimum were incorporated into the fast release microcapsules. It seems likely that the reasoning which applied to the individual variables would also apply to the combined conditions.

Polysorbate 20 may have interfered with encapsulation because of its orientation at the solid–liquid interface (1). However, this may not be the case with the dispersing agent. Here it seems likely that the increased release of solid from the capsule was due to an increase in the number of particles which resulted from better dispersion of the solid and thus in more individual capsules having been formed. (See Fig. 4.) With the increased number of particles present, it would seem that the ratio of solid surface to encapsulating agents has been increased. As shown previously, this too would decrease the capsule strength.

Studies are now being carried out in order to determine the degree to which surface orientation and particle dispersion or size affect capsule strength.

CONCLUSIONS

Polysorbate 20, in the higher concentration used, seems to enhance the release of pentobarbituric acid to simulated gastrointestinal fluids.

Photomicrographs indicate that the polyelectrolyte dispersing agent aids in the dispersion of solid containing microcapsules and that at higher concentrations the encapsulations are sometimes incomplete.

It is possible to control the rate of release of pentobarbituric acid to gastrointestinal fluids by varying certain conditions in the encapsulation process.

REFERENCES

(1) Luzzi, L. A., and Gerraughty, R. J., *J. Pharm. Sci.*, **53**, 429(1964).
(2) *Ibid.*, **56**, 634(1967).
(3) Green, B. K., and Schleicher, L., U. S. pat. 2,703,457 (1956).
(4) Green, B. K., U. S. pat. 2,722,507(1955).