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Report

Nylon Microcapsules. II. Effect of Selected Variables on Theophylline Release[1]

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The effect of selected variables on the release characteristics of theophylline microcapsules prepared with 1,6-hexamethylene diamine and sebacoyl chloride via interfacial polycondensation has been investigated. The nature of the microcapsules and the release characteristics of theophylline from the microcapsules were affected by the type of organic phase, particle size, stirring speed, and rate of addition of sebacoyl chloride during the preparation of microcapsules. The aggregation of the final product was generally less at the lower speeds of stirring. Decreasing the rate of additon of sebacoyl chloride increased the aggregation of the final product as well as the release of theophylline. Decreasing the particle size of the microcapsules increased the release of theophylline from the microcapsules.

KEY WORDS: microcapsules; nylon microcapsules; theophylline microcapsules; theophylline release from microcapsules; effect of variables on release.

INTRODUCTION

The feasibility of using interfacial polycondensation as a means of preparing nylon microcapsules has been demonstrated by various investigations (1–6). The Schotten–Baumann reaction between a diamine in an aqueous solution and an acid dihalide in a water-immiscible organic solution results in the formation of a polymer film at the interface of the two immiscible liquids. A variety of diamines (e.g., ethylenediamine, ethylenetetramine, hexamethylenediamine, tetramethylenediamine, etc.) and acid dihalides (e.g., adipoyl chloride, phthaloyl chloride, sebacoyl chloride, succinyl chloride, etc.) can be used in preparing various types of polymer membranes (7).

Among the various encapsulating membranes that have been investigated, polyhexamethylene sebacamide (popularly known as nylon 6-10 membrane) has been extensively used to form the microcapsule wall (1,6). The chemical reaction in the formation of the nylon 6-10 membrane is as follows.

$$\underset{\text{1,6-Hexamethylene-diamine}}{H_2N(CH_2)_6NH_2} + \underset{\text{Sebacoyl chloride}}{ClCO(CH_2)_8COCl} \rightarrow \underset{\text{Nylon 6-10}}{\{HN(CH_2)_6NHCO(CH_2)_8CO\}_x}$$

Since the interfacial reaction takes place on the organic side of the interface (7), the monomers whose rate of hydrolysis is faster than the interfacial reaction are unable to produce microcapsules. Therefore, the lower aliphatic acid chlorides are unable to give satisfactory microcapsules (8). In the case of polyamide microcapsules, it has been reported that acid chlorides with fewer than eight carbon atoms do not produce satisfactory microcapsules, while tough membranes are produced when acid chlorides with more then eight carbon atoms are used (8), suggesting that eight-carbon acid dichloride (sebacoyl chloride) is an optimum requirement for microencapsulation.

In most studies dealing with microencapsulation via interfacial polycondensation, the product has exhibited a tendency to agglomerate rather strongly during preparation and/or drying. Attempts to separate the microcapsules usually resulted in damage and rupture of the microcapsules. Some authors used special techniques such as spray-drying (1) or matrix inclusion (2) in order to prevent agglomeration. It was demonstrated in an earlier report (3) that the use of mineral oil, singly and in combination with varying amounts of carbon tetrachloride, cyclohexane, or chloroform, yielded discrete free-flowing microcapsules. Mineral oil is a good lubricating agent and has been used successfully to prevent aggregation of gelatin microcapsules prepared by the capillary drop method (9).

This study investigates the effect of organic phase, stirring speeds, particle size, and rate of addition of sebacoyl chloride on the release characteristics of theophylline microcapsules prepared by interfacial polycondensation.

MATERIALS AND METHODS

The following materials were used as received from the manufacturer without further treatment or purification: car-

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bon tetrachloride (Ashland Chemicals, Columbus, Ohio), chloroform, cyclohexane (J. T. Baker Chemical Co., Philipsburgh, N.J.), 1,6-hexamethylenediamine, sebacoyl chloride (Eastman Kodak, Rochester, N.Y.), theophylline anhydrous (Knoll Fine Chemicals Inc., New York, N.Y.), and light mineral oil, USP (Ruger Chemical Co., Irvington, N.J.).

According to the manufacturer, sebacoyl chloride and 1,6-hexamethylenediamine had a minimum purity of 98%.

Preparation of Microcapsules

Nylon microcapsules containing theophylline were prepared utilizing interfacial polycondensation by a method similar to the one reported previously (3). The method consisted of adding 20 ml of an aqueous solution containing 7% (w/v) 1,6-hexamethylenediamine, 4.8% (w/v) sodium hydroxide, and 1 g of anhydrous theophylline to 120 ml of the organic phase contained in a 600-ml beaker. The mixture was stirred (Talboy Stirrer Model 102, Talboy Engineering Co., Emerson, N.J.) for 20 sec to form a w/o emulsion. Without stopping the stirring, 120 ml of a 3.17% (w/v) solution of sebacoyl chloride in the organic phase was added and the stirring was continued for a total of 10 min. The microcapsules formed were collected by filtration and air-dried for 24 hr. The dried microcapsules were then washed with chloroform, filtered, and dried at 35°C for 15 hr.

Nine different organic phases were studied in this investigation (Table I). Triplicate batches of microcapsules were prepared for each variable studied. The singularity and continuous coating of the microcapsules was verified by examining samples from each batch under an optical microscope.

Effect of Stirring Speed

Stirring speeds of 770, 980, or 1400 rpm (representing low, medium, and high rates of mixing, respectively) were used when 120 ml of the 3.17% (w/v) solution of sebacoyl chloride in the organic phase was added to the water-in-oil emulsion. The dial setting on the stirrer was adjusted to obtain the desired stirring speed using a digital phototachometer (Power Instruments Inc., Skokie, Ill.). The organic phase used for these experiments was 10% chloroform in mineral oil.

Effect of Rate of Addition of Sebacoyl Chloride

To study the effect of the rate of addition of sebacoyl chloride on the characteristics of the microcapsules produced, the 3.17% (w/v) solution of sebacoyl chloride in 15% chloroform in mineral oil was delivered at the rate of 14.7, 20.0, 27.9, 46.1, or 58.2 ml/min while stirring the oil-in-water emulsion at the stirring speed of 770 rpm.

Table I. Organic Phases Investigated in this Study

1. 5% carbon tetrachloride in mineral oil
2. 10% carbon tetrachloride in mineral oil
3. 15% carbon tetrachloride in mineral oil
4. 5% cyclohexane in mineral oil
5. 10% cyclohexane in mineral oil
6. 15% cyclohexane in mineral oil
7. 5% chloroform in mineral oil
8. 10% chloroform in mineral oil
9. 15% chloroform in mineral oil

Effect of Particle Size

A nest of sieves was used to obtain the various particle size fractions. USA standard testing sieves (W. J. Tyler Inc., Mentor, Ohio) numbers 45, 50, 60, 80, and 100 were used. The product was placed on sieve number 45 and the nest of sieves was shaken on a Cenco-Meinzer sieve shaker (Central Scientific Co., Chicago) for 7 min at an amplitude of 1 in order to obtain four fractions of microcapsules having an average particle size of 165, 215, 275, and 363 μm. The average particle size of each fraction was computed by taking an average of the sieve opening through which the particles passed and the sieve opening on which the particles were retained. The average particle size in each fraction and the singularity of the microcapsules were established by viewing approximately 500 microcapsules under an optical microscope fitted with a micrometer. The microcapsules appeared to be continuously coated and singular and did not appear to have a tendency to form clusters or aggregates.

Release Rate Studies

The release characteristics of microcapsules containing theophylline were studied using the rotating bottle method employing a 10-bottle rotating assembly (Vanderkemp sustained release apparatus, Van-Kel Industries, Chatham, N.J.) fitted in a constant-temperature bath (Vanderkemp Model W-1115, Van Kel Industries, Edison, N.J.) set at 37 ± 1°C.

Approximately 30 mg of the microcapsules was placed in each bottle containing 60 ml of 0.1 *N* HCl or pH 7.4 phosphate buffer which had been previously warmed to 37°C. The bottles were rotated at a speed of 15 rpm. At predetermined times, each bottle was removed and the contents were filtered through a 0.45-μm membrane filter (Millipore Co., Bedford, Mass.). The concentration of theophylline released from the microcapsules was determined spectrophotometrically (Perkin Elmer Co., Saddle Brook, N.J.) at 271 nm. The wavelength of maximum absorbance for theophylline was found to be at 271 nm for both 0.1 *N* HCl and pH 7.4 buffer. Each release profile was determined based upon the average of triplicate determinations.

RESULTS AND DISCUSSION

All dissolution studies employed microcapsules having an average particle size of 275 μm prepared at 770 rpm and sebacoyl chloride added at a rate of 68.5 ml/min, unless stated otherwise. This particular microcapsule fraction was chosen for release studies primarily for practical reasons. As far as the particle size is concerned, either the 275- or the 315-μm-size fraction could have been used. The 165- and 215-μm-size fractions were not used because they rapidly released nearly 50% of the drug within the first 2 min. Similarly, microcapsules prepared at 900 and 1400 rpm released 70% drug within the first 2 min and nearly all their drug content within 10 min. The rate of addition of sebacoyl chloride was chosen at 68.5 ml/min because at lower rates the

microcapsules released 50% or more of their drug content within the first 2 min.

The release of theophylline from the microcapsules in 0.1 *N* HCl and pH 7.4 phosphate buffer is shown in Fig. 1. In a 21-min period about 95% of the encapsulated theophylline was released in 0.1 *N* HCl, whereas only 65% was released in the phosphate buffer. This release difference may be due to the varying ability of the acidic and the basic dissolution media to wet the microcapsules (1).

Effect of Stirring Speed

In an earlier investigation (3) it was found that increasing the stirring speed from 770 to 1400 rpm during the preparation of the microcapsules did not have any effect on the physical quality of the product (clumping and agglomeration of the microcapsules) in some cases but worsened the physical quality of the product in others. In general, however, the free-flowing property appeared to be improved by decreasing the stirring to a point where a sufficient degree of mixing and movement of the system was maintained.

Figure 2 shows the effect of stirring speed on the release of theophylline from the microcapsules. Microcapsules prepared at the low stirring speed (770 rpm) released theophylline slower than those prepared using either the medium (980 rpm) or the high stirring speed (1400 rpm). It is possible that higher stirring speeds produced microcapsules with weak and/or thin membranes. Alternatively the microcapsule wall ruptured because of the high shearing force during preparation to form membrane pores which yielded faster release of the drug. Indeed, microcapsules prepared at the low stirring speed released only 35% theophylline in the first 3 min, compared to 70% from the microcapsules prepared at higher stirring speeds.

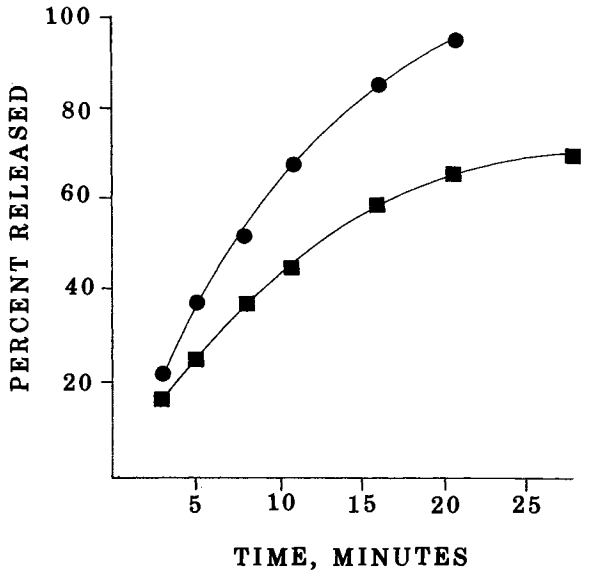

Fig. 1. Release of theophylline from 275-μm microcapsules in 0.1 *N* HCl (●) and pH 7.4 phosphate buffer (■) at 37°C. Microcapsules were prepared at 770 rpm using 15% chloroform in mineral oil delivered at 68.5 ml/min. Each point in this and all subsequent figures represents an average of three determinations. The standard deviations were smaller than the symbols and are therefore not shown.

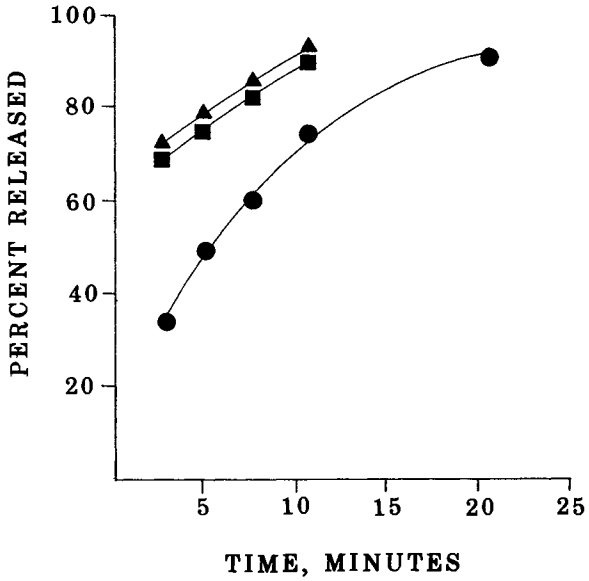

Fig. 2. Effect of stirring speed (▲, 1400 rpm; ■, 980 rpm; ●, 770 rpm) on the release of theophylline from 275-μm microcapsules in 0.1 *N* HCl at 37°C. Microcapsules were prepared using 10% chloroform in mineral delivered at 68.5 ml/min.

Effect of Rate of Addition of Sebacoyl Chloride

The rate of sebacoyl chloride addition to the diamine-organic phase emulsion is another variable of interfacial polycondensation that has not been specifically investigated previously. McGinity *et al.* (10) employed an undefined "slower addition" of sebacoyl chloride, while Luzzi *et al.* (1) and Degennaro *et al.* (4) did not mention the rate of addition of sebacoyl chloride. Table II documents that the nature of microcapsules was influenced by the rate of sebacoyl chloride addition. Microcapsules prepared at 68.5, 58.2, or 46.1 ml/min were free flowing, while those prepared at 20.0 or 14.7 ml/min formed aggregates. Some aggregation was noticed when the rate of addition of sebacoyl chloride was reduced to 27.9 ml/min. Thus, the physical quality of the product improved with increasing rates of sebacoyl chloride addition.

The release of theophylline from the microcapsules produced at various rates of addition of sebacoyl chloride is shown in Fig. 3. The release of theophylline from the micro-

Table II. Effect of the Rate of Addition of Sebacoyl Chloride on the Nature of Microcapsules

Rate of addition[a]	Nature of microcapsules[b]
14.7	−
20.0	−
27.9	+ +
46.1	+ + +
58.2	+ + +
68.5	+ + +

[a] 3.17% (w/v) sebacoyl chloride in mineral oil containing 15% chloroform. The stirring speed was 770 rpm.

[b] (+ + +) Free-flowing powder; (+ +) loose aggregates, yielding free-flowing powder upon sieving; (−) large clumps, microcapsules not separable.

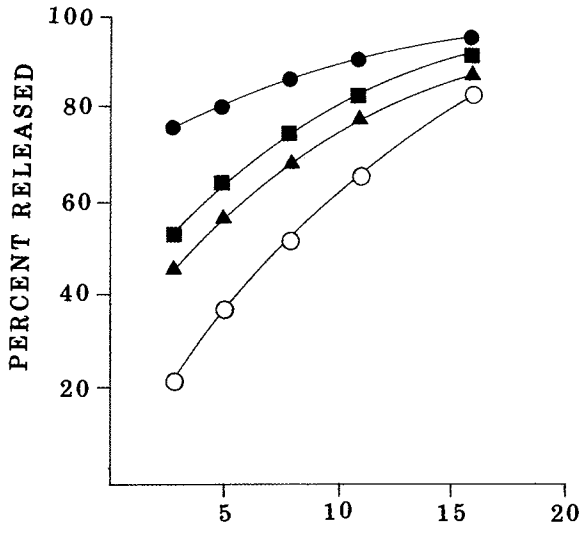

Fig. 3. Effect of rate of addition of 3.17% solution of sebacoyl chloride in 15% chloroform in mineral oil (●, 27.1 ml/min; ■, 46.1 ml/min; ▲, 58.2 ml/min; ○, 68.5 ml/min) on the release of theophylline from 275-μm microcapsules in 0.1 *N* HCl at 37°C. Microcapsules were prepared at 770 rpm.

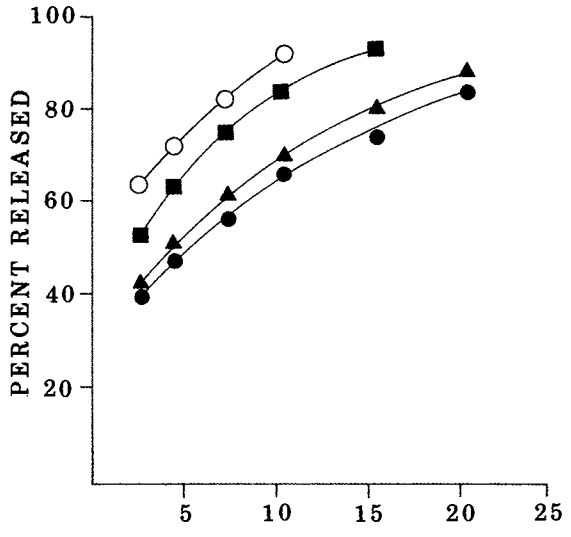

Fig. 4. Effect of particle size (○, 165 μm; ■, 215 μm; ▲, 275 μm; ●, 363 μm) on the release of theophylline in 0.1 *N* HCl at 37°C. Microcapsules were prepared at 770 rpm using 10% chloroform in mineral oil delivered at 68.5 ml/min.

capsules increased with the decreasing rate of sebacoyl chloride addition to the diamine-organic phase emulsion. The rate of sebacoyl chloride addition may have influenced the degree of polymerization which affected the structure as well as the thickness of the membrane resulting in different microcapsule walls and, therefore, different drug release from the microcapsules.

Effect of Particle Size

Figure 4 shows that the release of theophylline from the microcapsules increased as the particle size of the microcapsules was decreased. Because of the large surface area of the smaller particles, the smaller-sized microcapsules appeared to have less membrane-forming material available for the encapsulation of the individual particles (11,12), thus resulting in a thinner microcapsule shell. Also, a reduction in the particle size of the microcapsules results in a larger total surface area available for the dissolution medium to penetrate the microcapsules. Either one or the combination of the above mechanisms appears to be responsible for the faster release of the drug from the smaller-sized microcapsules.

Effect of Organic Phase on Release Characteristics

Figure 5 shows the effect of the organic phase on the release profiles of theophylline from the microcapsules. Three organic solvents (chloroform, cyclohexane, and carbon tetrachloride) were incorporated into mineral oil at 5, 10, and 15% concentration levels. Figure 5A shows that the microcapsules prepared in mineral oil containing 15% chloroform released theophylline more slowly than those prepared with 10 or 5% chloroform in mineral oil. However, the rank order of release was reversed in the system using similar concentrations of carbon tetrachloride (Fig. 5B) and cyclohexane (Fig. 5C).

The difference in the theophylline release from the microcapsules prepared in various organic phases may be accounted for by the mechanisms of the formation of the microcapsule wall. The partitioning of diamine into the organic phase appears to be the important factor in the formation of the nylon membrane, which can vary from smooth and thin when the organic phase is cyclohexane to coarse and thick when chloroform is used as the organic phase (5,6). Morgan *et al.* (13) reported that the partition coefficient of diamine in water/chloroform was 0.9, compared to 104 in water/cyclohexane and 56 in water/carbon tetrachloride. Hence the diamine distributes very well into the chloroform phase and partitions moderately into carbon tetrachloride and poorly into cyclohexane. Since the partition coefficient of the diamine varies with the organic solvent present in the system, it is reasonable to assume that the incorporation of organic

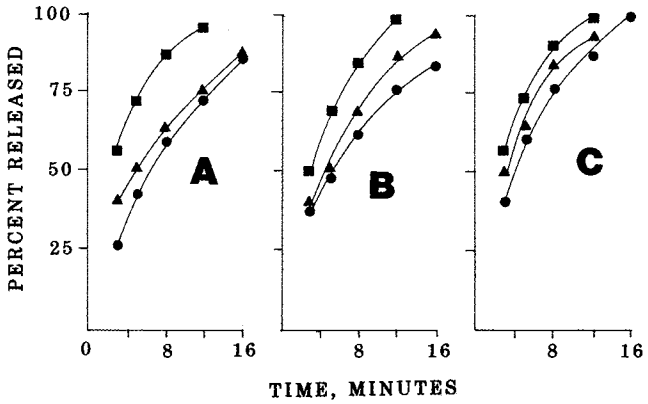

Fig. 5. Effect of chloroform (A), cyclohexane (B), and carbon tetrachloride (C) concentration in mineral oil on the release of theophylline from 275-μm microcapsules in 0.1 *N* HCl at 37°C. Microcapsules were prepared at 770 rpm and the organic phase was delivered at 68.5 ml/min. (■) 5%; (▲) 10±; (●) 15%.

solvents would affect the formation of the nylon membrane. Similarly, the concentration of the organic solvent in mineral oil would affect the drug release from the microcapsules. This view is supported by the data shown in Fig. 6, which compares the theophylline release from the microcapsules when similar quantities of the organic solvents were incorporated into mineral oil. In the system containing 5% of the organic solvent in mineral oil (Fig. 6A), the rate of theophylline release from the microcapsules was similar, although microcapsules prepared using chloroform released theophylline faster than those prepared with cyclohexane or carbon tetrachloride. When the concentration of the organic solvent was increased to 10 or 15%, the release of theophylline from the microcapsules prepared with chloroform decreased sharply (Figs. 6B and C). This result is expected on the basis of the excellent partition coefficient of diamine in water/chloroform compared to the poor partitioning of diamine in either cyclohexane or carbon tetrachloride.

In conclusion, this study was undertaken to investigate the use of mineral oil to minimize aggregation of microcapsules prepared by interfacial polycondensation and to determine the effect of selected variables on the release characteristics of theophylline from the microcapsules. The nature of the microcapsules and the release characteristics of theophylline from the microcapsules were affected by the type of organic phase, the stirring speed, and the rate of sebacoyl chloride addition to the diamine-organic phase emulsion. The aggregation of the final product was generally less at lower speeds of stirring than at higher speeds of stirring. Decreasing the rate of addition of sebacoyl chloride increased the aggregation of the final product. Decreasing the particle size of microcapsules increased the release of theophylline from the microcapsules. The release of theophylline from the microcapsules was governed by the partition coefficient of diamine in the water/organic phase. Faster-releasing microcapsules were produced in the organic phase in which diamine partitioned poorly and slower-releasing microcapsules were produced with an organic phase that exhibited a greater partition coefficient for the diamine.

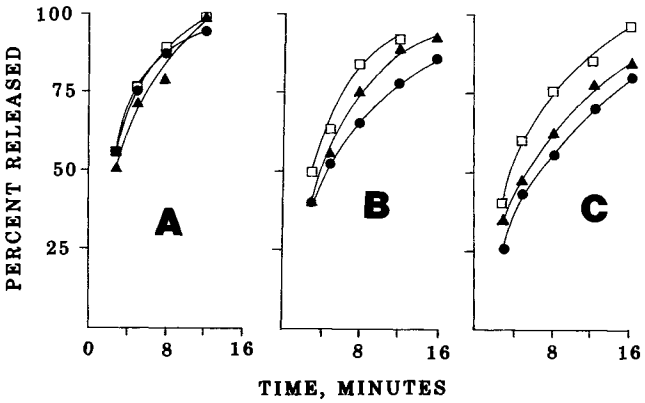

Fig. 6. Effect of similar levels (A = 5%, B = 10%, C = 15%) of organic solvents (●, chloroform; □, carbon tetrachloride; ▲, cyclohexane) in mineral oil on the release of theophylline from 275-μm microcapsules in 0.1 *N* HCl at 37°C. Microcapsules were prepared at 770 rpm and the organic phase was delivered at 68.5 ml/min.

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