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NYLON MICROCAPSULES: I. EFFECT OF ORGANIC PHASE AND STIRRING SPEED

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ABSTRACT

The effect of organic phase and stirring speed on the preparation of nylon microcapsules using 1,6-hexamethylene diamine and sebacyl chloride in the interfacial polycondensation reaction has been investigated. Carbon tetrachloride alone and the traditional 20% chloroform in cyclohexane were found to be poor solvents producing non-separable clumps of microcapsules. Mineral oil, singly, and in combination with varying amounts of carbon tetrachloride, cyclohexane, or chloroform yielded discrete free-flowing microcapsules.

In general, lower speeds of stirring produced products which were more discrete and free flowing than those prepared at higher stirring rates.

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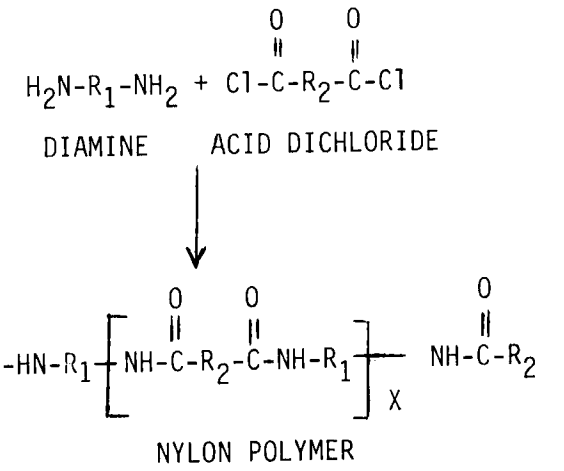
INTRODUCTION

The feasibility of using interfacial reaction as a means of preparing microcapsules has been demonstrated in preparing semipermeable microcapsules containing enzymes used in the treatment of enzyme deficiencies (1) and the use of nylon microcapsules in an extracorporeal shunt system (2,3). The basic chemistry in this reaction is the interaction between a diamine in an aqueous solution with an acid dihalide contained in the water immiscible organic solution resulting in the formation of a film at the interface of the two immiscible liquids. The chemical reaction in the formation of nylon membrane, for example, may be depicted as follows:



NYLON POLYMER

Reports in the literature (4) suggest that a variety of diamines and acid halides can be used in preparing various types of polymers (Table 1). A number of encapsulating membranes have been investigated and used in preparing micro-

TABLE 1

Alphabetical Listing of Some Examples of Acid Halides and Diamines Used in Interfacial Polycondensation

Acid Halides	Diamines
Adipoyl Chloride	Bis (4-Aminocyclohexyl) Methane
4,4-Biphenyldicarbonyl Chloride	1,4-Bis (aminomethyl) Cyclohexane
1.4-Cyclohexanedicarbonyl Chloride	Bis (p-aminophenyl) Methane
1,2-Ethanedisulphonyl Chloride	Ethylenediamine
1,6-hexanedisulphonyl Chloride	Ethylene Tetramine
Phosgene	Hexamethylenediamine
Phthaloyl Chloride	p-phenylenediamine
Sebacyl Chloride	Piperazine
Succinyl Chloride	1,3-Propylenediamine
4,4-Sulphonyldibenzoyl Chloride	Tetramethylenediamine

capsules via interfacial polycondensation (5-8). For the encapsulation of pharmaceuticals, however, polyhexamethylene sebacamide (nylon 6-10) membrane has been extensively used to form the microcapsule wall (9-11).

One of the major problems encountered in the production of nylon 6-10 membrane has been the recovery of the final product as a free flowing powder. The product usually tends to agglomerate forming either a hard cake or large clumps of microcapsules at best (9-11).

This investigation was therefore undertaken to prepare discrete, free-flowing microcapsules utilizing polyhexamethylene sebacamide membrane to encapsulate a water soluble drug. The effect of stirring speed and the type of organic phase used was studied to investigate whether discrete, free-flowing microcapsules can be easily prepared.

EXPERIMENTAL

Material: The following materials were used as received from the manufacturer without further treatment or purification: carbon tetrachloride[1], sebacyl chloride[2] 1,6-hexamethylenediamine[2], chloroform[3], cyclohexane[3], sodium salicylate[3], and light mineral oil USP[4].

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

Preparation of Microcapsules:

Nylon microcapsules containing sodium salicylate were prepared utilizing interfacial polycondensation. The procedure consisted of adding 20 ml of an aqueous solution containing 7% w/v, 1,6-hexamethylenediamine, 4.8% w/v sodium hydroxide and 1.0g of sodium salicylate to 120 ml of the organic phase contained in a 600 ml beaker. The mixture was then stirred[5] for 20 seconds to form a w/o emulsion. Without stopping the stirring, 120 ml of a 3.17% w/v solution of sebacyl chloride in the organic phase was added and the stirring was continued for a total of 10 minutes. Various organic phases were studied in this investigation. These are listed in Table 2.

TABLE 2

Organic Phases Investigated

Solvent	Co-Solvent
Carbon Tetrachloride	None
Cyclohexane	5% Chloroform
Cyclohexane	10% Chloroform
Cyclohexane	20% Chloroform
Mineral Oil	None
Mineral Oil	5% Carbon Tetrachloride
Mineral Oil	10% Carbon Tetrachloride
Mineral Oil	15% Carbon Tetrachloride
Mineral Oil	5% Cyclohexane
Mineral Oil	10% Cyclohexane
Mineral Oil	15% Cyclohexane
Mineral Oil	5% Chloroform
Mineral Oil	10% Chloroform
Mineral Oil	15% Chloroform
Mineral Oil	20% Chloroform

The microcapsules formed were collected by filtration and air-dried for 24 hours. The microcapsules were then washed with chloroform, filtered, and dried at 35° for 15 hours.

RESULTS AND DISCUSSION

Effect of Organic Phase:

Previous studies dealing with the encapsulation of drugs in 1,6-hexamethylenediamine and sebacyl chloride microcapsules have used either carbon tetrachloride (10) or a 20% solution of chloroform in cyclohexane (9,11) as the organic phase. The final product in such systems produced non-discrete microcapsules which agglomerate to form clumps unless special techniques such as spray drying (9), or matrix inclusion (11) were used.

Mineral oil, singly and in combination with carbon tetrachloride, cyclohexane, or chloroform was investigated as a substitute for the traditionally used organic phase because previous studies dealing with microencapsulation via congealing (12,13) revealed that the use of mineral oil minimized agglomeration and clumping of the microcapsules.

From the results found in Table 3 it can be seen that the use of mineral oil as the organic phase did in fact minimize or eliminate clumping and agglomeration of the final product. Discrete, free-flowing microcapsules were obtained in the systems using 5% chloroform in cyclohexane compared with 10% or 15% chloroform in cyclohexane. Similarly, mineral oil containing 10% chloroform, 10% cyclohexane, or 15% cyclohexane produced

TABLE 3

Effect of Organic Phase and Stirring Speed on the Nature of Microcapsules

Organic Phase	Nature[a] of Microcapsules at 770 RPM	980 RPM	1400 RPM
Carbon Tetrachloride	+	-	-
5% Chloroform in Cyclohexane	+ + +	+ + +	+ +
10% Chloroform in Cyclohexane	+	-	-
20% Chloroform in Cyclohexane	-	-	-
Mineral Oil	+ +	+ +	+ +
5% Carbon Tetrachloride in Mineral Oil	+ +	+ +	+ +
10%Carbon Tetrachloride in Mineral Oil	+ +	+ +	+ +
15%Carbon Tetrachloride in Mineral Oil	+ +	+ +	+ +
5% Cyclohexane in Mineral Oil	+ + +	+ +	+ +
10% Cyclohexane in Mineral Oil	+ + +	+ + +	+ + +
15% Cyclohexane in Mineral Oil	+ + +	+ + +	+ + +
5% Chloroform in Mineral Oil	+ + +	+ + +	+ + +
10% Chloroform in Mineral Oil	+ + +	+ + +	+ + +
15% Chloroform in Mineral Oil	+ + +	+	-
20% Chloroform in Mineral Oil	-	-	-

[a] + + + indicates free-flowing powder

+ + indicates some aggregation but the aggregates could be easily separated into discrete particles

+ indicates aggregates which could not be separated without possible damage to the microcapsules

- indicates clumps, microcapsules were not separable

microcapsules which were discrete and free-flowing. It would therefore appear that the quantity of organic solvent needed for the organic phase can be minimized when mineral oil is incorporated into the system. This is a definite advantage because reducing the quantity of organic solvents minimizes the use of possible hazardous contaminants. Also, substitution with mineral oil provides an economical and safer medium.

In all mineral oil systems studied, the quality of product obtained was either acceptable or excellent. Some degree of agglomeration was observed when mineral oil was used alone but these agglomerates could be easily separated to give discrete particles of the product. Incorporation of either cyclohexane or chloroform at 5%, 10%, or 15% concentration levels prevented the agglomeration and yielded a product which consisted of discrete free-flowing particles. When the concentration of chloroform in mineral oil was increased to 20%, the product obtained was unacceptable. The microcapsules produced agglomerated into large clumps which could not be separated into individual entities. It therefore appears that incorporation of large quantities of organic solvents may be undesirable since large quantities of these solvents may tend to negate the physicochemical properties of mineral oil.

Effect of Stirring Speed

The previously published reports describing nylon 6-10 microcapsules are either not very specific about the stirring

speeds used in the preparation of microcapsules (11), or have usually indicated the stirring speed with reference to the dial setting on the stirring device (9,10). In this study we have investigated the effect of the number of revolutions (per minute) of the propeller on the quality of the product.

Three stirring speeds were selected to represent slow, medium, and high rates of mixing. The lowest speed chosen was such that the two phases formed the emulsion and droplets were mobile enough to prevent coalescence even after the organic phase had been added to the system. The medium speed was based upon experience and represented better mixing than that obtained at low speed. The high rate of stirring approached turbulent mixing. These speeds were measured using a digital phototachometer.[6]

In all cases studied, increasing the speed of mixing did not favor a better product. Either the quality of the product remained the same or it exhibited deterioration. In the case of carbon tetrachloride alone, for example, the product was poor at low speed and unacceptable when the mixing speed was increased indicating that this organic solvent is not a good material to be used as the organic phase in preparing nylon microcapsules. Similar results were seen in the system containing 10% chloroform in cyclohexane.

From the results found in Table 3 it can be seen that increasing the speed of stirring did not have any effect on the

quality of the product in some cases, and worsened the 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 sufficient degree of mixing and movement of the system was maintained.

SUMMARY AND CONCLUSIONS

The results of this investigation show that the type of organic phase used and the degree of mixing played an important role in the quality of the formed microcapsules. Further studies are in progress to examine the factors contributing to the behavior of the release of the drug from the microcapsules and will be the subject of a future communication.

FOOTNOTES

1 Ashland Chemical Company, Columbus, Ohio

2 Eastman, Rochester, NY

3 J. T. Baker Chemical Company, Philipsburgh, NJ

4 Ruger Chemical Company, Irvington, NJ

5 Talboy Stirrer Model 102, Talboy Engineering Company, Emerson, NJ

6 Digital Phototachometer, Power Instruments Inc., Skokie, IL

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