

계면중합을 이용한 살충제의 마이크로캡슐화에 관한 연구 : 2. 수용성 약제가 들어있는 폴리아미드 마이크로캡슐의 제조

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Microencapsulation of Pesticides by Interfacial Polymerization : 2. Polyamide Microcapsules Containing Water-Soluble Drug

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요 약 : 다관능성 아민과 이염기산 클로라이드를 계면중합하여 살충제인 5-메틸이소옥사졸-3-올 (Hymexazol) 수용액이 들어있는 폴리아미드 마이크로캡슐을 제조하였다. 얻어진 마이크로캡슐의 크기분포, 기계적 강도 및 응집현상은 피막구성물질과 유기상의 성질, 교반속도 그리고 분산제에 의하여 큰 영향을 받음을 알 수 있었다. 그리고 마이크로캡슐의 기계적 강도는 다관능성 아민을 이용하여 폴리아미드를 가교시킴으로써 향상시킬 수 있었으며 또한 교반속도 및 분산제 (Antaron V-216)의 양을 조정함으로써 마이크로캡슐의 크기분포 및 응집현상을 조절할 수 있었다. 마이크로캡슐의 크기가 약 300 μm 일때가 캡슐 입자의 응집방지나 입자 크기 분포면에서 가장 좋은 결과를 얻을 수 있었다. 약제의 방출실험 결과, 마이크로캡슐 내부의 약제가 이를 이내에 거의 대부분 방출되는 것으로부터 제조된 캡슐은 다공성이 매우 큰 피막으로 되어 있음을 알 수 있었다. 따라서 방출거동을 조절하기 위하여 마이크로캡슐을 여러가지 탄소사슬길이의 지방산으로 코팅하였으며 방출거동을 6일 이상으로 증가시킬 수 있었다. 그러나 이 실험의 코팅조건에서 지방산의 탄소사슬길이의 변화는 살충제의 방출거동에 뚜렷한 영향을 미치지 않았다.

Abstract : Polyamide microcapsules containing aqueous solution of a pesticide, 5-methylisoxazol-3-ol (Hymexazol), were prepared by the interfacial polymerization of multifunctional amines and diacid chlorides. Size distribution, mechanical strength, and agglomeration phenomena of the obtained microcapsules were found to be strongly influenced by the nature of wall-forming materials and organic phase, stirring speed, and dispersing agents. While mechanical strength of microcapsules were improved by crosslinking the polyamide by use of multifunctional amines, size distribution and agglomeration of microcapsules could be controlled by adjusting stirring speed and amount of polymeric dispersing agent, Antaron V-216. The best results with respect to anti-agglomeration and particle size distri-

bution were obtained when the microcapsule size was about 300 μ m. Upon release test of the drug, it was found that the polyamide capsule wall was porous and all the drugs were completely released within 2 days. For further control of the release behavior, the microcapsules were coated with various fatty acids having different carbon chain lengths and it could prolong the release behavior longer than 6 days. Under our coating conditions, however, no significant effect on the release behavior of the pesticide was noticed as the carbon chain length of fatty acid changed.

INTRODUCTION

In the previous communication,¹ we reported a study on the polyurethane microcapsules containing oil-soluble pesticide and their drug release behavior. The microcapsules were prepared by interfacial polymerization of two monomers at the oil/water interface where the oil phase containing one of the monomers was suspended as droplets in continuous aqueous solution of the other monomer during the polymerization process (o/w microcapsule).^{2,3} Therefore, application of this method was limited for oil-soluble drugs only, however, one might be able to find more versatile applications for water-soluble materials.

In this work, we have studied on microcapsules containing water (w/o microcapsules) for the purpose of controlled delivery of water-soluble materials. In principle, the same interfacial polymerization procedure could be applied for the preparation of microcapsules containing water.^{2,3} In fact, w/o microcapsules have been prepared through interfacial polymerization by a number of researchers and their characteristics have been studied.^{4~7} Most of these studies have been carried out with the emulsion state of aqueous phase so that one can obtain a few micron size microcapsules partly because one of the principal aim of these studies has been to mimic biological cells.^{4,8} In this case, the barrier property of interest is somewhat different from the view of controlled release application. Also the required physical strength of microcapsules is quite different from the microcapsules of the size of a few tens to hundreds microns prepared from the suspension state of aqueous phase in this study.

Here, we report a study on the preparation of w/o polyamide microcapsules and their controlled release behavior of a water-soluble drug.

EXPERIMENTAL

Materials

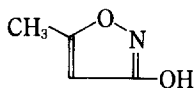
As mentioned earlier, any monomer pairs having suitable reactivities and solubilities for two phases can be used, in principle, for the preparation of microcapsules through interfacial polymerization.^{2,3} However, it was found that the results strongly depend on the choice of monomer, oil phase, and reaction conditions.

In this work, polyamide was chosen as the wall-forming material of w/o microcapsules from the following reasons. First of all, the reaction between amine and acid chloride is sufficiently fast even in mild reaction condition, which was found to be critical to obtain microcapsules without a serious loss due to agglomeration. Secondly, wide variety of the monomers are easily available. Also polyamide microcapsules are probably the most widely studied system among the microcapsules made by w/o type interfacial polymerization.^{8~16} In order to investigate the effect of wall-forming material on the release characteristics, we have used four different amines, namely 1,6-hexamethylenediamine, 1,12-dodecanediamine, diethylenetriamine, and tetraethylenepentamine expecting the variation of the degree of crosslinking. Also we employed two kinds of acid chlorides, sebacoyl chloride and terephthaloyl chloride for the same purpose.

For the oil phase, we have chosen 1 : 4 mixture (in volume) of chloroform and cyclohexane which

has been widely used in the preparation of polyamide microcapsules. Addition of a small amount of polar chloroform to nonpolar cyclohexane enhances the solubility of polyamide so that the molecular weight of polyamide is increased necessary to form an adequate strength membrane round the droplet.³ We had used 5-methylisoxazol-3-ol, a fungicide effective to soil-borne disease caused by various fungi, as the test drug for the controlled release study.¹⁷

5-methylisoxazol-3-ol
(Hymexazol)

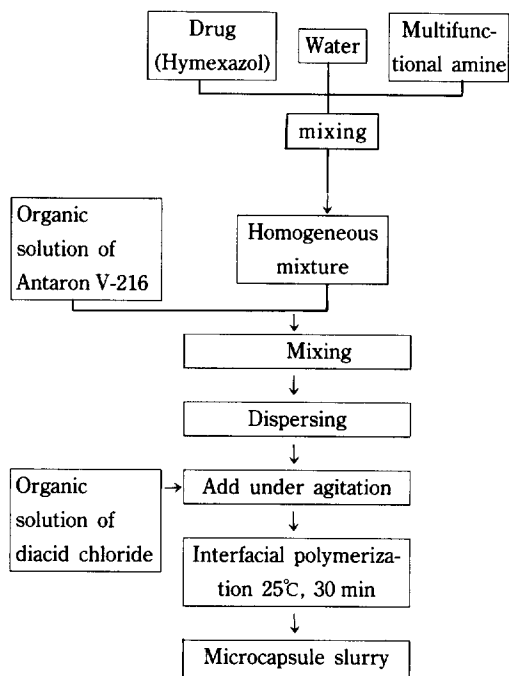


It has a reasonable solubility to water of 85 g/L at 25°C and also quite soluble in most of organic solvents. Due to its solubility for organic solvents, this drug may not be an ideal model drug for w/o microcapsule study, however, it was found that the drug could be encapsulated in w/o microcapsules without significant loss. Furthermore, it can be quantitatively analyzed with ease by spectrophotometer and the presence of hydroxyl group allows chemical modification readily so that it can be utilized for chemically controlled release system^{18,19} as will be reported in the subsequent paper in this series.²⁰

We used Antaron V-216 as the suspending agent which is an N-alkylated polyvinyl pyrrolidone with 16 carbon chains. All the chemicals used were reagent grades except Hymexazol and Antaron V-216 which were obtained from Oriental Chemical Industry and GAF Chemical Corporation, respectively.

Microencapsulation

The preparation procedure of w/o microcapsules was practically the same as that of o/w type microcapsules¹ and is illustrated in Scheme 1. A 500 mL round-bottom flask with an attached mechanical stirrer was used as the reactor. The stirring speed of the mechanical stirrer was adjustable and monitored by a strobe light detector. The continuous organic phase was a homogenous 1 : 4 mixture of



* Organic solvent : Chloroform/Cyclohexane = 1/4(V/V)

Scheme 1. Procedure for the preparation of w/o polyamide microcapsules.

chloroform and cyclohexane containing a small amount of the dispersing agent, Antaron V-216, and the dispersed aqueous phase consisted of water, drug, and a multifunctional amine. After a steady dispersion was obtained by stirring, a portion of a diacid chloride solution in the same 1 : 4 mixture of chloroform and cyclohexane was slowly added dropwise with the use of a liquid dropping funnel to initiate the interfacial polymerization. The polymerization reaction proceeded fast and was usually allowed to react completely for 30 minutes. The w/o microcapsules were collected by filtration and washed a few times with ethanol and finally with water.

Coating with Fatty Acids

In order for further control of the release behavior, the surface of microcapsules were coated with fatty acids having different carbon chain lengths. Microcapsules were coated by immersing in a 10 wt% chloroform solution of a fatty acid for a short

period (typically 1-2 minutes) in order to avoid the loss of drug during the coating process. It was found that the coating period of one minute was long enough to obtain the reproducible release behaviors. Coated microcapsules were collected by filtration and dried by gentle blowing of N_2 gas.

Release Test

One gram of microcapsules were put into dialysis bag (SIGMA Diagnostics) and located in a 25 mL deionized water of which temperature was maintained at 30°C in a shaking bath under steady agitation. At a regular interval, the deionized water was replaced with a fresh water and a 10 μ l aliquot of water was sampled to analyze the drug released. The drug content in the aliquot was determined from the absorbance at 200 nm wavelength by the use of a UV-VIS spectrophotometer (Shimadzu UV-240). The calibration curve was obtained by separate spectrophotometric measurements of aqueous solutions of Hymexazol.

RESULTS and DISCUSSION

Preparation of Microcapsules

For the interfacial polymerization between water and organic solvents, the capsule wall is known to grow toward the phase which has a better solvent quality for the growing polymer chain.^{3,21} Since the organic phase is a better solvent for the case of polyamide in this study, capsule wall of w/o microcapsules grew outside toward the continuous oil phase contrary to the case of o/w microcapsules. Therefore, it resulted in a diffuse wall structure and the suspending agent could not effectively surround the surface of droplets during the polymerization process. This caused poor mechanical strength of microcapsules, and severe agglomeration took place during the reaction. Mechanical strength of capsule wall could be improved by crosslinking the wall-forming materials and only the multifunctional amines, diethylenetriamine and tetraethylenepentamine, produced useful microcapsules.

Also it was found that the agitation speed and

the concentration of dispersing agent were the crucial factors in acquiring quality microcapsules. Similar to the o/w microcapsules,¹ the average size of microcapsules was reduced with increase of stirring speed as displayed in Fig. 1. Reaction conditions of microencapsulation process is summarized in Table 1 and the results shown in Fig. 1 was obtained under the condition (a) at stirring speeds of 200, 300 and 400 rpm etc. The best result was obtained at the stirring speed around 300 rpm in terms of size distribution and agglomeration. At higher speeds, agglomeration of microcapsules became serious while the size of microcapsules was large and the size distribution became broad at lower speeds, similar to the o/w microcapsules. The concentration effect of dispersing agent is displayed in Fig. 2 where the reaction condition was the same as before at the stirring speed at 300 rpm, but the concentrations of Antaron V-216 were varied at 0.1, 0.3, 0.5 and 1 parts. It showed a strong effect of dispersing agent on the capsule size. We found that the optimum condition was near 0.4 part of the dispersing agent judging from the agglomeration and size distribution. At higher concentration, agglomeration became severe while the size distribution of microcapsules became larger at

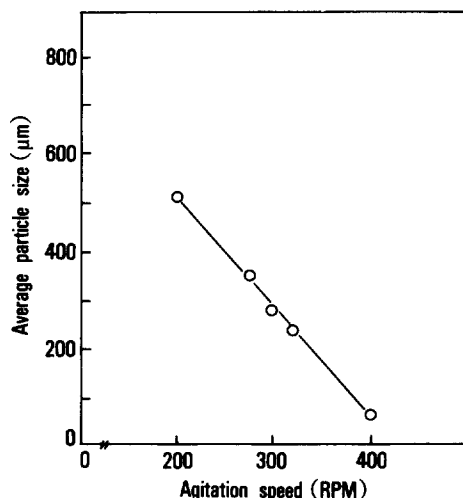


Fig. 1. Dependence of average size of microcapsules on stirring speed.

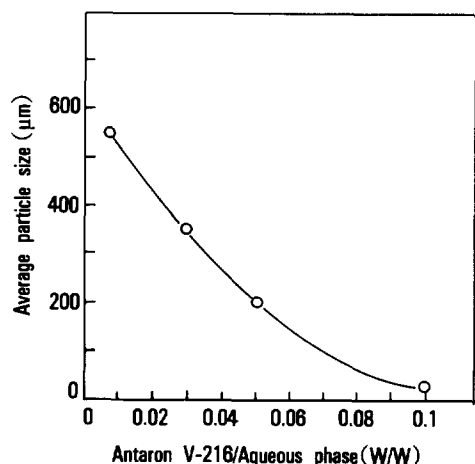


Fig. 2. Dependence of average size of microcapsules on concentration of dispersing agent, Antaron V-216.

Table 1. Preparation Conditions of Polyamide Microcapsules

Component	a	b	Sample c	d
Organic Solution	90	90	90	90
Water	10	10	10	10
Antaron V-216	0.4	0.4	0.4	0.4
Hymexazol	1	1	1	1
DETA	0.72	0.72	—	—
TEPA	—	—	0.95	0.95
SBC	2.39	—	2.39	—
TPC	—	2.03	—	2.03
NaOH	0.8	0.8	0.8	0.8

Organic solution : chloroform/cyclohexane =
1/4 (부피비)

DETA : diethylenetriamine

TEPA : tetraethylenepentamine

SBC : sebacoyl chloride

TPC : terephthaloyl chloride

lower concentration. Most of microcapsules prepared at optimum condition, i. e. at stirring speed of 300 rpm and at dispersing agent concentration of 0.4 part, had a average diameter of ca. 300 μm. This size was too large to be sprayable, but it was the best result achieved at the moment. Practical encapsulated pesticides had better to be sprayable

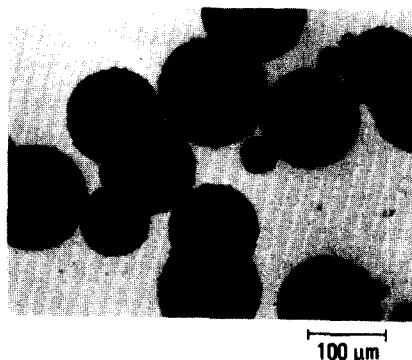


Fig. 3. An optical micrograph of polyamide microcapsules.

but most of commercially available ones are o/w microcapsules.^{22~24} We presume that the same difficulty prevails for other type of w/o microcapsules too. An optical microscope picture of microcapsules made at 300 rpm stirring speed is shown in Fig. 3.

Surface Coating and Release Behavior

In Fig. 4 is shown the release behaviors of uncoated microcapsules with various wall-forming materials. The recipe of microencapsulation is given in Table 1. Although they showed somewhat different release behavior, we thought that the difference in the total release amount observed for different wall-forming materials was not significant and the difference was mainly due to the loss during the filtration and washing steps as well as initial burst effect. For most of the release tests performed in this study, rather large initial burst effects were always observed. We suspected that this came from the drug accumulated in the pores and surface of the capsule wall during the filtration, washing, coating, and drying process.

Otherwise their release patterns were similar and all the drug was released in about two days. This results indicated that the polyamide capsule walls were porous and could not act as an effective barrier for controlled release and it was supported by the rough surface structure viewed by scanning electron microscope (SEM) as shown in Fig. 5(A). In the same figure, 5(B) is also shown the SEM

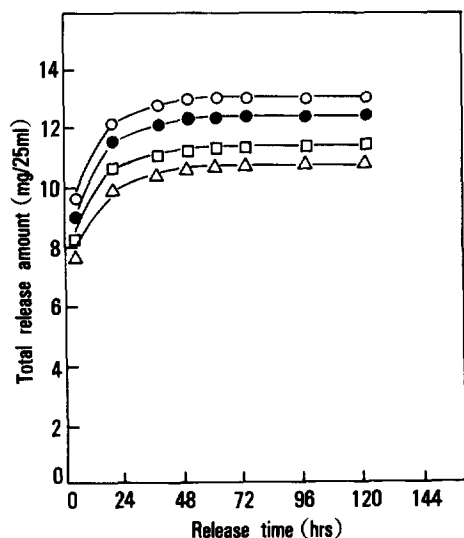


Fig. 4. Release behavior of Hymexazol from polyamide microcapsules with various wall materials : (Δ) diethylenetriamine-sebacoyl chloride base, (□) diethylenetriamine-terephthaloyl chloride base, (○) tetraethylenepentamine-sebacoyl chloride base, (●) tetraethylenepentamine-terephthaloyl chloride base.

picture of the microcapsule surface coated with stearic acid which is significantly different from the uncoated surface. The coating of microcapsules with lipid had been tried before for mostly the permeability control of wall membranes.²⁵⁻²⁷ The surface characteristics were further investigated by X-ray photoelectron spectroscopy (XPS, VG Scientific Co.) and the results are displayed in Fig. 6. Effective surface coating with fatty acids was confirmed from the observation that the nitrogen 1s electron was detected at the binding energy of ca. 400 eV for the uncoated capsules whereas the peak was no longer found from the coated ones. This also indicated that stearic acids not only filled the pores but coated entire microcapsule surface under our coating condition. We had not tried to determine the amount of coating material quantitatively, however, it was sufficient at the moment to note that the drug release behavior was modified significantly by surface coating as can be seen in Fig. 7. For this test, microcapsules were prepared

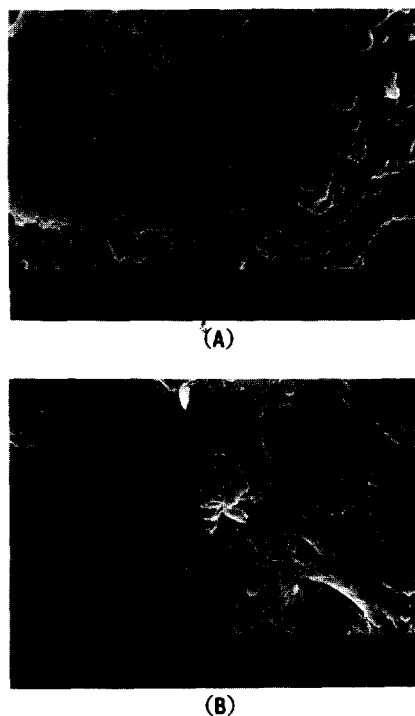


Fig. 5. Scanning electron micrograph of uncoated (A) and stearic acid coated (B) polyamide microcapsules prepared from diethylenetriamine and sebacoyl chloride.

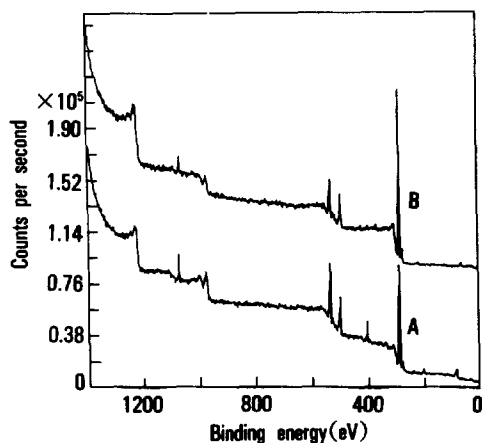


Fig. 6. XPS spectra for uncoated (A) and coated (B) polyamide microcapsules.

according to the recipe (a) in Table 1 and the stearic acid concentration was varied from 0 to 15

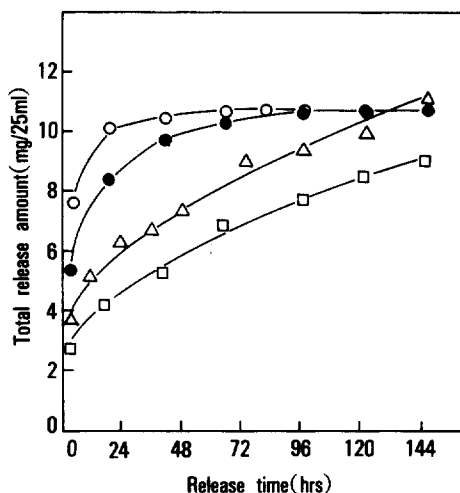


Fig. 7. Dependence of the release behavior of Hymexazol from stearic acid coated polyamide microcapsules on the amount of coating. The microcapsules are made of diethylenetriamine and sebacyl chloride : (○) 0%, (●) 5%, (△) 10%, (□) 15%.

% for the surface coating. It was evident that the release rate was controlled efficiently depending on the amount of surface coating and the controlled release period extended longer than 6 days with the coating in 10% solution. Again they showed the initial burst effect which also decreased as the amount of coating was increased.

In Fig. 8 is shown the effect of carbon chain length of fatty acids on the release behavior of hymexazol. Used microcapsules were the same as that of experiments shown in Fig. 7 except that four different fatty acids were employed at the coating concentration of 10%. Release pattern of coated microcapsules appeared more or less the same regardless the fatty acids used. It was difficult to conclude from this result that the permeability of the drug was independent of the carbon chain length of fatty acids because the quantitative amounts of coating were not available. Also we could not sure whether the microcapsules were uniformly coated with fatty acids so that we monitored the permeation of drug through fatty acid layer or there still existed pores through which drug

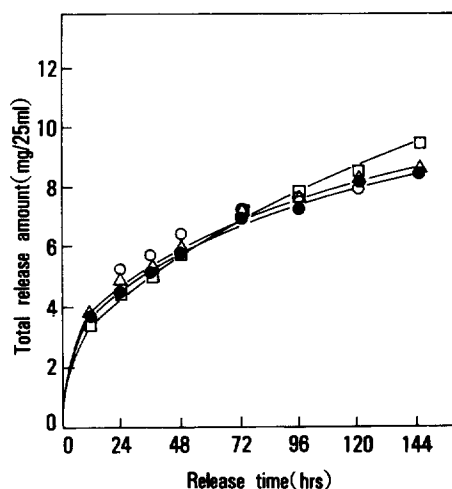


Fig. 8. Release behavior of Hymexazol from polyamide microcapsules coated with various fatty acids having different carbon chain lengths : (□) Stearic acid, (△) Palmitic acid, (●) Myristic acid, (○) Lauric acid.

was released. However it seemed to be clear that the nature of fatty acids did not have a significant effect on the permeability of the drug tested at our coating condition.

In conclusion, our results could be summarized as following.

1. Polyamide microcapsules of a few hundreds micrometer in diameter could be prepared by interfacial polymerization of multifunctional amines and diacid chlorides from the suspension of water droplets containing water-soluble drug in organic continuous phase with the aid of a polymeric suspending agent.
2. The size distribution, mechanical strength and agglomeration phenomena of microcapsules could be controlled by employing multifunctional amines and adjusting stirring speed and the amount of suspending agent.
3. Resulting capsules were found to be porous and the surface coating with fatty acids was effective in controlling the permeability of drugs through capsule wall.
4. It was found that carbon chain length of fatty

acids did not show a significant effect on the permeability of the drug tested at our coating condition.

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