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계면중합을 이용한 살충제의 마이크로캡슐화에 관한 연구 1. 유용성 약제가 들어있는 폴리우레탄 마이크로 캡슐의 제조

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Microencapsulation of Pesticides by Interfacial Polymerization 1. Polyurethane Microcapsules Containing Oil-Soluble Drug

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요 약 : 말단에 이소시아네이트기가 있는 프리폴리머와 에틸렌 글리콜을 물과 시클로헥산온의 계면에서 계면부가중합하여 살충제인 2,2′-디클로로에테닐디메틸포스페이트 (DDVP)가 내부에 들어있는 폴리우레탄 마이크로캡슐을 제조하였다. 얻어진 마이크로캡슐의 크기는 분산제의 농도와 교반속도가 증가함에 따라 작아졌다. 그러나 입도분포는 프리폴리머의 화학적 조성이나 유기층의 농도변화에는 거의 영향을 받지 않았다. 따라서 마이크로캡슐의 막두께는 유기층내의 프리폴리머의 농도를 변화시킴으로써 효과적으로 조절이 가능하였다. 제조한 마이크로캡슐로부터 DDVP의 방출속도는 전형적인 영차 방출거동을 따랐으며 막두께가 증가할 수록 감소되는 경향을 나타내었다. 그러나 막의 조성물질의 화학구조는 방출속도에 뚜렷한 영향을 미치지 않았다. 따라서 약제의 방출은 고분자 매트릭스를 통한 확산에 의한 것이라기 보다는 폴리우레탄 마이크로캡슐막의 다공성 구조를 통한 것으로 생각된다.

Abstract : Polyurethane microcapsules containing pesticide, 2,2′-dichloroethenyldimethylphosphate (DDVP), were prepared by the interfacial addition polymerization of isocyanate-terminated prepolymer with ethylene glycol in the interface between water and cyclohexanone. The sizes of the obtained microcapsules were decreased as the concentration of suspending agent and agitation speed increased. But the size distribution was not sensitive with the variations of chemical compositions of prepolymer and concentration in oil phase. Therefore, the wall thickness of microcapsule could be effectively controlled by the amount of prepolymer in oil phase. The release rate of DDVP from the prepared microcapsules showed a typical zero-order release behavior and was decreased as the wall thickness increased. However, no significant variation in release rate was noticed as the chemical structure of wall material changed. Thus it is believed that the major path of drug fumigation is due to the porous structure of polyurethane microcapsule wall rather than the diffusion through polymer matrix.

INTRODUCTION

In a controlled release system, bioactive materials such as pharmaceuticals and pesticides are incorporated into a carrier so that these materials can be delivered in a more effective, longer, and safer manner.[1~6] Through controlled release, existing agent with established activity prove more efficacious, and newer agents whose toxicity or low stabilities have limited use may prove more suitable.

Among the numerous methods devised for the purpose, microcapsule is one of the most useful devices which find immense applications in the various fields.[1,2] Although carbonless copypaper is one of the largest application field of microcapsules, its applications for pharmaceuticals, food ingredients and pesticides are increasing rapidly.[1~8]

Microcapsules are minute containers enclosing active materials with wall materials. The wall is often made of thin synthetic or natural polymeric membranes which can control the release of the core material. The release rate of the core materials from the microcapsules can be controlled by the chemical structure of the capsule wall, its thickness and the particle size of the microcapsule.[7,11]

Microencapsulation processes can be largely divided into three categories, physical coating, phase separation, and interfacial reaction.[1,2,5] In the interfacial reaction methods, microcapsules are formed by emulsifying or dispersing the core material in an immiscible continuous phase and then by interfacial polymerization reaction in the interface between phases forming wall membrane.

Some microencapsulated pesticides are already on the market such as Pencap M (methylparathion), Knox Out 2 FM (diazinon), and Sectrol TM (pyethrin) etc.[1,2] Characteristics of these encapsulated formulations are decrease of mammalian toxicity and longer residual activity.

Recently Fuyama et. al.[7] showed that polyurethane microcapsule exhibited a good mechanical strength and controlled release behavior when it was used as a substitution of a wettable powder formulation for Sumithion. In this paper, we present a microencapsulation study based on interfacial addition polymerization of diisocyanate and polyol monomers to give a polyurethane microcapsules. We are interested in the efficacy of polyurethane wall in controlling delivery through fumigation process. Also the influence of the various experimental conditions on the final properties of microcapsule is discussed.

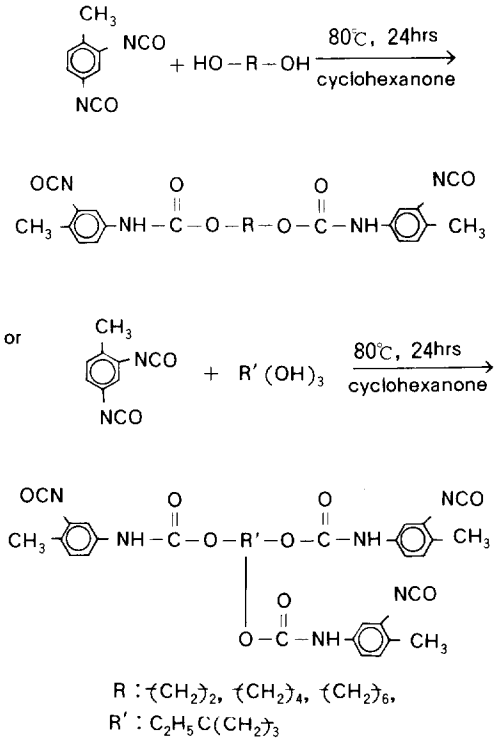
EXPERIMENTAL

Materials and Methods.

Microencapsulation : In this study we used 2,2'-dichloroethenyldimethylphosphate(DDVP) as the material for controlled release. In order to control the release rate of the pesticide, we varied the wall materials systematically by preparing isocyanate terminated prepolymers of tolylene-2, 4-diisocyanate(TDI) and various polyols such as ethylene glycol, 1, 4-butanediol, 1, 6-hexanediol, trimethylol propane. Then ethylene glycol was used as the chain extender for interfacial polymerization. The prepolymers were prepared by the reaction between 1 equivalent of a diol and 2.2 equivalents of TDI so that the prepolymer have isocynate functional groups at both ends. Since the reactivity of second isocyanate group drops markedly after the first isocyanate group reacted, 10% stoichiometric excess was found to be enough to yield a quantitative results. First, the appropriate amounts of TDI were mixed in cyclohexanone so that the final adduct concentration was to be 15%. Then a polyol was slowly added with stirring at 80℃ and the reaction was allowed to proceed to completion for overnight. Excess TDI and cyclohexanone were distilled out under reduced pressure.

The syntheses of prepolymers are shown in Eq. 1. The triol also acts as a crosslinking agent and 3.3 equivalents of TDI was used for completely isocyanate terminated 1 equivalent of triol prepolymer. All the chemicals used were reagent

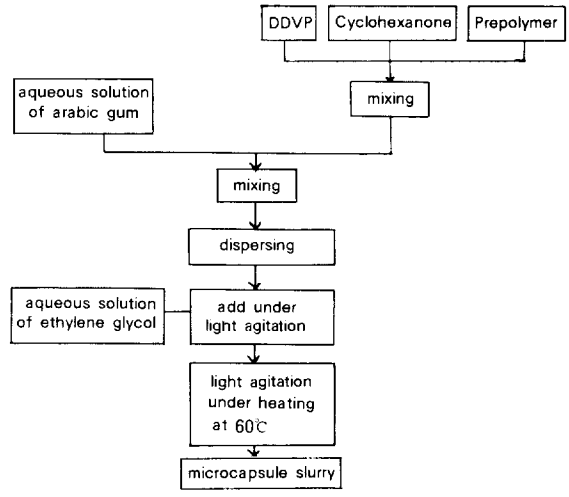
grades and used without further purification.



Eq. 1. Preparation of Prepolymers.

Polyurethane microcapsules were made by interfacial polymerization of a TDI/polyol-based prepolymers in oil phase and ethylene glycol in aqueous phase at the water/cyclohexanone interface using arabic gum as the suspending agent. The microencapsulation procedure are schematically shown in Eq. 2. and Scheme 1.

The oil phase, cyclohexanone containing DDVP and TDI/polyol-based prepolymer, was suspended by agitation in the aqueous solution of arabic gum at room temperature. After complete dispersion of oil phase was obtained, the reaction flask was immersed into a water bath at 60℃ and aqueous solution of ethylene glycol was added slowly under continuous agitation. After 2 hours of reaction, the microencapsulation was completed and the sedimented microcapsule slurry was collected by decanting the supernatent and washing several times with water.



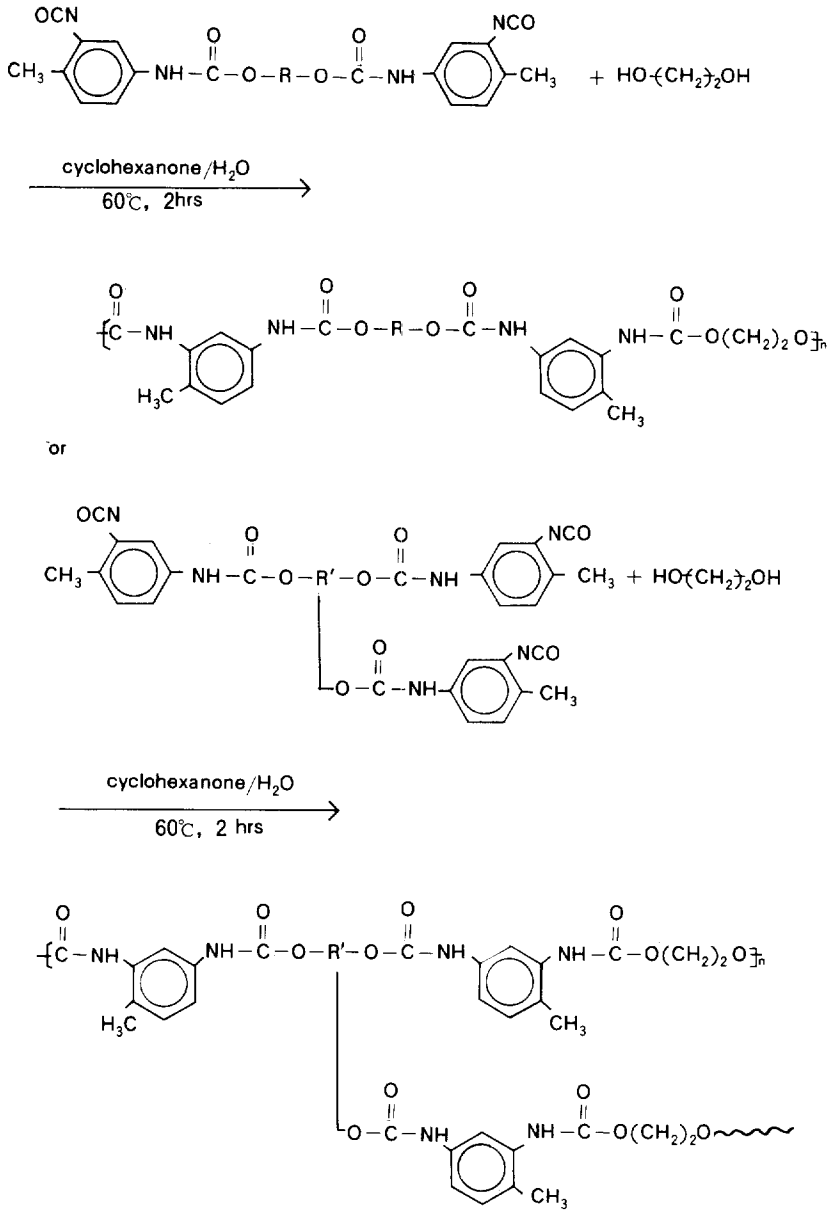
Scheme 1. Procedure for the preparation of DDVP/PU microcapsules.

We also have varied the following factors in the microencapsulation process[9~12,16] which may affect the release rate of DDVP. Those factors included variation of crosslinking density, capsule wall thickness, capsule size, and concentration of drug. The variation of crosslinking density was carried out by employing TDI/triol-based prepolymers as described in Eq. 1 and Eq. 2.

And the variation of the capsule wall thickness was investigated by changing the prepolymer concentration in organic phase. We also examined the effects of dispersing agent concentration and agitation speed upon the capsule sizes.

The particle size and the distribution of microcapsules were determined by the optical microscope. For the statistical treatments, more than three pictures taken at different places were used and the sizes of more than 100 microcapsules were measured.

Wall thickness of the microcapsule was varied by changing the relative amount of TDI/polyol-based prepolymer in the organic phase and the wall thickness was estimated from the average particle size and the amount of polymer formed.



R : $-(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_6-$,

R' : $C_2H_5C(CH_2)_3$

Eq. 2. Synthesis of Polyurethane by Interfacial Polymerization.

Release Test of DDVP

The release rate of DDVP from microcapsules was measured by use of the apparatus as shown in Fig. 1. In the lower part of the apparatus 3 grams of microcapsules were loaded and 5 grams of absorbent, Amberlite XAD-4, were filled at the upper part. Then nitrogen gas was allowed to flow through the apparatus.

The N_2 gas flow was controlled at 20 ml/min by use of a metering valve and the flow rate was monitored by a flow meter. After a given period of release experiment, the absorbent was replaced with a fresh batch and the absorbed DDVP was extracted from the collected batch of the absorbent by ethyl acetate. The extract was concentrated to 2 ml by evaporation of excess ethyl acetate under reduced pressure and the amount of released DDVP was measured by a gas chromatography equipped with thermionic selective detector.

RESULTS AND DISCUSSION

Characterization of Polyurethane Microcapsule

As mentioned, DDVP was used as the pesticide in this research. DDVP is an insecticide commonly used for household pest control. Also it is a liquid at room temperature with a suitable solubility for interfacial polymerization and a reasonable vapor pressure for controlled fumigation formulation. The general properties of DDVP are summarized in Table 1.

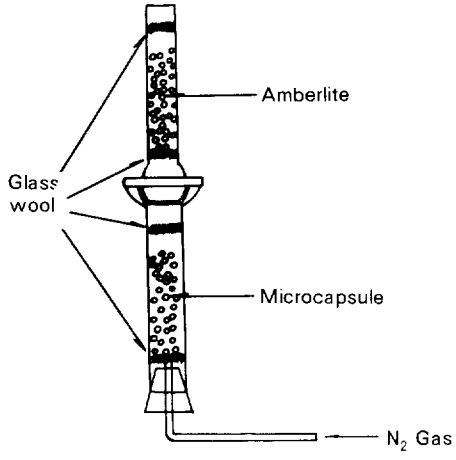


Fig. 1. Diffusion apparatus for DDVP.

The characterization of the polyurethane microcapsule wall materials was carried out by infrared spectroscopy and gel permeation chromatography. The complete disappearance of characteristic absorption band of $-NCO$ at 2270 cm^{-1} and appearance of absorption bands of NH and C=O stretchings at 3300 cm^{-1} and 1700 cm^{-1}, respectively, indicated almost the complete reaction between TDI and polyols. Also the GPC analysis showed a fairly high molecular weight, Mw being about 40,000 (calibrated for polystyrene standards). Fig. 2 shows a scanning electron microscope picture of the typical microcapsules which had such a good mechanical strength that it could be treated as hard particles without any special care. The appearance of the microcapsules was practically the same except the size distribution regardless of the variation of the experimental factors mentioned previously.

The Size distribution of Microcapsules

The particle size distribution of the microcapsules were not much affected with the variations of prepolymers as shown in Fig. 3. For this experiments, the oil phase (2 g of DDVP and 2 g of

Table 1. The properties of DDVP

Structural Formula	$Cl_2C=CHOP(OCH_3)_2$
Appearance	A colourless to amber liquid, with an aromatic odour.
Uses	A contact and stomach-acting insecticide with fumigant and penetrant action. Especially effective against diptera and mosquitoes.
BP	35℃/0.05 mmHg
P_v	1.6 Pa (20℃)
Density	1.415
Solubility	10 g/L H_2O, 2~3 g/kg Kerosene Miscible with organic solvents
Toxicology (LD_{50})	66~108 mg/kg (rat)

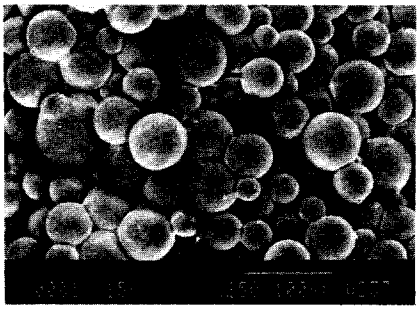


Fig. 2. Scanning electron micrograph of prepared polyurethane microcapsules(ethyleneglycol-TDI base).

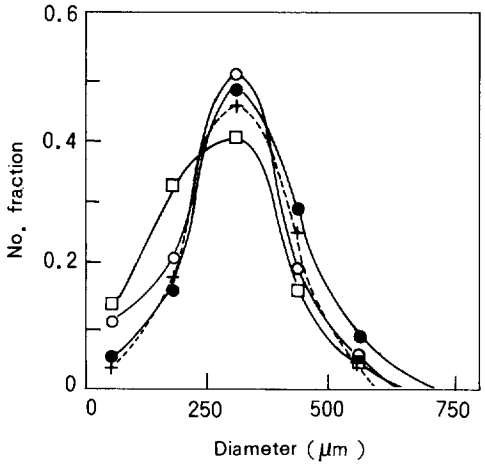


Fig. 3. Effect of prepolymer compoition upon particle size distribution of PU microcapsules : (○) ethyleneglycol-TDI base, (●) 1, 4-butanediol-TDI base, (+) 1, 6-hexanediol-TDI base, (□) trimethylolpropane-TDI base.

polyol/TDI prepolymers in 6 g of cyclohexanone) was suspended in 90 g of water containing 1.5 g of arabic gum first, then 2 g of ethylene glycol mixed with 10 g of water was added for interfacial polymerization. It appeared that the trimethylolpropane/TDI-based microcapsule had slightly more population of smaller sized microcapsule. However, their amount was not significant in terms of their volume which should be a direct measure of the pesticide contents.

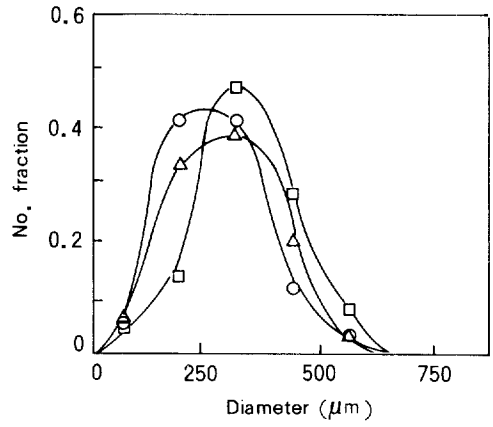


Fig. 4. Variation of particle size distribution of PU microcapsules with organic phase composition (1, 4-butanediol-TDI base), prepolymer/organic phase : (○) 1/10, (□) 2/10, (△) 4/10.

Also we found the size distribution was not sensitive with the variation of the prepolymer solid content. Namely, the particle size distribution of the microcapsules were not much affected with the variation of organic phase compostion as shown in Fig. 4. This behavior allowed us to vary the wall thickness of the microcapsule easily since the volume of the wall material would be proportional to the prepolymer solid content and the average wall thickness could be estimated from the volume of the polymeric material and the average size of the microcapsules.

On the other hand, the particle size was strongly affected by the concentration of suspending agents. In Fig. 5 are shown the size distributions of butanediol/TDI-based microcapsules at three different concentration of the suspending agent. All the experimental conditions are the same as before except that the amount of arabic gum was varied as indicated. In order to eliminate the effect of stirring speed, we fixed the agitation speed of a mechanical stirrer (300 rpm). It is clear that the distribution becomes broader as the concentration of suspending agent decreases as shown in Fig. 5. In addition, the particle size was remarkable affected by the agitation speed. Namely, the particle

size diminished with the agitation speed increased as shown in Fig. 6. Accordingly, the particle size distributions of PU microcapsules were controlled by the amount of the suspending agent as well as the agitation speed.

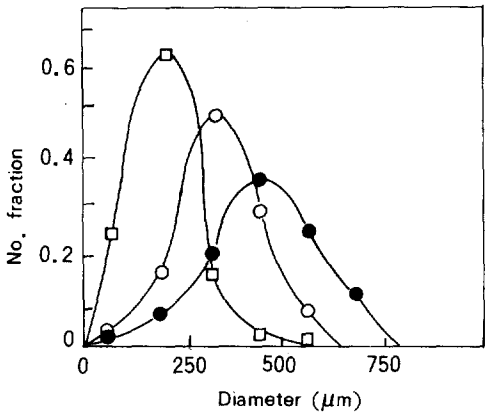


Fig. 5. Effect of dispersing agent upon particle size of DDVP/PU microcapsules (1, 4-butanediol-TDI base), arabic gum/organic phase : (●) 0.5/10, (○) 1/10, (□) 1.5/10.

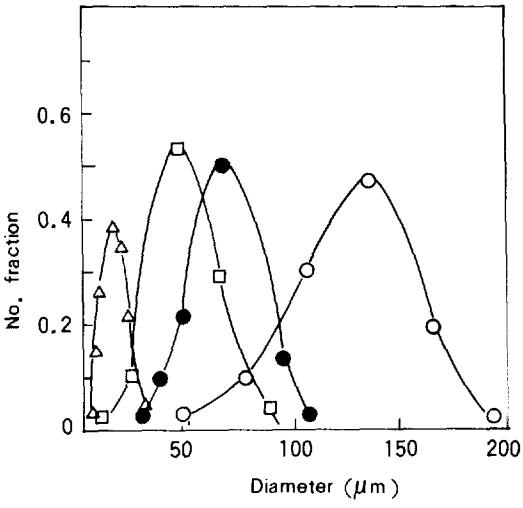


Fig. 6. Effect of agitation speed upon particle size of DDVP/PU microcapsules (ethyleneglycol-TDI base), agitation speed (RPM) : (○) 200, (●) 300, (□) 400, (△) 500.

Release Test of DDVP

Influence of Wall Materials : Fig. 7 shows the release rate of DDVP over a few days from the microcapsules having different wall materials. For this study the ethylene glycol, 1, 4-butanediol, 1, 6-hexanediol, and trimethylol propane were used to make polyol/TDI-based prepolymers for oil phase reactants. First of all, we could noticed that the release rates could be well represented with zero-order release pattern[11,13~16] which is one of the characteristics of the reservoir system up to 4 days. Although, there existed a small difference in release rate depending on prepolymers used as represented in Fig. 7. But it scarecely exceeded experimental uncertainty. Therefore we might regard this as independence of release rate upon the nature of wall materials. It seems that the fumigation of DDVP does not take place by diffusion through homogeneous polymeric walls, but mainly by diffusion through porous structure of wall materials. The porous structure of microcapsule wall was taken by electron microscope support this view as shown in Fig. 8.

Influence of Capsule Wall Thickness : We also investigated the effect of wall thickness on the re-

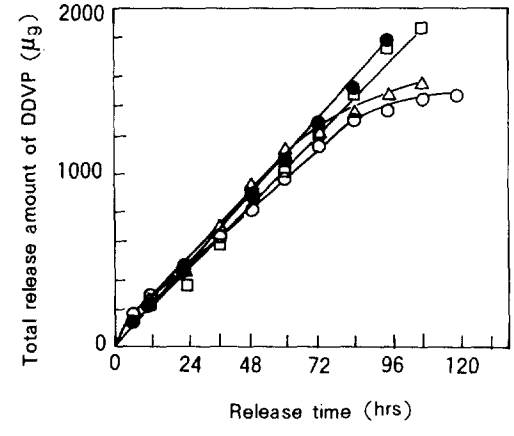


Fig. 7. Dependence of release behavior of DDVP from PU microcapsules upon prepolymer composition (Capsule amount : 3 g) : (○) ethyleneglycol-TDI base, (●) 1, 4-butanediol-TDI base, (△) 1, 6-hexanediol-TDI base, (□) trimethylolpropane-TDI base.

Fig. 8. Scanning electron micrograph of prepared PU microcapsule surface (ethyleneglycol-TDI base).

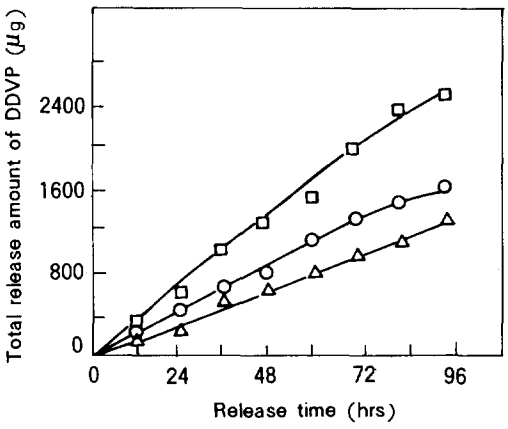


Fig. 9. Influence of wall thickness upon release behavior of DDVP from PU microcapsules (capsule amount : 3 g), prepolymer/organic phase : (□) 1/10, (○) 2/10, (△) 3/10, prepolymer : ethyleneglycol-TDI base.

lease rate of DDVP as shown on Fig. 9. As mentioned, the variation of prepolymer solid content did not affect on the particle size of the microcapsule. Rather it is believed that the prepolymer concentration influences upon the wall thickness. Actually, the effect of prepolymer concentration in organic phase upon capsule wall thickness should be measured directly from the cross-section by using electron microscope. However, it was very difficult to cut the microcapsule by using microtome due to the somewhat elastic property of polyurethane. So, in this figure, we used the relative amount of polyol/TDI-based prepolymer instead of the wall thickness. It was clear from the figure that the release rate became smaller as the wall thickness increased.

CONCLUSION

In summary, we can conclude our study as follows.

1. Polyurethane microcapsules are easily prepared by the interfacial polymerization of diisocyanate and polyols at the interface between water and cyclohexanone.

2. The size of the microcapsule can be controlled by the concentration of the suspending agent (arabic gum in this study) as well as agitation speed. Also it is found that the concentration of either monomer or drug does not affect the size of the microcapsules. Therefore we can effectively control the wall thickness of the microcapsules by simply changing the prepolymer solid content of the reaction mixture.

3. The release rate of the encapsulated drug is not influenced on the chemical structure of wall materials but clearly depends on wall thickness of the microcapsules. We believe this phenomena is due to the porous structure of the polyurethane wall and the major path of the drug fumigation is the diffusion through the pores rather than polymer matrix.

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