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Preparation of Aqueous Suspension of Porous Polyurethane Microspheres by Suspension Polycondensation

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In this paper, polyurethane (PU) microspheres are prepared via suspension polycondensation technique and through the reaction of methylene diphenyl diisocyanate (MDI) and polyethylene glycol (PEG400) in a high speed homogenizer. A chain extending agent, namely, 1,4-butanediol, was used to increase the ratio of hard to soft segments of the PU chains. The effects of type and concentration of suspending agent and homogenizer speed on particle size are also investigated. Results indicate that the type of suspending agent has little effect on particle size; however, particle size substantially decreased when mixing rate or concentration of suspending agent was increased. The structure of microspheres was porous due to the formation of carbon dioxide by the reaction of MDI with water. Nevertheless, the porosity was significantly affected by the concentration of chain extending agent. The release behavior of microspheres is investigated with diazinon as the active agent. After an initial burst, corresponding to 3% of the amount of active agent, the release rate was of zero order.

INTRODUCTION

Polymeric microspheres have found widespread applications in biomedical, biochemical, pharmaceutical and agricultural fields [1-4]. One of the most novel applications of these microspheres is in controlled and targeted delivery of biologically active agents [5-7]. Polymeric microspheres can be prepared by a variety of methods [8]. These methods include emulsion [9], suspension [10], semi-suspension [11], precipitation [12], dispersion [13], interfacial polymerization [14-17] and suspension polycondensation [18,19]. Among these methods, interfacial polymerization is used extensively in industry for preparation of microcapsules [20-25]. In this method, the monomer in the oil phase polymerizes through condensation reaction while the other monomer in the aqueous phase forms a polymeric membrane around the active agent at the interface between the two phases. Membrane devices are characterized by zero order release rate, however, a major disadvantage of these devices is dose dumping due to a rupture of the capsule shell or membrane [26,27]. On the other hand, although in matrix devices the release rate decreases with time, because the active agent is distributed homogeneously throughout the matrix, the problem of dose dumping is reduced to a minimum [28,29]. As a result, matrix devices are the preferred choice, especially for delivery of biologically active agents where dose dumping can be fatal or can damage the environment.

In preparation of microspheres through the method of suspension polycondensation, two monomers in the suspended oil particles, containing the active agent, polymerize by condensation reaction to form a polymeric matrix in which the active agent is dissolved or distributed homogeneously throughout the matrix [6]. In most applications, an isocyanate monomer reacts with a diol in the suspended oil phase to form a polyurethane microsphere with the active agent distributed in the matrix. Polyurethanes, due to their excellent biocompatibility and a wide range of mechanical properties, are used extensively in medicine [30]. Therefore, preparation of polyurethane microspheres with controlled microstructure and morphology is particularly important in designing delivery systems for biologically active agents.

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In the last few decades, significant progress has been made in the synthesis and characterization of microcapsules prepared by condensation polymerization for controlled release applications [31-34]. In comparison, most of the work on preparation and characterization of polyurethane microspheres for controlled release applications is in patented form. More specifically, the morphology and microstructure of these microspheres have not been well characterized [35]. Shanta and Panduranga Rao [36] have recently prepared polyurethane microspheres using suspension polycondensation technique with tolylene 2,4-diisocyanate (TDI) or methylene diphenyl diisocyanate (MDI) and polyethylene glycol (PEG). According to their results, the chemical nature of the monomers has a significant effect on morphology and release behavior of the microspheres. When TDI was used as the reactant, the resulting microspheres were non-porous and release of the active agent was relatively slow. On the other hand, when MDI was used, the resulting microspheres had a porous morphology and release of the active agent was relatively fast.

The objective of this work was to prepare porous polyurethane microspheres in an aqueous media using the method of suspension polycondensation with MDI as the isocyanate monomer, PEG400 as the diol and 1,4-butanediol as the chain extending agent. Furthermore, the effect of chain extending agent on morphology of these microspheres was investigated.

EXPERIMENTAL

Materials

4,4'-methylene bisphenyl isocyanate (MDI) with functionality of 2.2 and equivalent weight of 113.6, polyethylene glycol 400 (PEG400) as a difunctional alcohol with hydroxyl number of 280.5 and equivalent weight of 200, and 1,4-butanediol (BD), a difunctional alcohol, as a chain extending agent with hydroxyl number of 1245 and equivalent weight of 45.06 were obtained from Merck Chemical Co., Germany. The composition of isocyanate used was 60%w/w difunctional MDI, 30% w/w trifunctional isocyanates, and 10% w/w other difunctional isocyanates. The purity of 1,4-butanediol used was higher than 98% on a weight basis, as reported by the supplier. Polyvinyl pyrrolidone, as a stabilizer, in three different grades of PVPK15, PVPK25 and PVPK30 with M_v of 10000, 24000 and 38000 g/mol, respectively and Polyvinyl alcohol, also as a stabilizer, in two grades of PVA80 and PVA88 with M_v of 9500 and 18000 g/mol and degree of hydrolysis of 80% and 88%, respectively, were obtained from Aldrich Chemical Co. Ultra low viscosity sodium carboxy methyl cellulose (NaCMC), as a stabilizer, was also obtained from Aldrich Chemical Co. Technical grade diazinon, o,o-diethyl-o- (2-isopropyl -6-methyl -4-pyromedinyl) phosphoro thioate was purchased from Ciba-Geigy Co. and used as an active agent to study the release behavior of the microspheres. All chemicals were used as received without further purification.

Preparation of PU Microspheres

PU aqueous suspension was prepared in four steps which consisted of preparation of the aqueous phase, preparation of the prepolymer, homogenization and polycondensation. A typical procedure for preparing PU microspheres was as follows. To prepare the aqueous phase, in a beaker containing 148.5 g of distilled water, 1.5 g of PVPK25 was added to get a 1.0% solution. The solution was mixed for at least one hour with a magnetic stirrer while the temperature was kept constant at 40°C to allow complete dissolution of PVP.

To prepare the prepolymer, 9.6 g MDI (3.84×10^{-2} mol) was mixed in a beaker with 8.45 g PEG400 (2.11×10^{-2} mol) and 1.90 g BD (2.12×10^{-2} mol) in a stoichiometric ratio to give a dispersed oil phase containing 48%, 42% and 10% w/w MDI, PEG400 and BD, respectively. For release studies, 1.8 g diazinon, as the active agent, was added to the prepolymer mixture to get a 10% w/w concentration of diazinon in the dispersed phase. The mixture was allowed to react partially for approximately 3 min at ambient conditions in order to convert most of the PEG400 and BD to isocyanate-polyol dimers and trimers. This corresponded to approximately 50% conversion of the isocyanate groups. PEG400 and BD are relatively soluble in water, therefore, if the oil phase were dispersed in the aqueous phase before prepolymer formation, then a significant fraction of PEG400 and BD would diffuse to the aqueous phase and polycondensation reaction would not reach completion. On the other hand, if partial condensation reaction were proceeded to much higher than 50% conversion, the viscosity of the prepolymer would become excessively high and homogenization and particle formation would become difficult.

In the next step, the prepolymer was added dropwise to the aqueous phase in a reaction vessel equipped with a homogenizer (DIAX 600, Heidolph). Maximum permissible rotor speed was 25000 rpm and the maximum volume of solution that could be homogenized was 100 ml. The use of homogenizer to prepare microspheres is a new technique. (Maa and Hsu have recently investigated the effect of homogenization speed and time on particle size distribution [37].) The homogenization continued for 45 min while the reaction proceeded. The solid content of the suspen-

sion was approximately 11% w/w. After completion of polycondensation reaction, the microspheres were filtered, washed twice with distilled water to remove the suspending agent and allowed to dry for at least 24 hrs at ambient conditions.

Microsphere Characterization

The extent of polycondensation reaction was determined by Fourier transform infrared spectroscopy (FTIR) in the Attenuated Total Reflection (ATR) mode. The microspheres, in a dry powder form, were sprinkled on an ATR crystal and spectra was recorded using a Bruker IFS88 spectrometer. A strong absorption band with peak location at 2272 cm^{-1}, due to N=C=O stretching vibration, was used to monitor the disappearance of isocyanate groups of MDI. The absorption band between 1000 and 1300 cm^{-1}, due to C-O-C stretching vibration, was used to monitor PEG400. A strong absorption band with peak location at 3400 cm^{-1} (due to stretching vibration of N-H groups) and another absorption band between 1650 and 1700 cm^{-1} (due to stretching vibration of C=O groups), were used to monitor the appearance of urethane group during polycondensation reaction.

The average diameter of microspheres was determined with an optical microscope (Euromex). A drop of the suspension was placed on a microscope glass slide, diluted with distilled water and examined at a magnification of 1650. Samples of the microspheres were selected at random from different locations on the glass slide and the diameter of 100 particles was measured. The sampling procedure was repeated three times and the average value was reported as the diameter of microspheres. To determine the breadth of the particle size distribution for each sample, the polydispersity index, PDI, of each distribution was calculated using the following equation:

$$PDI = \sigma / < D_n >= (< D_w > / < D_n > -1.0)^{1/2}. \quad (1)$$

In the above equation, $< D_n >$ and $< D_w >$ are the number (mean) and weight averaged particle diameter and σ is the standard deviation of the distribution. Based on Equation 1, the PDI of different distributions in Figures 1, 2 and 3 were determined. It should be mentioned that all of the samples had mono-modal particle size distributions.

The structure and morphology of polyurethane microspheres were studied with a Scanning Electron Microscope (SEM). A drop of the suspension was placed on a double stick tape which was affixed to an SEM mount. After drying, the sample was sputter coated with gold and examined with Leica Cambridge S360 SEM at an accelerating voltage of 10 KeV.

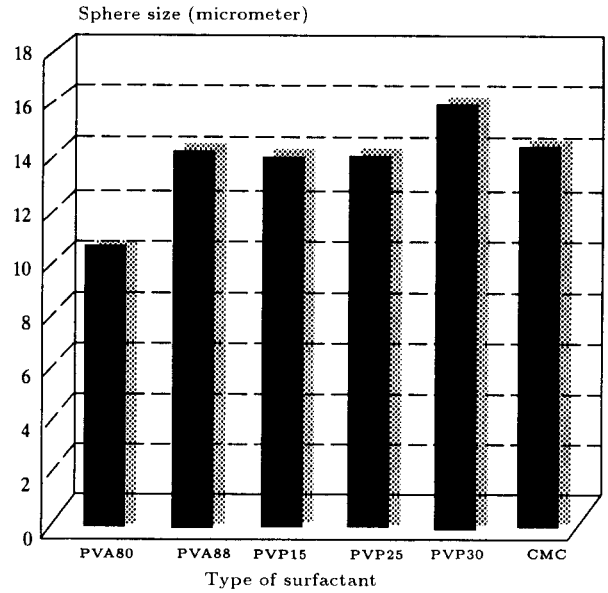

Figure 1. The effect of stabilizer type on microsphere size at constant homogenization speed of 13500 rpm. NaCMC is ultra low viscosity sodium carboxy methyl cellulose.

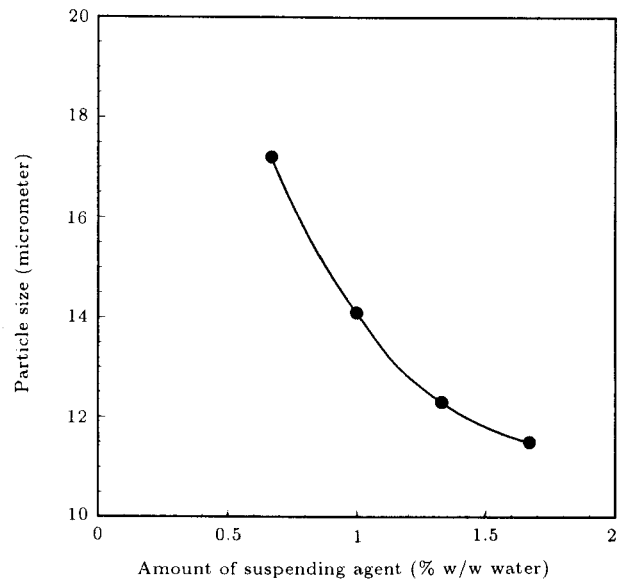

Figure 2. The effect of stabilizer concentration on microsphere size at constant homogenization speed of 13500 rpm.

Release Measurements

The release behavior of the microspheres was studied with ultraviolet (UV) spectroscopy using diazinon, an agricultural pesticide, as the active agent. The peak absorption of diazinon in the UV region, obtained through scanning, was at 246 nm. For calibration, solutions of diazinon in distilled water with concentrations ranging from 2 to 40 ppm were prepared and their absorption was measured at 246 nm with a Milton Roy Spectronic 601 spectrophotometer. The calibration line

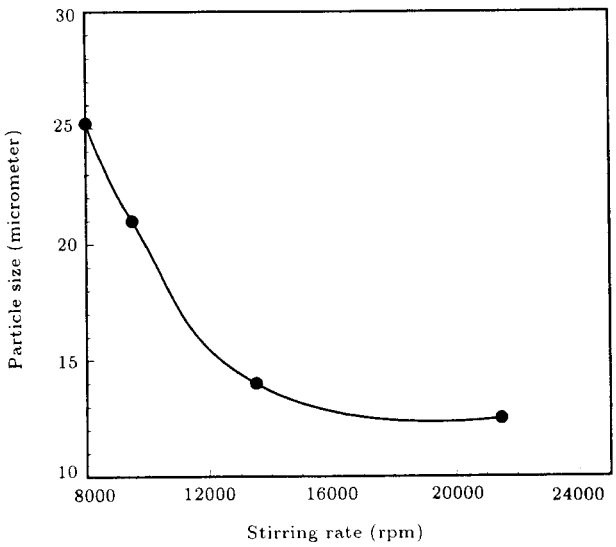

Figure 3. The effect of homogenization speed on particle size at constant stabilizer concentration of 1.0% w/w.

was linear with a slope of 44.07 ppm/a.u. For release studies, 1.0 g of dried PU powder containing 10% w/w diazinon was dispersed in 1500 ml of distilled water. The suspension was stirred gently while temperature was kept constant at 25°C. Samples were taken from the suspension with time, centrifuged for 10 min at 5000 rpm to separate the microspheres and their absorption was measured.

RESULTS AND DISCUSSION

Polycondensation Reactions

The oil phase suspended in the continuous aqueous phase contained MDI, PEG400, BD and the active agent, diazinon. Water could also diffuse into the oil phase and participate in the polycondensation reaction. The following reactions could occur in the oil phase [38-40]:

$$O{=}\,C{=}N\text{-}R\text{-}N{=}C{=}O + HO\text{-}R' - OH \longrightarrow$$

$$- [-C(O)N(H)\text{-}R\text{-}N(H)C(O)O\text{-}R' - O-]_n - \quad (2)$$

$$- RN{=}\,C{=}O + HOH \longrightarrow$$

$$- [RN(H)COOH] \longrightarrow -RNH_2 + CO_2 \quad (3)$$

$$- RNH_2 + -R'N{=}C{=}O \longrightarrow$$

$$- RN(H)C(O)N(H)R' - \quad (4)$$

$$- RN{=}C{=}O + R'N(H)C(O)OR'' \longrightarrow$$

$$- RN(H)C(O)N(R')C(O)OR'' \quad (5)$$

$$- RN{=}\,C{=}O + R'N(H)C(O)N(H)R'' \longrightarrow$$

$$- RN(H)C(O)N(R')C(O)N(H)R'' \quad (6)$$

In the first reaction, isocyanate groups react with hydroxyl groups of PEG400 or BD to form urethane linkages and polyurethane chains. In the second reaction, isocyanate groups react with water that diffused from the aqueous phase to form an amino acid group which is unstable and dissociates into a chain with amine end-group and carbon dioxide. The extent of carbon dioxide formation by this reaction contributes significantly to the porosity of microspheres. In the third reaction, a chain with amine end-group reacts with a chain with isocyanate end-group to form urea linkages (NHCONH). In reaction 5, a chain with isocyanate end-group reacts with a NH group of the urethane linkage to form an allophanate. In reaction 6, a chain with isocyanate end-group reacts with a NH group of the urea linkage to form a biuret. Reactions 5 and 6 cause interconnection and crosslinking of PU chains. The functionality of MDI, which was 2.2, also contributed to the extent of crosslinking and network formation.

The extent of polycondensation reaction between MDI and polyol was monitored by ATR-FTIR. The FTIR spectrum of PU microspheres is shown in Figure 4. A strong absorption band with peak location at 2272 cm^{-1}, due to NCO stretching vibration of isocyanate group of MDI, was absent in the spectra of PU microspheres. The absorption band between 1000 to 1300 cm^{-1}, due to stretching vibration of ether group of PEG400, was present in the spectra of PU microspheres. A strong absorption band with peak location at 3400 cm^{-1}, due to stretching vibration of NH groups and the absorption band between 1650 and 1700 cm^{-1}, due to stretching vibration of CO groups, were absent in the MDI and PEG400 spectra but present in the spectrum of PU microspheres, as shown in Figure 4. The absence of absorption due to isocyanate groups and the presence of urethane groups absorption band in the spectrum of PU microspheres clearly indicated that the reaction reached completion after 45 min.

Effect of Suspending Agent

Different classes of stabilizers including non-ionic PVP and PVA and ionic NaCMC were used in this study. Three different grades, PVPK15, PVPK25 and PVPK30 of PVP with M_v of 10000, 24000 and 38000 g/mol, respectively, were used to study the effect of stabilizer size on particle size and suspension stability. Two different grades, PVA80 and PVA88 of PVA, were used to study the effect of degree of hydrolysis on suspension stability. The effect of stabilizer type on

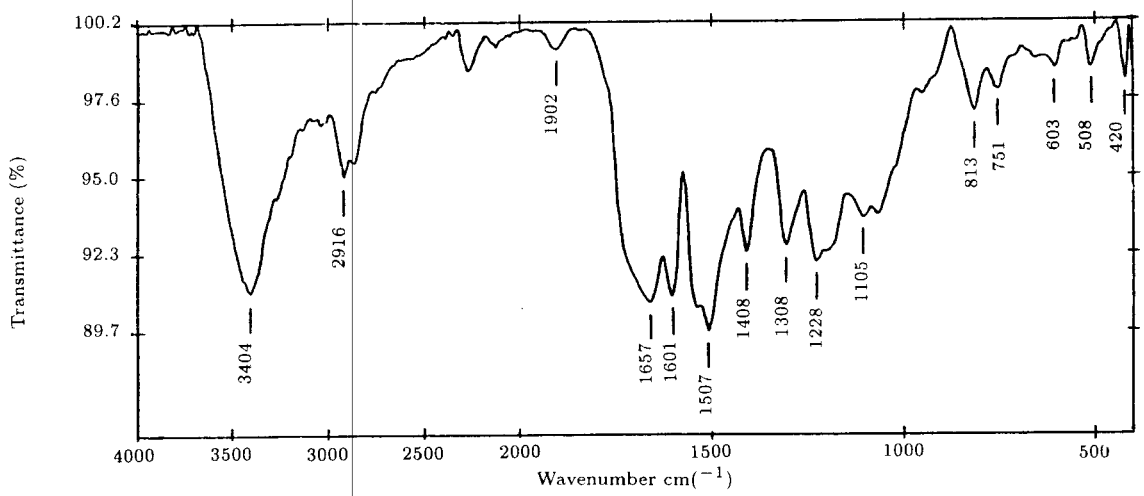

Figure 4. ATR-FTIR absorption spectrum of the PU powder prepared by suspension polycondensation of MDI and PEG400 with 1,4-butanediol as the chain extending agent.

particle size at constant rotor speed of 13500 rpm and 1% w/w stabilizer concentration based on the aqueous phase is shown in Figure 1. As the PVP molecular weight was changed from 10000 to 24000 to 38000 g/mol, the average particle size changed from 14.3 to 14.1 to 15.8 μm and the *PDI* changed from 0.46 to 0.46 to 0.45, respectively. As the degree of hydrolysis of PVA was changed from 80% to 88%, the particle size changed from 11 to 14.5 μm and the *PDI* changed from 0.8 to 0.5, respectively. For the ionic NaCMC, the particle size was 15 μm and the *PDI* was 0.49. As the stabilizer type was changed, no trend in the variation of particle size was observed. However, the *PDI*s of PVP type stabilizers were lower than PVA and NaCMC type stabilizers. Therefore, PVP type stabilizers provided the sharpest particle size distribution. Ross and Morrison [41] also studied the effect of stabilizer type on particle size and observed no significant effect when agitation rate was above 10000 rpm. However, long-term stability of the suspension was affected by stabilizer type. The stability of suspensions prepared with PVP and NaCMC was higher than PVA. The low stability of PVA based suspensions was due to the reaction of hydroxyl groups of PVA with the isocyanate groups of MDI with subsequent reduction of stabilizer concentration. This effect was also observed by Almog and Levy [42] for suspensions stabilized with PVA. Due to the lower degree of hydrolysis, PVA80 based suspension had higher long-term stability compared to PVA88.

In general, the molecular weight of the suspending agent affects the rate of absorption and desorption of the suspending agent from the surface of the particles. As the molecular weight increases, the rate of particle formation and short-term stability of emulsion slightly decreases but the long-term stability increases. However, in the range of molecular weight of PVP studied in Figure 1, no trend was observed for the effect of stabilizer molecular weight on mean particle diameter and breadth of distribution.

The effect of stabilizer concentration on particle size was investigated with PVPK25 at constant homogenization speed of 13500 rpm by varying the concentration from 0.67% to 1.67% w/w of the aqueous phase. The results are shown in Figure 2. According to this figure, as the stabilizer concentration increased from 0.67 to 1.0 to 1.33 to 1.67%, the mean particle diameter decreased exponentially from 17.2 to 14.0 to 12.1 to 11.5 μm, respectively, and the *PDI* changed from 0.49 to 0.46 to 0.55 to 0.62, respectively. Moreover, as the stabilizer concentration increased, the mean particle diameter decreased exponentially but the breadth of particle size distribution increased slightly. Therefore, in suspensions prepared by homogenization at speeds greater than 10000 rpm, the effect of stabilizer concentration on particle size is much greater than stabilizer type. Long-term stability of suspensions increased as the concentration of stabilizer increased.

In general, as the amount of suspending agent is increased, more agent is available to fill the interface between the dispersed and continuous phase and, therefore, more surface can be created. This means that, on the basis of constant volume of the dispersed phase, particle size can become smaller as the amount of suspending agent is increased because, on the basis of constant volume of dispersed phase, as the size of particles decreases the surface area increases. However, as the particle size decreases, excess Gibbs free energy of the particle increases and it becomes infinite in the limit of zero particle size. Therefore, as the amount of suspending agent increases, initially the particle size decreases sharply until a plateau is reached due to increase in excess Gibbs free energy.

The effect of homogenization speed on particle

size was investigated with PVPK25 at constant stabilizer concentration of 1% w/w by varying the agitation rate from 8000 to 21000 rpm. The results are shown in Figure 3. According to this figure, as the agitation rate increased from 8000 to 9500 to 13500 to 21000 rpm, the mean particle diameter decreased exponentially from 25.2 to 21.0 to 14.1 to 12.3 μm and the PDI changed from 0.35 to 0.32 to 0.46 to 0.47, respectively. Agitation rates of 8000 and 9500 rpm gave the highest mean particle diameter and more narrow distributions. On the other hand, agitation rates of 13500 and 21000 rpm gave the lowest mean particle diameter and wider distributions.

Microsphere Morphology

The morphology of PU microspheres was investigated with SEM. Due to the reaction of isocyanate groups of MDI with water and formation of carbon dioxide (reaction 2), it was anticipated that the microspheres would have a porous structure. Chain extending agent, BD, was used to increase the ratio of hard to soft segments of the PU chains which also increased the viscosity of the prepolymer and the density and hardness of the microspheres. Figure 5 shows the SEM picture of a microsphere prepared without BD at homogenization speed of 13500 rpm and 1% w/w PVPK25 stabilizer, at 2660 magnification. Figures 6 to 8 show the SEM pictures of a microsphere prepared with 50%, 60% and 67% by mol of PEG400 polyol substituted with BD at 3650, 800 and 1400 magnification, respectively, with the same homogenization speed and stabilizer concentration. According to these figures, microspheres with no BD and 50% BD had porous structures, whereas microspheres with 60% and 67% BD had non-porous structures. As the amount of BD increased from zero to 50% by mol, the number of pores on the surface of the microspheres decreased and the average pore diameter decreased from 947 to 604 nm. As the amount of BD increased to 60% and 67% by mol, no pores were observed on the surface of microspheres, as shown in Figures 7 and 8. With the substitution

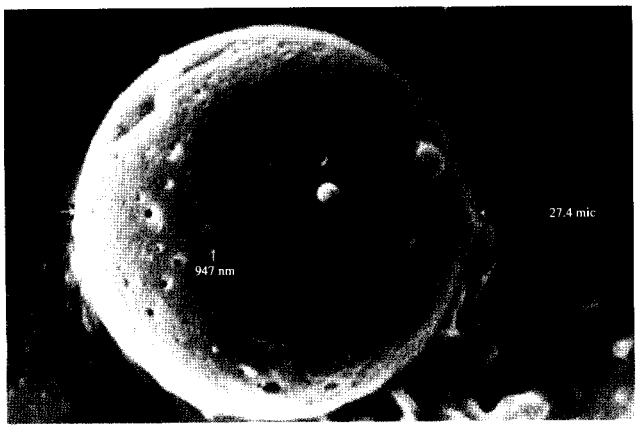

Figure 5. SEM micrograph of a microsphere prepared by suspension polycondensation without chain extending agent at magnification of 2660. Average pore size was 947 nm.

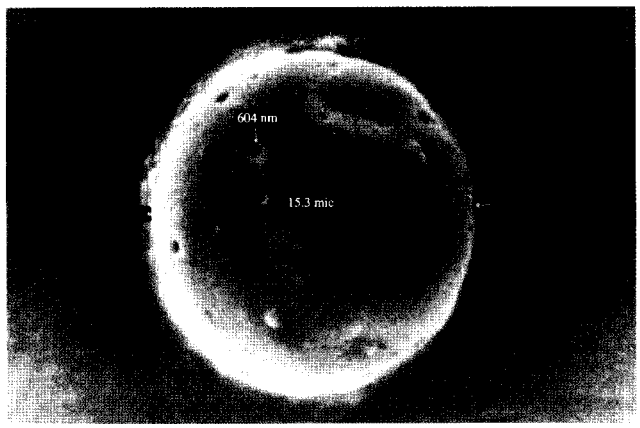

Figure 6. SEM micrograph of a microsphere prepared by suspension polycondensation. Average pore size was 604 nm.

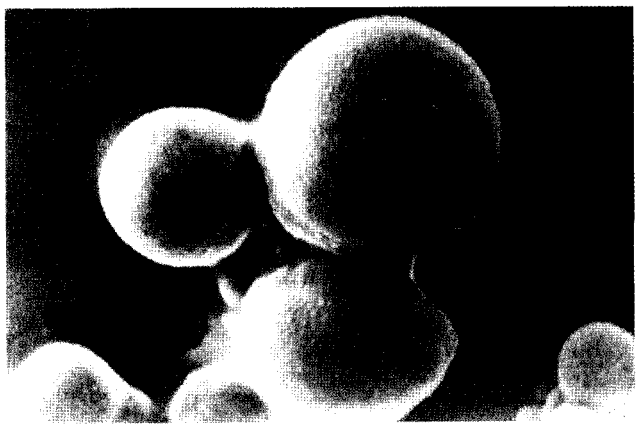

Figure 7. SEM micrograph of a microsphere prepared by suspension polycondensation at magnification of 800.

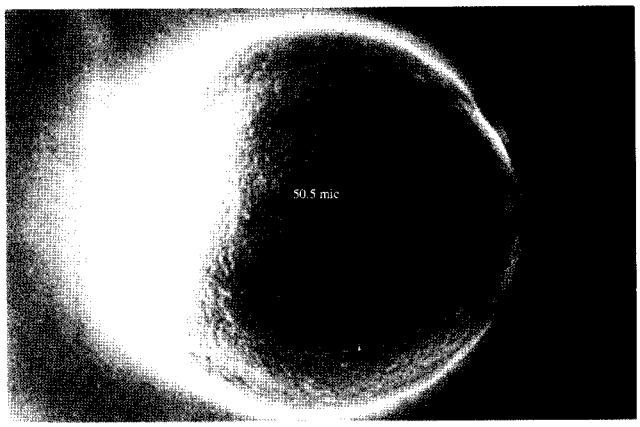

Figure 8. SEM micrograph of a microsphere prepared by suspension polycondensation at magnification of 1400.

of BD for PEG400, due to increase in the ratio of hard to soft segments, viscosity of the reacting polymer mixture increased which lowered the diffusivity of carbon dioxide formed by reaction 2. Therefore, the number and size of the pores decreased with increase of BD from zero to 50%. With further increase of chain extending agent to 60% and 67%, the PU chains became stiff, the microspheres became hard and the diffusion coefficient decreased such that the formation of pores was inhibited. Also as the chains became stiff, solubility of monomers in the crosslinked PU chains decreased and partial phase separation and collapse of the microsphere structure took place. Therefore, the number and size of the pores formed during the polycondensation reaction depended strongly on the microstructure of PU chains.

Release Behavior

The release behavior of PU microspheres was investigated with diazinon, an agricultural pesticide, as the active agent. 1.0 g of dried PU powder containing 10% w/w diazinon (0.1 g) was dispersed in 1500 ml of distilled water. The PU powder contained 50% by mole chain extending agent. The suspension was stirred gently while temperature was kept constant at 25°C. Figure 9 shows the release of diazinon versus time for up to 480 hrs. Microspheres were prepared by suspension polycondensation with 50% by mole of the PEG400 diol substituted with chain extending agent, 1,4-butanediol. The homogenization speed was 13500 rpm. The stabilizer was PVPK25 with concentration of 1% w/w of the aqueous phase. Temperature was kept constant at 25°C. Release was measured with ultraviolet spectroscopy at a wavelength of 246 nm.

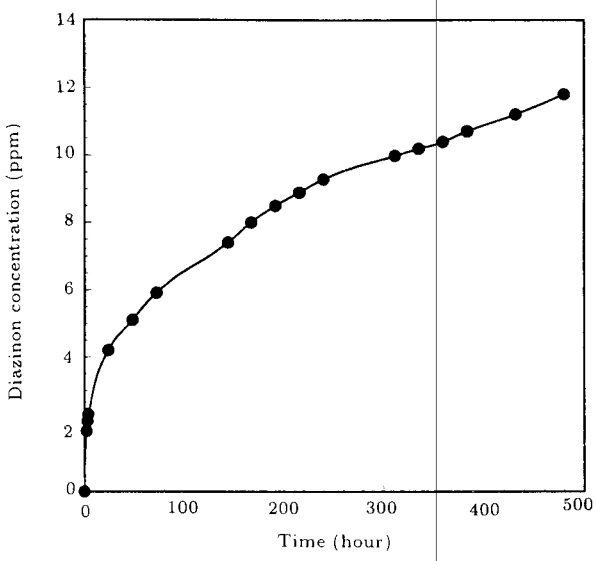

Figure 9. Release of diazinon versus time.

About 3% of diazinon (3×10^{-3} g) was released from the microspheres initially at zero time. This indicated that 3% of the total diazinon was absorbed on the surface and 97% trapped within the microspheres. After the initial burst, the release was linear with time, having a slope of 0.017 ppm/h, equivalent to 25 μg/h. After 480 hrs, 18% of diazinon (1.8×10^{-2} g) was released from the microspheres. Therefore, microspheres prepared by suspension polycondensation of MDI and PEG400 with 1,2-butanediol as the chain extending agent can be used for constant delivery of active agents for long periods of time.

After the initial transient, the diffusion of diazinon appears to be linear. If the flux is proportional to square root of time, then the release is controlled by Fickian diffusion of the active agent. On the other hand, if the flux is linearly proportional to time, then the release is non-Fickian. Since in Figure 9 the release of diazinon is linearly proportional to time, the release process is non-Fickian. It is assumed that since the solubility of diazinon is very low in water (40 ppm), the release is controlled by the partition of diazinon between the PU particle phase and the water phase filling the pores inside the particles. Work is in progress to find the effect of preparation parameters on release behavior.

CONCLUSIONS

Porous polyurethane microspheres were prepared by suspension polycondensation of an isocyanate, MDI and a diol, PEG400, with 1,4-butanediol as the chain extending agent using a high speed homogenizer. The microsphere size was independent of stabilizer type but depended strongly on concentration of stabilizer and speed of homogenization. The structure of microspheres was porous due to the reaction of isocyanate groups with water and formation of carbon dioxide. The porous structure of the microspheres depended on the amount of chain extending agent. As the amount of chain extending agent increased from zero to 50% by mol, the number of pores on the surface of the microspheres decreased and the average diameter decreased from 947 to 604 nm. As the amount of chain extending agent increased to 60% and 67%, the microsphere structure became non-porous. With the substitution of BD for PEG400, viscosity of the reacting polymer mixture increased, due to increase in the ratio of hard to soft segments, which lowered the diffusivity of carbon dioxide formed. Therefore, the number and size of the pores decreased with increase in the concentration of chain extending agent from zero to 50%. With further increase in the concentration of chain extending agent to 60% and 67%, the PU chains became stiff, the microspheres became hard and the diffusion coefficient of the reacting species

decreased such that pore formation was inhibited. The release behavior of PU microspheres containing 50% by mol chain extending agent was investigated with diazinon. About 3% of diazinon was released from the microspheres initially at zero time. After the initial burst, the release was linear with time.

REFERENCES

1. Domb, A.J., Ed., in *Polymeric Site-Specific Pharmacotherapy*, John Wiley, New York, USA (1994).
2. El-Nokaly, M.A. et al., Eds., in *Polymeric Delivery Systems: Properties and Applications*, ACS Symposium Series, San Francisco, CA, USA (1992).
3. Langer, R.S. and Wise, D.L., Eds., in *Medical Applications of Controlled Release*, **II**, CRC Press, Boca Raton, Florida, USA, pp 1-189 (1985).
4. Cardarelli, N., *Controlled Release Pesticides Formulations*, CRC Press, Cleveland, Ohio, USA, pp 93-156 (1976).
5. Arshady, R. "Preparation of polymer nano- and microspheres by vinyl polymerization techniques", *J. Microencapsulation*, **5**, p 101 (1988).
6. Arshady, R. "Preparation of polymer nano- and microspheres by polycondensation techniques", *J. Microencapsulation*, **6**, p 1 (1989).
7. Arshady, R. and George, M.H. "Suspension, dispersion and interfacial polycondensation: A methodological survey", *Polym. Eng. Sci.*, **33**, p 865 (1993).
8. Thompson, M.W. "Types of polymerization", in *Polymer Colloids*, R. Buscall, et al., Eds., Elsevier Applied Science, London, UK (1985).
9. Poehlein, G.W. "Emulsion polymerization", in *Encyclopedia of Polymer Science and Engineering*, H.F. Mark, Ed., **6**, John Wiley, New York, USA (1987).
10. Grulke, E.A. "Suspension polymerization", in *Encyclopedia of Polymer Science and Engineering*, H.F. Mark, Ed., **6**, John Wiley, New York, USA (1987).
11. Mahabadi, K.K. and Wright, D. "Semi-suspension polymerization process", *Macromol. Symp.*, **111**, p 133 (1996).
12. Barrett, K.E.J. and Thompson, M.W. "The preparation of polymer dispersions prepared in organic media", in *Dispersion Polymerization in Organic Media*, K.E.J. Barrett, Ed., John Wiley, London, UK (1975).
13. Arshady, R. "Preparation of microspheres and microcapsules by interfacial polycondensation techniques", *J. Microencapsulation*, **6**, p 13 (1989).
14. Morgan, P.W. "Interfacial polymerization", in *Encyclopedia of Polymer Science and Engineering*, H.F. Mark, Ed., **8**, John Wiley, New York, USA (1987).
15. Morgan, P.W. "Comments on the status and future of interfacial polycondensation", *J. Macromol. Sci. Macromol. Chem.*, **A15**, p 683 (1982).
16. Thies, C. "Microencapsulation", in *Encyclopedia of Polymer Science and Engineering*, H.F. Mark, Ed., **9**, John Wiley, New York, USA (1987).
17. Luckham, P.F. "Microencapsulation: Techniques of formation and characterization", in *Controlled Particle, Droplet and Bubble Formation*, D.J. Wedlock, Ed., Butterworth-Heinemann, Oxford, UK (1994).
18. Brode, G.L. et al. "Phenolics: The new way", *Chemtech*, p 676 (1983).
19. Santosusso, T.M. "Process for the preparation of granular urethane-urea polymers", U.S. Patent 4,083,831 (1978).
20. Dahme, M. et al. "Microcapsules and their preparation", U.S. Patent 4,299,723 (1981).
21. Kiritani, M. et al. "Pressure sensitive recording sheet", U.S. Patent 4,021,595 (1977).
22. DeSavigny, C.B. "Microencapsulated methyl and ethyl parathion insecticide in aqueous carrier", U.S. Patent 3,959,464 (1976).
23. Beestman, G.B. and Deming, J.M. "Encapsulation by interfacial polycondensation and aqueous herbicidal composition containing microcapsules produced thereby", U.S. Patent 4,280,833 (1981).
24. Beestman, G.B. and Deming, J.M. "Encapsulation by interfacial polycondensation", U.S. Patent 4,417,916 (1983).
25. Scher, H.B. "Encapsulation process and capsules produced thereby", U.S. Patent 4,285,720 (1981).
26. Fan, L.T. and Singh, S.K., *Controlled Release: A Quantitative Treatment*, Springer-Verlag, Berlin, pp 9-83 (1989).
27. Baker, R.W., *Controlled Release of Biologically Active Agents*, John Wiley, New York, USA, pp 39-74 (1987).
28. Price, J.C. "Diffusion controlled systems: Polymeric microcapsules", in *Polymers in Controlled Drug Delivery*, P.J. Tarcha, Ed., CRC Press, Boca Raton, Florida, USA, pp 4-10 (1991).
29. Good, W.R. and Lee, P.I. "Membrane controlled reservoir drug delivery systems", in *Medical Applications of Controlled Release*, R.S. Langer and D.L. Wise, Eds., **I**, CRC Press, Boca Raton, Florida, USA, pp 1-68 (1985).
30. Francois, P. et al. "Physical and biological effects of a surface coating procedure on polyurethane catheter", *Biomaterials*, **17**(7), p 667 (1996).
31. Ichikawa, K. "Dynamic mechanical properties of polyurethane-urea microcapsules on coated paper", *J. Appl. Polym. Sci.*, **54**, p 1321 (1994).
32. Yui, N. et al. "Drug release from monolithic devices of segmented polyether poly(urethane-urea)s having both hydrophobic and hydrophilic soft segments", *Makromol. Chem., Rapid Commun.*, **7**, p 747 (1986).
33. Yadav, S.K. et al. "Microencapsulation in polyurea shell by interfacial polycondensation", *AIChE J.*, **36**, p 431 (1990).

34. Pearson, R.G. and Williams, E.L. "Interfacial polymerization of an isocyanate and a diol", *J. Polym. Sci. Polym. Chem.*, Ed., **23**, p 9 (1985).
35. Matsuda, K. et al. "Emulsion polyurethane having thermosetting properties: I. Preparation", *J. Appl. Polym. Sci.*, **23**, p 141 (1979).
36. Shantha, S.Y. and Panduranga, R.-K. "Drug-release behavior of polyurethane microspheres", *J. Appl. Polym. Sci.*, **50**, p 1863 (1993).
37. Maa, Y.F. and Hsu, C. "Liquid-liquid emulsification by rotor/stator homogenization", *J. Controlled Release*, **38**, p 219 (1996).
38. Backus, J.K. et al. "Polyurethanes", in *Encyclopedia of Polymer Science and Engineering*, H.F. Mark, Ed., **13**, John Wiley, New York, USA (1987).
39. Lyman, D.L. "Polyurethanes: The chemistry of the diisocyanate-diol reaction", in *Step Growth Polymerization*, D.H. Solomon, Ed., Marcel Dekker, New York, USA (1972).
40. Woods, G., *The ICI Polyurethane Book*, John Wiley, London, UK (1987).
41. Ross, S. and Morrison, I.D., *Colloidal Systems and Interfaces*, John Wiley, New York, USA (1988).
42. Almog, Y. and Levy, M. "Studies of particle size distribution and adsorption of stabilizers in dispersion polymerization", *J. Polym. Sci. Polym. Chem.*, Ed., **20**, p 417 (1982).