Sustained-release microsphere formulation containing an agrochemical by polyurethane polymerization during an agitation granulation process

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Abbreviations: CTD, clothianidin; LAC, linear attenuation coefficient; PU, polyurethane; SEM, scanning electron microscopy; HPLC, high-performance liquid chromatography.

ABSTRACT

In this report, a new solventless microencapsulation method by synthesizing polyurethane (PU) from polyol and isocyanate during an agglomeration process in a high-speed mixing apparatus was developed. Clothianidin (CTD), which is a neonicotinoid insecticide and highly effective against a wide variety of insect pests, was used as the model compound. The microencapsulated samples covered with PU (CTD microspheres) had a median diameter of < 75 μm and sustained-release properties. The CTD microspheres were analyzed by synchrotron X-ray computed tomography measurements. Multiple cores of CTD and other solid excipient were dispersed in PU. Although voids appeared in the CTD microspheres after CTD release, the spherical shape of the microspheres remained stable and no change in its framework was observed. The experimental release data were highly consistent with the Baker–Lonsdale model derived from drug release of spherical monolithic dispersions and consistent with the computed tomography measurements.

Keywords:

Sustained release, agrochemical, polyurethane, microsphere, agitation granulation

1. Introduction

Microencapsulation is a technique where solid particles or liquid droplets as core material are covered by a shell material, such as a polymer or inorganic compound, and the particle size of the product is on the micron scale. The products prepared by this process are called microcapsules, microspheres, and microparticles which differentiate in morphology and internal structure (Arshady, 1999; Ghosh, 2006). Microencapsulation provides controlled release of active ingredients, masks the taste and odor of the substances, improves handling of toxic materials, and protects core materials from the external environmental. Consequently, microencapsulation is used in pharmaceutical, agricultural, printing, and food industries (Chang et al., 2003; Hirech et al., 2003; Takada et al., 2003; Shaikh et al., 2006; Gu et al., 2010). In agriculture, reducing application frequency is required because it improves operational efficiency and prevents excess release of agrochemicals into the environment (Tsuji 2001). Thus, a number of microencapsulation studies have been reported that aim to address the abovementioned drawbacks of agrochemical use (Ohtsubo et al., 1991; Kök et al., 1999; Asrar et al., 2004; Takei et al., 2008; Zhang et al., 2013).

In general, microencapsulation can be classified into three technical methods: (i) chemical methods, such as interfacial polymerization and *in situ* polymerization; (ii) physico-chemical methods, such as coacervation, phase separation, and sol-gel encapsulation; and (iii) physico-mechanical methods, such as spray drying and congealing, solvent evaporation, and fluid bed coating (Jyothi et al., 2010).

In chemical methods, polyurethane (PU), polyurea, and epoxy resin are used as polymer shells. Chemical methods have the advantage that the polymer shell can be designed using different monomers with unique functional groups and/or different chain lengths. The procedure using a chemical method involves core materials dispersed in dispersion media such as water or organic solvent being covered with shell material by polymerization. Therefore, there are some

disadvantages: (i) difficulty in preparing high content formulation owing to the presence of excipients indispensable for stabilizing the cores in dispersion media; (ii) low encapsulation efficiency when the core material is highly soluble in dispersion media; and (iii) insufficient product performance because the thickness of the shell material is limited. Furthermore, when products encapsulated by the chemical methods require removal of the dispersion media, there are some demerits such as extra costs for evaporating the dispersion media and safety issues associated with the removal of possible flammable organic solvents used. As an alternative approach that circumvents these issues, solventless microencapsulation has recently been studied (Luo et al., 2008; Otles et al., 2011; Capece and Davé, 2014). However, these reports used physico-chemical or physico-mechanical methods, and there is negligible information available that describes possible chemical methods.

In this study, we have developed a new solventless microencapsulation method for core materials containing agrochemicals. The core materials are covered with polyurethane (Fig. 1 (A)) synthesized from polyol and isocyanate during an agglomeration process in a high-speed mixing apparatus. The physico-chemical properties and the internal structures of the microencapsulated samples manufactured were investigated. Clothianidin (CTD; Fig. 1 (B)) was used as a model compound for this study. CTD is a water-soluble neonicotinoid insecticide possessing a thiazolyl ring and is highly effective against a wide variety of insect pests (Uneme, 2011).

2. Materials and methods

2.1. Materials

Clothianidin (CTD) and CTD pre-mix (CTD/clay = 70/30, d_{50} = 10–20 μm) was procured from Sumitomo Chemical Co. Ltd (Tokyo, Japan). Poly(phenylene methylene isocyanate) (polymeric MDI) (Sumidur 44V-10; Functionality, 2.3–2.5) was procured from Sumika Bayer Urethane Co. Ltd

(Hyogo, Japan). Trifunctional polyether polyol (Sumiphen S429, Mw: 700) was procured from Sumika Bayer Urethane Co. Ltd. 2,4,6-Tris(dimethylaminomethyl)phenol was procured from Kayaku Akzo Corporation (Tokyo, Japan). Fumed silica (AEROSIL300) was procured from Nippon Aerosil Co., Ltd (Tokyo, Japan).

2.2. Preparation of CTD microspheres

Batch manufacturing was performed with a high-speed mixer (Earth Techinica Co., Ltd., Tokyo, Japan) with a horizontal bowl and a capacity of 2 L. The apparatus was equipped with agitator blades on the bottom and chopper blades on the side. The injection site was located at the top of the equipment and the bowl was covered with a jacket. A schematic is shown in Fig. 2 (A).

The polymer compositions and an outline of the manufacturing method are shown in Table 1 and Fig. 2 (B), respectively. The reactant ratio of isocyanate to hydroxyl was set at 1.0: 1.0. Three hundred grams of CTD pre-mix (CTD content: 69.1%) was loaded into the apparatus and heated to 80 ± 5 °C. The CTD pre-mix was maintained at this temperature while the agitator blades and chopper blades set at 850 and 2,500 rpm, respectively, mixed the material. The predetermined amount of polyol, which is composed of 98.5% (*w*/*w*) of Sumiphen S429 and 1.5% (*w*/*w*) 2,4,6-tris(dimethylaminomethyl)phenol, was added over 2 min to the pre-mix and mixing continued for 3 min. A predetermined amount of Sumidur 44V-10 was then added over 2 min and the sample mixed for 6 min to encapsulate the CTD pre-mix by PU, which is a reaction product of isocyanate and polyol. The additions of Sumiphen S429 and Sumidur 44V-10 were repeated at predetermined times. The weight ratio of isocyanate and polyol added per cycle to the CTD premix was defined as the addition ratio. The encapsulated samples were annealed for 30 min at 80 ± 5 °C to complete PU polymerization (Watanabe et al., 2009). A predetermined amount of AEROSIL300 was added to the sample and mixed for 3 min to prevent agglomeration. After cooling to an ambient temperature, the

samples were removed from the high-speed mixer. Finally, the samples were sieved thorough a JIS standard sieve No. 50 (sieve size 300 μm); the sieved samples were defined as CTD microspheres. Microsphere yield was calculated by the following equation:

$$\text{Microsphere yield (\%)} = \frac{\text{Amount of encapsulated samples passed through No.50 sieve}}{\text{Total amount of encapsulated samples before sieving}} \times 100 \quad (1)$$

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2.3. Particle size distribution

Five grams of each CTD microsphere sample was vibrated for 5 min by a sieve shaker (Vibratory Sieve Shaker AS 200, Retsch) with No. 100 (150 μm) and No. 200 (75 μm) sieves. The sieved samples were weighed. Three replicates were carried out for each CTD microsphere sample.

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2.4. Scanning electron microscopy (SEM)

The surface structures of the CTD microspheres were observed by SEM (S-3000N, Hitachi, Ltd., Tokyo, Japan). Each CTD microsphere was sputter coated with Pt-Pd alloy by an ion sputter before observation by SEM.

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2.5. CTD content in CTD microspheres

One hundred milligrams of each CTD microsphere sample was placed in a glass vial and extracted by 100 mL of tetrahydrofuran. The suspension was filtered through a syringe filter (pore size = 0.45 μm) and the filtrate was analyzed for CTD by high-performance liquid chromatography

125 (HPLC) with a reversed-phase column (Inertsil ODS-EP 5 μm, φ 4.6 × 150 mm; GL Sciences, Tokyo, Japan). The mobile phase consisted of water/acetonitrile/phosphoric acid = 800/200/1 (v/v). The wavelength for CTD detection by ultraviolet absorption was set at 270 nm and flow rate was 1.0 mL/min. Three measurements were carried out for each CTD microsphere sample. The encapsulation ratio was calculated by the following equation:

$$\text{Encapsulation ratio (\%)} = \frac{\text{CTD content in CTD microspheres}}{\text{Theoretical CTD content in CTD microspheres}} \times 100. \quad (2)$$

2.6. Release test

CTD microspheres equivalent to 22.5 mg of CTD were add to 450 mL of three-degree hard water, and stirred with a stirring bar at a constant speed of 100 rpm. The degree hard water was general test solution to evaluate agrochemical formulation in Japan and prepared by dissolving 47.4 mg $CaCl_2$ and 21.7 mg $MgCl_2$ to 1 L of distilled water. The temperature of the test solution was kept at 25.0 ± 0.3 °C. Two milliliters of the test solution was taken at a predetermined time and the CTD concentration in the solution was quantified by HPLC, as described above. The release amount of CTD was calculated by the following equation:

$$\text{Release amount of CTD } (w/w\%) = \frac{\text{CTD content in the solution}}{\text{CTD content in the weighed CTD microspheres}} \times 100. \quad (3)$$

Three replicates were carried out for each CTD microsphere sample.

2.7. Statistical analysis of release profiles

The difference factor (f_1) was used to evaluate the difference between release profiles of two CTD microspheres (Moore and Flanner, 1996). The f_1 was calculated by the following equation:

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n}|R_t|}\right\} \times 100. \quad (4)$$

where n is the number of time points, R_t is the release amount of the Sample 1 at time t, and T_t is the release amount of Sample 2 at time t. According to the FDA's guidance (FDA, 1997), release data time points below 85% CTD release and only one sampling time point above 85% were used to calculate f_1. The f_1 values up to 15 (0–15) generally indicate the equivalence of two release profiles, and values over 15 indicate a significant difference between two release profiles.

2.8. Synchrotron X-ray μCT measurements

CTD microspheres before the release test were sieved through No. 200 sieve (75 μm). CTD microspheres after the release test were collected from the beaker of the release test after 14 or 56 days, and were dried at ambient temperature for a few days. The CTD microspheres were placed in Lindemann glass capillaries with a diameter of 0.2–0.5 mm. The synchrotron X-ray computed microtomography (μCT) measurements were performed at the SPring-8 BL37XU equipped with a μCT instrument (Uesugi et al., 2012; Suzuki et al., 2011; Noguchi et al., 2013; Kajihara et al., 2015). The X-ray energy was set to 8 keV. Nine hundred X-ray transmission-images, in parallel projection geometry, were recorded in 0.2° steps with continuous rotation of the CTD microspheres. The exposure time per transmission image was 150 ms. The distance between the detector and the CTD microspheres was 3 mm. Cross-sectional images were calculated by the CBP software package (Uesugi, 2004). One pixel size was equivalent to 0.507 × 0.507 μm. The cross-sectional images were analyzed using SLICE (Nakano et al., 2006) and Fiji (Schindelin et al., 2012; Schneider et al., 2012). The linear attenuation coefficient (LAC) values of drugs and excipients were calculated using the software MU_4 (Kato, 2011; Hubbell and Seltzer, 1996).

2.9. Comparison of the consistency between experimental data and the release profile by kinetic equations

Akaike's information criterion (AIC; Akaike, 1973) was used as a measurement of goodness of fit of the experimental data to the release model equation. AIC is given by:

$$AIC = N \ln(RSS) + 2P, \tag{5}$$

where N, RSS, and P are the number of experimental data, residual sum of squares, and number of parameters, respectively. A lower AIC value means that the release data are more consistent with the release model.

The Higuchi model, which represents drug release from a homogeneous planar matrix (Higuchi, 1963), the Hixson–Crowel model, which represents drug release involved in erosion (Hixson and Crowel, 1931), and the Baker–Lonsdale model, which represents drug release from spherical monolithic dispersions (Baker and Lonsdale, 1974), were selected as the release models. The three model equations are given by:

Higuchi model $$Q = k \cdot t^{1/2}, \quad (6)$$

Hixson–Crowell model $$1 - (1-Q)^{1/3} = k \cdot t, \quad (7)$$

Baker–Lonsdale model $$3[1 - (1-Q)^{2/3}] /2 - Q = k \cdot t, \quad (8)$$

where Q, k, and t are the released CTD ratio ($0 < Q \leqq 1$), dissolution constant, and time, respectively. Data points with Q less than 0.80 were used for the analyses.

3. Results and discussion

3.1. Effect of the addition ratio per cycle on the physicochemical properties of CTD microspheres

Six samples with the same coating ratio, 60%, were prepared by different addition ratios (Table 1). Table 2 shows the physicochemical properties of the samples, such as microsphere yield and encapsulation ratio. Besides the 60% coat (7.5% × 8), the microsphere yields of the other five samples were > 90%, and the microsphere yields of the samples increased as the addition ratio decreased (Table 2). The results indicated that CTD microspheres were mainly composed of particles that passed 300μm sieve. Encapsulation ratios of all samples were larger than 95%. The encapsulation ratio of 60% coat (2.5% × 24), which was prepared for the longest time among those samples, was almost 100%. It indicated that CTD was stable during preparation. Results of microsphere yields and encapsulation ratios for six CTD microsphere samples suggested that our technology is an effective, efficient and robust microencapsulation method. The samples prepared with a lower addition ratio showed a higher encapsulation ratio. Table 3 shows each CTD content in

CTD microspheres with different particle size range, less than 75μm, 75–150μm, and 150–300μm. CTD content in CTD microspheres with larger particle size range was higher than CTD content in CTD microspheres with smaller particle size range. Elimination of CTD microspheres > 300 μm in manufacturing process, which were assumed to contain a higher CTD content, would cause the lowering of encapsulation ratio to under 100%. As shown in Fig. 3, the results of the particle size frequency showed that the median diameters of all samples were < 75 μm, and the ratios of particles with the diameter < 75 μm in samples increased as the addition ratio decreased.

Fig. 4 (A) and (B) show SEM images of microspheres. The sizes of all samples were larger than the CTD premix, and the shapes and the surfaces of all samples were more spherical and smoother than those of the CTD premix. These particle characteristics suggest that the granulation process of our methods consisted of two phases: one is an ‘’aggregation phase’’ where primary particles are aggregated by PU and the other is a ‘’coating phase’’ in which aggregated particles were covered by PU. In addition, the sizes of samples became larger and the shapes and the surfaces of all samples became smoother and more spherical as the addition ratio increased. The higher addition ratio was considered to produce larger aggregated particles via larger PU amount per cycle in the aggregation phase, and to be sufficient amount to cover the aggregated particles in the coating phase.

In the case of 60% coat samples, those prepared by lower addition ratios showed longer sustained release, except for the 60% coat (7.5% × 8), as shown in Fig. 5, Table 4 and 5. Although a smaller specific surface area of the controlled-release product is thought to contribute to longer sustained release in general, our results were found to be inconsistent with this principle. This inconsistency with previous observations was assumed to arise from the difference of the total coating ratio required for shifting from the aggregation phase to the coating phase at each addition ratio. However, the release profile of the 60% coat (7.5% × 8) was comparable to the release profile of the coat 60% coat (3% × 20) and was longer sustained-release than the release profile of the coat 60% coat (4% ×

15). As mentioned above, the diameter < 75 μm in CTD microspheres was dominant particle size distribution (Fig. 3), and the CTD content of the 60% coat (7.5% × 8) with < 75 μm was the lowest among the other five samples with < 75 μm. It would be contributed to have a longer sustained-release performance for 60% coat (7.5% × 8). Through the result of the release test, the coat 60% coat (2.5% × 24) was the longest sustained-release period among the 60% coat samples.

3.2. Effect of coating ratio on physicochemical properties of CTD microspheres

As described above, the two phases of microencapsulation are the aggregation phase and coating phase. The results of the release tests were found to be inconsistent with the general theory that as the specific surface area increases the release rate increases. To elucidate the mechanism and explain this apparent inconsistency, four samples with an addition ratio of 2.5% and different coating ratios were prepared, and six samples with an addition ratio of 5.0% and different coating ratios were prepared (Table 1). As shown in Table 2, the microsphere yields and the encapsulation ratios of these samples were high, over 90% and 95%, respectively. In particular, the microsphere yields of samples with lower coating ratios were higher than those with higher coating ratios. As shown in Fig. 3, the median diameters of all samples except for the 90% coat (5% × 18) were < 75 μm. The particle sizes of the four samples with a 2.5% addition ratio were comparable. For the six samples with a 5.0% addition ratio, the particle sizes of three samples with coating ratios of 15–45% were comparable; however, the three samples with a coating ratio > 60% showed larger particle sizes and the sizes were found to increase as the coating ratio increased.

SEM results revealed that particle sizes of 15% coat (2.5% × 6) and 15% coat (5% × 3) were larger than the CTD premix, indicating that aggregation occurred in the initial phase of the microencapsulation (Fig. 4 (B) and (C)). The samples with a 2.5% addition ratio showed rugged surfaces, irrespective of the coating ratio. The six samples with the 5.0% addition ratio; however,

showed different surface appearances that were dependent on the coating ratio. Here, the 15% coat (5% × 3) and 30% coat (5% × 6) had concavity and convexity on their surface, but the 60% coat (5% × 12) showed reduced asperity on the surface of the particles, and the shape and size were more spherical and larger. From the SEM observations, our assumption of a two-phase mechanism, i.e., aggregation phase and coating phase, was proven. This shows that shifting from the aggregation phase to the coating phase is dependent on the coating ratio.

As shown in Fig. 6 and Table 4, the CTD release ratios of the 15% coat (2.5% × 6), 30% coat (2.5% × 12), 15% coat (5% × 3), and 30% coat (5% × 6) were over 80% within 1 day. Thus, these samples were likely to be only aggregates and not covered with PU. This is consistent with SEM observations. The samples with > 45% coat showed increasing sustained-release performance as the coating ratio increased. This suggests that the coating phase starts when the coating ratio reaches 45%. The 45% coat (2.5% × 18) sample (Fig. 6 (A)) showed extended sustained release performance when compared with the 45% coat (5% × 9) sample (Fig. 6 (B)). This indicates that the coating phase would be initiated at a lower coating ratio when an addition ratio of 2.5% is used. In addition, the sustained-release performance of the 90% coat (5% × 18) was attained by using lower coating and addition ratios, e.g., 60% coat (2.5% × 24), demonstrating that the desired sustained-release performances, as well as particle size, could be manufactured by designing the coating and addition ratios properly.

3.3. Internal structures of CTD microspheres

As above, the particle growing process of CTD microspheres was clarified by SEM images and evaluation of the release tests. To further understand CTD microencapsulation into microspheres, the internal structures of the microspheres were investigated non-destructively by synchrotron X-ray μCT measurements. The internal structure of all samples prepared with the 5.0% addition ratio could

be visualized clearly, as shown in Fig. 7. However, the internal structures of the microspheres prepared by the 2.5% addition ratio were not visualized because the particle sizes were too small. PU was found to exist between CTD and/or clay particles inside the microspheres and negligible PU was found at the surfaces of the 15% coat (5% × 3) and 30% coat (5% × 6). Meanwhile, PU covered partially the surfaces of the 45% coat (5% × 9) and 60% coat (5% × 12), and covered completely the surfaces of the 75% coat (5% × 15) and 90% coat (5% × 18). The CTD microspheres obtained formed spherical monolithic dispersions with multiple cores made of PU, in which CTD and clay were randomly dispersed, and no void was observed in the CTD microspheres (Siepmann and Siepmann, 2012).

3.4. Change in the internal structure of CTD microspheres during the dissolution process

The internal structures of the 90% coat (5% × 18) microspheres were visualized before and after the release test (Fig. 8). Before the release test, CTD and clay were dispersed in PU and there was no void observed, as described above. However, samples that released more than 50% of CTD after 14 days displayed some voids in the CTD microspheres. Samples that released more than 90% of CTD after 54 days showed a large increase in the number of voids. Although voids emerged in CTD microspheres following the release of CTD, the spherical shape of the microspheres was maintained and no change in the framework of the microspheres was observed. This is probably because of the water-insoluble property of PU and that there was a sufficient amount of PU to stabilize the framework of the microspheres following complete release of CTD. As a result, the 90% coat (5% × 18) showed a long sustained release over 2 months and the structure of the microsphere remained stable following the completion of the release test.

3.5. Release model and kinetic mechanism

To elucidate the release mechanism of CTD microspheres, mathematical release model equations were fitted to the experimental release data. Three equations were used: the Higuchi model, the Hixson–Crowell model, and the Baker–Lonsdale model. These models were evaluated by AIC (Table 6). AIC values of the Baker–Lonsdale model were the lowest among the models, except for the 60% coat (6% × 10), in which the number of experimental release data to be analyzed was the smallest. In addition, the differences of AIC values between the Baker–Lonsdale model and the other two models were larger for samples with longer sustained-release periods. Figure 9 shows that the Baker–Lonsdale model was the most coincident with the experimental release data among the three models. This would be reasonable since the structures of the CTD microspheres, spherical monolithic dispersions as revealed by CT analyses (Fig. 7), were coincident with the microsphere structure assumed in the Baker–Lonsdale model. The Higuchi model was less suitable because the structure of the CTD microspheres was not a homogenous planar matrix assumed in the Higuchi model. The Hixon-Crowell model was also less suitable because no erosion was observed during the drug elution from the CTD microspheres as is evident from their internal structures (Fig. 8).

4. Conclusions

In the present study, we have developed solventless microencapsulation using a high-speed mixer and polyurethane polymerization with polyol and isocyanate. In this method, the particle size and the sustained-release performance of agrochemical microspheres were modulated by adjustment of the addition ratio and coating ratio. CT analysis of the CTD microspheres showed that with different coating ratios the internal structures of CTD microspheres differ. Moreover, the CT analysis revealed that multiple cores of CTD and clay were dispersed in PU and the mechanism of producing CTD microspheres involved in two phases, an aggregation phase and a coating phase. The experimental release data were highly consistent with the Baker–Lonsdale model derived from drug

release of spherical monolithic dispersions, and this model choice was supported by CT analysis of the CTD microspheres before and after the release test. This microencapsulation approach has the advantages of being an eco-friendly and economical process that does not require solvent and water, and the particle size and sustained-release performance can be modulated easily by process factors.

Acknowledgments

The synchrotron radiation experiments at BL37XU were performed with the approval of the Japan Synchrotron Radiation Research Institute (Proposal Nos. 2014B1119 and 2014A1205). This work was partly supported by the Japan Society for the Promotion of Science KAKENHI (Grant Nos. 26460224, 26460039, and 26460226).

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Figure captions

Fig. 1. General reaction formula of polyurethane (A) and the chemical structure of CTD (B).

Fig. 2. Schematic of (A) high-speed mixer apparatus and (B) manufacturing process flow chart.

Fig. 3. Particle size distribution of CTD microspheres.

Fig. 4. Surface images of CTD microspheres by SEM. (A) 60% coat samples at different addition ratio, (B) different coating ratio samples at 2.5% addition ratio, and (C) different coating ratio samples at 5.0% addition ratio

Fig. 5. Effect of the addition ratio per cycle on the release ratio of CTD from 60% coat CTD microspheres.

Fig. 6. Effect of the coating ratio on the release ratio of CTD from CTD microspheres. (A) Addition ratio: 2.5% and (B) addition ratio: 5.0%

Fig. 7. Internal structure images of CTD microspheres by CT analysis. LAC values between 0 and 70.0 are shown in 8-bit grayscale, with LAC values 70 or higher shown as white. Calculated LAC values of PU, CTD, and clay were 7.0, 53.4, and 90.7 cm^{-1}, respectively.

Fig. 8. Internal structure images of CTD microspheres before and after release test by CT analyses.

Fig. 9. Comparison between the data of the release test and the mathematical models. Symbols:

experimental values; red solid curve: Baker–Lonsdale model; dotted green curve: Higuchi model; dashed blue curve: Hixson–Crowell model.