



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



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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 <math><75\ \mu\text{m}</math> 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.

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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 environment. 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; K ok 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

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

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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 Technica 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 $80 \pm 5^\circ\text{C}$. The CTD pre-mix was maintained at this temperature while the agitator blades and

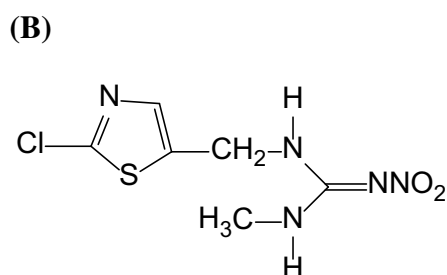
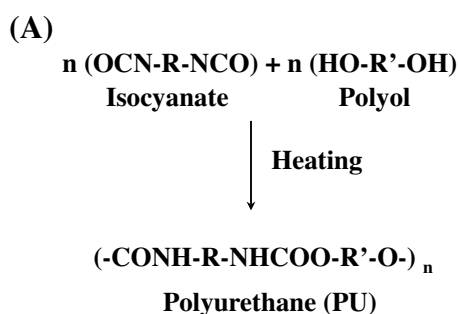


Fig. 1. General reaction formula of polyurethane (A) and the chemical structure of CTD (B).

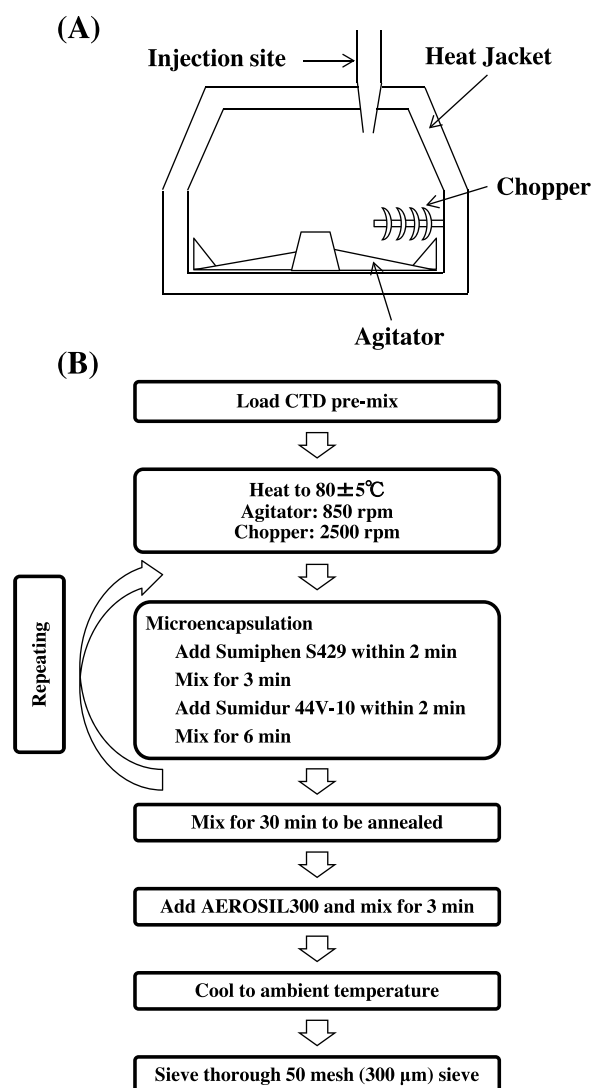


Fig. 2. Schematic of (A) high-speed mixer apparatus and (B) manufacturing process flow chart.

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