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# Two-stage controlled release system possesses excellent initial and long-term efficacy

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ABSTRACT

In this work, a series of polyurea-based lambda-cyhalothrin-loaded microcapsules (MCs) with three different size distributions (average diameters of 1.35 μm, MC-S; 5.13 μm, MC-M; and 21.48 μm, MC-L) were prepared and characterized. The results indicated that MCs with a smaller particle size distribution had a faster release rate and excellent initial efficacy against pests. MC-L had a remarkably slow incipient release rate, outstanding photostability and better later-stage efficacy than that of the other tested MCs. The results clarified that the diameter distribution of MCs is the key factor in determining the release property and bioactivity of the MC formulations. Subsequently, the binary mixture MC formulations of MC(+M), MC(S+L) and MC(M+L) were obtained by mixing MC-S, MC-M or MC-L at 1:1 to establish a two-stage release system utilized for foliar application situations. Greenhouse and field experiments showed that MC(S+L) provided an optimal efficacy, and its effective duration was much longer than that of the emulsifiable concentrate (EC) group. Therefore, the release system established in this study was simple and workable for regulating the initial and long-term efficacy by adjusting the particle size distribution; in addition, this system has potential applications in other fields such as drug delivery devices.

## 1. Introduction

Microencapsulation technology plays an important role in controlled release formulations and has attracted increasing attention over the past few decades [1–5]. Due to the formation of the capsule wall, MCs provide a physical barrier between the core cargo and the external environment [6] that can minimize the degradation of the pesticide inside by sunlight, water and microorganisms, thereby prolonging the duration of efficacy [7–9]. Many MC formulations of pesticides, such as insecticides, fungicides, herbicides and plant growth regulators, have been registered and commercialized and can be sprayed, dusted or coated in/on soil, foliage and seeds in the same way as conventional pesticides.

Mogul et al. suggested that an excellent pesticide controlled release system should have favorable efficacy in the field [10]. In many applications, the biological activity of MCs is closely related to the MC release profile. The release of the core material can be achieved through a number of mechanisms, such as encapsulation of the cargo via the diffusion permeability that is determined by the size, MC wall structure and solubility of the core in the wall [11], or release that is triggered by temperature [12], light [13,14], pH [15], or enzymes [16]. However, the pesticide MCs applied on the surface of the organism is simultaneously stimulated by various environmental factors such as temperature, light and humidity, while the factor of diffusion permeability of the core exists at the same time. In such a complex and vacillating release environment, it is very hard to achieve the release rate or cargo concentration that satisfies the demand to control pests, so that the proper control period is frequently missed. Therefore, a controlled release system with persistent insecticidal activity is urgently needed. At present, interfacial polymerization is one of the most popular encapsulation methods for pesticide MC products, and polyurea is widely used as the wall material due to its relatively mild technology conditions and simple production process [17]. However, in a previous study, we found that a majority of polyurea MCs with nonporous and stable polymer membranes provided only one release course, either an initial or later performance, which could not meet the requirements of foliar application. This phenomenon could be because most MC formulations were generally equipped with a single peak distribution of particles [8], thus providing only one release behavior. However, there have been no reports on the construction of a pesticide controlled release system that

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possesses excellent initial efficacy and long-term efficacy for foliar application [18–20].

As an important pyrethroid insecticide, lambda-cyhalothrin (LC) presents effective control over a variety of agricultural and sanitary pests. Nevertheless, the stinging skin irritation by LC experienced by operators needs to be alleviated via microencapsulation technology [21]. It has been reported that the MCs of LC encapsulated by various materials have been used to control public health pests, but their application in agriculture has rarely been reported [22,23]. In the present study, LC-loaded polyurea MCs with different size distributions were prepared and used to control agricultural pests. In addition, based on the characteristics of the MC formulation with a single peak distribution, combination formulations with a bimodal size distribution of MCs were obtained. Then, the two-stage release behavior, initial efficacy and long-term efficacy of the formulations were investigated. The persistent period of the pesticide is expected to be increased through the development of a novel and innovative pesticide delivery system that possesses satisfactory initial and long-term efficacies to improve the utilization and application effect of pesticides. Ultimately, a new combinatorial strategy based on the relationship between the release profiles and size distribution was developed to establish a two-stage release delivery system for foliar application. In addition, the research results are expected to enrich the release theory of controlled release formulations.

## 2. Materials and methods

### 2.1. Chemicals

Technical grade LC (purity = 96%) was provided by Shandong Weifang Rainbow Chemical Co., Ltd. (Shandong, China). Other chemicals used to fabricate the MCs are listed in the Supporting Information.

### 2.2. Insect source

The test insects were *Pieris rapae* Linne. The insects were successively raised in the laboratory and fed fresh cabbage leaves at 25–28 °C, 60%–70% relative humidity and 16:8 light/dark cycles [24]. Fourth-instar larvae were selected for the bioassay and greenhouse experiments.

### 2.3. Preparation of the MCs

MCs were obtained using the interfacial polymerization method according to previously reported procedures [25], and the detailed fabrication process is described in the Supporting Information.

### 2.4. Microcapsule characterization

The size distribution and specific surface area of the MC samples were evaluated by a laser particle size analyzer (LS-POP 6, Zhuhai OMEC Instrument Co., Ltd., Guangdong, China). MC-S (average diameter of 1.35 μm), MC-M (average diameter of 5.13 μm) and MC-L (average diameter of 21.48 μm) were the MCs with different particle sizes. The surface morphology of the MCs was observed using scanning electron microscopy (SEM) (JSM-6610LV, JEOL, Tokyo, Japan). The atomic force microscopy (AFM) experiments were performed using an NT-MDT-PRIMA scanning probe microscope (NT-MDT, Moscow, Russia). Prior to the AFM experiment, the core material encapsulated in the MCs was dissolved in excess methanol to produce hollow MCs for thickness analysis [26]. Then, the hollow MCs were allowed to air dry on a silicon wafer (washed with methanol). The membrane thicknesses were analyzed using NOVA 1138 image processing software. The release properties of the MCs were tested according to previous methods, with modifications [27]. The standard procedures used are described in the Supporting Information.

### 2.5. Field experiments

Field validation experiments were performed at the experimental field of Shandong Agricultural University, China (N 36°09′, E117°09′), from August to September in 2016 and 2017. The daily rainfall and mean temperature are described in the Supporting Information (Fig. S2). One-meter-wide buffer zones were intended to separate each plot. The pesticides (EC and MCs of LC) were applied at 15 g a.i./ha with a spray volume of 450 Liters per hectare. To promote foliage spreadability, 0.05% Silwet 408 (silicone additive, Momentive Performance Materials, USA) was added to diluted solutions. Cabbages in the untreated group were sprayed with an aqueous solution containing 0.05% Silwet 408. Each treatment had three replicates. Before treatment, the basic number of *P. rapae* was counted. After treatment for 1, 3, 7, 14 and 21 days, the number of *P. rapae* was investigated, and the control efficacy was evaluated [28].

### 2.6. Greenhouse experiments

Greenhouse experiments were carried out to verify the results of the field test. MC containing LC was sprayed at 10 mg/L. To promote foliage spreadability, 0.05% Silwet 408 was added to the diluted solutions. The average temperature of the greenhouse where the experiments were carried out was maintained at 25–15 °C throughout the tests. The treated cabbage leaves were picked periodically and made into round samples with a diameter of 1 cm using a circular punch. Two roundels and one cabbage worm were placed into each hole of 24-hole cell culture plates. Each experiment was repeated three times. The temperature and relative humidity was maintained at 25 − 28° C and 60%-70%, respectively. Larval mortality was evaluated after 24 h [9].

### 2.7. UV irradiation experiment

The photostability of the MCs was tested according to a previously reported protocol [9]. The EC, MC-S, MC-M and MC-L samples were diluted with distilled water to a concentration of 1000 mg/L. Then, 1 mL of each diluted solution was evenly applied to dishes with a diameter of 6 cm. After the water was evaporated, the dish was exposed to ultraviolet rays with an average irradiation intensity of 25 $\mu W/cm^2$. Then, the dish was removed at regular intervals. The residue in the dish was washed with acetonitrile and transferred to a volumetric flask (100 mL). Then, the solution was filled to a constant volume of 100 mL using acetonitrile. The amount of LC was detected using an HPLC system. The residual content was calculated using the following Eq. (1):

$$\text{Residual content (\%)} = (c_r/c_1) \times 100 \quad (1)$$

where $c_1$ is the initial concentration and $c_r$ is the concentration after degradation.

### 2.8. Statistical analysis

The data from the field experiments, greenhouse experiments, release and photostability properties were statistically analyzed using SPSS software (version 16.0) and displayed as the means and the standard error (SE) by Tukey's multiple range test ($p < 0.05$). The figures were obtained using Sigmaplot 12.5 software, and data fitting analysis was obtained using OriginPro 2017 software.

## 3. Results and discussion

### 3.1. Microcapsule characterization

As depicted in Fig. 1A, the size distribution of the three MC samples