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Star Polymer-Based Nanodelivery System for Pesticides: Enhanced Broad-Spectrum Toxicity and Selective Toxicity

Yuanrui Liu, Ying Wei, Meizhen Yin, Jie Shen, Xiangge Du, Shuo Yan,* and Min Dong*

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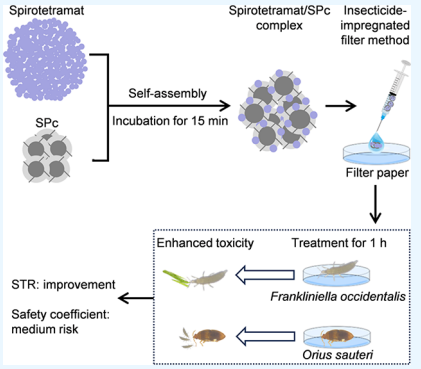
ABSTRACT: The application of nanotechnology in agriculture can break through many traditional problems of synthetic pesticides, especially for increasing bioactivity and reducing application amount. However, the safety and selective toxicity of nanocarrier-loaded pesticides should be clarified toward natural predators. In this context, an efficient spirotetramat nanodelivery system was successfully constructed based on a star polymer (SPc). Spirotetramat could complex with SPc through hydrogen bonding and van der Waals forces spontaneously. The self-assembly of the spirotetramat/SPc complex decreased the particle size of spirotetramat from 1292 to 710 nm. After the complexation with SPc, the lethal concentration 50 (LC_{50}) values of spirotratemat decreased from 252.064 to 108.871 and 332.079 to 189.257 mg/L toward target pest *Frankliniella occidentalis* and nontarget predator *Orius sauteri* with the synergic ratios of 2.315 and 1.755, respectively. The possible reason might be due to the enhancement of the broad-spectrum toxicity of SPc-loaded pesticides. Importantly, the selective toxicity ratio (STR) of spirotetramat increased from 1.32 to 1.73 with the help of SPc, indicating the higher selectivity of the spirotratemat/SPc complex toward predators. Meanwhile, the safety coefficient (SC) of spirotratemat was not significantly changed after complexation with SPc, and the spirotratemat/SPc complex belonged to the medium risk pesticide. Overall, the assembly with SPc could not only improve the control efficacy of spirotetramat but also increase its selectivity as well as alleviate its negative effects on predators. The current study is beneficial for understanding the enhancement of broad-spectrum toxicity and the selective toxicity of nanocarrier-loaded pesticides.



1. INTRODUCTION

Synthetic pesticides have become the most popular and successful choice to combat plant pathogens and insect pests over the past 70 years. However, most synthetic pesticides present defects such as poor dispersibility, instability, and low utilization rate.[1,2] Moreover, the overuse of pesticides has caused various environmental problems and finally threatened to human health.[3−5] The application of nanotechnology in agriculture has become a recent developmental trend, which can break through many traditional problems of conventional pesticides.[6−9] Most synthetic pesticides contain hydrophobic active ingredients (AIs) that can be wrapped in nanoparticles or attached to peripheral groups of nanoparticles; thus, some nanocarriers have been successfully applied to construct nanodelivery systems for synthetic pesticides.[10,11] Compared to conventional pesticides, nanopesticides possess the smaller particle size and larger specific surface area, which can effectively improve the dispersibility and wettability of insoluble AIs, thereby increasing their stability and enhancing their bioactivity.[12−15]

Our group has designed and synthesized a star polymer (SPc) as an efficient nanocarrier for various substances.[16] The SPc-based nanodelivery system is fit for the efficient delivery of nucleic acids and synthetic/botanical pesticides.[17−19] The SPc can assemble with several synthetic/botanical pesticides spontaneously, including osthole, matrine, dinotefuran, thiocyclam, methoxyfenozide, etc.[17,20−23] The self-assembly with SPc can reduce the particle sizes of pesticides and improve their delivery efficiency for enhanced bioactivity. We have confirmed that the bioactivities of SPc-loaded pesticides can be improved by 20−40% compared with conventional pesticides. For instance, the lethal concentration 50 (LC_{50}) of SPc-loaded osthole decreases from 0.049 to 0.034 g/L with an efficiency ratio of 1.441 against aphids.[20] The control efficacy of matrine toward thrips increases to 76.8% with the help of SPc compared to 62.1% at 10 d after the treatment.[17] Therefore, SPc is regarded as an excellent adjuvant to improve the bioactivities of various agents for plant protection.

Although the control efficacies of pesticides can be remarkably increased with the help of nanodelivery system, the risks of nanopesticides toward nontargets need to be elucidated similarly as conventional pesticides.[24,25] Some

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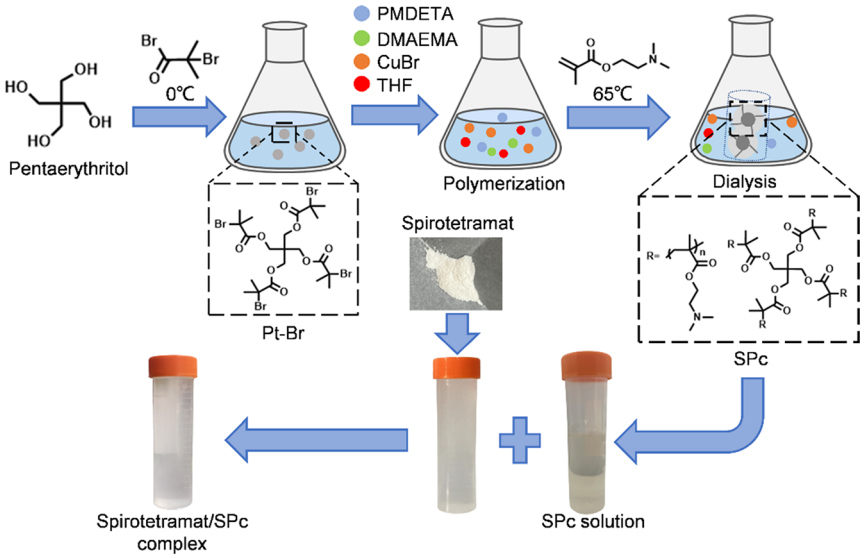
Scheme 1. Synthesis Route of SPc and Preparation of the Spirotetramat/SPc Complex



previous studies have evaluated the safety of nano insecticides against natural enemies.[26,27] However, only one study has tested the selective toxicity of nanopesticide, and it shows that the complexation with nanocarriers can improve the selective toxicity ratio (STR) of cyantraniliprole.[28] Due to the limited knowledge about the selective toxicity of SPc-loaded pesticides, more reliable experiment data and conclusions need to be obtained and complemented so that we could be clearer about two issues: (1) Whether the SPc-loaded pesticides exhibit the enhancement of broad-spectrum toxicity against both target pests and nontarget predators. (2) Whether the complexation with SPc changes the STR of pesticides and brings greater risk to nontargets. Western flower thrips, *Frankliniella occidentalis* (Thysanoptera: Thripidae), are important insect pests all over the world due to their wide range of hosts, which cause serious economic losses annually.[29] At present, synthetic pesticides are usually employed to control thrips, but the extensive use of pesticides has accelerated the resistance development of thrips to multiple insecticides.[30,31] As a kind of endosuctive insecticide, spirotetramat is particularly effective for controlling the thrips with the rasping mouthparts, especially for nymphs.[32,33] Although spirotetramat resistance in some thrip populations is also increasing, it basically remains at a low to moderate level, making it a commonly used pesticide.[34]

The current study aimed to construct the spiritetramat/SPc complex and examine its toxicity enhancement and selective toxicity toward target pest *F. occidentalis* and predator *Orius sauteri*. We first measured the pesticide loading content (PLC) of SPc toward spiritetramat, determined the dominate interaction force between SPc and spiritetramat, and examined the particle size and morphology of the spiritetramat/SPc complex to illustrate the self-assembly mechanism of the spiritetramat/SPc complex. We then employed the insecticide-impregnated filter method to determine the LC_{50} values of the spiratetramat/SPc complex and spiratetramat alone toward the second instar nymphs of *F. occidentalis* and the third instar nymphs of *O. sauteri*, respectively. We finally calculated the STR and safety coefficient (SC) of the spiratetramat/SPc complex toward *O. sauteri* to assess its safety. The current study is beneficial for understanding the enhancement of broad-spectrum toxicity via nanodelivery system. Besides, it brings more attention about the selective toxicity of nano-carrier-loaded pesticides and promotes their application in field.

2. MATERIALS AND METHODS

2.1. Chemical Reagents. Chemicals for SPc synthesis included 2-bromo-2-methylpropionyl bromide and triethylamine (TEA) bought from Heowns BioChemTechnologies (China), *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA) and CuBr bought from Sigma-Aldrich (USA), and 2-(dimethylamino) ethyl methacrylate (DMAEMA) bought from Energy Chemical (China). Pure spirotetramat (effective content: 97%) was purchased from Hebei Weiyuan Biological Chemical Co. (China).

2.2. Synthesis of SPc and Preparation of the Spirotetramat/SPc Complex. The SPc was synthesized through two steps following a previously described method.[16] The synthesis process of SPc is shown in Scheme 1. In briefly, pentaerythritol solution (10 g, 73.45 mmol) was added to anhydrous tetrahydrofuran (400 mL) along with TEA (100 mL, 721.42 mmol). A mixture of 2-bromo-2-methylpropanoyl bromide (100 mL, 809.04 mmol) and anhydrous THF (150 mL) was added dropwise, and the mixture was stirred for 5 h. Subsequently, the solvent was removed, followed by extraction with dichloromethane (DCM) and water. The star initiator Pt−Br (15 g, 30%) was obtained by washing with ice-cold acetone. The obtained Pt−Br (8 g, 10.9 mmol), DMAEMA (617 g, 3924 mmol), PMDETA (26.6 g, 153 mmol), and THF (1600 mL) were mixed, and then stirred under a nitrogen atmosphere, followed by the addition of CuBr (9.4 g, 65 mmol). The polymerization reaction was conducted at 65 °C in an oil bath for 10 h, and then quenched by cooling and air exposure. The THF was recycled to decrease the production cost of SPc. The crude polymer was dialyzed to obtain the SPc solution.

Spirotetramat and SPc were dissolved in ddH_2O at the mass ratio of 1:1, and then, they were incubated for 15 min at room temperature. The SPc could assemble with spirotetramat spontaneously in aqueous solution. The preparation of the spirotetramat/SPc complex is also shown in Scheme 1.

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2.3. Loading Capacity Measurement. The loading capacity of SPc toward spirotetramat was measured using the freeze-drying method.[22] Spirotetramat (104.2 mg) was suspended in 10 mL of ddH_2O, and 2 mL of a 10 mg/mL SPc aqueous solution was preprepared. The spirotetramat was incubated with SPc and then dialyzed using the regenerated cellulose with a molecular weight cut-off of 2000 Da (Shanghai Yuanye Bio-Technology Co., China) for 12 h to exclude the surplus spirotetramat. The dialysate was freeze-dried using the vacuum freeze-dryer (Beijing Songyuanhuaxing Technology Development Co., China) and weighed. The PLC was calculated using the following equation. PLC (%) = weight of spirotetramat loaded in complex ÷ weight of spirotetramat-loaded complex ×100%. The treatment was performed in triplicate.

2.4. Isothermal Titration Calorimetry (ITC) Assay. To determine the interaction of SPc with spirotetramat, 1 mL of spirotetramat (0.05356 mmol/L) was titrated with 250 μL of SPc aqueous solution (0.5 mmol/L) in Nano ITC (TA Instruments Waters, USA). The heat of interaction during each injection was calculated by integrating each titration peak via Launch NanoAnalyze software (USA). The test temperature was 25 °C, and ΔG was calculated using the formula $\Delta G = \Delta H - T\Delta S$.

2.5. Ultraviolet Spectra and ATR Spectra of the Spirotetramat/SPc Complex. The ultraviolet spectra of spirotetramat and spirotetramat/SPc complex were tested via UV−vis spectrophotometry (Genesys 180, USA). The spirotetramat was dissolved in ddH_2O to prepare a series of spirotetramat aqueous solutions that were used to determine the characteristic absorption peak. Besides, the freeze-dried sample of the spirotetramat/SPc complex obtained in the above experiment was dissolved with ddH_2O to test the ultraviolet. The solid phase of samples, including spirotetramat, SPc and spirotetramat/SPc complex, were used for ATR spectra test via ATR accessory (Nicolet 6700, USA).

2.6. Particle Size Measurement and Complex Morphology Characterization. The particle sizes of the spirotetramat/SPc complex at the mass ratio of 1:1 (0.8 mg/mL) and spirotetramat (0.8 mg/mL) in aqueous solution were measured using the Zetasizer Nano ZS (Malvern Instruments Ltd., UK) at 25 °C. Each treatment included three independent samples. The morphologies of the above samples were further examined using a scanning electron microscope (Regulus 8100, Japan). A few microliters of each sample were dropped on the silicon slice to dry naturally, and the two specimens were sprayed with platinum material before observation.

2.7. Toxicity Assay of the Spirotetramat/SPc Complex against *F. occidentalis*. The toxicity of the spirotetramat/SPc complex was tested toward pest *F. occidentalis*. *F. occidentalis* were collected from organic cucumbers in Beicaiyuan Agricultural Science and Technology Development Co. (China), fed with sword beans, and maintained at 25 ± 1 °C, 75 ± 10% relative humidity, and 14 L:10 D photoperiod in a constant-temperature incubator.

According to the national standard (Guideline for laboratory bioassay of pesticides part 8: insecticide-impregnated filter method), the insecticide-impregnated filter method was used for toxicity assay. The 1 mL of spirotetramat (30.19, 60.38, 120.75, 241.50, 483.10 mg/L) and spirotetramat/SPc complex (31.25, 62.50, 125.00, 250.00, and 500.00 mg/L) were dripped on the qualitative filter paper (9 cm diameter), respectively, and the filter paper was air-dried. The ddH_2O and SPc at the highest concentration were applied as controls. The second instar nymphs of *F. occidentalis* were released on the filter paper for 1 h, then removed to a clean dish, and fed on sufficient sword beans. Nymphs that did not move when pushed gently with a brush were scored as dead 48 h after the treatment. The concentration−mortality data were analyzed to obtain LC_{50} using the POLOPlus 2.0 (LeOra Software, USA). Each treatment contained 10 nymphs and was repeated 5 times. The synergic ratio was given as the ratio of spirotetramat LC_{50} to ÷ complex LC_{50}.

2.8. Bioactivity Assay of the Spirotetramat/SPc Complex toward *O. sauteri*. The bioactivity of the spirotetramat/SPc complex was examined toward predator *O. Sauteri*. *O. Sauteri* were purchased from Beijing Kuoye Tianyuan Biotechnology Co., Ltd. (China), fed on *F. occidentalis*, and reared under the same conditions as those for *F. occidentalis*. The bioassay of spirotetramat/SPc complex toward third instar nymphs of *O. Sauteri* was performed similarly as above. The LC_{50} and synergic ratio were also calculated to evaluate the potential negative effects of the spirotetramat/SPc complex. Each treatment included 10 nymphs and was repeated 5 times.

2.9. Assessment of the Selective Toxicity Ratio and Safety Coefficient of the Spirotetramat/SPc Complex. The STR was applied to assess the selective toxicity of the spirotetramat/SPc complex between pests and predators according to the method described by Shen et al.[35] STR was calculated as STR = predator's LC_{50} ÷ pest's LC_{50}, and the pesticide can be classified as a selective pesticide when STR > 1.

The safety of the complex was analyzed by calculating the SC according to the previous studies.[36,37] SC was calculated using the formula SC = predator's LC_{50} ÷ recommended concentration of pesticide for field application. The pesticide can be classified as high risk when SC > 5, medium risk when 0.5 < SC ≤ 5, and low risk when SC ≤ 0.5. The field recommended concentration of spirotetramat is 106.67−142.22 mg/L for controlling thrips.

2.10. Data Analysis. SPSS 27.0 software (SPSS Inc., USA) was used for statistical analysis. Duncan's test and independent *t* test were used to analyze the significant differences at the $P = 0.05$ level. The descriptive statistics are shown as the mean value and standard errors of the mean.

3. RESULTS AND DISCUSSION

3.1. Loading Capacity and Self-Assembly of SPc with Spirotetramat. As shown in Table 1, the PLC of SPc toward spirotetramat was examined using the freeze-drying method, and it was calculated to be 36.16%, which was comparable to

Table 1. Loading Capacity of SPc toward Spirotetramat Using the Freeze-Drying Method[a]

weight of applied pesticide (mg)	weight of applied SPc (mg)	weight of pesticide-loaded complex (mg)	weight of pesticide loaded in complex (mg)	pesticide-loading content (%)	average pesticide-loading content (%)
104.2	20.0	32.9	12.9	39.21	36.16 ± 1.57
104.2	20.0	30.9	10.9	35.28	
104.2	20.0	30.3	10.3	33.99	

[a]Mean ± SE.

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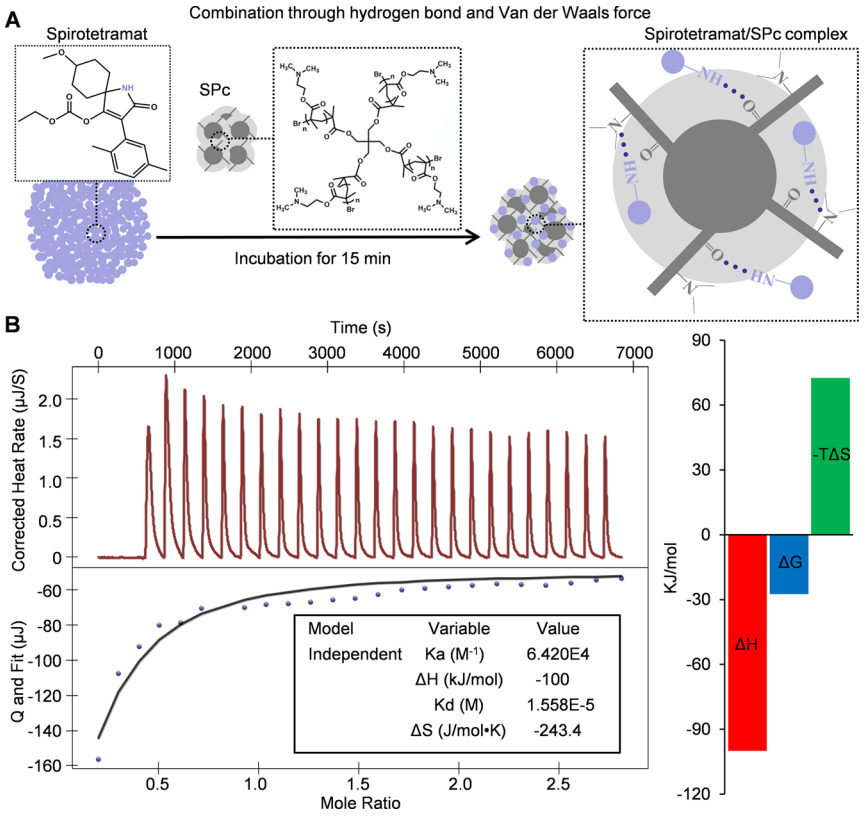

Figure 1. (A, B) ITC titration of SPc into the spirotetramat solution. The titration was performed by adding 250 μL of SPc solution (0.5 mmol/L) into a 2 mL solution of pure spirotetramat (0.05356 mmol/L).

Table 2. Polydispersity and Particle Size of the Spirotetramat/SPc Complex at the Mass Ratio of 1:1[a]

formulation	sample number	polydispersity	average polydispersity	size (nm)	average size (nm)
spirotetramat	1	0.372	0.353 ± 0.015	1277.14	1291.74 ± 52.70
	2	0.323		1389.45	
	3	0.363		1208.64	
spirotetramat/SPc complex	1	0.304	0.238 ± 0.033	703.64	710.14 ± 5.13
	2	0.201		720.27	
	3	0.209		706.50	
	t = 3.155, df = 4, P = 0.034 t = 10.983, df = 4, P < 0.001				

[a]The independent t test was used to analyze the data at P = 0.05 level of significance.

methoxyfenozide (32.66%) and higher than dinotefuran (17.41%) and thiamethoxam (20.63%).[19,21,23]

High PLC also revealed the successful assembly of SPc with spirotetramat, and their dominant interaction force was examined using ITC (Figure 1). According to the previous interpretation of ITC data,[38] the high affinity constant Ka (6.420×10^4 M^{-1}) suggested a strong interaction between SPc and spirotetramat. The negative ΔG value (−27.467 kJ/mol) indicated that this self-assembly was automatic. The negative values of ΔH (−100 kJ/mol) and ΔS (−243.4 J/mol·K) demonstrated that the self-complexation of SPc with spirotetramat was mainly driven by hydrogen bonding and van der Waals forces. Furthermore, the change in the characteristic absorption peak of the spirotetramat/SPc complex confirmed the successful self-assembly of the spirotetramat/SPc complex (Figure S1A). As shown in Figure S1B, the characteristic peaks of both spirotetramat and SPc could be found in the spirotetramat/SPc complex. The peaks at 1721 and 1391 cm^{-1} in SPc are attributed to the characteristic stretching vibrations of the carbonyl group and C−N bond in tertiary amines, respectively. The peak at 3402 cm^{-1} in spirotetramat is the stretching vibration of the N−H bond in secondary amine or the intermolecular hydrogen bonds. The increase of peak intensity at 3402 cm^{-1} in the spirotetramat/SPc complex indicated the formation of hydrogen bonds between spirotetramat and SPc. The dominant interaction force is dependent on the chemical structures, particularly the functional groups present in SPc and pesticides. Based on the chemical structures of spirotetramat and SPc, the binding sites for hydrogen bonding should be the amide NH of spirotetramat with carbonyl groups or tertiary amines of SPc. Similar to the current study, the tertiary amines of SPc can combine with the oxhydryl groups of chitosan via hydrogen bonding to achieve self-assembly.[39] Moreover, the SPc can also assemble with exogenous substances through other interaction forces such as electrostatic interaction, hydrophobic interaction, etc.[40−42] Thus, the SPc is a universal nanocarrier for delivering exogenous substances and has a promising prospect in agricultural application.[43,44]

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3.2. Reduced Particle Size and Morphology of the Spirotetramat/SPc Complex. As shown in Table 2, the combination of spirotetramat with SPc decreased the particle size of spirotetramat from 1292 to 710 nm at a mass ratio of 1:1. The representative SEM images also supported this conclusion (Figure 2). The spirotetramat aggregated into large

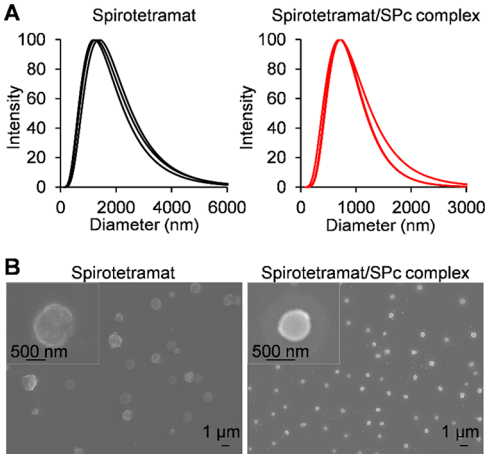

Figure 2. Particle size distributions (A) and SEM images (B) of spirotetramat and spirotetramat/SPc complex at the mass ratios of 1:1.

particles with an average diameter of approximately 1200 nm, whereas the assembly of the spirotetramat/SPc complex at the mass ratio of 1:1 disturbed the self-aggregated structure of spirotetramat, forming smaller spherical particles. Based on our previous research, SPc can be used as a common adjuvant for pesticide nanometerization to decrease the particle sizes of osthole, avermectin, and thiocyclam.[20,22,45] In the current study, the particle size of the spirotetramat/SPc complex was not decreased to the nanoscale, but the smaller particle size might increase the contact area of spirotetramat to pests for enhanced bioactivity.

3.3. Enhanced Bioactivity of the Spiratetramat/SPc Complex toward *F. occidentalis* and *O. sauteri*. To test the bioactivity of the spiratetramat/SPc complex toward target pests and predators, a series of spiratetramat/SPc complex dilutions were prepared, and the LC_{50} values of the spiratetramat/SPc complex were examined toward *F. occidentalis* and *O. sauteri* via the insecticide-impregnated filter method. As shown in Table 3, the LC_{50} of spiratetramat/SPc complex toward *F. occidentalis* decreased to 108.871 mg/L compared with 252.064 mg/L of spiratetramat alone and that toward *O. sauteri* decreased from 332.079 to 189.257 mg/L, demonstrating the enhanced bioactivity toward both pests and predators. The mortality of pests treated with the spiratetramat/SPc complex was consistently higher than that with spiratetramat alone at all tested concentrations, which increased by approximately 20% (Figure 3). The mortality of

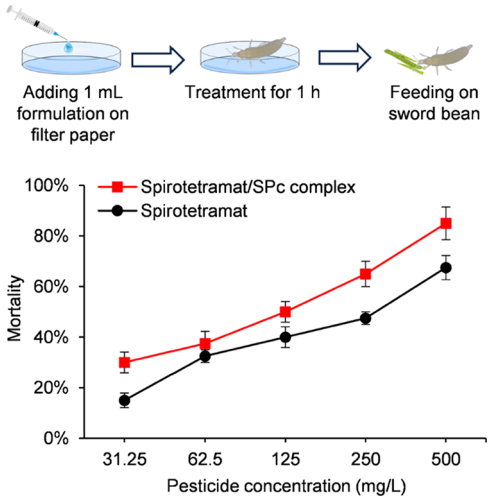

Figure 3. Toxicity of spiratetramat/SPc complex against the second instar nymphs of *F. occidentalis* through the insecticide-impregnated filter method. The nymphs were released on the filter paper treated with various formulations for 1 h, then removed to a clean dish. The mortality was recorded at 48 h after the treatment. Each treatment contained 10 nymphs and was repeated 5 times.

predators treated with the spiratetramat/SPc complex increased by approximately 10% (Figure 4). The synergic ratios toward pests and predators were calculated to be 2.315 and 1.755, respectively.

Previous publications have revealed that SPc can load various pesticides to increase their bioactivity. For instance, the toxicity of fluopyram can be remarkably increased against root-knot nematodes with the aid of SPc, with the LC_{50} decreasing from 8.63 to 5.70 mg/L.[41] The possible explanation for enhanced toxicity was that the nanocarrier SPc could decrease the particle size of spiratetramat, increase its contact area toward target insects, and then improve its permeability across the insect cuticle. In addition, the SPc could also promote the endocytosis processes, which facilitated the cellular uptake of spiratetramat.[37,39] Therefore, the toxicity of SPc-loaded spiratetramat was enhanced against both pests and predators, which led to the enhancement of broad-spectrum toxicity. The current findings were similar to a previous publication in that

Table 3. Enhanced Toxicity of the Spirotetramat/SPc Complex at the Mass Ratio of 1:1 Using the Insecticide-Impregnated Filter Method[a]

insect species	formulation	slope ± SE	LC_{50} (mg/L) (95% confidence limits)	$\chi 2$ (df)	*P*	synergic ratio
F. occidentalis	spirotetramat	1.194 ± 0.254	252.064 (170.700−461.231)	4.686 (18)	*	2.315
	spirotetramat/SPc complex	1.301 ± 0.245	108.871 (73.837−155.536)	8.295 (18)		
O. sauteri	spirotetramat	1.164 ± 0.272	332.079 (214.251−749.646)	2.869 (18)	*	1.755
	spirotetramat/SPc complex	1.224 ± 0.208	189.257 (90.409−204.809)	2.932 (18)		

[a] $\chi 2$ value and degrees of freedom (df) were calculated using the PoloPlus. The 2nd and 3rd instar nymphs were released on the filter paper treated with various formulations for 1 h, then removed to a clean dish, and fed on sufficient foods. The mortality was recorded at 48 h after the treatment. The synergic ratio was given as the ratio of spirotetramat LC_{50} ÷ complex LC_{50}. Each treatment included 10 nymphs and was repeated 5 times. The "*" indicates significant difference in bioactivity between spirotetramat and spirotetramat/SPc complex according to the independent *t* test ($P < 0.05$).

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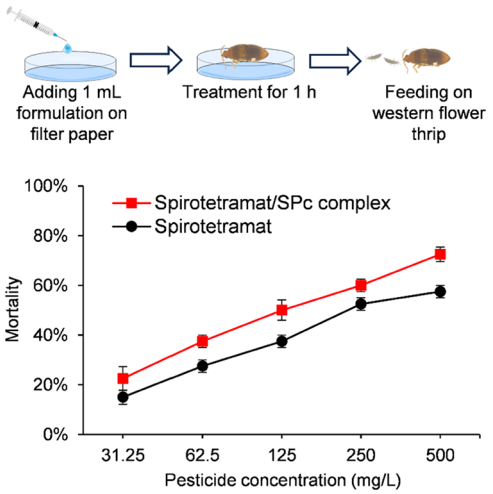

Figure 4. Bioactivity of spiratetramat/SPc complex toward the third instar nymphs of *O. sauteri* through the insecticide-impregnated filter method. The nymphs were released on the filter paper treated with various formulations for 1 h, then removed to a clean dish. The mortality was recorded at 48 h after the treatment. Each treatment contained 10 nymphs and was repeated 5 times.

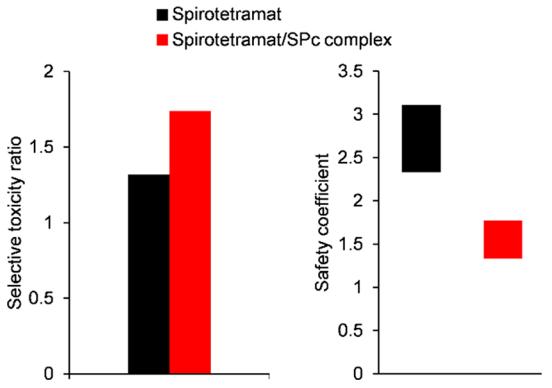

Figure 5. Selective toxicity ratio and safety coefficient of the spirotetramat/SPc complex toward *O. sauteri*. STR was calculated as STR = predator's LC_{50} ÷ pest's LC_{50}, and the pesticide can be classified as a selective pesticide when STR > 1. SC was calculated using the formula of SC = predator's LC_{50} ÷ recommended concentration of pesticide for field application. The pesticide can be classified as medium risk when 0.5 < SC ≤ 5.

the toxicity of SPc-loaded dinotefuran is slightly improved against predatory ladybirds.[21] Furthermore, the SPc-based nanodelivery system can expand the insecticidal target of thiamethoxam toward fall armyworms.[46]

As expected, the application of SPc at the highest concentration exhibited no lethal effects on the two insect species. A previous study has examined the potential negative effects of SPc on model insect *Drosophila melanogaster*.[47] Exposure to SPc at high concentrations adversely influences *Drosophila* lifespan, fertility, and climbing ability with the LC_{50} values of 2.14 and 26.33 g/L toward larvae and adults, respectively. Dong et al.[48] have investigated the biotoxicity of SPc toward predatory ladybirds. The oral feeding of SPc at extremely high concentrations can down-regulate many membrane protein genes and damage the cell membrane and nucleus. The LC_{50} of SPc toward ladybirds is 9925 times that of the SPc's working concentration. Thus, the SPc at working concentration exhibits negligible toxicity toward insects, suggesting the biosafety of SPc in agricultural applications.

3.4. Improved Selective Toxicity and Safety of the Spirotetramat/SPc Complex toward *O. sauteri*. The enhanced toxicity of the spirotratemat/SPc complex was demonstrated above; however, it was necessary to explore whether the safety of SPc-loaded spirotratemat changed toward predators. Thus, the STR and SC were used to assess the complex safety toward predators (Figure 5). The STR of the spirotratemat/SPc complex increased to 1.73 compared to 1.32 of spirotratemat alone, indicating the higher selectivity of the spirotratemat/SPc complex. The possible reason was that the synergistic function of SPc was more obvious toward pests than predators. The different synergistic degrees of the spirotratemat/SPc complex might be related with the action mechanism of spirotratemat. Moreover, the SC values of the spirotratemat/SPc complex and spirotratemat alone were 1.77−1.33 and 3.11−2.33, respectively. Both pesticides can be classified as medium risk pesticides toward *O. sauteri*. These data demonstrated that the application of SPc did not significantly change the risk of spirotratemat. The current data was consistent with a previous publication that the selective toxicity of SPc-loaded cyantraniliprole is improved toward *O. sauteri*.[26]

A previous publication has evaluated the safety of spirotratemat toward predator *Chrysoperla zastrowisillemi*, and there are no adverse effects on its egg hatching percentage, pupation rate, adult emergence, and fecundity, hence considered as a safe pesticide.[49] The sublethal effects of spirotratemat on parasitoid *Eretmocerus mundus* have also been investigated, and the spirotetramat is proved less harmful than cypermethrin.[50] Alexander et al.[51] have assessed the relative toxicity of 8 insecticides toward nontargets, and spirotratemat is found safe to *Cryptolaemus montrouzieri* and *Scymnus coccivora* among tested insecticides. Thus, the selectivity improvement of spirotratemat via SPc-based nanodelivery system was further expected to decrease the toxicity against natural enemies, which in turn improved the safety of spirotratemat in agricultural applications.

4. CONCLUSIONS

The current study developed an efficient nanodelivery system to prepare the spirotetramat/SPc complex. Spirotetramat can complex with SPc through hydrogen bonding and van der Waals forces. This nanodelivery system could break the self-aggregated structure of spirotetramat and significantly decrease its particle size from 1292 to 710 nm. Bioassay data indicated that the bioactivity of spirotetramat was remarkably increased with the aid of SPc toward both the pest *F. occidentalis* and the predator *O. sauteri*. More specifically, the synergic ratios were calculated to be 2.315 and 1.755 toward two insect species, respectively. The possible reason might be due to the enhancement of broad-spectrum toxicity of SPc-loaded pesticides. Considering the safety in agricultural application, the STR and SC of the spirotratemat/SPc complex were analyzed toward predators, which demonstrated that the selectivity of the spirotratemat/SPc complex was improved and it can be classified as a medium risk pesticide. Overall, the current study applied a SPc-based nanodelivery system to increase the control efficacy of spirotetramat toward pests, which could also increase the selectivity of spirotetramat as well as alleviate its negative effects on predators.

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■ ASSOCIATED CONTENT

Supporting Information

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Ultraviolet spectrum and ATR spectrum of spirotetramat, SPc, and spirotetramat/SPc complex (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Shuo Yan − *Department of Plant Biosecurity and MARA Key Laboratory of Surveillance and Management for Plant Quarantine Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China;* orcid.org/0000-0001-9685-9810; Email: yanshuo2011@foxmail.com

Min Dong − *Department of Plant Biosecurity and MARA Key Laboratory of Surveillance and Management for Plant Quarantine Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China;* Email: dongmin@cau.edu.cn

Authors

Yuanrui Liu − *Department of Plant Biosecurity and MARA Key Laboratory of Surveillance and Management for Plant Quarantine Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China*

Ying Wei − *Department of Plant Biosecurity and MARA Key Laboratory of Surveillance and Management for Plant Quarantine Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China*

Meizhen Yin − *State Key Laboratory of Chemical Resource Engineering, Beijing Lab of Biomedical Materials, Beijing University of Chemical Technology, Beijing 100029, China;* orcid.org/0000-0001-8519-8578

Jie Shen − *Department of Plant Biosecurity and MARA Key Laboratory of Surveillance and Management for Plant Quarantine Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China*

Xiangge Du − *Department of Plant Biosecurity and MARA Key Laboratory of Surveillance and Management for Plant Quarantine Pests, College of Plant Protection, China Agricultural University, Beijing 100193, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c05722

Author Contributions

Y.L. and Y.W. contributed equally to this work. M.D. and S.Y. designed and supervised the research; Y.L. and Y.W. performed the research; M.Y., J.S., and X.D. provided the materials; all authors analyzed the data; and S.Y., Y.L., and Y.W. wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Notes

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