Effect of White Carbon Contained in Water Insoluble Polymer Membrane of Time-Controlled Release Granule on Release Profile of Metominostrobin

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We investigated the effect of white carbon (hydrated silicon dioxide) contained in water insoluble polymer membrane on release profiles of metominostrobin from the time-controlled release granule (TCRG) containing metominostrobin. As the amount of white carbon increased, the lag time for release was shortened and the release rate became faster. Thus, the changes in both lag time and release rate were thought to be related to water permeability into the TCRG and tensile strength of the membrane induced by it. We also made a single regression model and a logistic model to predict release profile based on the amount of white carbon in TCRG using computer program NLIN procedure of SAS (Statistical Analysis Systems). As a result, the actual release profile fitted in a three parameter logistic model by non linear least-squares method.

Key words: metominostrobin, time-controlled release granule (TCRG), lag time, three parameter logistic model, white carbon.

INTRODUCTION

Establishment of simpler and more effective application methods in pest control can not only save cost but also decrease loading on the environment. For these objectives, the granules containing insecticide and/or fungicide have been applied in seedling box. In the case of rice blast disease caused by Pyricularia oryzae, fungicides applied into seedling box are expected to maintain the effect for a certain period needed. However, the efficacy of fungicides is not always sufficient in a duration of efficacy. Especially, in northern Japan, since the disease mostly occurs about two months after transplanting, their persistency is not often sufficient.1,2) Moreover, if a fungicide is released from formulation before development of rice blast symptom, there can occur some problems such as no effect on rice blast and injury on juvenile rice seedlings and environmental pollution. Therefore, we prepared a time-controlled release granule (TCRG) which was characterized by an active ingredient, metominostrobin3,4) to release with lag time.5,6)

In this report, we studied the effect of white carbon (hydrated silicon dioxide), which was contained in water insoluble polymer membrane of TCRG, on lag time and release rate of metominostrobin.

MATERIALS AND METHODS

1. Chemicals

The chemical structure of metominostrobin (molecular weight: 284.32) was shown in Fig. 1. It was synthesized at Aburahi Laboratories, Shionogi & Co., Ltd. (Shiga, Japan). The compound dissolves at 128 mg/l in water at 20°C and easily dissolves in various organic solvents. The melting point is 87.0–89.0°C. Silica sand (8.6–20 mesh; silica sand No.3) as a core particle, low-substituted hydroxypropylcellulose (Nisso, HPC-SL®, HPC) as a binding agent and hydrated silicon dioxide (CARPLEX® # 80, white carbon) as an anti-blocking agent among particles were supplied by Takeori Mineral Mining Co., Ltd. (Tokyo, Japan), Nisso & Co., Ltd. (Tokyo, Japan) and Shionogi & Co., Ltd. (Osaka, Japan), respectively. Acrylate starch (Sunfresh ST-100MPS®), which swells in water, was supplied by...
Sanyo Kasei Co., Ltd. (Kyoto, Japan). For a water insoluble membrane-forming agent, aqueous dispersion of polyvinylidene chloride [PVC] (polymer content 50%; Kurehalon® DO-821S) was supplied by Kureha Co., Ltd. (Tokyo, Japan). As a filler, talc was purchased from Wako Pure Chemicals Co. Ltd. (Osaka, Japan). All the other chemicals were of analytical grade and used without further purification.

2. Preparation of Granules
Formula of TCRG was shown in Table 1. The granule was prepared as described previously. The white carbon of 1.0% (PU-119), 0.75% (PU-120) and 0.5% (PU-121) was contained in water insoluble polymer membrane, respectively.

3. Measurement of Release Rate
Metominostrobin released from granules was measured as described previously.

4. Preparation of PVC Cast Film
PVC solution was diluted to one-half with distilled water followed by adding 0.5, 0.75 or 1.0% white carbon. The PVC solution was cast on glass share at 40°C for 1 hr to make a film. The resulting film was put in a desiccator over silica gel at room temperature for 24 hrs. The film thickness was determined at five different positions on the specimen with the dimension of 4.5×4.5 cm using a micrometer dial gauge (Ozeki Seisakusho Co., Ltd. Japan).

5. Measurement of Water Permeability through Film
Water permeability through film was measured as follows. As shown in Fig. 2, prepared film was placed on the upper portion of glass container (diameter: 4.0 cm, height: 2.8 cm) containing calcium chloride. This container was placed in a desiccator with saturated KNO₃ solution (relative humidity 92% at 20°C). The container was weighed periodically and the increase of weight was defined as the amount of water permeability through film.

6. Measurement of Tensile Strength of Film
A tensile testing machine (Imada Digital force gauge, DPS-50) was used to evaluate the mechanical property of PVC films. The PVC film, 10 mm wide and 25 mm long, was mounted between the grips in the tensile testing machine. The extension rate during tensile testing was 10 mm/min. Tensile strength was determined according to Eq. (1).

\[
\text{Tensile strength (N/cm²)} = \frac{(\text{strength of film when film was broken down})}{(\text{a} \times b)} \times \left[1 + \left(\frac{\Delta L}{L}\right)\right]
\]

where \(a\) is thickness of film (mm), \(b\) width of film (mm), \(\Delta L\) extension of film (mm) when film was broken down and \(L\) length of film (mm).

7. Prediction of Release Profile
The following three models using NLIN procedure of SAS were examined to predict release profile by the various amount of white carbon in the granules. In the following equations, the release percent (%) was \(n\), the amount of white carbon was \(x\), determined time (days) was \(t\) and the day when release percent reached \(n\%) was \(Tn\). \(\alpha\) and \(\beta\) were defined as parameters of intercept and slope of line, respectively.

Model 1: Simultaneous fitting of a two step single regression model

\[
Tn = (\beta_1 x + \alpha_1) + n/(\beta_2 x + \alpha_2)
\]

The parameters \(\beta_1, \alpha_1, \beta_2\) and \(\alpha_2\) could be estimated simultaneously.

Model 2: Fitting of a two parameter logistic model

\[
Tn = \frac{1}{1 + e^{-(\beta x + \alpha)}}
\]
\[
\log \left( \frac{n}{100-n} \right) = a + \beta t \quad (3)
\]

When the lower and upper limit of \( n \) were defined as zero and 100, respectively, the parameters, \( a \) and \( \beta \), can be estimated.

Model 3: Fitting of a three parameter logistic model

\[
\log \left( \frac{n}{C_1-n} \right) = a + \beta t \quad (4)
\]

When the lower limit of \( n \) was defined as zero and the upper limit was parameterised, the parameters, \( a \) and \( \beta \), can be estimated.

RESULTS AND DISCUSSION

1. Effect of White Carbon on Lag Time and Release Rate

Figure 3 showed the schematic structure of TCRG. White carbon was included in water insoluble polymer membrane (PVC membrane) as an anti-blocking agent.

As the amount of white carbon decreased, lag time was prolonged and release rate decreased (Fig. 4). If lag time was defined as the time (\( T_{5\%} \)) required to release within 5% of the loaded pesticide, \(^{11}\) there was a relationship between \( T_{5\%} \) and the amount of white carbon

\[
Y = -44X + 47.33, \quad Y: \text{ days}, \quad X: \text{ amount of white carbon (\%), correlation coefficient: 0.9673}. \]

The relationship between the release rate and the amount of white carbon was also examined. A good correlation was between logistically remaining percent of metominostrobin in granules and days after initiation of release, so the slope of line in the graph was defined as the constant of release rate. \(^{12}\) The constant was correlated with the amount of white carbon

\[
Y = 0.38X - 0.171, \quad Y: \text{ constant of release rate (days/\%), } X: \text{ amount of white carbon (%), correlation coefficient: 0.9730}. \]

From the above result, it appeared that lag time and release rate could be controlled by the amount of white carbon contained in the membrane.

In the previous report, \(^{5}\) it was described that lag time and release rate could be controlled by the amount of water insoluble polymer membrane and swelling agent. In the study, as these amount increased, the yield of granules tended to decrease because of agglomeration among granules. However, even though the amount of white carbon increased, an almost quantitative yield of granules was obtained. Therefore, it was suggested that this preparation of TCRG was practically useful.

2. Water Permeability through Film

Figure 5 showed the relationship between the amount of white carbon and the water permeability through film. Thickness of each film was 452±12 \( \mu m \). It was found that the linear slope in graph, that is, the rate of water permeability became faster with increase in the white carbon content in the film. A good correlation was between the amount of white carbon and the rate of water permeability

\[
Y = 0.195X - 0.0019, \quad Y: \text{ rate of water permeability (g/days), } X: \text{ amount of white carbon (%), correlation coefficient : 0.9945}. \]

Fig. 3 Schematic structure of time-controlled release granule (TCRG).

a : core particle (silica sand), b : mixed powder layer containing active ingredient (metominostrobin), swelling agent (acrylate starch) and filler (talc), c : water-insoluble polymer membrane layer (PVC) containing white carbon.

Fig. 4 Effect of white carbon contained in water insoluble polymer membrane on release profile. The amount of white carbon was designated in parentheses.

Fig. 5 Effect of white carbon on water permeability through film.
3. Tensile Strength of Film

Figure 6 showed the relationship between the amount of white carbon and tensile strength of film. It was found that the tensile strength of film decreased with increase in the white carbon content in film. A good correlation was between the amount of white carbon and tensile strength of film \[ Y = 1031 e^{-2.71x}, \] where \( Y \): tensile strength of film \( (N/cm^2) \), \( X \): amount of white carbon\( (\%) \), correlation coefficient: 0.9904.

After water insoluble polymer membrane is destroyed, metominostrobin is released rapidly from TCRG. The release of active ingredient from TCRG is dependent on swelling rate and tensile strength of membrane. The swelling rate is influenced by the water permeability through membrane. Therefore, it is thought that the release profile of active ingredient from TCRG can be controlled by the amount of white carbon which regulates water permeability and tensile strength of film.

4. Prediction of Release Profile by the Amount of White Carbon

We studied whether release profile could be predicted by the amount of white carbon using a statistical method.

4.1 Simultaneous fitting of two step single regression model

In Eq. (2), \( \beta_1, \alpha_1, \beta_2 \) and \( \alpha_2 \) were estimated as \( -34.59 \pm 5.88, \alpha_1 \) \(-35.59 \pm 4.55, \beta_2 \) \( 5.74 \pm 1.09 \) and \( \alpha_2 \) \( 1.21 \pm 0.63 \). As shown in the fitting plot, Fig. 7, there was a significant difference between the actual release profile and two step single regression model.

4.2 Fitting of two parameter logistic model

As the equation of two parameter logistic model, Eq. (3) was applied. In this model, when the lower and upper limits of \( n \) were defined as zero and 100, \( \alpha \) and \( \beta \) were estimated. Eq.(3) was converted into the following equation which estimated \( n \),

\[ n=100 \cdot \exp (\alpha + \beta t)/[\exp(\alpha + \beta t)+1] \] (6)

If there is a linear relationship between the amount of white carbon and parameter (reparametrization), Eq.(6) was converted by model fitting as follows.

![Fig. 6 Effect of white carbon on tensile strength of film.](image)

![Fig. 7 Prediction of release profile by single regression model fitting.](image)

### Table 2 Estimated value, standard deviation, 95% confidential interval and residual dispersion of parameters in the case of fitting two parameter logistic model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated value</th>
<th>Standard deviation</th>
<th>95% confidential interval</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_0 )</td>
<td>-8.838</td>
<td>1.457</td>
<td>-11.833</td>
<td>-5.844</td>
<td></td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>5.604</td>
<td>1.558</td>
<td>2.402</td>
<td>8.807</td>
<td></td>
</tr>
<tr>
<td>( \beta_0 )</td>
<td>-0.033</td>
<td>0.037</td>
<td>-0.109</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>( \beta_1 )</td>
<td>0.313</td>
<td>0.061</td>
<td>0.188</td>
<td>0.439</td>
<td></td>
</tr>
</tbody>
</table>

Residual dispersion: 57.29.
\[ n = 100 \cdot \exp \left( a_0 + a_1 x + (\beta_0 + \beta_1 x) t \right) \]
\[ / \left( \exp \left( a_0 + a_1 x + (\beta_0 + \beta_1 x) t \right) + 1 \right) \]  

(7)

Since this model was fitted, the estimated value of parameter, standard deviation and 95% confidential interval (lower limit, upper limit) were shown in Table 2. The graph fitted in this model was shown in Fig. 8. In this graph, there was a better suitability between actual release profile and two parameter logistic model at the white carbon amount of 1.0 and 0.75% as compared with two step single regression model. However, there was little suitability at the white carbon amount of 0.5% and residual dispersion which showed the suitability of model was 57.30.

4.3 Fitting of three parameter logistic model

As the equation of three parameter logistic model, Eq. (4) was applied. In this model, when the lower limit of \( n \) was defined as zero and the upper limit was parameterised, \( a \) and \( b \) were estimated. Eq. (4) was converted into the following equation to estimate \( n \).

\[ n = C_1 \exp(\alpha + \beta t) / [\exp(\alpha + \beta t) + 1] \]  

(8)

If there was a linear relationship between the amount of white carbon and regression parameters (reparametriza-
eq.(8) was converted by model fitting as follows.

\[
\frac{n = (u_0 + u_1 x) \cdot \exp[a_0 + a_1 x + (b_0 + b_1 x) t]}{\exp[a_0 + a_1 x + (b_0 + b_1 x) t] + 1}
\]  \hspace{1cm} (9)

In the case of this model fitting, standard deviation and 95% confidential interval (lower limit and upper limit) were shown in Table 3. The graph fitted in this model was shown in Fig. 9. The residual dispersion value was 28.23, which was smaller than that of two parameter logistic model. Consequently, the suitability of this model was well compared with the other models and the application of three parameter logistic model led us to predict release profile of TCRG by the amount of white carbon in the membrane.

As conclusion, it appeared that the release profile of active ingredient from TCRG could be controlled by the amount of white carbon contained in the membrane. This can be considered as the reason for change of water permeability and tensile strength of water insoluble polymer membrane by white carbon. When the reparameterization model of three parameter logistic model by non linear least-squares method was applied, the release profile could be predicted based on the amount of white carbon.

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要約

メトノストロピンの溶出挙動におよぼす時間制御型溶出性格子の硫性高分子皮膜中に含まれるホワイトカーボンの影響

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メトノストロピンを含有する時間制御型溶出性格子 (TCRG) からの溶出挙動におよぼす硫性高分子皮膜中に含まれるホワイトカーボン (含水無晶形二酸化ケイ素) の影響を調べた。ホワイトカーボンの量が増大するに従って、ラグタイムが短くなり、溶出速度が速くなった。このように、ホワイトカーボンの量によって、ラグタイムおよび溶出速度が変化したのは、その量によって皮膜の水透過性および引張り強度に変化が生じたためと考えられた。また、統計的手法によりホワイトカーボンの量から溶出挙動を予測した結果、非線形最小二乗法による 3 パラメータモデルによって予測が可能であった。

*メトノストロピン含有時間制御型溶出性格子の開発（第 3 報）