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2 **Regular Article**

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4 **Evaluation of the thermosensitive release properties of microspheres containing**
5 **an agrochemical compound**

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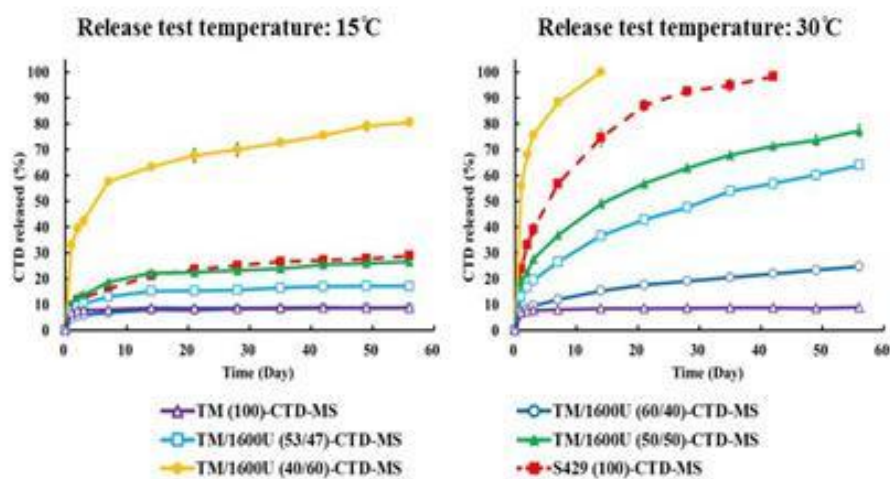
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Graphical abstract

| Sample name (Polyurethane (PU) film) | Extrapolated onset temperature T_o (°C) | Glass transition temperature T_g (°C) | Extrapolated end temperature T_e (°C) |
|-----------------------------------------|----------------------------------------------|--------------------------------------------|--------------------------------------------|
| TM (100)-PU film | 67.5 | 78.7 | 90.0 |
| TM/1600U (60/40)-PU film | 15.1 | 30.4 | 45.7 |
| TM/1600U (53/47)-PU film | 3.5 | 21.3 | 39.1 |
| TM/1600U (50/50)-PU film | -2.6 | 16.2 | 35.0 |
| TM/1600U (40/60)-PU film | -12.3 | 5.3 | 22.8 |
| S429 (100)-PU film | 3.1 | 15.4 | 27.6 |



CTD-MS: Clothianidin Microsphere

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36 **Summary**

37 The purpose of this study was to develop a deeper understanding of the key physicochemical
38 parameters involved in the release profiles of microsphere-encapsulated agrochemicals at different
39 temperatures. Microspheres consisting of different polyurethanes (PUs) were prepared using our
40 previously reported solventless microencapsulation technique. Notably, these microspheres exhibited
41 considerable differences in their thermodynamic characteristics, including their glass transition
42 temperature (T_g), extrapolated onset temperature (T_o) and extrapolated end temperature (T_e). At test
43 temperatures below the T_o of the PU, only 5%–10% of the agrochemical was rapidly released from
44 the microspheres within 1 day, and none was released thereafter. However, at test temperatures
45 above the T_o of the PU, the rate of agrochemical release gradually increased with increasing
46 temperatures, and the rate of release from the microspheres was dependent on the composition of the
47 PU. Taken together, these results show that the release profiles of the microspheres were dependent
48 on their thermodynamic characteristics and changes in their PU composition.

49
50 **Keywords:** Sustained release; agrochemical; polyurethane; microspheres; thermodynamic
51 characteristics.

52
53 **Abbreviations:** PU, polyurethane; CTD, clothianidin; TAP, 2,4,6-Tris(dimethylaminomethyl)phenol;
54 DSC, differential scanning calorimetry; T_g , glass transition temperature; T_o , extrapolated onset
55 temperature; T_e , extrapolated end temperature; CTD-MS, clothianidin microspheres; SEM, scanning
56 electron microscopy; PXRD, powder X-ray diffraction.

57

58 **1. Introduction**

59 Developing sustained-release formulations for agrochemicals is required to diminish the need for the
60 frequent application of these materials, to reduce the environmental exposure, as well as to improve
61 overall agricultural efficiency.¹⁾ Numerous studies have been reported pertaining to
62 microencapsulation, which is a well-known technique for the controlled release of small molecules.²⁻
63 ⁶⁾ Microencapsulation involves the use of liquid droplets or solid particles as core materials, which
64 are covered with a shell-like material, such as an inorganic compound or polymer, to give
65 microencapsulated particles on the micron scale. Products prepared in this way are known as
66 microcapsules, microspheres or microparticles, depending on their morphological characteristics and
67 internal structure.^{7,8)} Microencapsulation has been used to mask the taste and odor characteristics of
68 specific substances, control the release of active ingredients, protect core materials from external
69 environmental factors and improve the ease with which toxic materials can be handled in the
70 pharmaceutical, agricultural, printing and food industries.⁹⁻¹³⁾

71 Solventless microencapsulation processes have recently been studied by several groups
72 because they are simple, cost effective and environmentally friendly.¹⁴⁻¹⁶⁾ We previously reported the
73 development of a new solventless microencapsulation process involving agitation granulation and
74 chemical reaction steps.¹⁷⁾ In our previous report, solid agrochemicals were agglomerated and
75 covered with polyurethane (PU), which was synthesized *in situ* from polyol and isocyanate monomer
76 units (Fig.1 (A)) during the agglomeration process. The resulting PU-covered microencapsulated
77 samples had a median diameter of less than 75 μm and showed sustained release over several months
78 at 25 °C. From a result of inner structural analysis by synchrotron X-ray computed tomography,
79 multiple cores of agrochemical compound and other solid excipient were dispersed in PU. In
80 addition, after agrochemical compound was released, no change in its framework was observed,
81 although voids emerged in the microencapsulated following the release of agrochemical compound.
82 The experimental release data were highly consistent with the Baker– Lonsdale model derived from
83 drug release of spherical monolithic dispersions. These results therefore suggest that our solventless

84 microencapsulation techniques could be used to address some of the issues described above for the
85 formulation of agricultural materials.

86 The optimal temperature for agricultural cultivation can vary considerably depending on the
87 nature of the crop targeted. The optimum daytime cultivation temperatures of many Japanese crops
88 are in the range of 15–30 °C. To ensure that agrochemicals reach their maximum efficacy, further
89 drug release studies are necessary to develop a deeper understanding of their release characteristics
90 from microencapsulated samples at a variety of different temperatures consistent with the optimum
91 cultivation temperature. It was envisaged that the release profiles of agrochemicals from
92 microencapsulated samples would change depending on the temperature, according to the
93 thermodynamic characteristics of the polymer used to coat the core structure. However, there have
94 been very few reports pertaining to the relationship between the release profiles of
95 microencapsulated materials at different temperatures. Furthermore, very little is known about the
96 roles played by the thermodynamic characteristics of the polymeric shell during the release process
97 in terms of its transition from a glass state to a rubber state. Further work is also required to develop
98 a deeper understanding of the key physicochemical parameters affecting the release profiles of
99 microencapsulated materials.

100 In this study, we used our previously reported microencapsulation method to prepare several
101 microencapsulated samples with different PU compositions and a wide variety of thermodynamic
102 characteristics. All of these samples were prepared using one isocyanate and two trifunctional and
103 one bifunctional polyol. The physicochemical properties and release profiles of these
104 microencapsulated samples were determined at a variety of different temperatures. The ultimate goal
105 of this study was to not only evaluate the effects of the PU composition on the physicochemical
106 properties of the microencapsulated samples, but to also develop a deeper understanding of the
107 thermosensitive release properties of these materials.

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109

110 **2. Materials and methods**

111 *2.1. Materials*

112 Clothianidin (CTD), which is an agrochemical compound (Fig. 1 (B)), and CTD pre-mix
113 (CTD/clay = 70/30, d_{50} = 10–20 μm) were supplied by Sumitomo Chemical Co., Ltd (Tokyo, Japan).
114 Fumed silica (AEROSIL300) was procured from Nippon Aerosil Co., Ltd (Tokyo, Japan).
115 Trifunctional polyether polyol (Sumiphen S429 (polyol S429), Mw: 700; Sumiphen TM (polyol TM),
116 Mw: 450) and bifunctional polyether polyol (Sumiphen 1600U (polyol 1600U), Mw: 1000) were
117 procured from Sumika Bayer Urethane Co. Ltd (Hyogo, Japan). Poly(phenylene methylene
118 isocyanate) (polymeric MDI) (Sumidur 44V-10; Functionality, 2.3–2.5) was procured from Sumika
119 Bayer Urethane Co. Ltd. 2,4,6-Tris(dimethylaminomethyl)phenol (TAP) was procured from Kayaku
120 Akzo Corporation (Tokyo, Japan).

121

122 *2.2. Preparation of PU films*

123 The PU films were prepared according to the following method to prevent the occurrence of
124 any thermodynamic effects on the CTD in the microspheres. The compositions of these materials are
125 shown in Table 1. The reactant ratio of isocyanate to hydroxyl moieties was set to one. Isocyanate
126 was added to the polyols, and the resulting mixture was vigorously stirred for 1 min to give a
127 homogenous mixture. The mixture was then cast onto a glass plate using an applicator set at 375 μm .
128 The glass plate was then held in an oven at 80 °C for over 3 h to terminate the urethane reaction.

129

130 *2.3. Differential scanning calorimetry (DSC)*

131 DSC thermograms of PU were measured in an aluminum pan using a DSC Q100 system (TA
132 instruments, New Castle, DE, USA). The DSC curves were recorded a temperature in the range of
133 –90 to 200 °C at a heating rate of 10 °C min^{-1} under a nitrogen atmosphere. The extrapolated onset
134 temperature (T_o), extrapolated end-point temperature (T_e) and midpoint temperature were determined
135 from the DSC curves.¹⁹⁾ The midpoint temperature is commonly used as the glass transition

136 temperature (T_g).

137

138 2.4. Preparation of CTD microsphere (CTD-MS) samples using an agitation granulation process

139 All of these samples were prepared according to the agitation granulation process (Fig. 2)
140 reported in our previous study.¹⁷⁾ Briefly, 300 g of CTD pre-mix (CTD content: 69.1%) was loaded
141 into a high-speed mixer (EarthTechnica Co., Ltd, Tokyo, Japan) and heated to 80 ± 5 °C with the
142 agitator and chopper blades set at 850 and 2,500 rpm, respectively, to mix the material. A
143 predetermined amount of polyol mixture (Table 1) was added over 2 min to the pre-mixed material,
144 and mixing was continued for 3 min. A predetermined amount of isocyanate (Table 1) was then
145 added to the mixture over 2 min, and mixing was continued for 6 min. This sequential addition
146 process (i.e., polyol mixture and isocyanate) was repeated totally 24 times. The encapsulated samples
147 were then annealed for 30 min at 80 ± 5 °C to complete the PU polymerization process. Fumed silica
148 (2.4 g) was then added to the encapsulated sample, and the resulting mixture was mixed for 3 min to
149 prevent agglomeration. After cooling to ambient temperature, the encapsulated samples were sieved
150 thorough a JIS standard sieve (sieve size 300 μm); the sieved samples were defined as CTD-MS. The
151 coating ratio and microsphere yield were calculated using the following equations:

$$152 \quad \text{Coating ratio (\%)} = \frac{\text{Total amount of polyol mixture and isocyanate}}{\text{Amount of CTD pre-mix}} \times 100 \quad (1)$$

$$153 \quad \text{Microsphere yield (\%)} = \frac{\text{Amount of encapsulated sample passed through the sieve}}{\text{Total amount of encapsulated sample before sieving}} \times 100 \quad (2)$$

154

155 2.5. Particle size distribution

156 Five grams of each CTD-MS sample was sieved for 5 min on a sieve shaker (Vibratory Sieve
157 Shaker AS 200, Retsch) equipped with two sieves (75 and 150 μm). The sieved samples were
158 weighed. Each CTD-MS sample was evaluated in triplicate.

159

160 2.6. Scanning electron microscopy (SEM)

161 The surface morphologies of the CTD-MS samples were observed by SEM (S-3000N, Hitachi,
162 Ltd., Tokyo, Japan). Each CTD-MS sample was sputter-coated with a Pt-Pd alloy in an ion sputter
163 before being observed by SEM.

164

165 2.7. CTD content in CTD-MS

166 One hundred milligrams of each CTD-MS sample was extracted with 100 mL of
167 tetrahydrofuran in a glass vial. The resulting suspension was filtered through a syringe filter (pore
168 size = 0.45 μm) and the filtrate was analyzed by HPLC with a reversed-phase column (Inertsil
169 ODS-EP 5 μm , ϕ 4.6 \times 150 mm; GL Sciences, Tokyo, Japan). A wavelength of 270 nm was selected
170 for the detection of the CTD by ultraviolet absorption. The column was eluted with a mobile phase
171 consisting of acetonitrile/water/phosphoric acid = 200/800/1 (v/v) at a flow rate of 1.0 mL/min.
172 Three measurements were carried out for each of the CTD-MS samples. The encapsulation ratio was
173 calculated using equation (3):

$$174 \text{ Encapsulation ratio (\%)} = \frac{\text{CTD content in the CTD microspheres}}{\text{Theoretical CTD content in the CTD microspheres}} \times 100. \quad (3)$$

175

176 2.8. Release test

177 A small portion (52 mg) of each CTD-MS sample was added to 450 mL of three-degree hard
178 water, which was prepared by dissolving MgCl_2 (21.7 mg) and CaCl_2 (47.4 mg) in 1000 mL of
179 distilled water under stirring at 100 rpm. The temperature of the test solution was kept at 15.0 ± 0.3 ,
180 20.0 ± 0.3 , 25.0 ± 0.3 or 30.0 ± 0.3 $^\circ\text{C}$. Two milliliters of the test solution was taken at a
181 predetermined time and the CTD content in the solution was quantified by HPLC, as described above.
182 The release amount of CTD was determined using equation (4):

$$183 \text{ Release amount of CTD (w/w\%)} = \frac{\text{CTD content in the solution}}{\text{CTD content in the weighed CTD microspheres}} \times 100. \quad (4)$$

184 Each CTD-MS sample was evaluated in triplicate. Release tests were continued up to 56 days
185 until almost 100% of the CTD was released.

186

187 2.9. Statistical analysis of release profiles

188 The difference factor (f_1) was used to evaluate the difference between two release profiles.²⁰⁾

189 The f_1 was calculated by the following equation:

$$190 f_1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n |R_t|} \right\} \times 100. \quad (5)$$

191 where n is the number of time points, R_t is the release amount of the Release profile 1 at time t , and
192 T_t is the release amount of Release profile 2 at time t . According to the FDA's guidance²¹⁾, release
193 data time points below 85% release amount of CTD and only one sampling time point above 85%
194 release amount of CTD were used to calculate f_1 . The calculated f_1 values up to 15 (0–15) indicate
195 the equivalence of two release profiles, and the calculated f_1 values over 15 indicate a significant
196 difference between two release profiles.

197

198 2.10. Powder X- ray diffraction (PXRD)

199 CTD pre-mix and CTD-MS samples were analyzed by PXRD (Rigaku Rotaflex RU-200B,
200 Rigaku Corp, Tokyo, Japan) under the following operating conditions: voltage: 30 kV, current: 15
201 mA; target: Cu; scanning speed: 4 °/min; 2 θ range: 3–40°.

202

203 3. Results and discussion

204 3.1. Thermodynamic characteristics of PU films

205 Six different PU films (Table 1) were prepared and analyzed by DSC to determine some of
206 their thermodynamic characteristics, including their T_o , T_g and T_e values. The results in Tables 3
207 show that the PU films containing larger amounts of isocyanate had higher T_o , T_g and T_e values. As
208 shown in Fig. 3, there was a linear relationship between the amount of isocyanate in the PU films and
209 their T_g values. This result therefore indicated that the thermodynamic characteristics of PU films
210 could be tailored by adjusting the amount of isocyanate in the PU composition. However, a

211 comparison of the TM/1600U (50/50)-film with the S429 (100)-film, which both contained the same
212 amount of isocyanate, revealed that whilst both of these films had the same T_g value, the S429
213 (100)-film had higher T_o and lower T_e values. The S429 (100)-film was therefore found to change in
214 a narrow range from the glass state to the rubber state. This change could be attributed to differences
215 in the chemical structures of these films. For example, the PU used to prepare the S429 (100)-film
216 was composed entirely of trifunctional polyol, making its structure much more uniform than that of
217 the TM/1600U (50/50)-film.

218

219 ***3.2. Effects of the PU composition on the physicochemical properties of the CTD-MS samples***

220 Six CTD-MS samples with different PU compositions but the same coating ratio were prepared
221 using our solventless microencapsulation process. Table 4 shows the physicochemical properties of
222 these six CTD-MS samples, including their microsphere yield and encapsulation ratio data. With the
223 exception of the TM/1600U (40/60)-CTD-MS, the microsphere yields of the other five samples were
224 >95%. The encapsulation ratios of all six samples were >98%. Our previous result also showed all
225 encapsulation ratios of 14 samples using this technique were > 95%¹⁷⁾, indicating that this
226 microencapsulation process would be robust even if the PU compositions changed. As shown in Fig.
227 4, the median diameters of all the CTD-MS samples were less than 75 μm , except for TM/1600U
228 (40/60)-CTD-MS. Furthermore, the median diameter increased as the amount of isocyanate in the
229 PU composition increased. The results of our previous report¹⁷⁾ showed that the solventless
230 microencapsulation process involved two phases, including (i) an aggregation phase, where the
231 primary particles were aggregated by PU; and (ii) a coating phase, where the aggregated particles
232 were covered by PU. Given that PU materials with low isocyanate contents are highly adhesiveness
233 because of their low T_g values, they can form large aggregates in their aggregation phase. Fig. 5
234 shows SEM images of the different CTD-MS samples. These images revealed that there were no
235 discernible differences between the different samples. The PU composition was therefore found to
236 have very little impact on the surface morphology of the CTD-MS samples.

237

238 **3.3. Effect of the PU composition on the release profiles of the CTD-MSs**

239 Fig. 6 shows the release profiles of six different CTD-MS samples at four different test
240 temperatures (15–30 °C), and Table 5 shows the differences between two release profiles. As for the
241 five CTD-MS samples with PU containing polyol TM, CTD was released at a much greater rate from
242 CTD-MS samples containing lower amounts of polyol TM for all of the temperatures tested in the
243 current study. The amount of CTD released from the CTD-MS samples increased with increasing
244 temperature, except for TM (100)-CTD-MS. Notably, the differences observed in the release profiles
245 of the different CTD-MS samples at different temperatures were much more pronounced for the
246 CTD-MS prepared with lower amounts of polyol TM. The results of the release tests for these
247 samples showed that their release temperatures were greater than their T_o values, except for TM
248 (100)-CTD-MS. The thermodynamic characteristics of the PU materials changed from those of a
249 glass state to a rubber state across all of the temperature ranges tested in the current study. The
250 increase in the free volume within the PU as a result of the transition to the rubber state made it much
251 easier for the CTD to diffuse through the PU. Furthermore, pronounced changes in the
252 thermodynamic characteristics of the PU led to considerable differences in the release profiles of
253 CTD-MSs at different temperatures. In contrast, the release profile of TM (100)-CTD-MS remained
254 largely unchanged for all of the temperatures tested in the current study, with 5%–10% of the CTD
255 being released within 1 day, followed by negligible CTD releases thereafter. The glass state of the
256 PU probably prevented the diffusion of CTD through its structure, only allowing for the CTD near to
257 the surface of the CTD-MS to be released, as exemplified by the T_e values being higher than all of
258 the test temperatures.

259 We also compared TM/1600U (50/50)-CTD-MS and S429 (100)-CTD-MS, which contained
260 the same amount of isocyanate in their PU. Although the release profiles of these two materials were
261 almost identical at 15 °C, CTD was released at a much greater rate from S429 (100)-CTD-MS at
262 temperatures higher than 20 °C (Fig. 6 and Table 6).

263 As shown in Table 3, the T_g value of the S429 (100)-film was almost identical to that of the
264 TM/1600U (50/50)-film, but the difference between the T_g and T_e values of the S429
265 (100)-CTD-film was narrower than that of the TM/1600U (50/50)-film. The differences in
266 thermodynamic characteristics of these PU films may be responsible for the differences observed in
267 the release profiles of S429 (100)-CTD-MS and TM/1600U (50/50)-CTD-MS at temperatures above
268 20 °C ($>T_g$). As shown in Fig. 7, the PXRD patterns between CTD pre-mix and two CTD-MSs were
269 almost same, indicating that the changes of crystallinity of CTD before and after microencapsulation
270 did not occur and this was not involved in the changes of release behaviors of CTD from the
271 CTD-MSs.

272

273 **4. Conclusion**

274 We have investigated the thermodynamic characteristics of the PU materials used during the
275 microencapsulation of CTD by adjusting their composition. The release profiles of the CTD-MS
276 were found to be strongly affected by the thermodynamic characteristics of the PU. At test
277 temperatures below the T_o of the PU, around 5%–10% of the CTD was rapidly released from the
278 CTD-MS within 1 day, and none was released thereafter. In contrast, at test temperatures above the
279 T_o of the PU, the rate of the release of CTD from the CTD-MS gradually increased with increasing
280 temperatures, and the rate of release was dependent on the composition of the PU. This could be
281 attributed to changes in the thermodynamic characteristics of the PU as it transitioned from a glass
282 state to a rubber state, leading to an increase in its free volume. In addition, the particle size and
283 surface morphology characteristics of the CTD-MS showed very little dependence on the
284 composition of the PU, except for PUs with very low glass temperatures. In conclusion, we have
285 developed an optimized procedure for the microencapsulation of agrochemicals using a specially
286 designed PU.

287

288 **Conflict of Interest References**

289 The authors declare no conflict of interest.

290

291 **References**

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323

324 **Figure captions**

325 **Fig. 1.** Reaction formula of PU (A) and chemical structure of CTD (B).

326

327 **Fig. 2.** Manufacturing process flow chart.

328

329 **Fig. 3.** Relationship between the ratio of isocyanate and T_g .

330

331 **Fig. 4.** Particle size distributions of the different CTD-MS samples.

332

333 **Fig. 5.** SEM surface images of CTD-MS with different PU compositions.

334

335 **Fig. 6.** Release profiles of CTD-MSs with different PU compositions at different temperatures. (A)

336 15 °C, (B) 20 °C, (C) 25 °C and (D) 30 °C. The release data of S429 (100)-CTD-MS at 25 °C was

337 obtained from our previous report.¹⁷⁾

338

339 **Fig. 7.** PXRD patterns of CTD pre-mix (A), S429 (100)-CTD-MS (B) and TM/1600U

340 (50/50)-CTD-MS (C).

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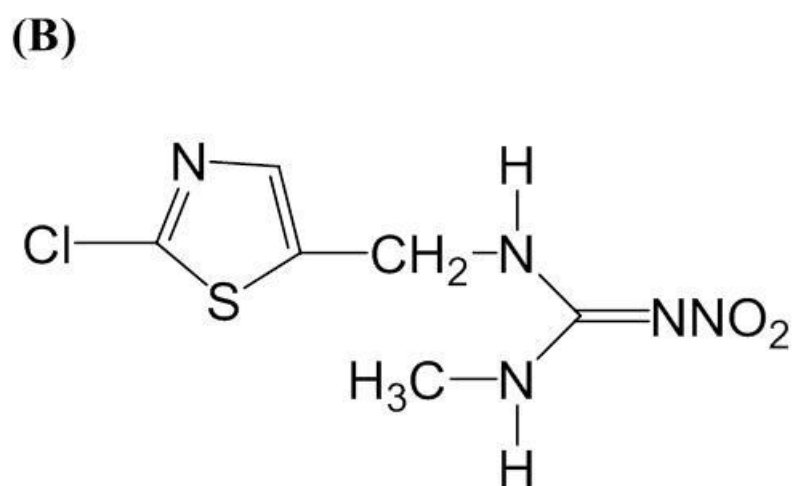
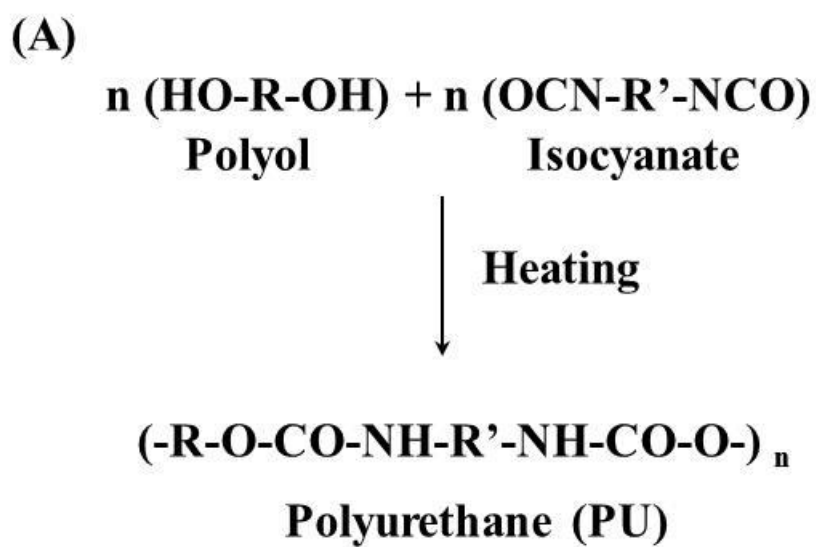


Fig.1

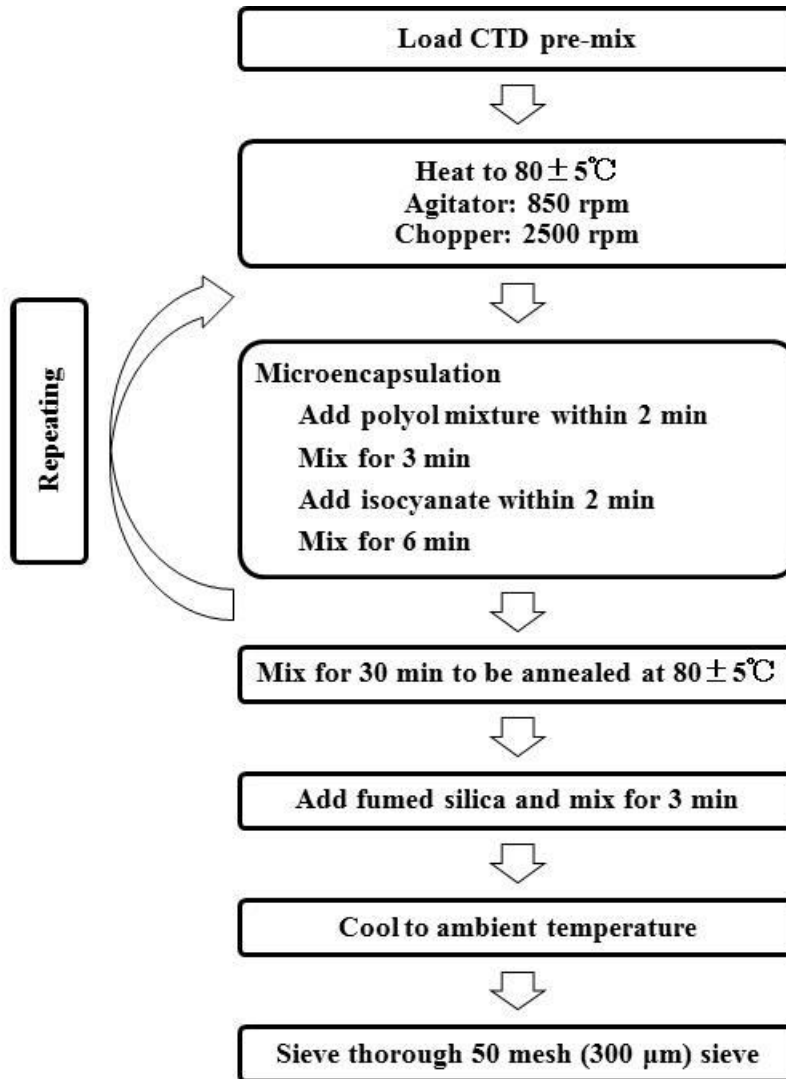


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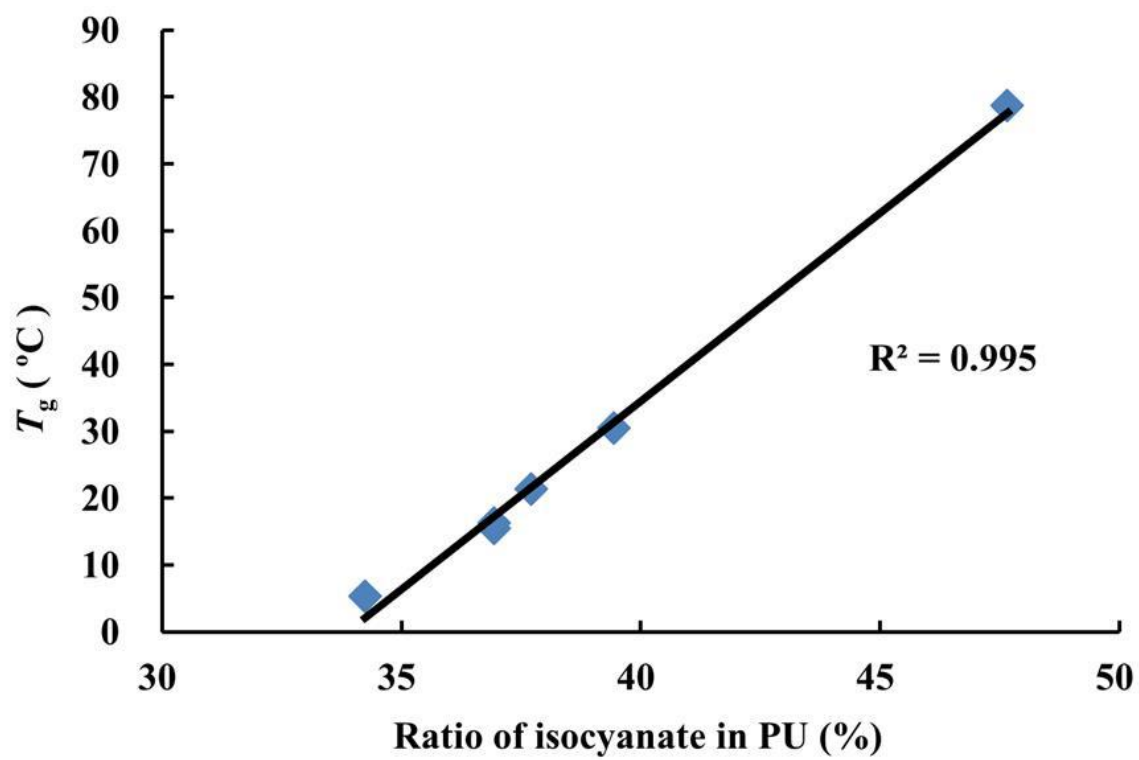


Fig.3

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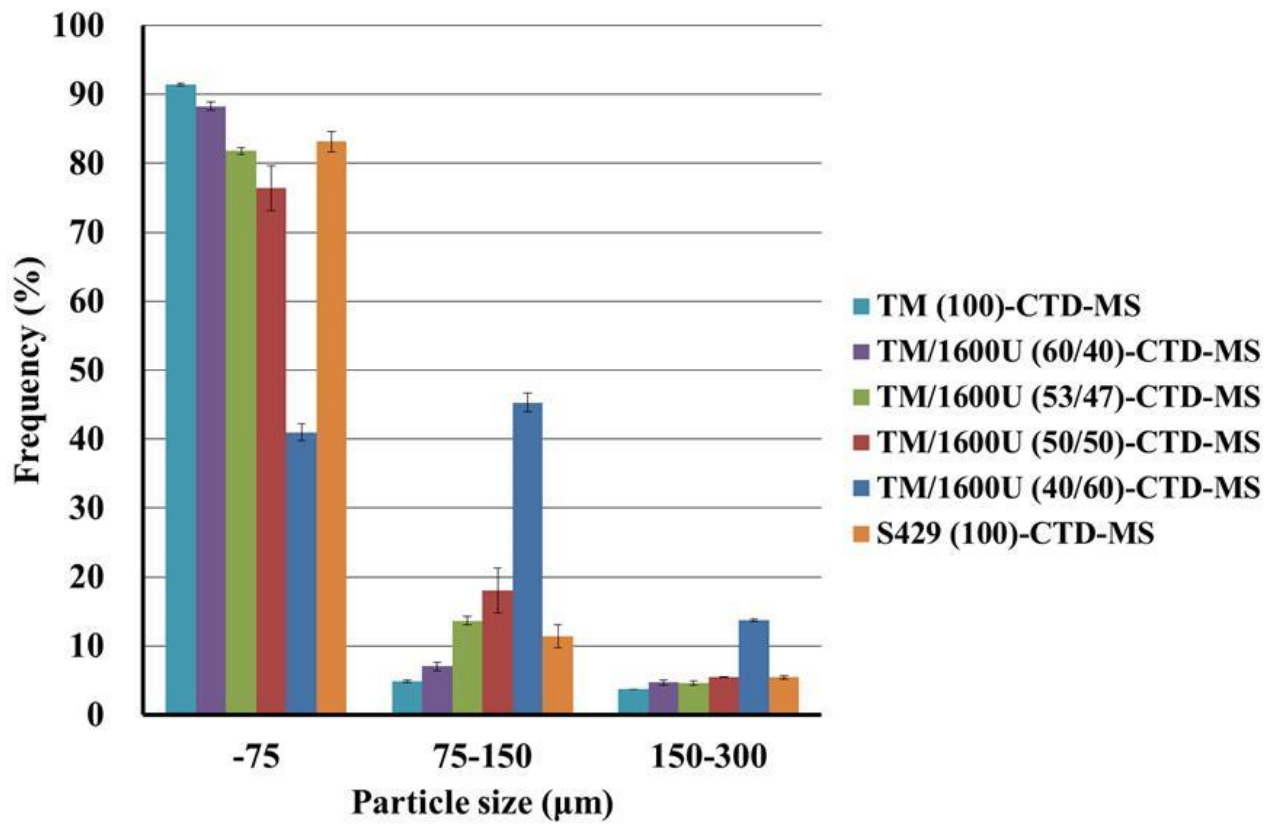
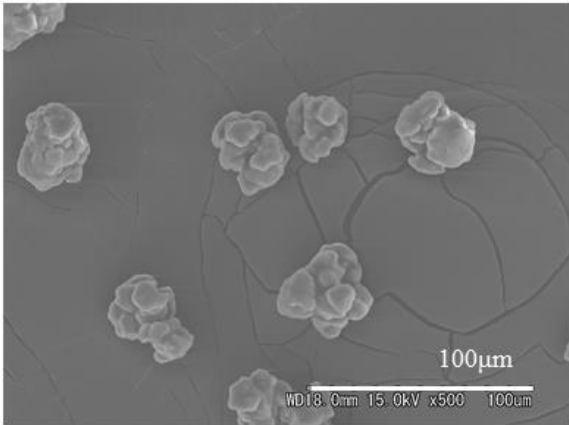


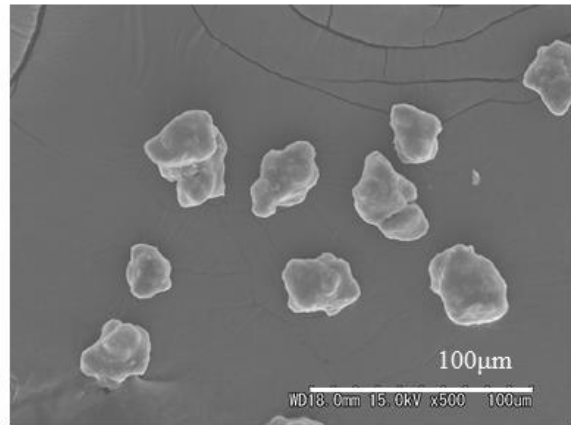
Fig.4

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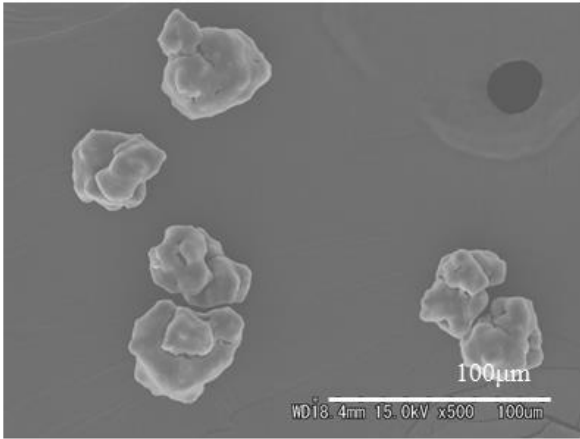
TM (100)-CTD-MS



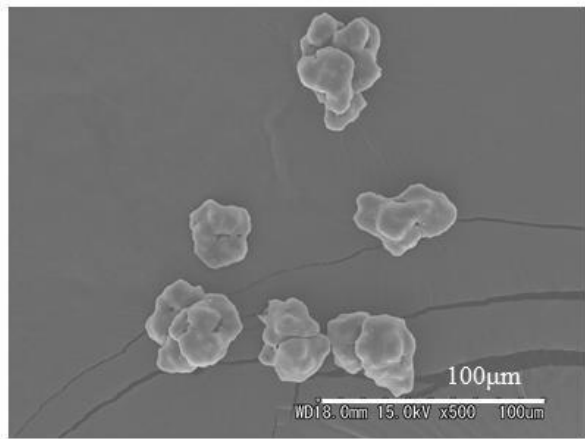
TM/1600U (60/40)-CTD-MS



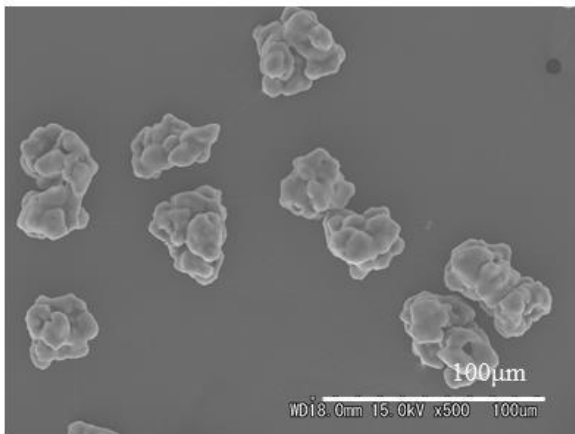
TM/1600U (53/47)-CTD-MS



TM/1600U (50/50)-CTD-MS



TM/1600U (40/60)-CTD-MS



S429 (100)-CTD-MS

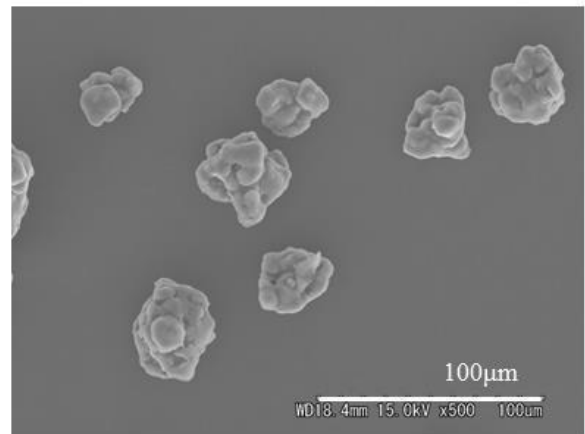


Fig.5

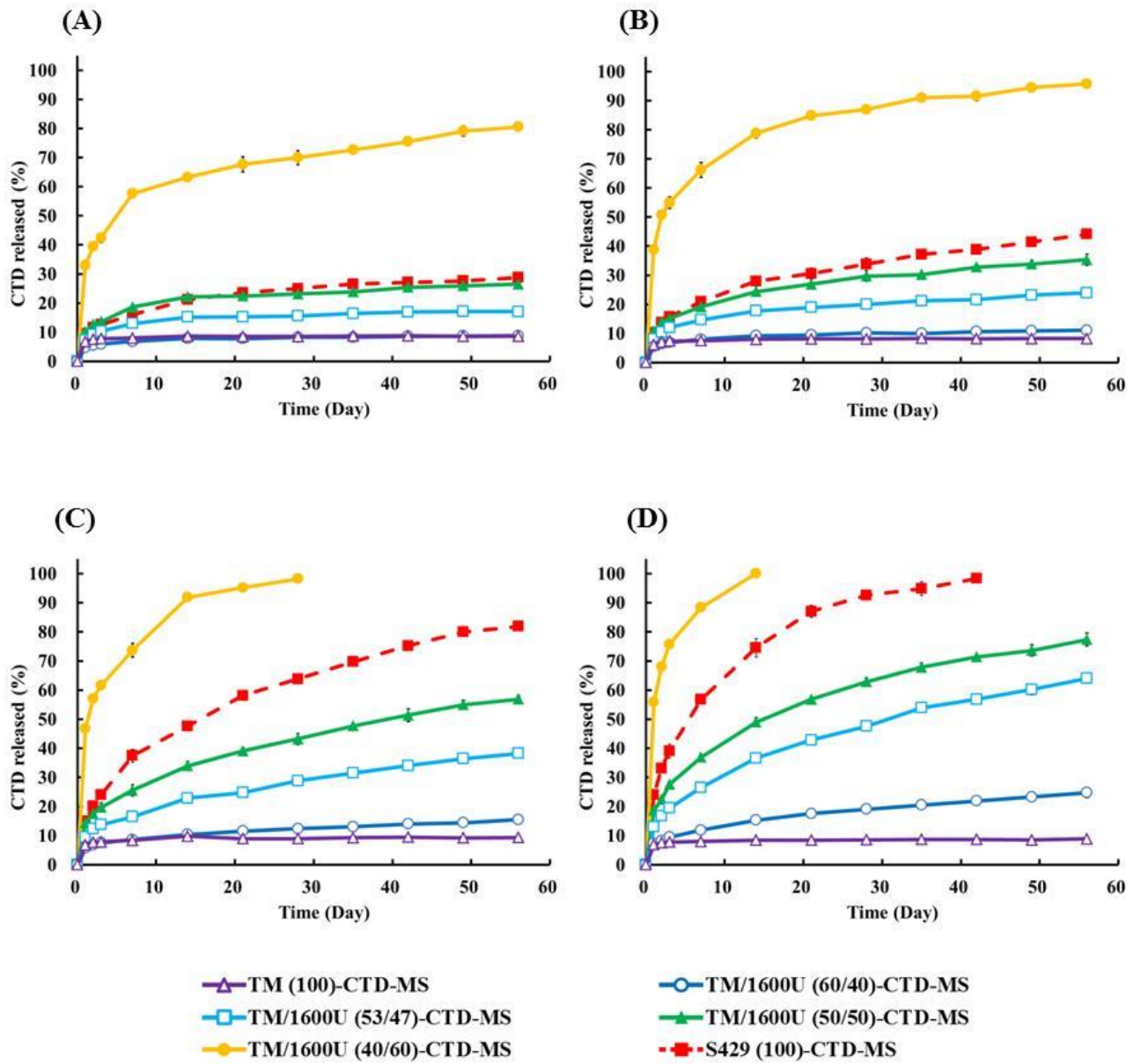


Fig.6

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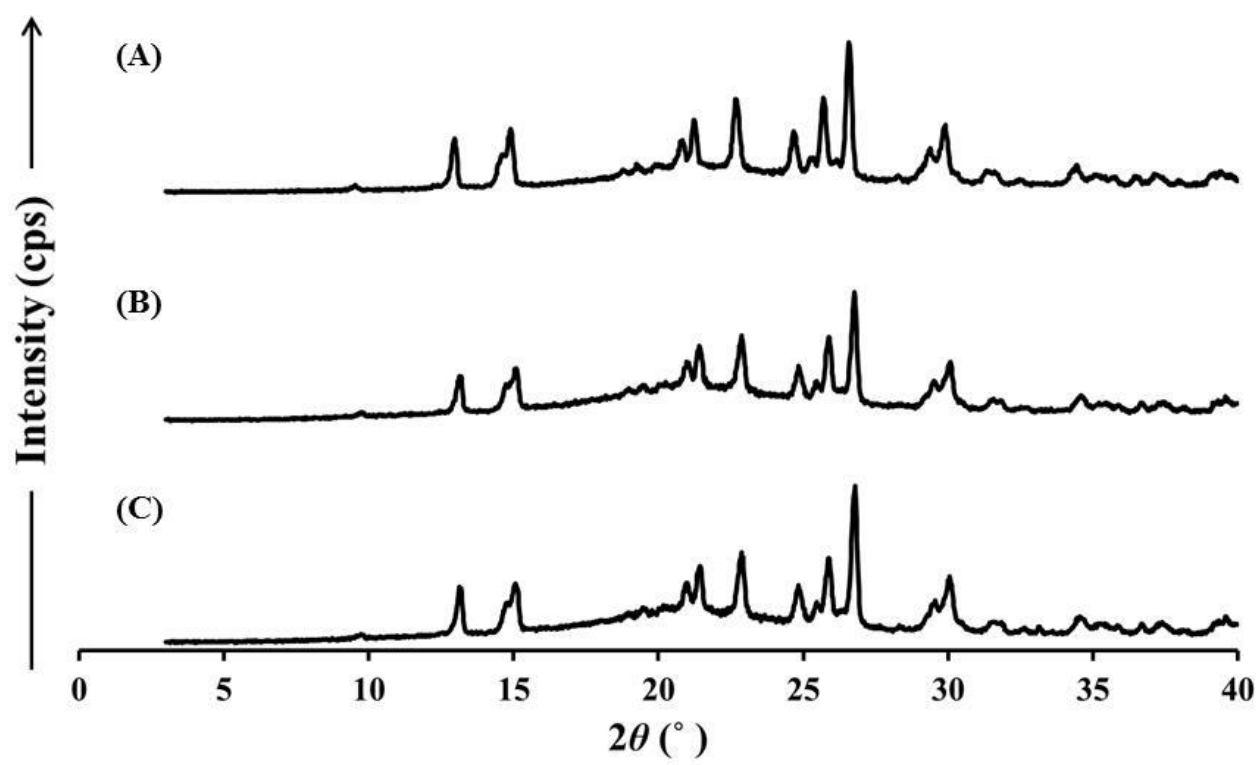


Fig.7