RSC Advances

1 **The in situ monitoring of transformation of Moxidectin Ethanol Solvate to**

2 **Form Ⅰ in Ethanol-Water Mixture**

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19   **Abstract**: Moxidectin is single-component and semisynthetic macrocyclic lactone antibiotic，

20   which has been widely used in the prevention and treatment of parasites in farm animals. In

21   this paper, the transformation of ethanol solvate to form Ⅰ of moxidectin in ethanol-water

22   mixture was studied. Offline methods and online instruments were used to monitor and

23   identify the transformation process，and influence of water content and temperature were

24   discussed. It is noted that the transformation kinetics is highly sensitive to both the solvent

25   composition and temperature and the transformation rate is a function of ethanol content in

26   aqueous ethanol mixtures. The solvent-mediated polymorphic transformation mechanism

27   from ethanol solvate to form Ⅰ was suggested，and the process is controlled by the

28   nucleation and growth rate of the stable form. Understanding these effects can aid

29   optimization and improve process control in the crystallization of moxidectin.

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1. Introduction

The arrangement of molecules or atoms in lattice will be changed due to kinetic and thermodynamic factors during crystallization, and different crystal structure will be formed, which means that the same organic molecule has two or more kinds of spatial arrangement pattern. This phenomenon is called polymorphism[1,2] which can be widely found in pharmaceutical substances. Solvate and hydrate are known as pseudopolymorphic[2,3], which combines the solvent/water molecule into the unit cell during the crystallization. Different crystal forms usually have different physical and chemical properties[4,5], such as solubility, bioactivity, melt point, dissolution rate and so on. Thus the process control of polymorphic drugs and the transformation study between different crystal forms are always the research hotspots in pharmaceutical industry[6,7]. The widely accepted mechanism of the transformation between different crystal forms can be described as solution-mediated transformation (SMT)[8] or solid-state transformation (SST)[9].

In the traditional research, off line techniques including Powder X-ray diffraction (PXRD)[10]、 differential scanning calorimetry (DSC)[11,12]and thermogravimetric analysis (TGA)[13] were widely used to identify the polymorphic transformation. Recently, online technologies including Focused beam reflectance measurement (FBRM), Particle vision measurement (PVM), Fourier transform infrared (FTIR) and online Raman spectroscopy have been introduced to monitor the phase transformation in situ. FBRM[14], for an example, can be applied to in situ record the change of the chord length distribution and particle counts during the transformation. PVM[6] and FTIR[15] have been used to trace the morphology of solid phase and concentration of the liquid phase in real time. Moreover，Online Raman spectroscopy[7,16] is a useful on-line technique which can be used to analyze the composition of the solid phase in situ.

58   Moxidectin[17,18] is single-component and semisynthetic macrocyclic lactone agricultural

59   antibiotic belonging to the class of milbemycin, which is the derivative of nemadectin and

60   produced by fermentation of Streptomyces. Because of its broad-spectrum，high efficiency

61   and safety, moxidectin is widely used in the prevention and treatment of parasites in

62   mammals such as cattle and sheep etc. The structure of moxidectin is shown in Fig.1. As it

63   can be seen moxidectin has Methoxine in C-23, which makes it has higher solubility in

64   organic solvent compared with ivermectin, so it can be made into different drugs with

65   different excipients such as injection[19]、 paste[20]、 pour-on solution[21] etc.

66   Two forms of moxidectin have been reported including a single crystal structure named

67   form Ⅰ[22,23] in 1988, and an ethanol solvate[24] in 2013. In our study we found that when the

68   temperature was equal or higher than 308.15 K, solid-state transformation of ethanol solvate

69   to amorphous form of moxidectin would occur, indicating that ethanol solvate was not stable

70   during the drying、 formation、 storage and transport of moxidectin. However we also found

71   that form Ⅰ could be prepared in ethanol with water as anti-solvent, due to its good solubility

72   in ethanol and insolubility in water. The hydrogen bonds between moxidectin and water

73   molecular would drive the formation of sticky gel product, which could debase the quality of

74   crystals and make the process operation difficult[25]. In our research, we have found that after

75   ethanol solvate was obtained by cooling crystallization, it would transform to form Ⅰ when it

76   was heated up to 308.15 K. It is very important to study the transformation of ethanol solvate

77   to form Ⅰ in order to obtain form Ⅰ without gelation. No reference was found on the

78   transformation of these two forms of moxidectin by far.

79   In this paper, the transformation of ethanol solvate to form Ⅰ of moxidecitn in

80   ethanol-water mixture was studied. FBRM、 PVM and on-line FTIR were introduced to in

81   situ monitor the transformation process and the factors affecting the transformation were

82   investigated. This work gives better understanding on the polymorphic transformation

83   mechanism of moxidecitn, as well as offers a novel way and critical information to control the

84   manufacture process of commercial form I products.

85   **2. Experimental section**

86   **2.1 Materials**

87   Ethanol solvate of moxidectin (provide by Hisun Pharmaceutical Co., Ltd) was prepared

88   by cooling crystallization in ethanol as follow: adding 5 g moxidectin into 10 ml ethanol and

89   heating up the slurry to 50 ℃. After 30 min of dissolution, the saturated solution was cooled

90   to 10 ℃ at a cooling rate of 0.5 ℃/min. Ethanol of analytical grade was supplied by Tianjin

91   KeWei Chemical Reagent Co., Ltd in China. The distilled deionized water was used to

92   prepare mixture of ethanol and water in all experiments.

93   **2.2 Characterization of ethanol solvate and form Ⅰ of moxidectin.**

94   Ethanol solvate and form Ⅰ of moxidectin were characterized by several off-line

95   techniques, including PXRD、 FTIR and optical microscope.

96   PXRD experiments were conducted by a D/max-2500 diffracometer (Rigku, Japan) at 40

97   Kv, 100 mA with a Cu Kα radiation (1.5406 Å). The diffraction data were collected from 2°

98   to 35° in 2θ, with a scan speed of 8° /min.

99   The FTIR spectra were obtained by a TENSOR 27 spectrometer (Bruker, Germany)

100   using KBr powder as the background, with wavenumber ranges from 3600 to 400 cm^{-1}.

101   The crystal morphologies were captured by a BX51 optical microscope (Olympus, Japan)

102   with a 40× objective lens and a 10× ocular lens.

103   **2.3 Transformation experiments.**

104   The transformation experiments of ethanol solvate to form Ⅰ of moxidectin were carried

105   out on an Easymax TM 102 (Mettler Toledo, Switzerland) with a 100 ml vessel. The

106   transformation processes were investigated by adding certain amount of ethanol solvate into

107   40 ml ethanol-water mixtures (with different water contents) under specific temperature, and

108   the experimental conditions are showed in Table 1.

109   A M400LF FBRM probe (Mettler Toledo, Switzerland) was inserted in the vessel to

110   record the change of particle counts at an interval of 60 seconds. The crystal morphologies

111   were investigated by HNK250 PVM (Mettler Toledo, Switzerland) once a minute. ReactIR

112   4000 FTIR (Mettler Toledo, Switzerland) was introduced to trace the concentration of

113   solution in real time with an interval of 60 seconds, with wavenumber from 3600 to 400 cm^{-1}.

114   During the transformation, the slurry was sampled and filtered by a Buchner funnel at

115   different time. The solid was dried at 303.15 K and measured by XRD to analyze the solid

116   composition.

117   **3. Results and discussion**

118   **3.1 Characterization of ethanol solvate and form Ⅰ of moxidectin.**

119   The experimental data are shown in Fig. 2, and compared with the single crystal data

120   obtained from CCDC. It can be seen from Fig. 2 that the form Ⅰ crystals prepared in our

121   study has the same crystal structure with that reported by Beddall *et al*. It also can be seen that

122   the characteristic peaks of ethanol solvate and form Ⅰ are totally different from each other.

123   There are characteristic peaks with 7.099, 8.916, 9.700, 11.120 12.041, 12.822, 15.180,

124   16.542, 17.880 for form Ⅰ and 7.740, 8.121, 8.501, 10.522, 11.599 for ethanol solvate,

125   respectively. Therefore, the two forms of moxidectin can be identified effectively by PXRD.

126   The FTIR spectra of ethanol solvate and form Ⅰ are presented in Fig. 3, which can be

127   used to further identify the two forms of moxidectin. It can be seen that the C=O stretching

128   vibration occurs at 1734 cm−1 for ethanol solvate and shifts to 1707 cm−1 for form Ⅰ. Two

129   hydroxyl groups in moxidectin molecule can form hydrogen bonds with two ethanol

130 molecules respectively. Hydroxyl group on C-5 is as a donor and Hydroxyl group on C-7 is as

131 an acceptor. The presence of hydrogen bonds makes the crystal structures of ethanol solvate

132 and form Ⅰ are different, which changes the C=O stretching vibration position.

133   The morphologies of ethanol solvate and form Ⅰ crystals were captured by optical

134 microscope and shown in Fig. 4. It is found that ethanol solvate is plate-shaped, while form

135 Ⅰ is needle-shaped. Therefore, PVM can be introduced to trace the change of crystal

136 morphologies in the transformation process.

137 **3.2 Transformation process on line monitoring.**

138   Compared with form Ⅰ of moxidectin, two ethanol in ethanol solvate crystal structure

139 are located in lattice channels to form hydrogen bonds between moxidectin and ethanol in

140 each asymmetric unit of ethanol solvate. The location of ethanol makes them easily to lose

141 along the lattice channels as compared with the other two locations, as the isolated site and

142 ion-associated hydrates, proposed by Inna Miroshnyk[26]. Therfore ethanol cannot exist in

143 ethanol solvate stably under high temperature. During the transformation, the removal of

144 ethanol from ethanol solvate results in the destruction of the structure of the metastable form

145 and formation of the stable form through the rearrangement of moxidectin molecule.

146   The transformation of ethanol solvate to form Ⅰ of moxidectin in ethanol-water mixture

147 was studied by FBRM, PVM, and on-line FTIR in real time and the result are shown in Fig

148 5,Fig 6 and Fig 7, respectively.

149   Fig 5 shows the change of particle counts of moxidectin for various size ranges during

150 the transformation. It can be seen that there is an obvious increase of particle counts after the

151 adding of moxidectin ethanol solvate, followed by a rapid decrease due to the dissolution of

152 the solid for various size ranges. The dissolution of ethanol solvate makes the solution to be

153 supersaturated with regard to form Ⅰ, and drives the nucleation and growth of form Ⅰ. As

154   time goes on, there appears an increase of small particle counts monitored by FBRM due to

155   the nucleation and growth of form Ⅰ. Fig 5 also demonstrates that the particle counts are

156   almost unchanged until after 5 h, which means there exists delay time before the

157   transformation, followed by a rapid increase of particle number, which suggests the

158   nucleation of form Ⅰ and the start of the transformation. After about 20 hours, all of the

159   particle counts are almost constant, indicating that the system reached thermodynamic

160   equilibrium, and the transformation is completed. The transformation process starts from fifth

161   hour and finishes at twentieth hour, and the whole process lasts for about fifteen hours.

162   Fig 6 shows the change of morphology of moxidectin during the transformation captured

163   by PVM. It can be seen that the plate-shaped ethanol solvate crystals are dominated in the

164   solution at the beginning of the transformation. After about 5 hours, a small number of

165   needle-shaped form Ⅰ crystals appear in the solution, demonstrating the nucleation and

166   growth of the stable form. With the transformation processing, the number of the

167   needle-shaped form Ⅰ increases and its crystal size becomes bigger. Mainly large

168   needle-shaped form Ⅰ crystals are captured 18 h after seeding. The change of crystal

169   morphology during the transformation provided by PVM is consistent with the FBRM data

170   discussed above, which reveals that the transformation process consisted of the dissolution of

171   the metastable form and the nucleation and growth of the stable form.

172   Fig 8 shows the XRD diffraction patterns of moxidectin solid sampled at different time

173   during the transformation, which confirms the complete transformation from ethanol solvate

174   of moxidectin to form Ⅰ in the solution within 20 h. At the beginning of the transformation,

175   only character peaks of ethanol solvate (7.740, 8.121, 8.501, 10.522, 11.599) could be

176   detected, and after 5 h there appears small weak character peaks of form Ⅰ. The relative

177   intensities of character peaks of ethanol solvate decrease along with time, in the meanwhile

178   those of form Ⅰ increase gradually. After about 20 h, only character peaks of form Ⅰ

179   (7.099, 8.916, 9.700, 11.120 12.041, 12.822, 15.180, 16.542, 17.880) exist without those of

180   ethanol solvate in the solid, indicating that ethanol solvate has completely transformed to

181   form Ⅰ, and the result is consistent with the PVM images and FBRM data.

182   **3.3 Rate Limiting Steps Identification.**

183   The concentration of moxidectin in the liquid phase during the transformation process

184   was detected by on-line FTIR, and the result is showed in Fig 7. It can be seen that the

185   concentration of the solution maintains at the solubility of the metastable form since the

186   moxidecitn solids be added, and then drops to the solubility of the stable form as the

187   transformation ended. FBRM and PVM detect the stable form after the induction time of 5 h,

188   while the concentration of the solution keeps no obvious change until the transformation

189   processing 12 h when the solids in the suspension are mainly form Ⅰ. It can be drawn the

190   conclusion from above results that the dissolution rate of the metastable form is faster than the

191   nucleation and growth rate of the stable form, thus the nucleation and growth of stable form is

192   the rate limiting step of the transformation, which means the transformation of ethanol solvate

193   to form Ⅰ of moxidectin is controlled by the nucleation and growth rate of the stable form.

194   **3.4 The effect of water content.**

195   In this work, excess moxidectin crystals were added into ethanol-water mixtures (with

196   different water contents: 0.10、0.20、0.30、0.40、0.50、0.60、0.70、0.80、0.90、1.00 mol %)

197   and shaked the suspension at a speed of 250 rpm in a thermostat at different temperatures

198   (293.15, 298.15, 303.15, 308.15 and 313.15 K) for 24 h and then the suspension was filtered

199   by a Buchner funnel. After that, the solid was further analyzed by XRD to identify the crystal

200   form. The result shows that when the temperature is equal or higher than 308.15 K, regardless

201   of the solvent composition, form Ⅰ is the stable form. It can also be found that when the

202   water content is equal or higher than 0.40 mol %, form Ⅰ is the stable form at all

203   temperatures investigated. When the water content is lower than 0.4 mol % and the

204   temperature is lower than 308.15 K, the transformation between form Ⅰ and ethanol solvate

205   is enantiotropic.

206   Since the solvent composition has a significant effect on solvent-mediated

207   transformation, the transformation experiments of ethanol solvate to form Ⅰ of moxidectin

208   in ethanol-water mixtures with different water contents were carried out to study the effect of

209   water content on the transformation and the results were shown in Fig 9.

210   FBRM data shows that the transformation times vary a lot at different water contents.

211   The particle counts of small particle begin to increase after about 5 h, and then it take 16 h to

212   complete the transformation in ethanol-water mixture containing 0.6 mol % water. The

213   transformation will be completed in 12 h when water content reached to 0.65 mol %. When

214   the transformation experiment is carried out in ethanol-water mixture containing 0.7 mol %

215   water, the small particle of form Ⅰ appears in the solution just after 4 h, and it take 8 h for the

216   system to reach thermodynamic equilibrium. From the FBRM data, it can be concluded that it

217   takes less time for ethanol solvate to transform to form Ⅰ as water content increases.

218   As there exists interaction between ethanol in ethanol solvate and water molecule in the

219   solution, water content in the mixture plays an important role in the transformation process,

220   just as the same phenomena many studies have pointed out in anhydrous/hydrate system[27,28].

221   During the transformation, since the interaction between ethanol molecule and water molecule

222   is stronger than the hydrogen bond formed between ethanol molecule and moxidectin

223   molecule, desolvation of ethanol solvate will happen and then ethanol molecule is released

224   into ethanol-water mixture, then followed by the nucleation of form Ⅰ through the structural

225   rearrangement of moxidectin. The interaction between water and ethanol increases as water

226 content in ethanol-water mixture increases, which can promote the removal of ethanol, and

227 then accordingly accelerate the transformation process.

228 In this binary solvent system, the transformation between ethanol solvate and form Ⅰ is

229 enantiotropic, and there existes a water content called equilibrium water content (x^*), at which

230 both of the metastable form and the stable form could coexist in the suspension. When the

231 water content is higher than x^*, form Ⅰ is the stable form. Otherwise, ethanol solvate is the

232 stable one. The difference between x and x^* is the driving force of the transformation. "x- x^*"

233 increases as water content increases in ethanol-water mixture. As a consequence, compared

234 with the transformation experiments carried out in mixture containing 0.60 and 0.65 mol %

235 water, the nucleation and growth of form Ⅰ in mixture containing 0.70 mol % water was

236 much faster.

237 **3.5 The effect of temperature.**

238 In order to reveal the influence of temperature on the transformation of ethanol solvate to

239 form Ⅰ, transformation experiments under different temperatures were carried out and the

240 result were shown in Fig 10.

241 Fig 10 shows that transformation rate is highly related with experimental temperature.

242 When the transformation experiments are carried out at 298.15 K, 303.15 K and 308.15 K, the

243 induced period are 42 h, 5 h and 1 h, respectively, and the corresponding transformation time

244 are 52 h, 8 h and 3 h, respectively. It could be concluded that it takes less time for

245 transformation of ethanol solvate to form Ⅰ as the temperature increases.

246 For the enantiotropic polymorphic system, there exists an equilibrium temperature under

247 a certain solvent composition. When the temperature is lower than the equilibrium

248 temperature, ethanol solvate is the stable form, otherwise, form Ⅰ is the stable one. When the

249 temperature is higher than the equivalent temperature, the difference between the solubility of

250 ethanol solvate and form Ⅰ becomes larger as the temperature increases, which will

251 accelerate the dissolution of ethanol solvate. Higher temperature would break the hydrogen

252 bonds much easier due to faster molecule motion, which would make the desolvation of

253 ethanol solvate much easier, and accordingly result in shorter transformation time. Higher

254 temperature would accelerate molecule motion and reduce the interfacial energy between the

255 solid and liquid phase. Both of the effects caused by higher temperature was beneficial to the

256 nucleation of form Ⅰ, which could shorten the transformation time obviously. It is can be

257 seen that temperature is the key factor whether ethanol molecules can exist in ethanol solvate

258 stably, and it affects the transformation process significantly.

259 **4. Conclusions**

260 Transformation of ethanol solvate to form Ⅰ of moxidectin in ethanol-water mixture is

261 studied by FBRM, PVM and on-line FTIR. It is found that the ethanol solvate can completely

262 transform to form Ⅰ under experiment condition, and the process is controlled by the

263 nucleation and growth rate of the stable form. The effects of water content and temperature on

264 the transformation process are also investigated. The hydrogen bonds between moxidectin and

265 ethanol become weaker along with the increase of water content and temperature, which

266 promote the desolvation of moxidectin ethanol solvate and shorten the transformation time

267 obviously. Meanwhile, the lower water content and temperature will promote the nucleation

268 and growth of the stable form, and accelerate the transformation process. Water content in the

269 solvent mixture and experimental temperature are the main factors which dominate the

270 transformation time significantly. This work gives better understanding on the polymorphic

271 transformation mechanism of moxidecitn, as well as offers a novel way and critical

272 information to control the manufacture process of commercial form I products.

273 **Acknowledgements**

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279 **References**

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322   Table 1. Transformation experiments

	Temperature (K)	Water content (mol %)	Stirrer speed (rpm)	Solid loading (g)
1	303.15	0.60	500	3.0
2	303.15	0.65	500	3.0
3	303.15	0.70	500	3.0
4	298.15	0.70	500	1.6
5	303.15	0.70	500	1.6
6	308.15	0.70	500	1.6

323

324

325   **Figure Legends:**

326

327   **Figure 1.** The molecular structure of moxidectin.

328

329   **Figure 2.** The X-ray powder diffraction patterns of form Ⅰ (a) and ethanol solvate (b) of

330   moxidectin.

331

332   **Figure 3.** The FTIR spectroscopies of ethanol solvate and form Ⅰ of moxidectin.

333

334   **Figure 4.** The optical microscope images of ethanol solvate (a) and form Ⅰ (b) of

335   moxidectin.

336

337   **Figure 5.** Trend of particle counts for various size ranges over time at an initial water content

338   of 0.60 mol %, a temperature of 303.15 K, and a stirrer speed of 500 rpm

339

340   **Figure 6.** Change of morphology of solid phase with time at an initial water content of 0.60

341   mol %, a temperature of 303.15 K, and a stirrer speed of 500 rpm.

342

343   **Figure 7.** Change of moxidectin concentration with time at an initial water content of 0.60

344   mol %, a temperature of 303.15 K, and a stirrer speed of 500 rpm.

345

346   **Figure 8.** The X-ray powder diffraction patterns of moxidectin during the transformation.

347

348   **Figure 9.** Change of particle counts (10 - 50 μm) over time at different water contents, a

349   temperature of 303.15 K, and a stirrer speed of 500 rpm.

350

351   **Figure 10.** Change of particle counts (10 - 50 μm) over time at different temperatures, an

352   initial water content of 0.70 mol %, and a stirrer speed of 500 rpm.

353

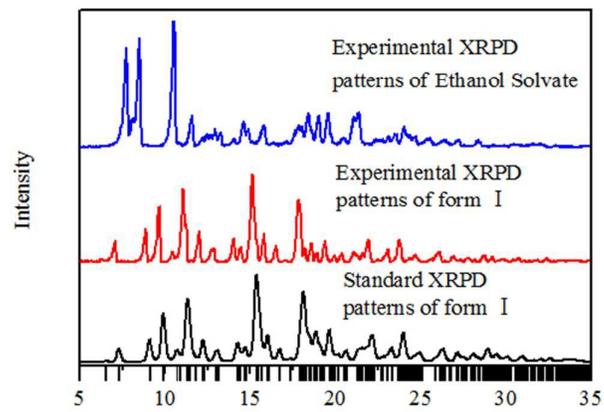354   **Figure 1.**

355

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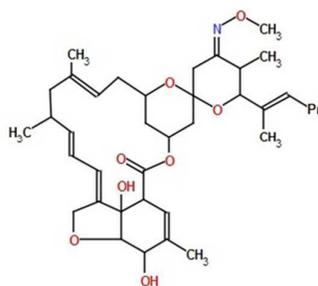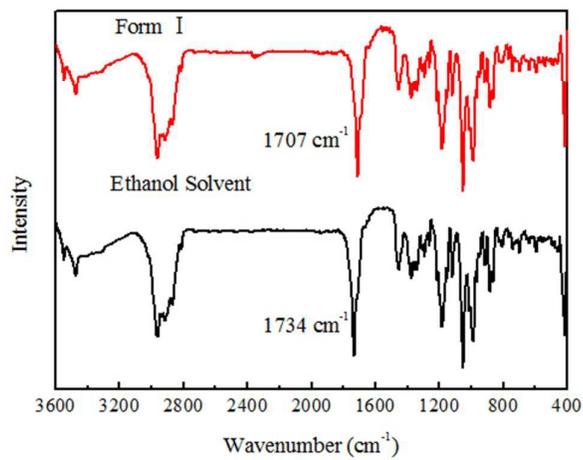

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359   **Figure 2.**
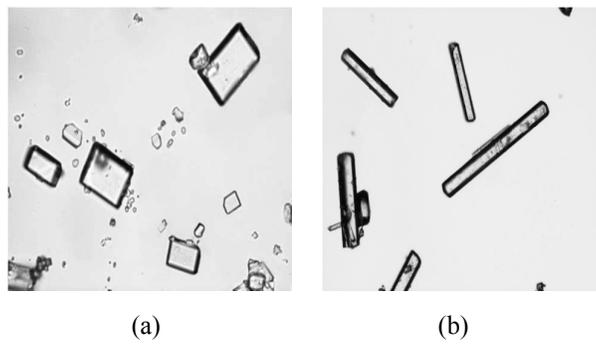
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364   **Figure 3.**

365

366

Form I

1707 cm^{-1}

Ethanol Solvent

1734 cm^{-1}

Intensity

Wavenumber (cm^{-1})

367

368

369 **Figure 4.**

370

371

(a)   (b)

372

373

374

375   **Figure 5.**

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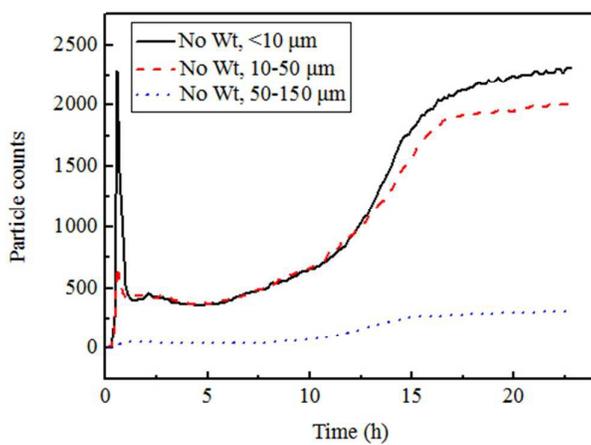
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379

380   **Figure 6.**
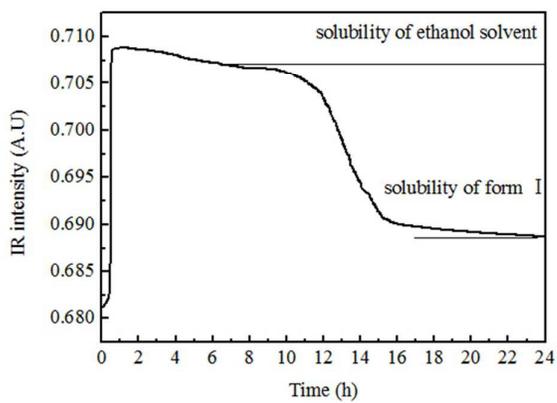
381

382

t=0 hour   t=5 hour   t=8 hour   t=10

t=12 hour   t=16 hour   t=18 hour   t=20
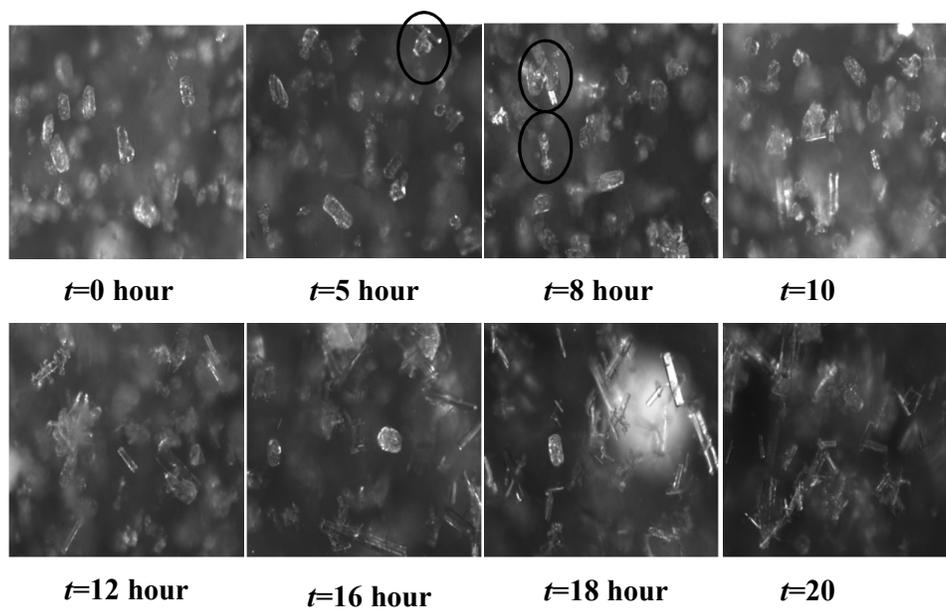
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386 **Figure 7.**

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392   **Figure 8.**

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394
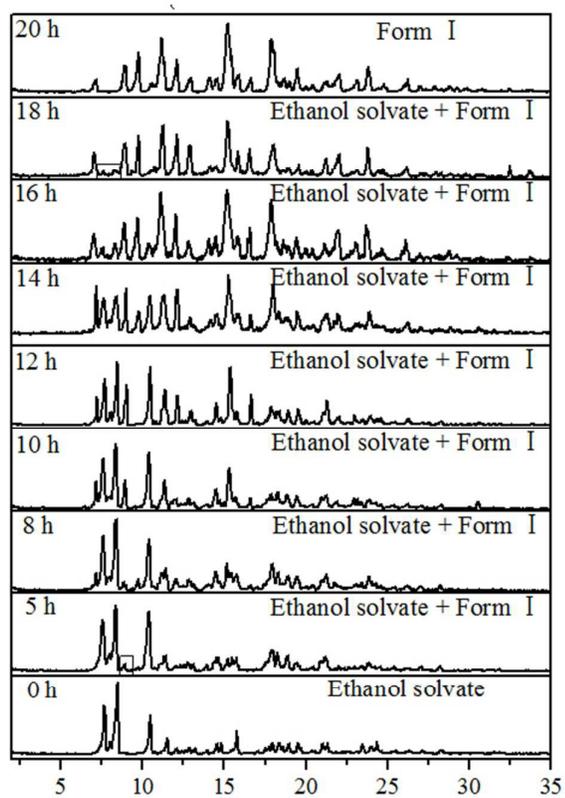
395

396

397   **Figure 9.**

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399
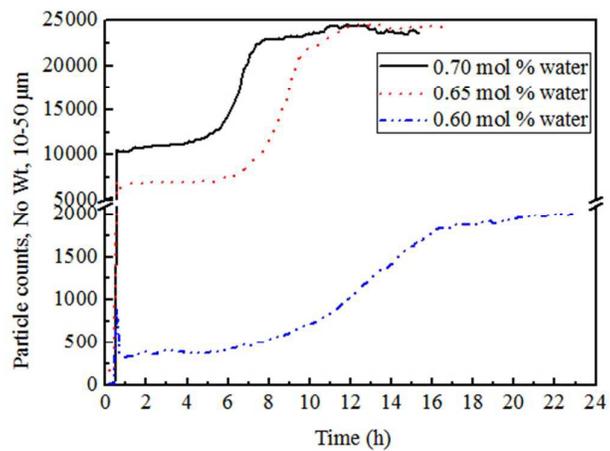
400

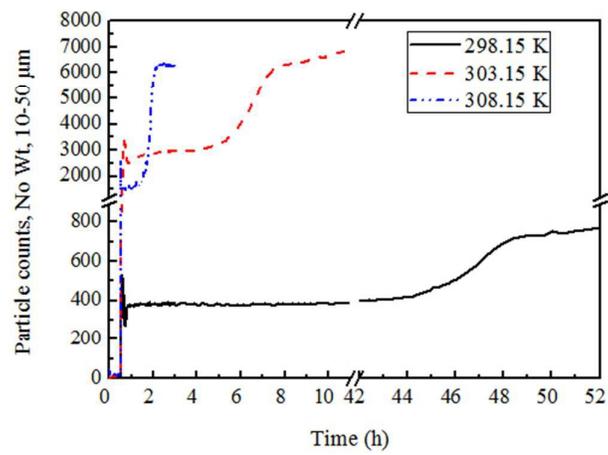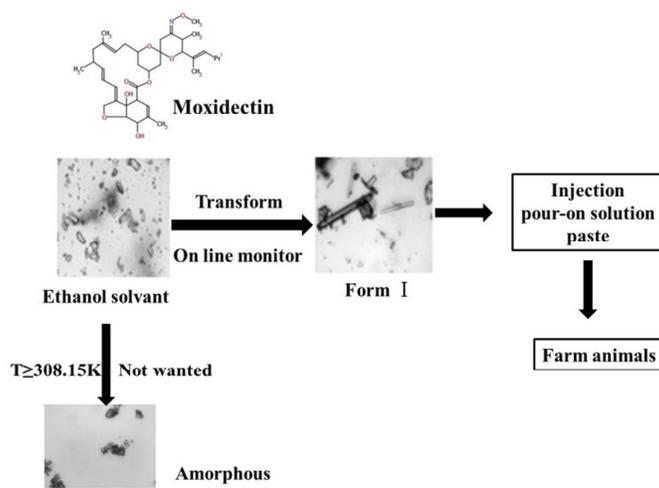401

402   **Figure 10.**

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407 **TOC Graphic**

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