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Effect of ethanol on water permeability of controlled release films composed of ethyl

cellulose and hydroxypropyl cellulose

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27 **Abstract**

28 Films for controlled release, composed of ethyl cellulose and hydroxypropyl cellulose were

29 prepared in various compositions and the effect of ethanol in the dissolution medium on the

30 water permeability of the films was studied using a modified Ussing chamber and tritiated

31 water. It was found that the effect of ethanol on the film permeability varied depending on the

32 composition of the films. The results were interpreted in terms of swelling of the ethyl

33 cellulose in the films, where the swelling increased with increasing ethanol concentration.

34 Thus, for films with low HPC content (non interconnected pores) the water permeability of

35 the films increased with increasing ethanol concentration as the diffusion through the ethyl

36 cellulose increased due to swelling. However, for films with higher HPC content (having

37 interconnected pores through the films) the permeability decreased, likely due to the swelling

38 of the ethyl cellulose blocking the pores. The interpretation of the results was supported by

39 dynamic mechanic analysis and SEM analysis.

40

41 **Keywords:** Ethyl cellulose, Hydroxypropyl cellulose, Permeability, Films, Controlled release

42

1. Introduction

Polymer film coatings are commonly used for controlling drug release from pellets and tablets (Shah and Sheth, 1972; Donbrow and Samuelov, 1980; Sakellariou and Rowe, 1995; Hyppoelae et al., 1996; Hjartstam and Hjertberg, 1999; Marucci et al., 2009;). In order to modify the release, different ratios of water insoluble film forming polymer and water soluble pore forming agent are used. Ethyl cellulose (EC) is a commonly used film forming agent (Hyppoelae et al., 1996) because it has good film forming properties and is generally regarded as non-toxic and non-allergenic (Hjartstam and Hjertberg, 1998; Marucci et al., 2009). Water soluble cellulose derivates, such as hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) are commonly used as pore forming agents in controlled release films (Sakellariou and Rowe, 1995; Hjartstam and Hjertberg, 1998; Marucci et al., 2009). HPC has low toxicity, is biodegradable and has good film forming properties (Marucci et al., 2009). Furthermore, HPC holds a great benefit over HPMC in industrial film spraying processes. HPC can be co-dissolved with EC in ethanol, while HPMC requires the use of other more hazardous solvents. Films composed of EC and HPC have been studied both with regard to structure and permeability. It has been shown that EC and HPC phase separate in the films (Sakellariou et al., 1986, 1988) and that the permeability of the films and the release rate from formulations increases with increasing HPC content (Thombre et al., 1994; Marucci et al., 2009). Furthermore, the permeability of the films as well as the release of the pore forming HPC has been shown to be low below a critical HPC content, this being explained by that at low HPC concentrations the pore forming network is not interconnected through the film (Sakellariou et al., 1988; Marucci et al., 2009).

Recently, regulatory authorities have expressed concerns over the effects of alcohol on extended release dosage (ER) forms, with potential dose dumping as a consequence (FDA,

67 2005; Meyer and Hussain, 2005). A regulatory framework regarding the effects of ethanol on

68 product performance and classification is currently being developed (Meyer and Hussain,

69 2005). Levina et al. (2007) have investigated the influence of ethanol on drug release from

70 HPMC based ER matrices, and reported that none of the investigated formulations exhibited

71 dose dumping when exposed to hydro-alcoholic solutions. However, Fadda et al. (2008)

72 investigated the influence of ethanol in the dissolution media on modified release tablets

73 coated with enteric methacrylic acid and methyl methacrylate ester copolymer. They found

74 that the influence of ethanol on the drug release was complicated, and concluded that several

75 tests are needed before making a decision on a formulations susceptibility to ethanol

76 impairment. Given the recent interest in the effect of ethanol on controlled release

77 formulations and the fact that EC (ETHOCEL^{TM}) is soluble in alcohol (Dow Cellulosics,

78 2005), it was considered interesting to investigate the effects of hydro-alcoholic solutions on

79 EC-HPC films for controlled delivery.

80 The aim of this study was to evaluate how the water permeability of EC films with varying

81 HPC content was affected by the presence of ethanol in the dissolution medium, and explain

82 the mechanism by which the permeability was affected. The water permeability of the films

83 was determined using a modified Ussing chamber, utilizing tritiated water as the diffusing

84 probe. Swelling of the films and changes in mechanical properties upon exposure to ethanol

85 solutions were studied using dynamic mechanic analysis (DMA). Finally, the structure of

86 films exposed to ethanol solutions and subsequently dried was studied using scanning electron

87 microscopy (SEM).

88

89 **2. Materials and methods**

90 *2.1 Materials*

91   The films in this study were prepared from ethyl cellulose (ETHOCEL^{TM} 10, Dow Chemical,

92   USA) and hydroxypropyl cellulose (HPC LF, Ashland, USA). Ethanol used was of 95 % v/v

93   concentration (Kemetyl AB, Sweden), water used was ultra-pure deionized (Maxima USF,

94   Elga, UK). Tritiated water (PerkinElmer, USA) was used as the diffusant in the water

95   permeability measurements.

96

97   *2.2 Film preparation*

98   Films of EC with varying amount of HPC (0, 20, 30, 35, 40, 50 % w/w) were prepared as

99   follows. Desired amounts of EC and HPC were dissolved in ethanol (95 % v/v) to a total

100 polymer content of 6 % w/w. The solution was sprayed, using a moving nozzle (Schlick 970-

101 0, nozzle diameter 0.8 mm, Schlick, Germany), onto a rotating Teflon cylinder (In-house

102 manufactured, length 100 mm diameter 65 mm) in a controlled air flow. The process

103 conditions are presented in Table 1. The dry film was peeled off the cylinder and cut into

104 suitable geometries for permeability and DMA analysis. The thicknesses of the films were 70-

105 90 µm as measured with a micrometer (IP 54, Mitutoyo, Japan).

106

107 *2.3 Water permeability analysis*

108 The water permeability of the films was analyzed using a modified Ussing chamber with the

109 setup previously described (Hjartstam and Hjertberg, 1999). Briefly, a film sample was placed

110 between a donor and acceptor compartment. The film thickness was determined as the

111 average of five measurements. Initially 15 ml of dissolution medium with 0, 5, 20 or 40 % v/v

112 ethanol concentration was added to both the donor and the acceptor compartments and two

113 paddles were used to stir the dissolution medium at a speed of 200 rpm. After 5 minutes a

114   small amount of tritiated water (10 μl, 400 kBq) was added to the donor compartment. At

115   specified times 500 μl sample was taken from the acceptor compartment and was replaced by

116   the same amount of dissolution medium. The temperature was maintained at 37 °C through

117   the analysis. The samples extracted at the different times were weighed and analyzed in a

118   scintillator counter (1414 LSC, Win Spectral, Wallac). From the tritium activity registered in

119   the acceptor compartment at the different times, the amount of water that had diffused

120   through the film at each time could be determined, and thus the film permeability. Due to the

121   large difference in tritium activity between the donor and acceptor compartment any counter

122   diffusion was neglected.

123

124   *2.4 Dynamic mechanic analysis*

125   DMA measurements were performed using a Rheometrics RSAII (Rheometrics Scientific,

126   Piscataway, USA), equipped with an in house designed submersion cell (Edrud et al., 2003).

127   Samples were prepared to a width of 3 mm using a razor-edged punch. The sample thickness

128   was recorded as the average of three measurements. The effective initial sample length in the

129   DMA was 22-23 mm. The samples were mounted in the DMA and after about 3 minutes 40

130   ml of dissolution medium with 0, 5, 20 or 40 % v/v ethanol concentration was added.

131   The samples were analyzed in strain controlled stretching mode with a static force, keeping

132   the samples stretched, set to just exceed the amplitude of the harmonic dynamic force. The

133   deformation and the force response of the samples were monitored and from those parameters

134   the elastic modulus G' and the loss factor, tan(δ), were calculated. Equilibrium value of tan(δ)

135   was taken as the average of the plateau values. The swelling of the samples was monitored as

136   the percent length change.

137

138 *2.5 Scanning electron microscopy*

139 Free polymer films with varying EC and HPC content were placed in beakers with dissolution

140 media containing 0, 5, 20 and 40 % ethanol for two days. The films were subsequently dried

141 and analysed using a scanning electron microscope (Quanta200, FEI, Czech Republic).

142

143 **3. Results and discussion**

144 *3.1 Water permeability analysis*

145 In order to investigate the influence of ethanol in the dissolution medium on water

146 permeability of EC-HPC films for controlled drug delivery, film samples were subjected to

147 permeability analysis. The analyses were conducted in dissolution media with different

148 ethanol concentrations using a modified Ussing chamber. The film samples were placed

149 separating the two compartments of the cell, and from the transport of tritiated water from the

150 donor to the acceptor compartment the volume of water that had diffused across the

151 membrane was calculated at each time. As seen in the exemplifying graph in Fig. 1, the

152 volume of water that had diffused across the membrane showed a linear dependence on time.

153 From the slope of the graphs the volume flow was calculated and the water permeability,

154 normalized versus film thickness, was determined as:

155 $$P_N = \frac{J \cdot h}{A}$$ (1)

156 where P_N is the water permeability, J is the volume flow, h is the film thickness and A is the

157 area.

158   The permeability data (see Table 2 and Fig. 2) revealed that, in general, the water

159   permeability of the films increased with increasing HPC content. This is expected as HPC is

160   widely soluble both in water and in ethanol (Rowe et al., 2009), and thus should dissolve and

161   leave pores. Furthermore, the permeability was very low up to 20 % HPC content. This is in

162   agreement with a previous study on the permeability of EC-HPC films in non-ethanol

163   containing dissolution media (Marucci et al., 2009). For samples analyzed in the presence of

164   40 % v/v ethanol in the dissolution medium, some deviations from the trend were seen. If

165   instead looking at the permeability for a fixed HPC content and varying ethanol concentration

166   in the dissolution media, the permeability of films with low HPC contents (0 and 20 % w/w)

167   increases with increasing ethanol concentrations. However, at HPC contents higher than 20 %

168   w/w the permeability instead decreases with increasing concentration of ethanol in the

169   dissolution medium. Only one exception from the trend is seen, the permeability of the

170   samples with 30 % w/w HPC in 5 % v/v ethanol is higher than suggested by the trend.

171   We propose the following explanation for the changes in film permeability in ethanol

172   containing dissolution medium. At low HPC concentrations the dissolution of HPC will not

173   form a coherent pore network though the film, in accordance with previous studies (

174   Sakellariou et al., 1988; Marucci et al., 2009). Thus, the permeability of the films will be low.

175   Ethyl cellulose is however soluble in ethanol. It would be expected that upon increasing the

176   ethanol content in the dissolution medium, the solubility of EC is increased, with gelling and

177   in the extreme dissolution as a consequence. It is well known that the diffusion coefficient in

178   polymeric materials increases with decreasing polymer concentration (Masaro and Zhu,

179   1999). Thus, due to the swelling of the EC, the permeability of films with low HPC content is

180   expected to increase with increasing ethanol concentration in the dissolution medium. For

181   films with higher HPC content, the dissolution of HPC will lead to the formation of a

182   coherent pore network through the films, with dramatic increase in permeability as a

183   consequence. When the EC swells in the presence of ethanol the pores will become smaller,

184   and in the extreme cases filled with EC gel. As such, the permeability of the films with a high

185   HPC content is expected to decrease with increasing ethanol concentration in the dissolution

186   medium.

187

188   *3.2 Dynamic mechanic analysis*

189   In order to test the hypothesis that EC swells in ethanol containing dissolution medium, EC

190   film samples were subjected to DMA during submersion in dissolution media with varying

191   ethanol content. The length change, the elastic modulus, G', and the loss factor, tan(δ)*,* of the

192   samples were recorded during the analyses. In Fig. 3 the percent length change is plotted

193   versus time after submersion for different concentrations of ethanol in the dissolution

194   medium. The film samples expanded more with increasing concentration of ethanol. The

195   effect was rather small for samples exposed to dissolution medium with 0 and 5 % v/v

196   ethanol, but more significant for 20 % v/v ethanol. For films swollen in dissolution medium

197   containing 40 % v/v ethanol the samples displayed a quick and accelerating length expansion

198   up to about 20 % (result not shown), at which point the analyses were terminated due to the

199   instrumental expansion limit. The elastic modulus of the film samples was relatively

200   unaffected by the addition of dissolution medium for ethanol concentrations in the range 0 to

201   20 % v/v. However, for the films exposed to the dissolution medium containing 40 % v/v

202   ethanol G' decreased dramatically even before reaching the expansion limit of the instrument.

203   Further decrease of G' would be expected if the measurements could have been continued.

204   The large decrease in G' clearly indicates that the samples undergo a transition from a solid to

205   a gelled state in the presence of 40 % v/v ethanol. Thus, the dramatic change in sample length

206 is most likely a combination of swelling of the film and irreversible strain under the small

207 force applied in the DMA.

208 In Fig. 4 the tan(δ) values for EC films in dissolution media with different ethanol

209 concentrations are shown. The tan(δ) values are equilibrium values for samples exposed to

210 dissolution media with ethanol concentration ranging from 0 to 20 % v/v. For the films

211 exposed to the dissolution media with 40 % v/v ethanol, the reported tan(δ) value is acquired

212 from the last measurable values before reaching the instrumental expansion limit. It is seen

213 that the loss factor is small for low concentrations of ethanol, increasing slightly as the

214 ethanol concentration increases. However, for higher ethanol concentrations, the increment is

215 large. The loss factor correlates to the elastic and viscous, G'', modulus as (Craig and

216 Johnson, 1995):

217 $$\tan(\delta) = \frac{G''}{G'} \qquad\qquad (2)$$

218 As such tan(δ) can be regarded as a measurement of how much of a viscous liquid character a

219 material has, as compared to an elastic solid. An increase in tan(δ) is equivalent with that a

220 sample dissipates more of the applied energy of deformation as frictional heat, rather than

221 storing the energy as in purely elastic deformation. From the increase in tan(δ) with increasing

222 ethanol concentration in the dissolution medium, it can be concluded that the presence of

223 ethanol increases the mobility of the EC polymer chains, causing the samples to dissipate

224 more of the applied deformation energy as heat. The increase of tan(δ) with increasing

225 concentration of alcohol is coherent with the increase in sample length, discussed above.

226

227 *3.3 Scanning electron microscopy*

228 To investigate if any difference could be detected in the structure of films exposed to

229 dissolution media with varying ethanol content, film samples composed purely of EC and

230 containing 35 % w/w HPC were submerged in dissolution media with different ethanol

231 concentrations for two days. The samples were subsequently dried and analysed using SEM.

232 If the EC was unaffected by the dissolution medium, pure EC films would be unaffected by

233 the treatment and no change in structure should be detected. For the analysed EC-HPC films

234 the HPC should dissolve, leaving a porous network. As for pure EC films, the structure should

235 not be altered by the treatment if EC was not affected by the dissolution medium. However, if

236 the EC swelled in the dissolution medium, altered structures would be expected both for pure

237 EC films and for EC-HPC films.

238 As seen in Fig. 5 A-D, the structure of pure EC films is clearly affected by the ethanol

239 concentration in the dissolution medium. The films that were exposed to dissolution medium

240 containing 20 and 40 % v/v ethanol exhibit a different surface than films exposed to

241 dissolution medium with less ethanol, probably due to swelling and subsequent drying. For

242 HPC containing films it is hard to draw any certain conclusions due to the inherent

243 heterogeneity of the films (Fig 5 E-H). However, there is some resemblance between the pure

244 EC film and the HPC containing film submerged in dissolution medium containing 40 % v/v

245 ethanol. The results from the SEM analysis support the hypothesis that the performance of

246 EC-HPC films in ethanol containing dissolution medium is influenced by the ethanol

247 concentration through the swelling, and at sufficiently high ethanol concentrations the gelling,

248 of EC.

249

250 **4. Conclusion**

251 In this study it was shown that the water permeability of EC-HPC films for controlled drug

252 delivery was influenced by the concentration of ethanol in the dissolution medium. Ethanol

253 increased the water permeability for no and low amount of HPC in the films, but reduced the

254 permeability at higher HPC content. The effects on the permeability can be explained by that

255 the EC swells in the presence of ethanol, leading to an increased diffusion through the EC in

256 the films, but more importantly decreasing the size of the pores left by the dissolved HPC.

257 This explanation is supported by results from DMA and SEM analysis. The findings are

258 interesting and of great relevance, as the effect of ethanol on controlled release formulations is

259 a current concern expressed by regulatory authorities. The results in this study indicate that

260 the performance of EC-HPC films in controlled delivery applications is at risk with regard to

261 co-ingestion with ethanol. The results here presented mainly showed on a decrease in water

262 permeability. However, given that in most formulations there will be an osmotic pressure

263 difference over the films and that drug molecules are considerably larger than water

264 molecules; our results should not be seen as a proof that dose dumping will not occur.

265 Interesting further studies would be to investigate how the concentration of ethanol in the

266 dissolution medium affects the performance of coated pellets and tablets with different

267 osmotic pressure.

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Figure legends

Fig. 1. Exemplifying plot of the volume of water having diffused across the film, here for a sample with 35% HPC and a thickness of 86 µm in dissolution medium with 5 % ethanol.

Fig. 2. Plot of the water permeability, normalized versus film thickness, for EC films with varying HPC content, in dissolution media with the following ethanol concentrations (■) 0, (○) 5, (□) 20 and (●) 40 %. Error bars indicate one standard deviation.

Fig. 3 The percent length change over time for EC films during dynamic mechanic analysis in dissolution media with different ethanol concentration. Dashed lines indicate min/max, n = 2, where not visible the deviations are too small to be displayed.

Fig. 4. The loss factor of EC films in dissolution media with different ethanol concentration, detected using DMA. The values are equilibrium values for ethanol concentrations ranging from 0 to 20 % and the last value before reaching the expansion limit of the instrument for 40 % ethanol. Insert is magnification of the region with ethanol concentrations of 0-20 % Error bars indicate min/max, n = 2.
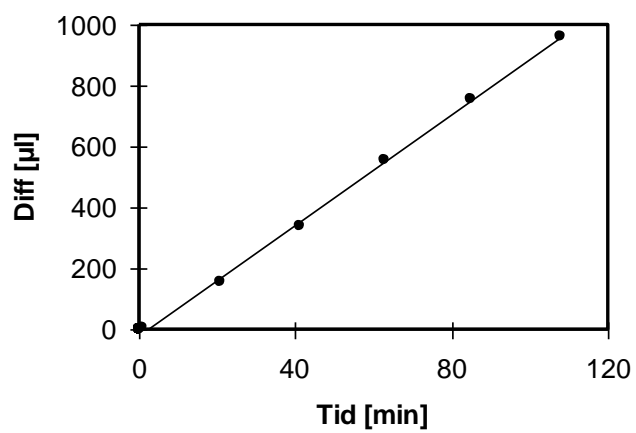
Fig. 5. SEM images of pure EC films (A-D) and films containing 35 % HPC (E-H) after being submerged in dissolution media with different ethanol concentrations (A, E = 0 %; B, F = 5 %; C, G = 20 % and D, H = 40 %) for two days. Scale bar is 20 µm.

356   Figure 1.
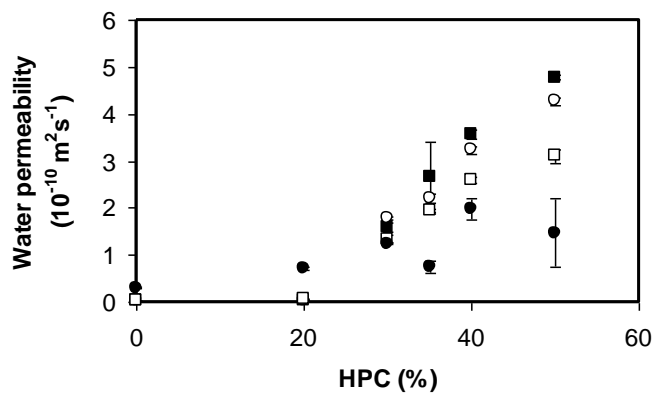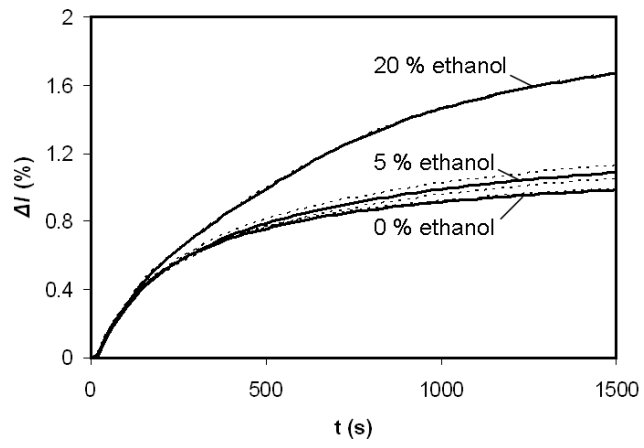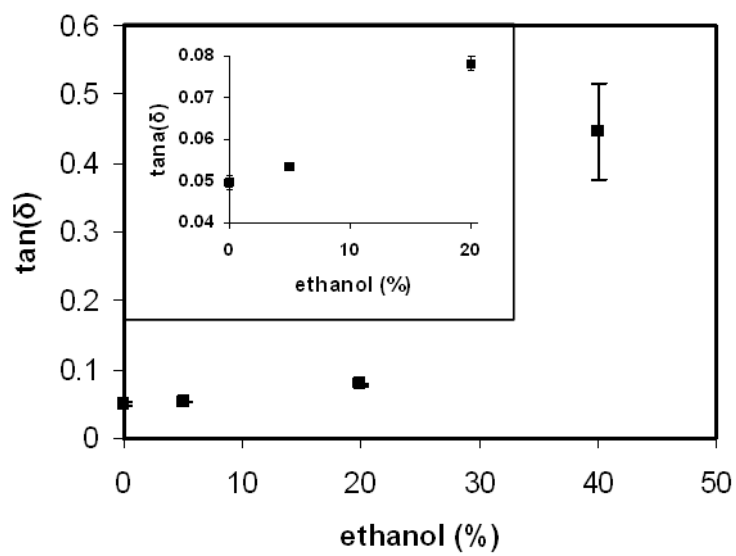357

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360   Figure 2.
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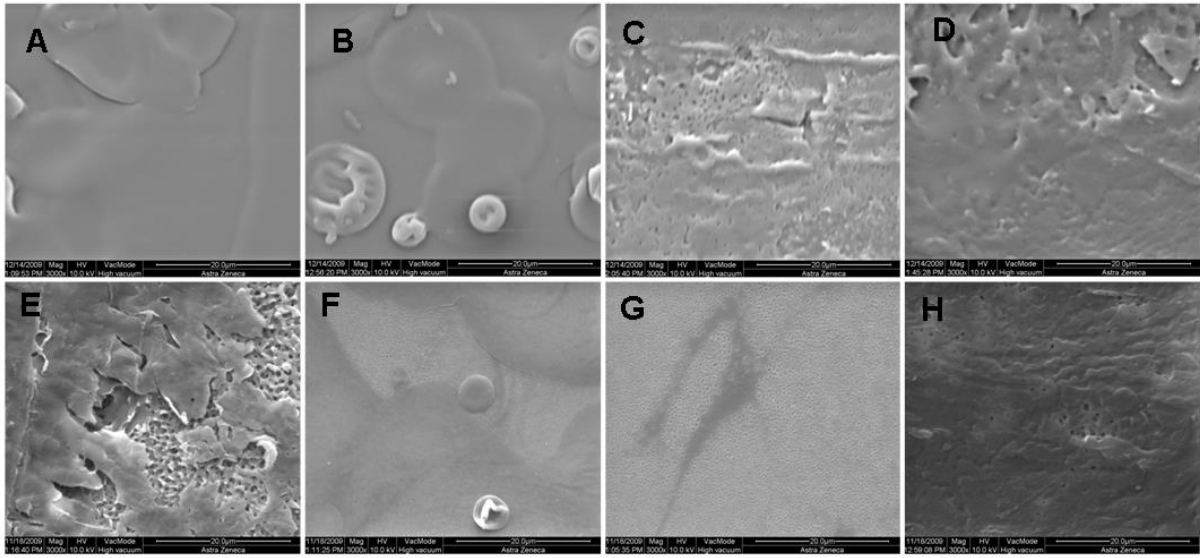365

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369   Figure 4.
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375   Figure 5.
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380   Table 1. Process parameters used in the preparation of films.

Process parameter	value
Inlet air temperature	72 °C
Outlet air temperature	45-47.5 °C
Fluidizing air flow rate	40 Nm^3/h
Atomizing air pressure	2.0 bar
Spraying rate	10 g/min

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386   Table 2. Water permeability normalized versus film thickness (10^{-12} m^2s^{-1}) for EC films with

387   varying HPC content, in dissolution media with different ethanol concentrations. One

388   standard deviation within parentheses, n = 2-5.

HPC (%)	0% EtOH	5% EtOH	20% EtOH	40% EtOH
0	2.3 (0.27)	2.40 (0.04)	3.9 (0.18)	30 (1.3)
20	3.4 (0.34)	3.61 (0.05)	7 (1.0)	70 (3.4)
30	158 (9.9)	177 (3.1)	134 (8.7)	124 (2.0)
35	270 (73)	221 (9.8)	193 (3.7)	70 (13)
40	356 (9.0)	324 (8.1)	260 (5.6)	200 (22)
50	478 (5.0)	427 (7.1)	310 (15)	150 (74)

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