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Abstract

Films for controlled release, composed of ethyl cellulose and hydroxypropyl cellulose were prepared in various compositions and the effect of ethanol in the dissolution medium on the water permeability of the films was studied using a modified Ussing chamber and tritiated water. It was found that the effect of ethanol on the film permeability varied depending on the composition of the films. The results were interpreted in terms of swelling of the ethyl cellulose in the films, where the swelling increased with increasing ethanol concentration. Thus, for films with low HPC content (non interconnected pores) the water permeability of the films increased with increasing ethanol concentration as the diffusion through the ethyl cellulose increased due to swelling. However, for films with higher HPC content (having interconnected pores through the films) the permeability decreased, likely due to the swelling of the ethyl cellulose blocking the pores. The interpretation of the results was supported by dynamic mechanic analysis and SEM analysis.

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

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,

2005; Meyer and Hussain, 2005). A regulatory framework regarding the effects of ethanol on product performance and classification is currently being developed (Meyer and Hussain, 2005). Levina et al. (2007) have investigated the influence of ethanol on drug release from HPMC based ER matrices, and reported that none of the investigated formulations exhibited dose dumping when exposed to hydro-alcoholic solutions. However, Fadda et al. (2008) investigated the influence of ethanol in the dissolution media on modified release tablets coated with enteric methacrylic acid and methyl methacrylate ester copolymer. They found that the influence of ethanol on the drug release was complicated, and concluded that several tests are needed before making a decision on a formulations susceptibility to ethanol impairment. Given the recent interest in the effect of ethanol on controlled release formulations and the fact that EC (ETHOCEL^{TM}) is soluble in alcohol (Dow Cellulosics, 2005), it was considered interesting to investigate the effects of hydro-alcoholic solutions on EC-HPC films for controlled delivery.

The aim of this study was to evaluate how the water permeability of EC films with varying HPC content was affected by the presence of ethanol in the dissolution medium, and explain the mechanism by which the permeability was affected. The water permeability of the films was determined using a modified Ussing chamber, utilizing tritiated water as the diffusing probe. Swelling of the films and changes in mechanical properties upon exposure to ethanol solutions were studied using dynamic mechanic analysis (DMA). Finally, the structure of films exposed to ethanol solutions and subsequently dried was studied using scanning electron microscopy (SEM).

2. Materials and methods

2.1 Materials

The films in this study were prepared from ethyl cellulose (ETHOCEL^{TM} 10, Dow Chemical, USA) and hydroxypropyl cellulose (HPC LF, Ashland, USA). Ethanol used was of 95 % v/v concentration (Kemetyl AB, Sweden), water used was ultra-pure deionized (Maxima USF, Elga, UK). Tritiated water (PerkinElmer, USA) was used as the diffusant in the water permeability measurements.

2.2 Film preparation

Films of EC with varying amount of HPC (0, 20, 30, 35, 40, 50 % w/w) were prepared as follows. Desired amounts of EC and HPC were dissolved in ethanol (95 % v/v) to a total polymer content of 6 % w/w. The solution was sprayed, using a moving nozzle (Schlick 970-0, nozzle diameter 0.8 mm, Schlick, Germany), onto a rotating Teflon cylinder (In-house manufactured, length 100 mm diameter 65 mm) in a controlled air flow. The process conditions are presented in Table 1. The dry film was peeled off the cylinder and cut into suitable geometries for permeability and DMA analysis. The thicknesses of the films were 70-90 µm as measured with a micrometer (IP 54, Mitutoyo, Japan).

2.3 Water permeability analysis

The water permeability of the films was analyzed using a modified Ussing chamber with the setup previously described (Hjartstam and Hjertberg, 1999). Briefly, a film sample was placed between a donor and acceptor compartment. The film thickness was determined as the average of five measurements. Initially 15 ml of dissolution medium with 0, 5, 20 or 40 % v/v ethanol concentration was added to both the donor and the acceptor compartments and two paddles were used to stir the dissolution medium at a speed of 200 rpm. After 5 minutes a

small amount of tritiated water (10 µl, 400 kBq) was added to the donor compartment. At specified times 500 µl sample was taken from the acceptor compartment and was replaced by the same amount of dissolution medium. The temperature was maintained at 37 °C through the analysis. The samples extracted at the different times were weighed and analyzed in a scintillator counter (1414 LSC, Win Spectral, Wallac). From the tritium activity registered in the acceptor compartment at the different times, the amount of water that had diffused through the film at each time could be determined, and thus the film permeability. Due to the large difference in tritium activity between the donor and acceptor compartment any counter diffusion was neglected.

2.4 Dynamic mechanic analysis

DMA measurements were performed using a Rheometrics RSAII (Rheometrics Scientific, Piscataway, USA), equipped with an in house designed submersion cell (Edrud et al., 2003). Samples were prepared to a width of 3 mm using a razor-edged punch. The sample thickness was recorded as the average of three measurements. The effective initial sample length in the DMA was 22-23 mm. The samples were mounted in the DMA and after about 3 minutes 40 ml of dissolution medium with 0, 5, 20 or 40 % v/v ethanol concentration was added.

The samples were analyzed in strain controlled stretching mode with a static force, keeping the samples stretched, set to just exceed the amplitude of the harmonic dynamic force. The deformation and the force response of the samples were monitored and from those parameters the elastic modulus *G'* and the loss factor, tan(δ), were calculated. Equilibrium value of tan(δ) was taken as the average of the plateau values. The swelling of the samples was monitored as the percent length change.

2.5 Scanning electron microscopy

Free polymer films with varying EC and HPC content were placed in beakers with dissolution media containing 0, 5, 20 and 40 % ethanol for two days. The films were subsequently dried and analysed using a scanning electron microscope (Quanta200, FEI, Czech Republic).

3. Results and discussion

3.1 Water permeability analysis

In order to investigate the influence of ethanol in the dissolution medium on water permeability of EC-HPC films for controlled drug delivery, film samples were subjected to permeability analysis. The analyses were conducted in dissolution media with different ethanol concentrations using a modified Ussing chamber. The film samples were placed separating the two compartments of the cell, and from the transport of tritiated water from the donor to the acceptor compartment the volume of water that had diffused across the membrane was calculated at each time. As seen in the exemplifying graph in Fig. 1, the volume of water that had diffused across the membrane showed a linear dependence on time. From the slope of the graphs the volume flow was calculated and the water permeability, normalized versus film thickness, was determined as:

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

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

The permeability data (see Table 2 and Fig. 2) revealed that, in general, the water permeability of the films increased with increasing HPC content. This is expected as HPC is widely soluble both in water and in ethanol (Rowe et al., 2009), and thus should dissolve and leave pores. Furthermore, the permeability was very low up to 20 % HPC content. This is in agreement with a previous study on the permeability of EC-HPC films in non-ethanol containing dissolution media (Marucci et al., 2009). For samples analyzed in the presence of 40 % v/v ethanol in the dissolution medium, some deviations from the trend were seen. If instead looking at the permeability for a fixed HPC content and varying ethanol concentration in the dissolution media, the permeability of films with low HPC contents (0 and 20 % w/w) increases with increasing ethanol concentrations. However, at HPC contents higher than 20 % w/w the permeability instead decreases with increasing concentration of ethanol in the dissolution medium. Only one exception from the trend is seen, the permeability of the samples with 30 % w/w HPC in 5 % v/v ethanol is higher than suggested by the trend.

We propose the following explanation for the changes in film permeability in ethanol containing dissolution medium. At low HPC concentrations the dissolution of HPC will not form a coherent pore network though the film, in accordance with previous studies (Sakellariou et al., 1988; Marucci et al., 2009). Thus, the permeability of the films will be low. Ethyl cellulose is however soluble in ethanol. It would be expected that upon increasing the ethanol content in the dissolution medium, the solubility of EC is increased, with gelling and in the extreme dissolution as a consequence. It is well known that the diffusion coefficient in polymeric materials increases with decreasing polymer concentration (Masaro and Zhu, 1999). Thus, due to the swelling of the EC, the permeability of films with low HPC content is expected to increase with increasing ethanol concentration in the dissolution medium. For films with higher HPC content, the dissolution of HPC will lead to the formation of a coherent pore network through the films, with dramatic increase in permeability as a

consequence. When the EC swells in the presence of ethanol the pores will become smaller, and in the extreme cases filled with EC gel. As such, the permeability of the films with a high HPC content is expected to decrease with increasing ethanol concentration in the dissolution medium.

3.2 Dynamic mechanic analysis

In order to test the hypothesis that EC swells in ethanol containing dissolution medium, EC film samples were subjected to DMA during submersion in dissolution media with varying ethanol content. The length change, the elastic modulus, *G'*, and the loss factor, tan(δ), of the samples were recorded during the analyses. In Fig. 3 the percent length change is plotted versus time after submersion for different concentrations of ethanol in the dissolution medium. The film samples expanded more with increasing concentration of ethanol. The effect was rather small for samples exposed to dissolution medium with 0 and 5 % v/v ethanol, but more significant for 20 % v/v ethanol. For films swollen in dissolution medium containing 40 % v/v ethanol the samples displayed a quick and accelerating length expansion up to about 20 % (result not shown), at which point the analyses were terminated due to the instrumental expansion limit. The elastic modulus of the film samples was relatively unaffected by the addition of dissolution medium for ethanol concentrations in the range 0 to 20 % v/v. However, for the films exposed to the dissolution medium containing 40 % v/v ethanol *G'* decreased dramatically even before reaching the expansion limit of the instrument. Further decrease of *G'* would be expected if the measurements could have been continued. The large decrease in *G*' clearly indicates that the samples undergo a transition from a solid to 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 $$\tan(\delta) = \frac{G''}{G'} \qquad (2)$$

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.

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227 *3.3 Scanning electron microscopy*

To investigate if any difference could be detected in the structure of films exposed to dissolution media with varying ethanol content, film samples composed purely of EC and containing 35 % w/w HPC were submerged in dissolution media with different ethanol concentrations for two days. The samples were subsequently dried and analysed using SEM. If the EC was unaffected by the dissolution medium, pure EC films would be unaffected by the treatment and no change in structure should be detected. For the analysed EC-HPC films the HPC should dissolve, leaving a porous network. As for pure EC films, the structure should not be altered by the treatment if EC was not affected by the dissolution medium. However, if the EC swelled in the dissolution medium, altered structures would be expected both for pure EC films and for EC-HPC films.

As seen in Fig. 5 A-D, the structure of pure EC films is clearly affected by the ethanol concentration in the dissolution medium. The films that were exposed to dissolution medium containing 20 and 40 % v/v ethanol exhibit a different surface than films exposed to dissolution medium with less ethanol, probably due to swelling and subsequent drying. For HPC containing films it is hard to draw any certain conclusions due to the inherent heterogeneity of the films (Fig 5 E-H). However, there is some resemblance between the pure EC film and the HPC containing film submerged in dissolution medium containing 40 % v/v ethanol. The results from the SEM analysis support the hypothesis that the performance of EC-HPC films in ethanol containing dissolution medium is influenced by the ethanol concentration through the swelling, and at sufficiently high ethanol concentrations the gelling, of EC.

4. Conclusion

In this study it was shown that the water permeability of EC-HPC films for controlled drug delivery was influenced by the concentration of ethanol in the dissolution medium. Ethanol increased the water permeability for no and low amount of HPC in the films, but reduced the permeability at higher HPC content. The effects on the permeability can be explained by that the EC swells in the presence of ethanol, leading to an increased diffusion through the EC in the films, but more importantly decreasing the size of the pores left by the dissolved HPC. This explanation is supported by results from DMA and SEM analysis. The findings are interesting and of great relevance, as the effect of ethanol on controlled release formulations is a current concern expressed by regulatory authorities. The results in this study indicate that the performance of EC-HPC films in controlled delivery applications is at risk with regard to co-ingestion with ethanol. The results here presented mainly showed on a decrease in water permeability. However, given that in most formulations there will be an osmotic pressure difference over the films and that drug molecules are considerably larger than water molecules; our results should not be seen as a proof that dose dumping will not occur. Interesting further studies would be to investigate how the concentration of ethanol in the dissolution medium affects the performance of coated pellets and tablets with different 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.
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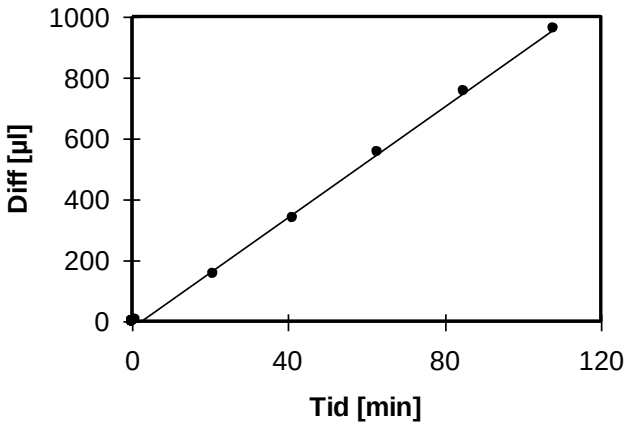

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360 Figure 2.
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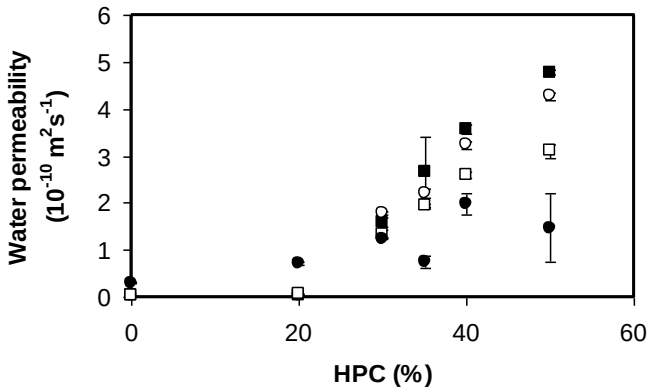

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364 Figure 3.
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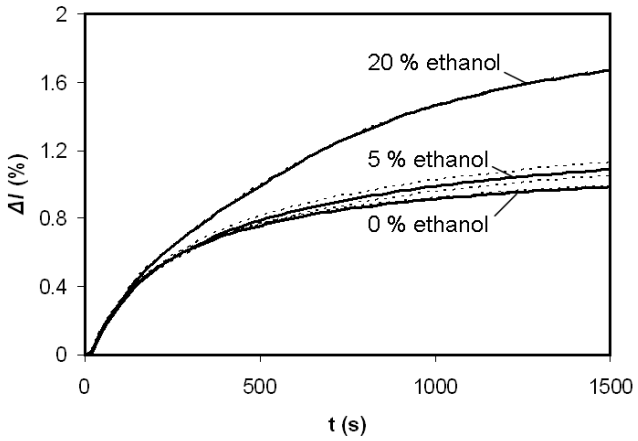

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Figure 4.

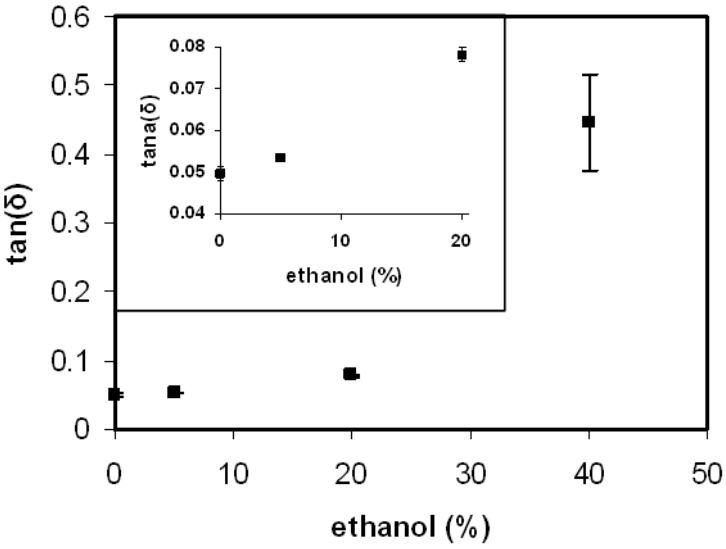
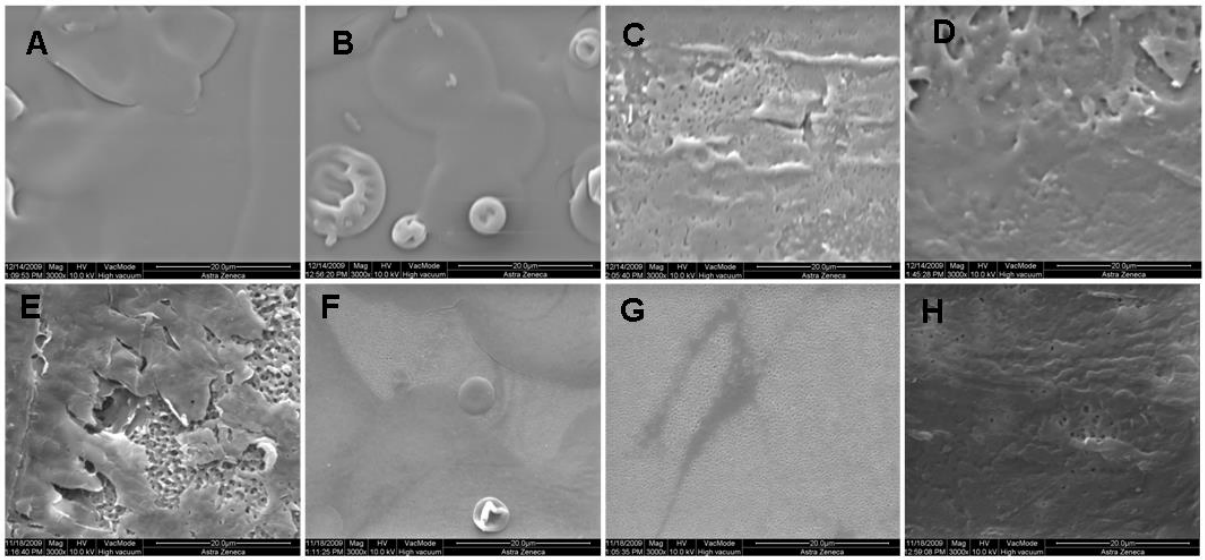


Figure 5.



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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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Table 2. Water permeability normalized versus film thickness (10^{-12} m^2s^{-1}) for EC films with varying HPC content, in dissolution media with different ethanol concentrations. One 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)