J Therm Anal Calorim (2012) 108:347–352
DOI 10.1007/s10973-011-1918-6

# Thermal study of ethyl cellulose coating films used for modified release (MR) dosage forms

**Géza Regdon Jr. · Diána Hegyesi · Klára Pintye-Hódi**

Received: 4 July 2011 / Accepted: 12 September 2011 / Published online: 23 September 2011


**Abstract** The aim of our research was to investigate the effect of the length of the polymer chain and the concentration of triethyl citrate used as a plasticizer on the thermal stability of the film structure in the case of two ethyl cellulose films (EC 10 and EC 45) used for preparing MR dosage forms. The influence of storage time was studied by monitoring the changes in the thermoanalytical parameters and by performing TG–MS examinations. It was found that the decomposition of the plasticizer from the arising film structure is retarded and a more homogeneous sample, therefore a better film can be prepared from EC 45. Mass spectrography performed as a coupled technique also proved that the films stayed stable until approximately 200 °C. Based on the above results, the composition prepared from EC 45 polymer with 5% triethyl citrate as plasticizer is recommended for making MR dosage forms.

**Keywords** Ethyl cellulose · Triethyl citrate · Free films · Physical–chemical investigations · MFT · Glass transition temperature · DSC · TG–MS

## Introduction

With the continuous development of biopharmacy and technology, the possibility arose to make controlled-release oral-modified release systems and thus to control the rate, place, or duration of drug release. Accordingly, modified, sustained, retarded, and periodic drug release can be achieved, and one possible way to realize this is to use a properly formed coat (pH-dependent dissolution, diffusion film, etc.). These solutions require film coats to meet higher expectations [1].

For this reason, it is indispensable to study the physicochemical and thermal behaviour of free films as part of the preformulation studies for developing a film coat composition, which is particularly important for the investigation of the stability of the preparations. Thermoanalysis is a very well used method in the preformulation tests of solid dosage forms [2–7].

There are some publications in literature on the thermoanalytical examination of free films or film-coated preparations, e.g. on the study of Eudragit containing polymethacrylate films [8–11], chitosan films [12], gelatin and poly(vinyl alcohol) containing films [13], biodegradable films [14–16] or cellulose-based films [9, 10, 17–19].

From amongst cellulose derivatives, EC is an ideal polymer for coating modified release (MR) preparations, yet few authors have studied its thermal properties in spite of the fact that more up-to-date preparations to be administered once/twice a day are of outstanding importance in choosing the therapy for reasons of patient compliance.

The aim of our experiments was to perform the preformulation tests of two EC film forming polymers with different chain lengths and different molecular weights (Ethocel Standard Premium 10®, Ethocel Standard Premium 45®, Colorcon Ltd.), and to study the thermal properties of the free films made from them. As polymer does not dissolve in water only in an organic solvent, 96% alcohol was used as a solvent. Polymers are best characterized by the viscosity of their solutions, the viscosity of Ethocel Standard Premium 10® and Ethocel Standard Premium 45® is 9–11 and 41–49 cP, respectively.

G. Regdon Jr. (✉) · D. Hegyesi · K. Pintye-Hódi
Department of Pharmaceutical Technology,
University of Szeged, Eötvös utca 6, 6720 Szeged, Hungary
e-mail: geza.regdon@pharm.u-szeged.hu

Viscosities are for 5% solutions measured at 25 °C in an Ubbelohde viscosimeter, and the solvent is 80% toluene and 20% alcohol [20]. We studied the effect of the length of the polymer molecule and the plasticizer used on important thermal properties such as, e.g. glass transition temperature, mass loss due to decomposition or thermal stability.

The polymer film has to form a uniform and continuous coat on the surface of the core to be coated; therefore, it has to have proper elasticity. In most of the cases films prepared only from a film forming polymer are rigid and break easily, so the use of plasticizers is indispensable to increase the elasticity of the coat. The quantity and quality of plasticizers can be checked with various physical–chemical investigations.

It is especially important to know the effect of the concentration of the plasticizer on the properties of the film structure, e.g. minimal film forming temperature (MFT), *Tg* [21] and the influence of storage time on the physical–chemical properties so that the polymer film can form an intact, properly elastic and uniform coat on the surface of the core. Plasticizers have to be used to ensure the proper elasticity of the coating. Plasticizers reduce the rigidity of the film. The molecules of the plasticizer are built in amongst the polymer chains, thereby preventing their interaction. Therefore, the polymer chains may shift along each other and the elasticity of the polymer film will increase.

With the examination of free films, we aimed to investigate the effect exerted not only by the chain length of the film forming polymer used and by the viscosity of its solution but also by the concentration of the plasticizer used on the thermal properties of the arising film structure to find the composition necessary for making films with optimal physical–chemical properties.

## Materials

Ethyl cellulose is a water insoluble cellulose ether which is prepared from cellulose, it is a partly *O*-ethylated cellulose, its ethoxy content (–OC2H5) is between 44 and 51%. Two different products of Colorcon Ltd. were used for the experiments, namely, EC labelled Ethocel Standard Premium 10® and Ethocel Standard Premium 45® (Colorcon Ltd, Dartford, England), which differed in the viscosity of their solutions and also in the length of the polymer chains. As polymer does not dissolve in water only in an organic solvent, 96% alcohol was used as a solvent.

Plasticizers have the capacity to alter the physical properties of a polymer film. Triethyl citrate, which was used as a plasticizer (Ph. Eur.), is the ethyl ester of citric acid, and it belongs in the group of organic esters.

## Methods

### Investigation of solutions

For the experiments, alcoholic solutions with 10% polymer content were prepared without plasticizer and with 1–3–5% triethyl citrate concentration. An MFT bar apparatus (Rhopoint Instrumentation Ltd.) was applied to determine the MFT and the film forming time of a 75-μm thick layer of solution at different temperatures. We had already worked out a method for determining film formation time earlier [19]. Six parallel measurements were performed.

### Preparation of free films

The solutions were sprayed on glass and Teflon surfaces placed in a rotating vessel, the conditions of spraying are presented in Table 1. The temperature of the drying air was set according to the MFT values presented in Table 2. During spraying, we continuously checked the temperature of the drying air, which was controlled with a laser temperature controller. The properties of the prepared free films were determined after preparation (fresh) and also after 2 and 4 weeks of storage (40 °C/50RH%) to monitor changes.

### Thermoanalytical measurements

The thermoanalytical examinations of the materials were carried out with a Mettler Toledo DSC 821e and TG/DSC1 instrument. During the DSC measurements, the start temperature was −40 °C, the end temperature was 300 °C and the applied heating rate was 10 °C $min^{-1}$. Argon atmosphere was used, and nitrogen was used as drying gas. 10 ± 1 mg of sample was measured into aluminium pans (40 μl). The data were calculated from the average of three parallel measurements and were evaluated with STARe Software.

For the TG measurements, the start temperature was +25 °C, the end temperature was 400 °C, and the applied heating rate was 10 °C $min^{-1}$. Nitrogen atmosphere was used. 10 ± 1 mg of sample was measured into aluminium pans (100 μl). The data were calculated from the average

**Table 1** Parameters of the preparation of free films

| Parameter | Value |
|---|---|
| Rotation rate of vessel | 22/min |
| Rate of liquid feeding | 5 ml/min |
| Pressure of spraying air | 1.5 bar |
| Diameter of nozzle | 0.8 mm |
| Temperature of drying air | According to MFT |

**Table 2** MFT values of EC 10 and EC 45 films

| | | Concentration of plasticizers | | | |
|---|---|---|---|---|---|
| | | 0% | 1% | 3% | 5% |
| EC 10 films | MFT (°C) | 26.1 | 20.7 | 20.3 | 17.7 |
| EC 45 films | MFT (°C) | 24.4 | 13.1 | 16.8 | 18.8 |

of three parallel measurements and were evaluated with STARe Software.

Mass spectrometric examinations

The stability examination of the films was supplemented with gas analysis. The TG instrument was coupled to a Thermo Star (Pfeiffer) quadruple mass spectrometer (maximum 500 amu) for gas analysis. The measurements were carried out in nitrogen atmosphere. Ions with various mass numbers were determined with the SEM MID measurement module of the Quadera software. The obtained results were exported and then plotted in one coordinate system with the TG curves using the Mettler Toledo Star software.

## Results and discussion

Before the preparation of free films, the minimum film forming temperature of EC films of various compositions were determined (see Table 2), so that the temperature of the drying air during spraying could be set accordingly. After the evaluation of the data shown in the table, it was found that the use of plasticizer decreased the value of the MFT in each case. The increase of triethyl citrate concentration decreased the MFT value proportionally to concentration in the case of EC 10 films and according to the minimum curve in the case of EC 45 films. The possible physical–chemical structural changes in the background of this phenomenon were already reported in another article [22].

The condition of the formation of a proper film structure is to know the glass transition temperature of the film forming polymer, which was determined with a DSC instrument. Both the structure and the glass transition temperature of the film are influenced greatly by the properties and concentration of the plasticizers used, therefore their role was studied.

The DSC curves of EC 10 fresh films containing various quantities of triethyl citrate are shown in Fig. 1. The glass transitions are indicated on the curve, and it is clear that the *Tg* value decreases with the increase of the plasticizer concentration.

The numerical data of glass transition are summarized in Table 3. The data clearly reveal that the *Tg* value in fresh films is not yet decreased by 1% of plasticizer but is definitely decreased by 3 and 5% of plasticizer.

**Table 3** Changes in the *Tg* values of EC 10 fresh films as a function of plasticizer concentration

| | Triethyl citrate concentration | | | |
|---|---|---|---|---|
| | 0% | 1% | 3% | 5% |
| Glass transition temperature (*Tg*)/°C (SD) | 126.4 (±2.22) | 126.9 (±2.74) | 118.6 (±7.89) | 105.1 (±8.95) |

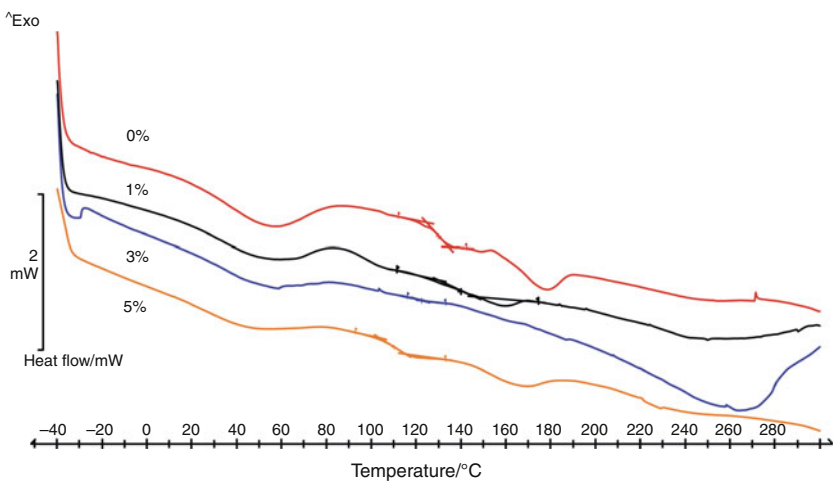


**Fig. 1** DSC curves of EC 10 fresh films

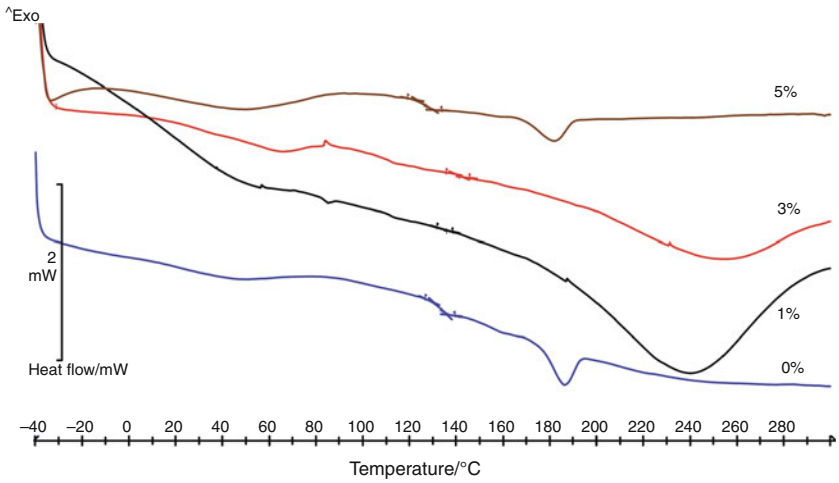


**Fig. 2** DSC curves of EC 45 fresh films

**Table 4** Changes in the *Tg* values of EC 45 fresh films as a function of plasticizer concentration

| | Triethyl citrate concentration | | | |
|---|---|---|---|---|
| | 0% | 1% | 3% | 5% |
| Glass transition temperature (*Tg*)/°C (SD) | 133.4 (±0.56) | 135.9 (±0.23) | 141.5 (±0.43) | 128.7 (±0.91) |

Figure 2 shows the DSC curves of EC 45 fresh films containing various quantities of triethyl citrate. The numerical data of glass transition are summarized in Table 4. It is clear from the data that the *Tg* value in fresh films is increased by 3% plasticizer, but is decreased by 5% of plasticizer in the case of EC 45 films, which is again due to structural changes.

The comparison of the glass transition temperature values of the two film forming polymers shows that the glass transition temperature of films prepared from the shorter-chain EC 10 polymer is slightly lower than for longer-chain EC 45 films. The reason for this is that in the "looser" structure transition can take place at a lower temperature than in the "more compact" structure formed by longer-chain polymers. The numerical data also show that in fresh films containing plasticizer the *Tg* value could be decreased by 3% plasticizer in the case of "looser" EC 10 films prepared from shorter-chain polymers, whilst 5% plasticizer was needed for "stronger" EC 45 films made from longer-chain polymers.

We also investigated whether the glass transition temperature, which is the most typical feature of the film structure, changed as a function of storage time for the free films we prepared.

**Table 6** Mass change of EC 10 and EC 45 films as a function of plasticizer concentration

| | | Triethyl citrate concentration | | | |
|---|---|---|---|---|---|
| | | 0% | 1% | 3% | 5% |
| Mass decrease/% | EC 10 films | 1.12 | 8.94 | 21.23 | 30.16 |
| | EC 45 films | 1.22 | 10.56 | 20.48 | 31.70 |

**Table 7** Mass change of EC 10 and EC 45 films as a function of plasticizer concentration after 4 weeks of storage

| | | Triethyl citrate concentration | | | |
|---|---|---|---|---|---|
| | | 0% | 1% | 3% | 5% |
| Mass decrease/% | EC 10 films | 2.59 | 1.16 | 21.00 | 27.03 |
| | EC 45 films | 0.53 | 11.51 | 20.25 | 28.14 |

**Table 5** Changes in the *Tg* values of EC 10 and EC 45 films as a function of storage time

| | Triethyl citrate concentration | *Tg*/°C | | |
|---|---|---|---|---|
| | | Storage time | | |
| | | Fresh | 2 weeks | 4 weeks |
| EC 10 films | 0% (SD) | 121.9 (±6.4) | 126.9 (±1.58) | 107.1 (±2.08) |
| | 5% (SD) | 108.3 (±7.11) | 104.2 (±6.16) | 101.1 (±11.1) |
| EC 45 films | 0% (SD) | 131.9 (±1.16) | 135.7 (±4.85) | 132.7 (±1.47) |
| | 5% (SD) | 127.5 (±0.74) | 127.9 (±2.16) | 128.5 (±0.16) |

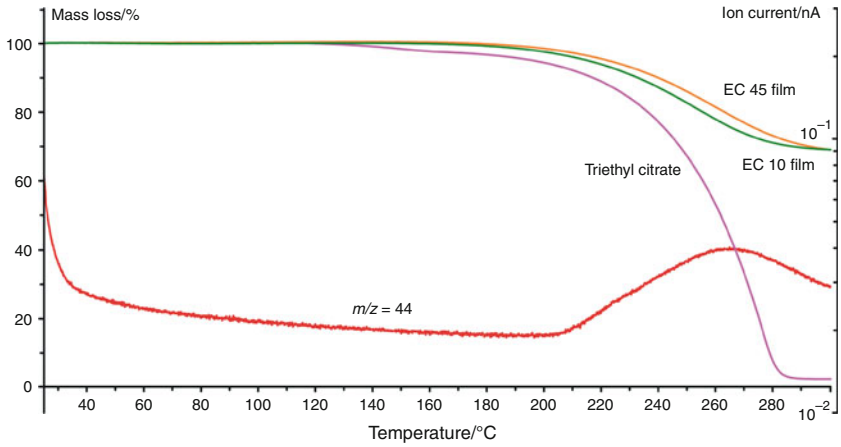


**Fig. 3** TG Curves of EC 10 and EC 45 films containing 5% triethyl citrate and their MS evaluation

The time course of the glass transition values is presented for the films without plasticizer and with the highest concentration in the case of both film forming polymers (see Table 5). The data show that EC 10 films underwent greater change during storage and they were less stable than EC 45 films, so EC 10 films are less suitable for forming MR dosage forms.

The thermal stability values of the fresh films were examined, and the results are summarized in Table 6. The analysis of the TG curves (Fig. 3) revealed that the two different film forming polymers are thermally stable, a mass decrease of only 0.5 and 1.2% could be detected until 100 and 300 °C, respectively. The decomposition process starts only later and a mass loss of about 10–20–30% can be detected, depending on the concentration of the plasticizer. There is practically no difference between the thermal stabilities of the two polymers, so mass change depends only on the plasticizer concentration.

The thermal behaviour of triethyl citrate and of films containing 5% plasticizer is shown in Fig. 3. The TG curves show that the decomposition of triethyl citrate starts as early as over 120 °C and becomes more intensive over 200 °C, and the material is fully decomposed before reaching 300 °C. The shape of the curves is a proof for triethyl citrate probably being built in the structure of the EC film, because its decomposition from the film starts only later, at about 180–200 °C.

Similarly, the results of the MS examinations are shown in Fig. 3, based on the analysis of the gases which evolve from the EC 10 film. Carbon dioxide gas ($m/z = 44$) starts to evolve at 200 °C and reaches its highest concentration at 260–270 °C.

The films were also examined after 4 weeks of storage (see Table 7), and the results were practically the same as those for the fresh film. The only exception was the EC 10 film containing 1% plasticizer, which is probably due to the inhomogeneity of the sample.

As a summary of the thermal investigations, it can be stated that the decomposition of the plasticizer from the arising film structure is retarded, and the polymer molecule itself stays stable until 300 °C. A more homogeneous sample, therefore a better film can be prepared from EC 45, but mass change depends basically on the material quality of the plasticizer. Mass spectrography performed as a coupled technique also proved that the films stayed stable until approximately 200 °C.

## Conclusions

It was found that the glass transition temperature of films prepared from the shorter-chain EC 10 polymer with a "looser" structure is slightly lower than for longer-chain, more "compact" EC 45 films. In fresh films containing plasticizer, the *Tg* value could be decreased by 3% plasticizer in the case of "looser" EC 10 films prepared from shorter-chain polymers, while 5% plasticizer was needed for "stronger" EC 45 films made from longer-chain polymers. EC 45 films were more stable during storage. The thermal stabilities of the two polymers are approximately the same.

The thermal investigations revealed that the decomposition of the plasticizer from the arising film structure is retarded. A more homogeneous sample, therefore a film of better quality (pore-free, properly elastic) can be prepared from EC 45. Mass spectrography performed as a coupled technique also proved that the films stayed stable until approximately 200 °C. Based on the above results, the composition prepared from EC 45 polymer with 5% triethyl citrate as plasticizer is recommended for making MR coats.

**Acknowledgements** This study was supported by TÁMOP-4.2.1/B-09/1/KONV-2010-0005 (Hungary).

## References


1. Bertelsen P, Christensen FN, Holm P, Jorgensen K. Comparison of organic solvent-based ethylcellulose coatings of KCl crystals applied by top and bottom spraying in fluidized-bed equipment. Int J Pharm. 1994;111:117–25.
2. Beretzky Á, Kása P Jr, Pintye-Hódi K, Bajdik J, Szabó-Révész P, Erős I. Pelletization of needle-shaped phenylbutazone crystals. J Therm Anal Calorim. 2002;69:529–39.
3. Zelkó R, Orbán Á, Nagy J, Csóka G, Rácz I. Coating polymer–plasticizer interaction in relation to the enthalpy relaxation of polymer. J Therm Anal Calorim. 2002;68:531–7.
4. Aigner Z, Szepesi E, Berkó S, Novák C, Regdon G Jr, Kata M. Investigation of ethacrynic acid and random-methyl-$\beta$-cyclodextrin binary complexes. J Incl Phenom Macro. 2002;42:219–26.
5. Kiekens F, Zelkó R, Remon JP. Effect of the storage conditions on the tensile strength of tablets in relation to the enthalpy relaxation of the binder. Pharm Res. 2000;17:490–3.
6. Peres-Filho MJ, Gaeti MPN, Oliveira SR, Marreto RN, Lima EM. Thermoanalytical investigation of olanzapine compatibility with excipients used in solid oral dosage forms. J Therm Anal Calorim. 2011;104:255–60.
7. Bhattacharjya S, Wurster DE. Investigation of the drug release and surface morphological properties of film-coated pellets, and physical, thermal and mechanical properties of free films as a function of various curing conditions. AAPS Pharm Sci Tech. 2008;9:449–57.
8. Melo EJ, Alves BRV, Freitas AA, Muniz EC, Cavalcanti OA. Influence of the addition of alpha or gamma-cyclodextrin on the formation of free films in the polymethacrylates eudragit (R) FS30D. Latin Am J Pharm. 2010;29:919–26.
9. Bley O, Siepmann I, Bodmeier R. Characterization of moisture-protective polymer coatings using differential scanning calorimetry and dynamic vapor sorption. J Pharm Sci. 2009;98:651–64.
10. Regdon G Jr, Kósa A, Erős I, Pintye-Hódi K. Study of thermoanalytical behaviour of some coating films. J Therm Anal and Calorim. 2007;89:793–7.
11. Bajdik J, Pintye-Hódi K, Regdon G Jr, Fazekas P, Szabó-Révész P, Erős I. The effect of storage on the behaviour of Eudragit NE free film. J Therm Anal Calorim. 2003;73:607–13.
12. Zen-aldeen EA, Hussein AK, Ibrahim MA, Amin MA. Physico-mechanical properties and release characteristics of ketorolac tromethamine from chitosan films: effect of inclusion of different polyols plasticizers. Bull Pharm Sci. 2008;31:229–47.
13. Mendieta-Taboada O, Sobral PJD, Carvalho RA, Habitante AMBQ. Thermomechanical properties of biodegradable films based on blends of gelatin and poly(vinyl alcohol). Food Hydrocolloids. 2008;22:1485–92.
14. Langmaier F, Mokrejs P, Mladek M. Heat-treated biodegradable films and foils of collagen hydrolysate crosslinked with dialdehyde starch. J Therm Anal Calorim. 2010;102:37–42.
15. Nunes PS, Bezerra MS, Costa LP, Cardoso JC, Albuquerque RLC Jr, Rodrigues MO, Barin GB, Amaral da Silva F, Araújo AAS. Thermal characterization of usnic acid/collagen-based films. J Therm Anal Calorim. 2010;99:1011–4.
16. Mokrejs P, Langmaier F, Janacova M, Mladek M, Kolomaznik K, Vasek V. Thermal study and solubility tests of films based on amaranth flour starch–protein hydrolysate. J Therm Anal Calorim. 2009;98:299–307.
17. Sahin NO, Arslan H. Formulation study for enteric microspheres of tenoxicam using cellulose acetate phthalate part-II: modulation of ulcerogenic effect. Asian J Chem. 2007;19:5718–26.
18. Regdon G Jr, Zsellér B, Pintye-Hódi K. Physical-chemical investigations of Metolose coating films. Composite Interfaces. 2010;17:581–94.
19. Bajdik J, Regdon G Jr, Marek T, Erős I, Süvegh K, Pintye-Hódi K. The effect of the solvent on the film-forming parameters of hydroxypropyl-cellulose. Int J Pharm. 2005;301:192–8.
20. Ethocel Standard Premium® Application Data, Colorcon Ltd. Dartford, England.
21. Bley O, Siepmann J, Bodmeier R. Importance of glassy-to-rubbery state transitions in moisture-protective polymer coatings. Eur J Pharm Biopharm. 2009;73:146–53.
22. Marek T, Süvegh K, Kéry I, Zelkó R, Regdon G Jr, Pintye-Hódi K, Vértes A. The effect of plasticizer on the ageing of Metolose films. Rad Phys Chem. 2007;76:165–8.