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Phase behaviour of the system estradiol/poly(ε-caprolactone)

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The temperature–concentration behaviour of the system 17-β-estradiol/poly(ε-caprolactone) has been investigated by calorimetry. An eutectic melting behaviour with the eutectic point lying on the pure poly(ε-caprolactone) axis is observed. The eutectic melting temperature coincides with the melting point of the polymer. The glass transition–concentration behaviour was also investigated. This transition is situated at 56°C for the pure 17-β-estradiol and at −71°C for the poly(ε-caprolactone). Consequently, the polymer act as a plasticizer for the 17-β-estradiol with a glass transition–concentration relationship that follows the Fox equation. The influence of this complex temperature–concentration behaviour on the crystallization of the constituents is discussed. © 1998 Elsevier Science Ltd. All rights reserved.

(Keywords: estradiol; ε-caprolactone; eutectic crystallization)

INTRODUCTION

Biodegradable polymers for controlled drug delivery have received much attention in recent years. Poly(ε-caprolactone) (PC), of which the repeat unit is shown in *Figure 1*, belongs to the group of aliphatic polyesters. Owing to its biocompatibility, biodegradability and permeability to many drugs, it is a valuable material for the use as drug-delivery matrix[1–3]. Several therapeutic agents have been incorporated. One of them is 17-β-estradiol (ED), shown in *Figure 2*, used in treatments for the prevention of postmenopausal bone loss[4,5]. As part of an ongoing programme on steroid-releasing implants, we are currently preparing polyester devices containing 17-β-estradiol. In a first approach, poly(ε-caprolactone) was studied as matrix material.

At room temperature, estradiol is a crystalline substance while PC is in the semicrystalline state. This means that a solution of ED in PC will phase separate at this temperature and that the system should consist of a dispersion of estradiol crystals in the PC matrix. The morphology of such a dispersion is of major importance for its use as a drug-delivery system since it will influence the diffusion characteristics. In order to understand and control such a process, it is imperative to get an insight in the different thermal transitions and the interactions that can take place. This kind of information can be obtained from the temperature–concentration phase diagram in which crystallization and melting of the different components is reported[6–8]. The diagram should also include the concentration dependence on the glass transition temperature(s), as their interference on crystallization and melting can strongly influence the behaviour of the system[7,9,10].

The investigation of this temperature–concentration behaviour will be the subject of the present study.

EXPERIMENTAL

17-β-Estradiol was obtained from Sigma and used as-received.

Poly(ε-caprolactone) was synthesized by ring-opening polymerization of the monomer ε-caprolactone with pentaerythritol as initiator. The monomer-to-initiator ratio was 450. Monomer, initiator and one drop of stannous octoate as a catalyst were added to a silanized flask. The polymerization was carried out in the bulk under nitrogen at 130°C. After 24 h, the resulting polymer was dissolved in methylene chloride and precipitated in cold methanol. It was dried at 40°C under vacuum.

The polymer was characterized by ^{1}H nuclear magnetic resonance (n.m.r.) spectroscopy by using a Brucker 360 MHz spectrometer with tetramethylsilane as internal standard.

The molecular weight of the polymer was determined by gel permeation chromatography (PLGel 5 μm MIXED-D column, polystyrene standards) with tetrahydrofuran as eluent. The values measured are $\overline{M}_n = 46\,500$ g/mol and $\overline{M}_w = 69\,700$ g/mol, $\overline{M}_w/\overline{M}_n = 1.49$.

Blends containing different weight fractions of ED in PC were prepared by evaporation at room temperature of a solution of both components in tetrahydrofuran (THF) at a concentration of 0.10 g in 10 ml solvent. The obtained film was then ground in a liquid-nitrogen-cooled mill to obtain a fine powder which was dried under vacuum. The concentrations are expressed in weight fraction of PC (w_1) and ED (w_2).

Calorimetric observations were performed with a Perkin–Elmer DSC-7. Samples weighing between 5 and 10 mg were used and the heating rate was set at 5°C min^{-1}.

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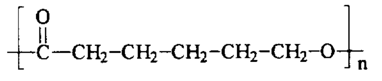
RESULTS

Experimental observations

The different thermal transitions have been evaluated by differential scanning calorimetry (DSC). Specific thermal treatments were applied in order to achieve the desired result. The pure components and the blends have been investigated. Three typical DSC scans are presented in *Figure 3* (ED), *Figure 4* (PC) and *Figure 5* (blend). The different transitions are indicated in these figures. The glass transition temperature (T_g) is taken as the temperature at the inflection point in the shift in the baseline (*Figure 3*). The choice of the melting temperature (T_m) depends on the type of melting as given by the Gibbs phase rule. For a pure component or an eutectic mixture, the temperature at the maximum of the melting endotherm is taken as the melting point (*Figures 3 and 4*). Both situations correspond to an invariant melting at constant pressure. In the case of a two-component system, the melting point of one of the components in the presence of the other one corresponds to the temperature at the end of the melting endotherm (*Figure 5*). This situation represents a variant melting or dissolution of one component in its solution with the other component. At constant pressure there is one independent variable, temperature or concentration. With these melting



$$\left[-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-CH_2-CH_2-CH_2-O-\right]_n$$

Figure 1 Repeating unit of poly(ε-caprolactone) (PC)

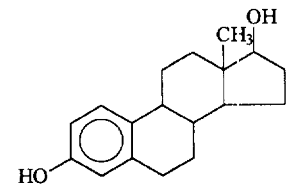


Figure 2 17-β-Estradiol (ED)

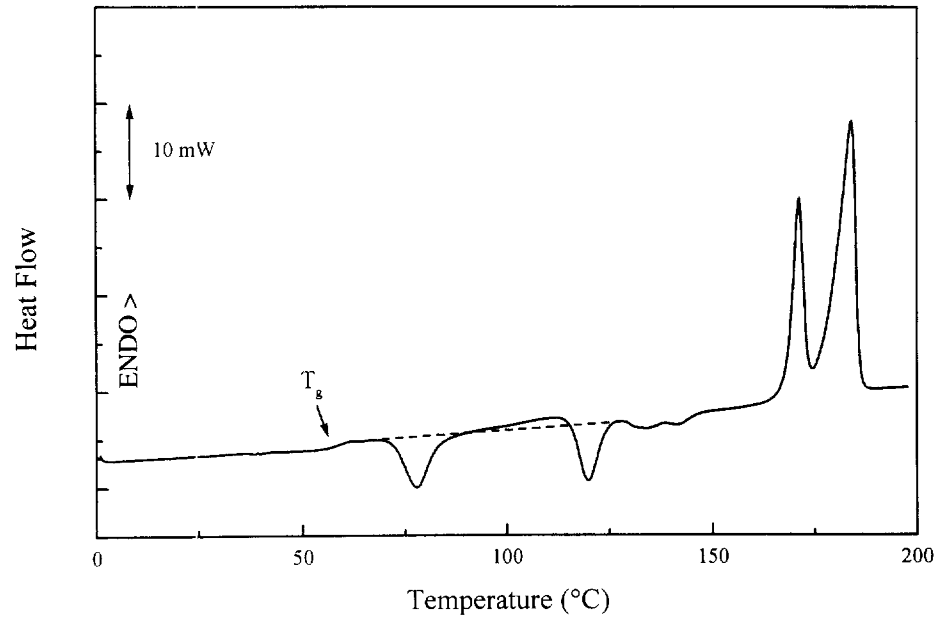


Figure 3 DSC thermogram of pure ED recorded at a heating rate of 5°C min^{-1}. Sample quenched in liquid nitrogen

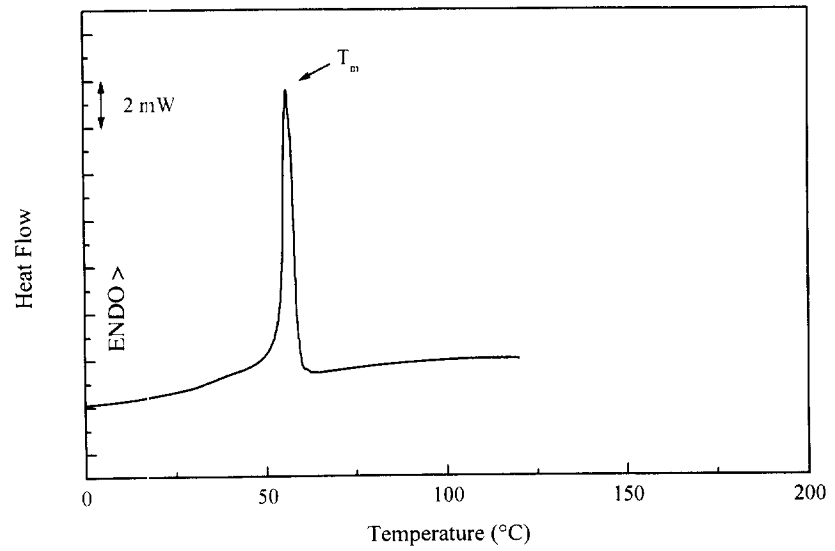


Figure 4 DSC thermogram of pure PC, recorded at a heating rate of 5°C min^{-1}. Sample crystallized isothermally at 27°C

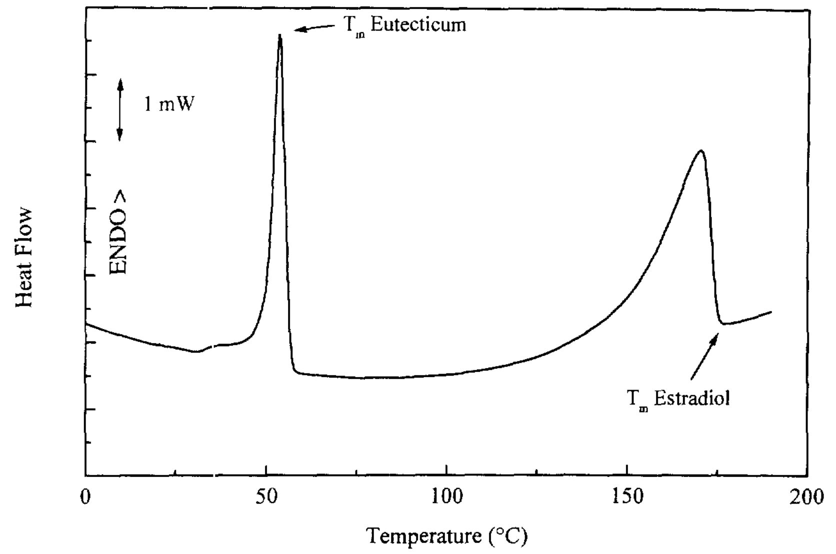


Figure 5 DSC thermogram of a blend $w_1 = 0.40$ recorded at a heating rate of 5°C min^{-1}. Sample isothermally crystallized at 90°C for 15 min, cooled to 27°C and also crystallized isothermally

temperatures, a temperature–concentration phase diagram can be constructed.

Glass transition temperature–concentration relationship

Figure 3 represents the DSC scan of ED. The sample was first heated at 190°C for several minutes outside the calorimeter in order to obtain a random melt. Then it was quenched in liquid nitrogen. This amorphous, glassy sample was then transferred to the calorimeter at −100°C and heated at 5°C min^{-1}. A glass transition at 59°C is followed by two exothermic and two endothermic signals. Those exo- and endothermic signals will be discussed below (see melting behaviour).

Figure 4 represents the DSC scan of PC recorded after the sample was quenched in liquid nitrogen. It was not possible to quench the pure polymer fast enough to obtain a completely amorphous sample. Therefore this scan does not show a shift in the baseline, characteristic for a T_g. The absence of a crystallization exotherm supports the fact that the sample is already crystalline after quenching. Consequently, only the melting could be observed. This problem, resulting from the very fast crystallization of the polymer, has been discussed previously in the literature by Koleske and Lundberg[11]. They localized the T_g around −71°C. This value will be used in this work.

By contrast, the glass transition of the blends was easily observed in a series of experiments with samples quenched in liquid nitrogen. These samples were treated as described above.

The experimentally observed T_g values are presented in *Figure 6*. The T_g–concentration relationship was calculated from the values of the glass transition temperatures of the pure components by means of the following Fox equation[12]:

$$1/T_g = w_1/T_{g1} + w_2/T_{g2} \qquad (1)$$

where w_1 and w_2 are the weight fractions of components 1 and 2, respectively, and T_{g1} and T_{g2} are the glass transition temperatures of the corresponding pure components. The previously discussed glass transition temperatures of the pure components, ED and PC, are used in these calculations. This calculated relationship is represented by the solid curve through the experimental points in *Figure 6*. The agreement between the experimental points and this calculated relationship is very good.

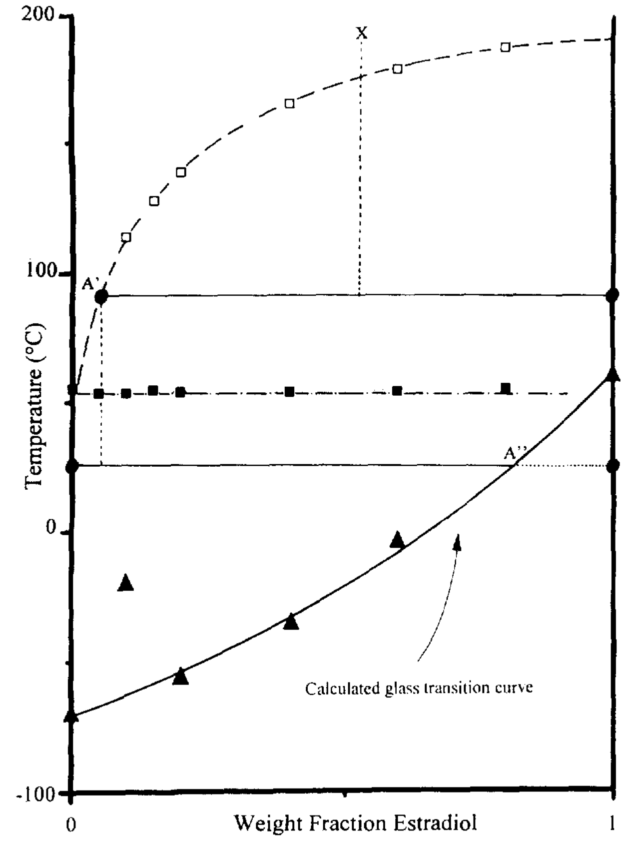


Figure 6 Temperature–composition diagram of the system PC/ED. □, Temperature at the end of the melting endotherm of ED in equilibrium with a solution ED/PC; ■, temperature at the maximum of the eutectic melting endotherm; ▲, experimentally observed glass transition temperatures; solid curve, calculated glass transition temperature–concentration relationship; ●–●, tie lines. X, composition of a homogeneous melt at 190°C; A′, composition of the melt coexisting with pure ED at 90°C; A″, composition of glassy phase coexisting with pure PC at 27°C

Only one of the experimentally observed values does not correspond to the calculated value. A blend containing only 10% estradiol has a T_g of −20°C. This high value for T_g is ascribed to the fact that the polymer is partially crystallized under the experimental conditions. As a consequence, pure crystalline PC is formed and this results in an increase of the ED content in the remaining melt. During crystallization, the melt composition shifts to the right (pure ED) until the glass transition–concentration curve is reached. Then the crystallization of the polymer stops and the crystalline PC coexists with a glassy phase with an ED content around $w_2 = 0.50$.

This problem does not arise with the blends that contain a higher fraction of ED. Quenching results in an amorphous, glassy sample which crystallizes when heated above T_g. The fact that a completely amorphous sample is obtained by quenching is supported by the value of the crystallization enthalpy, which equals the melting enthalpy.

The T_g of the 40/60 PC/ED blend equals −5°C. This is also in agreement with the estimated value of *Figure 6*. After passing the glass transition, crystallization of the PC does not take place. This is the direct consequence of the too narrow temperature gap between T_g and T_m. This leads to a too low crystallization rate in comparison with the heating rate. Consequently crystallization cannot take place under these conditions. The exothermic signal that set in at 56°C represents the crystallization of ED.

Melting behaviour

Melting data were obtained from two different sets of experiments. Information was obtained in the first place from the dynamic experiments discussed above. In a second series of experiments, the melting behaviour of isothermally crystallized samples was investigated. The samples were first melted inside the calorimeter at 190°C and then 'quenched' in the calorimeter to 90°C at a programmed rate of 200°C min^{-1}. This temperature is situated above the melting temperature of PC and below the crystallization temperature of ED. Isothermal annealing at this temperature will lead to the crystallization of ED. After 15 min the sample is cooled to 27°C and kept there for an additional 15 min. This induces the crystallization of the polymer. Then the sample is cooled to −20°C, and immediately heated to 190°C at 5°C min^{-1}. A typical DSC scan recorded during this heating procedure is reported in *Figure 5*.

The melting thermogram obtained for the pure polymer shows a broadened peak because of distribution in crystal size and perfection. Therefore the maximum of the endotherm is taken as the melting temperature. The maximum of the endotherm for the melting of pure PC is located at 56°C.

The thermogram for the melting (*Figure 3*) of pure estradiol shows a double endothermic peak. The first exotherm is ascribed to the crystallization of the amorphous sample. The second exotherm must correspond to a melting–recrystallization process. This overlap between a melting endotherm and crystallization exotherm can easily be seen when the baseline is continued to high temperature (dotted line). The occurrence of this melting–recrystallization process can also be responsible for the apparent instability of the baseline at higher temperature. Such a transition is characteristic for the occurrence of two different crystal morphologies and the transformation of one morphology into the other upon heating. The observation of two melting endotherms and only one melting endotherm when the sample is crystallized at 90°C (*Figure 7*), between the two exothermic signals of *Figure 3*, also supports the presence of these two morphologies.

The thermograms obtained by melting blends of several compositions of polycaprolactone and estradiol always show a rather sharp peak at 53°C followed by a much broader peak. This is independent of the thermal history of the experiment. Such a melting behaviour is characteristic for the occurrence of an eutectic melting[13,14]. The sharp, low-melting endotherm represents the eutectic melting of the system. In low-molecular-weight substances, the eutectic melting temperature corresponds to the temperature at the onset of this signal because of the invariant nature of the transition. When polymers are involved, an intrinsic broadening of the signal will take place and therefore the temperature at the maximum of this peak is the best approximation of the eutectic melting point. The melting temperature of one of the crystal phases in equilibrium with the melt corresponds to the temperature at the end of the

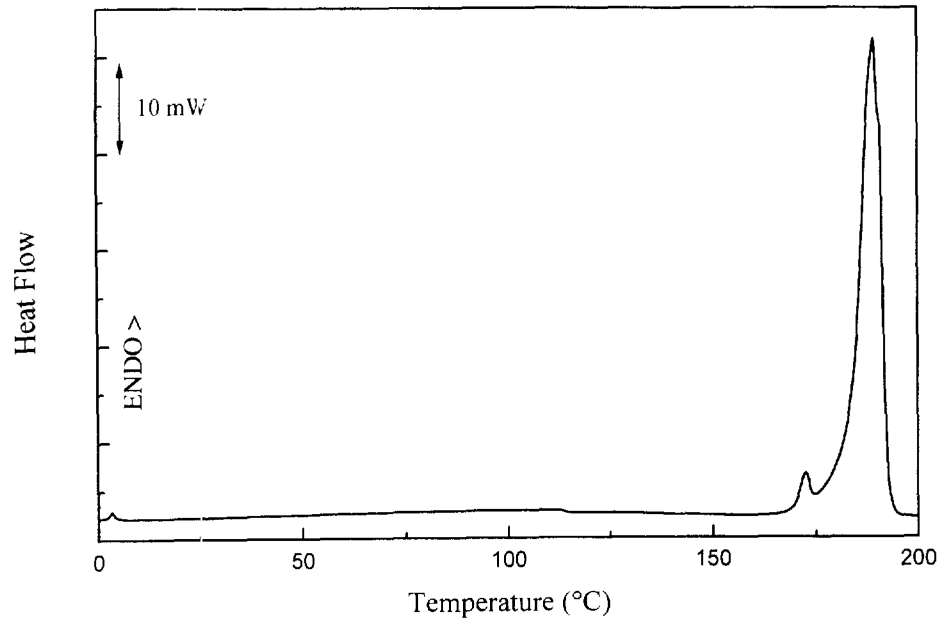


Figure 7 DSC thermogram of pure ED after crystallization at 90°C

second, high-temperature endotherm. This procedure should be followed not only in the case of solutions of small molecules, but also when one of the constituents is a polymer. The concentration dependence of these two melting points is also plotted in *Figure 6*. A eutectic melting diagram is obtained. Because of the difference in melting temperature between the two constituents and the observed concentration dependence of ED on the concentration of the polymer, only one liquidus is observed. This liquidus represents one branch of the eutectic diagram and corresponds to the concentration dependence of the melting point of ED. The eutectic point coincides with the axis of the pure PC. The eutectic melting therefore represents the melting of PC. This invariant, eutectic melting takes place at 53°C.

DISCUSSION

The temperature–concentration behaviour of the system PC/ED shows several interesting aspects.

(1) Both constituents are compatible over the whole concentration range, otherwise a different concentration dependence of the melting behaviour and glass transition would be observed.

(2) The glass transition–concentration behaviour is opposite to the behaviour generally observed when small molecules are dissolved in a polymer matrix. This generally results in the lowering of the glass transition of the polymer through plasticization by the small molecule. The opposite is observed here because PC has a lower T_g than ED. The T_g–concentration relationship follows the calculated relationship obtained with the Fox equation very well.

(3) An eutectic melting of the two constituents is observed. Because of the collegative character of a melting point depression and the difference in size between the molecules, the decrease of the melting point of ED is not very pronounced in the high w_2 region of this substance. A pronounced effect on the shape of the liquidus of ED is observed only for a polymer weight fraction $w_1 \geq 0.50$. The difference in melting point between the constituents shifts the eutectic point to the pure PC axis so that the eutectic temperature coincides with the melting temperature of the pure polymer and the eutectic melting peak represents the melting of PC.

(4) Such a complex phase behaviour will also influence the crystallization of the constituents. To what extent ED will crystallize quantitatively from the melt will depend, to a large extent, on the cooling procedure and the overall concentration.

Crystallization in samples quenched into the glassy region can only take place at room temperature at low ED content. A too high ED content increases T_g above room temperature and crystallization of ED can only take place above 56°C, the T_g of ED.

Crystallization from the melt at, for example, 90°C, preventing the crystallization of PC, will also lead to only partial crystallization. A melt with an overall composition X (see *Figure 6*) will be transformed at 90°C into ED crystals and a coexisting solution of ED in PC with composition A′. Quantitative crystallization of ED can only be realized when this sample is further slowly cooled to 53°C. This quantitative crystallization can, of course, also be realized by cooling a solution with any concentration from the molten state to 53°C.

Quenching to temperatures in the vicinity of room temperature will also result in partial crystallization. When the solution with composition A′ is cooled to 27°C as described before, PC will crystallize and the melt composition will shift to the pure ED axis. This component, however, will not crystallize as it will remain frozen in the glassy state with a composition A″ that is reached from the melt. The two-step crystallization used in this work will therefore result in the coexistence of three phases: crystalline ED, semicrystalline PC and a glass phase composed of PC and ED with composition A′. This is clearly illustrated by the DSC scan presented in *Figure 5*. A shift in the baseline around 27°C, characteristic for a glass transition, precedes the eutectic melting of PC (sharp endotherm). This eutectic melting is then followed by the dissolution of ED in the melt (broad endotherm).

Quenching from the melt to room temperature is therefore expected to result in limited or even completely suppressed crystallization of ED and the formation of crystalline PC, coexisting with a glassy phase composed of PC and ED. The exact situation that can be realized will depend strongly on the rate of crystallization of the different constituents in comparison with the cooling rate.

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REFERENCES

1. Pitt, C.G., in *Biodegradable Polymers as Drug Delivery Systems*, eds M. Chasin and R. Langer. Marcel Dekker, New York, 1990, Ch. 3.
2. Engelbert, I. and Kohn, J., *Biomaterials*, 1991, **12**, 292.
3. Holland, S. J., Tighe, B. L. and Gould, P. L., *J. Contr. Rel.*, 1986, **4**, 155.
4. Buntner, B., Nowak, M., Bero, M., Dobrzynski, P. and Kasperczyk, J., *J. Bioactive Compatible Polym.*, 1996, **11**, 110.
5. Ye, W.-P. and Chien, Y. W., *J. Contr. Rel.*, 1996, **41**, 259.
6. Aerts, L. and Berghmans, H., *Bull. Soc. Chim. Bel.*, 1990, **11-12**, 99.
7. Berghmans, H. and Deberdt, F., *Phil. Trans. Roy. Soc. Lond.*, 1994, **348**, 117.
8. Wunderlich, B., *Macromolecular Physics*. Academic Press, New York, 1973–1976. Ch. 3.
9. Arnouts, J. and Berghmans, H., *Polym. Commun.*, 1990, **31**, 343.
10. Roels, T., Deberdt, F. and Berghmans, H., *Macromolecules*, 1994, **27**, 6216.
11. Koleske, J. V. and Lundberg, R. D., *J. Polym. Sci., Part A2*, 1969, **7**, 795.
12. Fox, T. G., *Bull. Am. Phys. Soc.*, 1956, **2**, 123.
13. Smith, P. and Pennings, A. J., *J. Mater. Sci.*, 1976, **11**, 1450.
14. Gryte, C. C., Berghmans, H. and Smets, G., *J. Polym. Sci., Polym. Phys. Edn*, 1979, **17**, 1295.