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COMPARISON OF THE FRAGILITY INDEX OF DIFFERENT EUDRAGIT POLYMERS DETERMINED BY ACTIVATION ENTHALPIES

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The present study aimed to apply fragility index (m) of polymers in the determination of the optimal amount of plasticizer in polymer films. The fragility index of different Eudragit polymers (RS, RL, EPO) was assessed by differential scanning calorimerty (DSC), applying the Arrhenius connection ($\log q - 1/T_g$). The fragility of Eudragit EPO films proved to be the highest, while in the case of RS and RL, the increase of the alkyl-chain length caused the increase of fragility. Studying the effect of plasticizer (triethyl citrate, TEC) on the m value of Eudragit RL and RS films, a near linear reduction of the fragility index could be observed between 5–30% TEC concentration, but above 30%, this value leveled out to constant.

Keywords: *activation enthalpy, EPO, Eudragit RS, -RL, -EPO, fragility index, RL, RS, triethyl citrate*

Introduction

The optimization of the amount of plasticizer in the polymer film is a very important formulation task. There are some polymers, which can not be applied without plasticizer because of their fragility. When the amount of the applied plasticizer is too little, the polymer film remains fragile, and can not coat the tablet, capsule, or fit the skin properly. On the other hand too much plasticizer, can not diffuse into the film, it remains on the surface, so it can worsen the property of the film.

Polymers are often used in transdermal therapeutic systems (TTSs) as membrane and matrix forming agents. These systems are applied on the surface of the skin, and they are able to assure controlled drug release and constant blood level. TTSs must fit to skin, so flexibility and fragility are very important properties. Eudragits, which are commercial acrylate copolymers and are widely used in the pharmaceutical industry as film coating agents, can be applied in TTS preparations too, as matrix and membrane forming materials. Most of Eudragit polymers can not be used in TTSs without plasticizer because of the fragility. The used plasticizer changes the flexibility, tensile strength and adhesion properties of the resulting film and influences its appearance and different physical properties (glass transition temperature, minimal film forming temperature). The plasticizer not only affects the flexibility and reduces the brittleness of the film, but also can regulate the drug penetration through the polymeric film [1, 2]. These properties depend on the quality and concentration of the applied plasticizer, so the determination of the optimal amount of plasticizer plays an important role in the preparation of polymeric films. There are some possibilities to determine this optimal amount of plasticizer, e.g. measuring the enthalpy relaxation at the glass transition of the polymer [3].

Among the additives that are incorporated into aqueous polymeric dispersions, the plasticizer is the most critical component that determines proper film formation and quality of the resulting film [4]. For a plasticizer to be effective, it must be able to diffuse into and interact with the polymeric material. In vitro dissolution studies with cast films of Eudragits have demonstrated that water-soluble plasticizers were leached more readily from the film when the level of the hydrophilic polymer in the film was increased. Therefore, the selection of a plasticizer for a film formulation is a very important decision in order to develop and optimize the stability and drug release properties of a pharmaceutical dosage form. Plasticizers can affect the long term performance of amorphous polymers in pharmaceutical dosage forms due to the reduction of the glass transition temperature and minimal film forming temperature [3]. Plasticizers not only modify flexibility and fragility but they can also affect drug penetration through the film.

A relevant property of TTS films is fragility, because they have to fit to the skin surface. Fragility can

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be characterized by the fragility index (m), which can be affected by the type and concentration of the used polymer. Fragility parameters can be derived from either relaxation time or viscosity data, and by applying thermal methods, the fragility index can be determined from the temperature and activation enthalpy of glass transition [5–7]. Amorphous materials below T_g are in glassy state [8]. Glass transition is a change from equilibrium state to non-equilibrium state under heating or cooling processes. Molecular mobility of indomethacin as amorphous drug was characterized by determination of the fragility index [9–12]. Glass-former fragility describes the changing dynamics of a supercooled liquid with temperature [13].

Glass-forming liquids can be divided into two groups. The strong glass-forming liquids have Arrhenian behavior concerning the viscosity or relaxation time *vs*. T^*/T, while fragile glass-forming liquids exhibit non-Arrhenian behaviour, which can be described by the Vogel–Tamman–Flucher equation [14, 15]. Glass transition temperature highly depends on the rate of heating and cooling, which can be described by the following equation [16]:

$$\frac{\mathrm{d}\ln|q|}{\mathrm{d}1/T_g} = -\frac{\Delta H}{R} \tag{1}$$

where ΔH is the activation enthalpy, T_g is the glass transition temperature and q is the heating or cooling rate. When plotting the logarithm of rate *vs*. $1/T_g$ (K), a straight line is obtained (Arrhenius plot), and activation enthalpy is expressed as its slope. Fragility index (m) can be calculated substituting the calculated activation enthalpy into the following equation, as it can be set equal to the apparent activation energy of the original formula [16, 17]:

$$m = \frac{1}{2.303}\left[\frac{\Delta H_{T_g}}{RT_g}\right] \tag{2}$$

As the value of fragility index depends on the concentration of the plasticizer, it can be suitable to determine the concentration of this auxiliary material in a polymer film, above which fragility does not change any further. This, among other factors (e.g. drug liberation), is an important aspect of the determination of the optimal amount of plasticizer in a formulation.

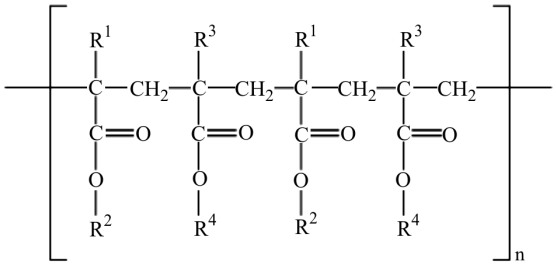
The aim of our work was to confirm this assumption, and three Eudragit type polymers applied in TTSs were studied. Eudragit EPO is the powder form of Eudragit E100 for fast disintegrating aqueous formulations. Eudragit E is a cationic type, gastrosoluble polymer (up to pH 5.0) which is swellable and permeable above pH 5.0. Eudragit RL and RS are zwitterionic copolymers with pH-independent properties. The chemical structure of these two polymers is similar, but the length of chains (carbon atoms on the alkyl chain) is different in R_1 and R_2, so Eudragit RL is a hydrophilic while RS is a lipophilic type polymer. Eudragit RL 30D is permeable pH independent aqueous polymer dispersion for sustained release aqueous formulations with good water permeability through the polymer. Eudragit RS 30D is a pH independent aqueous polymer dispersion with lower permeability for sustained release formulations.

The purpose of the present work was to calculate the fragility index of polymers commonly applied for different pharmaceutical formulations. The fragility index data of these polymers were compared. This parameter enabled the selection of the optimal type of the polymer and the required amount of plasticizer in TTSs.

Experimental

Materials

Eudragit RL 30D, RS 30D and EPO (Röhm GmbH, Darmstadt, Germany) were used as film-forming polymers. Their structural formulas are the following:



For Eudragit EPO:

R^1, R^3=CH_3, R^2=$CH_2CH_2N(CH_3)_2$, R^4=CH_3, C_4H_9

For Eudragit RL and Eudragit RS:

R^1=H, CH_3, R^2=CH_3, C_2H_5,
R^3=CH_3, R^4=$CH_2CH_2N(CH_3)_3^+Cl^-$

The permeability of the polymers depends on the ratio of ethylacrylate (EA), methyl methacrylate (MMA) and trimethylammonioethyl methacrylate chloride (TAMCl) groups in the polymer. Those polymers having EA:MMA:TAMCl ratios of 1:2:0.2 (Eudragit RL) are more permeable than those with ratios of 1:2:0.1 (Eudragit RS).

Triethyl citrate (TEC), (Fluka Chemie AG, Buchs, Switzerland) was selected as the plasticizer for the formulations.

Methods

Preparation of the membrane

Eudragit RS 30D and RL 30D membranes were made from polymer dispersions by mixing them with different amounts (0–40% mass/mass) of plasticizer. 10 g from the obtained solutions was poured on a glass plate of 10.0 cm diameter to achieve the required thickness and was dried at room temperature in a desiccator for 2 days. In the case of Eudragit EPO, a 30% mass/mass solution was prepared from the powder. The preparation of free films was the same as in the case of the other polymeric solution written above.

Determination of the glass transition temperature and activation enthalpy

The glass transition temperature of the polymers and films was studied by DSC method (HAAKE SII Exstar6000 DSC, Germany). 5 mg polymer or film was weighed into aluminum pans and hermetically closed. The DSC runs were conducted over a temperature range from 10 to 80°C at 10, 15, 20 and 25 K min^{-1} heating rates. In the present study, T_g values were determined from the onset temperature of the change in the heat capacity during the thermal event. The temperature calibration was performed taking the onset of the endothermic melting point (429.15 K) at a heating rate of q=10 K min^{-1} of indium standard. The enthalpy was also calibrated applying indium ($\Delta H_{\text{melting point}}$=27.15 J g^{-1}).

Results and discussion

An endothermic step on the DSC curve shows the glass transition. The thermal behavior of the three studied polymers is shown in Fig. 1, and the endothermic steps of the free polymers characterizing the glass transition can be well observed. Using the onset temperature of this endothermic step, we determined the values of T_g from these curves, Table 1. The determination of fragility index requires the knowledge of T_g and ΔH.

Figure 2 illustrates the connection between the heating rate and the measured glass transition temperature. The studied Eudragit polymers can be characterized well by the Arrhenius law. Plotting log$q$ as a function of $1/T_g$, they show good linear correlation. Calculated activation enthalpy and fragility index values are summarized in Table 1. These data were obtained from the heating curves. To characterize a strong or fragile property, fragility index is a useful tool, as larger m values are related to more fragile glasses. Comparing these three examined polymers, results show, that the m value of Eudragit EPO is higher, so it forms a more fragile film than Eudragit RL 30D and RS 30D. The two latter mentioned polymers have similar chemical structures (RL 30D, RS 30D), which explains the similarity of the fragility indices, but m decreased as the length of the R_1 or R_2 chains of the polymer (carbon atoms on the alkyl chain) increased.

The studied polymers are not suitable to form flexible films without plasticizers. Fragility of polymer films can be changed by using different plasticizers. These auxiliary materials increase the molecular mobility in polymers, because they can in-

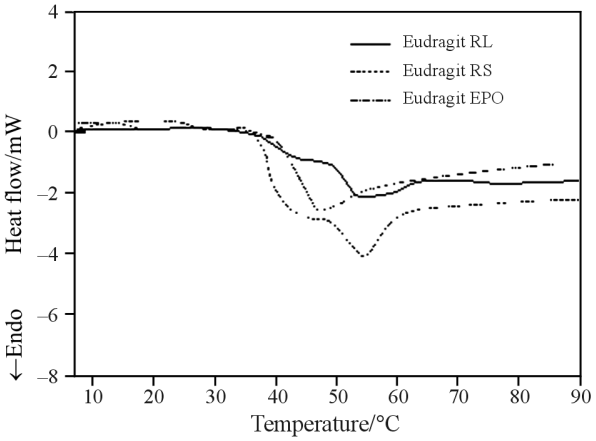


Fig. 1 DSC curves of different Eudragit polymers (heating rate=10 K min^{-1})

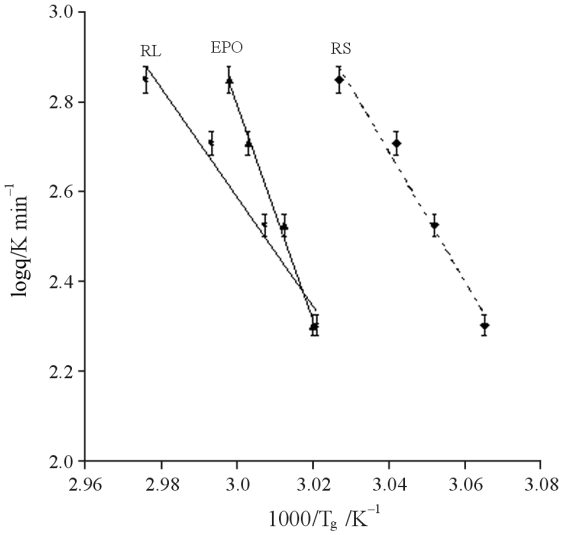


Fig. 2 Arrhenius plot of glass transition of different Eudragit polymers (heating rates: 10, 15, 20, 25 K min^{-1}; slope: –14.46 – RL, –23.98 – EPO, –11.70 – RS)

Table 1 Calculated activation enthalpy and fragility index values of different Eudragit polymers

Type of Eudragit	T_g/°C	ΔH/kJ mol^{-1}	m
Eudragit RS	55	99.63	15.7
Eudragit RL	51	122.73	19.7
Eudragit EPO	46	192.8	30.5

Table 2 Glass transition temperature (T_g) determined at 10 K min^{-1} heating rate and fragility index values of different Eudragit polymers

Type of Eudragit	TEC concentration /mass/mass%	T_g/°C	m
Eudragit RS	0	55	15.7
	10	37	10.6
	20	27	7.4
	30	24	4.2
	40	16	3.2
Eudragit RL	0	51	19.7
	10	35	12.7
	20	25	7.9
	30	24	4.8
	40	14	3.4

filtrate into the polymeric system. TEC is widely used as a plasticizer, thus converting rigid films to flexible ones. TEC was added to the Eudragit RL and RS films in different concentrations, and fragility indices were determined. As the fragility of Eudragit EPO proved to be the highest, it was not examined further with plasticizers. Table 2 summarizes the T_g values and the fragility indices of Eudragit polymers as a function of the concentration of the applied plasticizer. Results show a large dependence of m on the content of TEC – by increasing the plasticizer concentration, m decreased. The calculated fragility index was proportional to the plasticizer concentration in the polymer dispersion up to 30% mass/mass, but above this value it did not decrease any more (Fig. 3).

Plotting the fragility index as a function of TEC concentration, a linear reduction was obtained between 5–30% TEC concentration, above 30%, m leveled out to constant value.

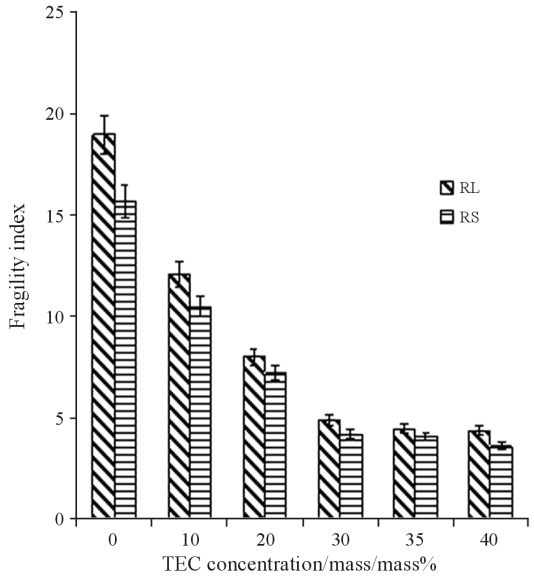


Fig. 3 Effect of TEC concentration on the fragility index values of Eudragit RL and RS films

A possible explanation for the above phenomena can be that as the plasticizer concentration increases, there is an increase in the free volume of the polymer film, as thus the total volume occupied by a given number of molecules increases [3]. The larger free volume inside the system allows enhanced molecular mobility, and consequently the formation of a less fragile film. After a certain concentration, however, the plasticizer is not miscible with the polymer, so more than 30% TEC cannot infiltrate completely into the Eudragit film, it remains on the surface, so it does not change the fragility index any more. These findings are in good correlation with some previous results of the authors concerning the interaction between film-forming agents and plasticizers [3, 18].

Our results show that calculation of the fragility index could be a new approach from the point of determination of the minimal necessary concentration of plasticizer in the polymer to form a flexible film.

Conclusions

Fragility index (m) values of three different Eudragit polymers potentially applicable in TTSs were determined and compared by DSC method from the glass transition temperature and activation enthalpy. As the fragility of Eudragit EPO proved to be the highest, it was not examined further. The fragility index values of Eudragit RL and RS are also high, so a plasticizer has to be applied, and m depends on the chemical structure of the polymer and length of the polymer chains. Increasing the concentration of the plasticizer, fragility index decreases, but after a certain amount of the auxiliary material, further changes can not be observed. As this can be explained with the fact that no more plasticizer can be incorporated into the film, this method can be applied to determine the amount of plasticizer that does not change the fragility of the polymer any further.

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References

1 S.-C. Shin and M.-K. Yoon, Int. J. Pharm., 232 (2002) 131.
2 J. Kim and S.-C. Shin, Int. J. Pharm., 273 (2004) 23.
3 R. Zelkó, Á. Orbán, J. Nagy, G. Csóka and I. Rácz, J. Therm. Anal. Cal., 68 (2002) 531.
4 S. Y. Lin, K. S. Chen and L. Run-Chu, J. Control Release, 68 (2003) 343.

5 J. J. Moura Ramos, C. A. M. Afonso and L. C. Branco, J. Therm. Anal. Cal., 71 (2003) 659.
6 L. Carpentier, S. Desprez and M. Descamps, J. Therm. Anal. Cal., 73 (2003) 577.
7 H. P. Diogo, S. S. Pinto and J. J. Moura Ramos, J. Therm. Anal. Cal., 83 (2006) 361.
8 B. C. Hancock and S. L. Shamblin, Thermochim. Acta, 380 (2001) 95.
9 J. J. Ramos, S. S. Pinto and H. P. Diogo, Pharm. Res., 22 (2005) 1142.
10 N. T. Correia, J. J. Ramos, M. Descamps and G. Collins, Pharm. Res., 18 (2001) 1767.
11 J. J. Ramos, R. Taveira-Marques and H. P. Diogo, J. Pharm. Sci., 93 (2004) 1503.
12 J. J. Ramos, N. T. Correia, R. Taveira-Marques and G. Collins, Pharm. Res., 19 (2002) 1879.
13 J. Kieran, G. Crowley and G. Zografi, Thermochim. Acta, 380 (2001) 79.
14 A. Saiter, J. M. Saiter and J. Grenet, Eur. Polym. J., 42 (2006) 213.
15 L. Delbreilh, A. Bernès, C. Lacabanne, J. Grenet and J. M. Saiter, Mater. Lett., 59 (2005) 2881.
16 J. Moura Ramos, R. Taveira-Marques and H. P. Diogo, J. Pharm. Sci., 93 (2004) 1503.
17 V. Andronis and G. Zografi, Pharm. Res., 15 (1998) 835.
18 R. Zelkó, Á. Orbán, K. Süvegh, Z. Riedl and I. Rácz, Int. J. Pharm., 244 (2002) 81.

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