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Note

# Quantification of the leaching of triethyl citrate/polysorbate 80 mixtures from Eudragit® RS films by differential scanning calorimetry

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**Abstract**

The influence of triethyl citrate and polysorbate 80 (Tween® 80) on the glass transition temperature ($T_G$) of Eudragit® RS membranes was investigated using differential scanning calorimetry (DSC). The $T_G$-decreasing effect of TEC and Tween® 80 displayed an almost identical performance in extent at a linear relationship between weight proportion and $T_G$ resulting in a specific $T_G$-decrease ($T_{G,spec.}$) of $-1.98(K/\%TEC)$ and $-1.86(K/\%Tween)$, respectively. Thus, the proportion of each adjuvant could be summarized as the plasticizer complex weight proportion (PC) with $T_{G,spec.} = 1.96(K/\%PC)$. Vice versa this linear relationship could be used to determine the proportion of plasticizer complex within the polymer membrane after swelling and diffusion processes, i.e. plasticizer leaching. For membranes containing 20% (w/w) TEC and 8% (w/w) Tween® 80 as plasticizer complex a fast leaching resulted during the dissolution test reaching an equilibrium at 6.08% ($\pm 0.5$) PC after 30 min in demineralised water. The DSC method proved to be a simple method to determine plasticizer leaching via $T_G$, however, without respect on the film forming properties of the two different excipients. Plasticizing with TEC or TEC/Tween® 80 mixtures led to smooth and continuous films, while plasticizing with Tween® 80 only resulted in mosaic like fissured films.


*Keywords:* Eudragit® RS; Plasticizer leaching; Triethyl citrate; Polysorbate 80; Glass transition temperature

## 1. Introduction

Most pharmaceutical polymers used as coating material for solid dosage forms need additives to enhance the film properties.

To decrease the minimum film forming temperature of aqueous polymer dispersions and the brittleness of the polymer film plasticizers are used, which are located between the polymer chains and increase the ductility of the film by decreasing the internal friction of the polymer chains. The effect of the plasticizer is specific for each plasticizer polymer blend and dependent on the polymer type and the plasticizer level. Usually, the effects stated above are related to the glass transition temperature ($T_G$) of the polymer plasticizer blend. Additionally, $T_G$ is not only a valuable measure in relation to the minimum film forming temperature but, furthermore related to thermo mechanical [1–3] and drug release properties [1,2]. While the influence of the plasticizer on the film properties and the drug release was investigated throughout the literature, the influence of additives like surfactants on the film properties still lacks on published data. For example the effect of triethyl citrate on the thermo mechanical properties of polymethacrylate polymers and on drug release from coated solid dosage forms is well described [1,4], while the influence of polysorbate surfactants on $T_G$ was published for the polymers ethylcellulose, Eudragit® L 30D-55 and Gantrez® AN139 (*n*-propyl and *n*-butyl half esters of polyvinyl methyl ether maleic anhydride copolymer) [5–7]. There are no published data for Eudragit® RS 30D. Nevertheless, the use of Tween® 80 as wetting agent in Eudragit® RS 30D dispersions is required if the film coating dispersion does not spread onto the solid dosage form's surface [8] or isolated films have to be prepared [9]. Due to an impact of both Tween® 80 and TEC on $T_G$ the purpose of this study was to

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(a) distinguish the single effects on $T_G$ of Eudragit RS membranes containing various concentrations of either TEC, Tween® 80 or TEC–Tween® 80 mixtures and
(b) to investigate the $T_G$ at distinct dissolution time steps, i.e. plasticizer leaching.

## 2. Materials and methods

### 2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received:

Eudragit® RS 30D [(poly-(ethacrylate-methylmethacrylate-trimethylammonio-ethyl methacrylate chloride) copolymer with ratio 1:2:0.1] (Röhm GmbH & Co. KG, Darmstadt, Germany), triethyl citrate (TEC; Röhm GmbH & Co. KG, Darmstadt, Germany), Tween® 80 V (Polysorbate 80; Uniquema, Wirral, UK), demineralized water.

### 2.2. Preparation of isolated films

Eudragit® RS membranes containing 0–25% of TEC (Series 1) or 0–20% Tween® 80 (Series 2) based on the dry polymer weight were prepared to investigate the influence of both excipients on the $T_G$. To prove the influence of mixtures of TEC and Tween® 80 films containing TEC (0–20%) plus 8% Tween® 80 (Series 3) were cast. Films containing 20% TEC and 8% Tween® 80 were used to investigate the plasticizer leaching from the Eudragit RS membranes. 10.0 g Eudragit® RS 30D together with TEC and/or Tween® 80 was diluted with purified water to a volume of 50 ml, warmed up to 50 °C and stirred for 30 min using a magnetic stirrer (IKA-Combimag-RCH, Janke and Kunkel KG, Staufen i. Br., Germany). Isolated films were cast using a self-constructed automatic film application apparatus. The films (12 mg/cm$^2$) were cast on the surface of exactly horizontal aligned PTFE coated glass plates of 180×350 mm. Glass plates were placed on a planar aluminium plate which was kept at a constant temperature of 30 °C controlled by a mobile electronic temperature control unit (KS 10-1 universal, PMA, Kassel, Germany) connected with a Pt 100 sensor (GTF 200, Greisinger electronic GmbH, Regenstrauf, Germany). The film dispersion was filled into a film applicator made of aluminium with a gap clearance of 0.8×150 mm. The film applicator moved at a constant speed of 2.5 mm/s on the upper surface of the PTFE coated glass plates. The film dispersion spread onto the glass plate and the film formation process started. Warming up the film dispersion to 50 °C resulted in enhanced spreading properties of the dispersion on the PTFE coated glass plates, due to the decreased hydrogen bonds forces at increased temperatures. To complete this process and for tempering purposes isolated films were cured for 24 h at 45 °C. The film thickness was determined using a micrometer screw (Mitutoyo Messgeräte GmbH, Neuss, Germany).

### 2.3. Determination of the glass transition temperature

The thermal analyses were performed using a Mettler TA 8000 with a TAS 811 system and a DSC 820 measuring cell (all Mettler-Toledo, Giessen, Germany) according to DIN 53765. Data acquisition and determination of $T_G$ was performed by the software Star 4.00 (Mettler-Toledo, Giessen, Germany). $T_G$ was calculated according to Eq. (1).

$$T_G = 0.5(T_{onset} + T_{endset}) \quad (1)$$

Dry film samples with a thickness of 110–130 μm and a mass of about 20 mg were sealed in aluminium pans, closed with perforated lids and run at a heating and cooling rate of 20 K/min using nitrogen gas at a flux of 20 ml/min as blanket gas. The rest-time in between heating and cooling process was 2 min. For determination of $T_G$ the second heating cycle was analysed.

### 2.4. Plasticizer leaching from isolated film

Eudragit® RS is a polymethacrylate copolymer containing quaternary ammonium groups (QAGs). These QAGs are interacting with the surrounding anions. The anion specie thereby governs the polymer permeability [9–11]. In order to elude the anions influence on the plasticizer leaching the investigation was performed in purified water. Samples of Eudragit® RS films were swollen in 900 ml purified water at 37 °C and stirred at 100 rpm using a paddle apparatus (Ph. Eur. 4/2002). The film samples were removed from the swelling medium after 5, 15, 30 and 60 min. Water droplets were removed carefully and the films were dried in an oven for 24 h at 45 °C. Afterwards their glass transition temperature was determined according to 2.2. Remaining water had no influence on the detection since all remaining water evaporated during the first heating cycle.

## 3. Results and discussion

### 3.1. Influence of additives on the glass transition temperature of Eudragit® RS films

The glass transition temperature of films from series 1 and 2 was determined to investigate the single effect of either TEC or Tween® 80 on $T_G$. Further the reciprocal value of $T_G$ ($T_G^{-1}$) was correlated with the amount of excipients within the film according to Binder et al. [12].

TEC lowered the $T_G$ as expected in accordance to Amighi and Moes [1]. A linear correlation of $T_G^{-1}$ versus the proportion of TEC within the film resulted in a high correlation coefficient ($r^2$) of 0.9962 (Fig. 1). The slope ($k$) of the linear regression of $T_G^{-1}$ versus the proportion of TEC

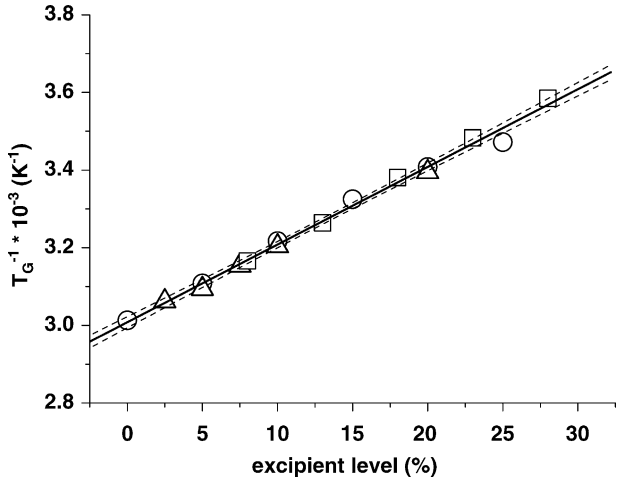


Fig. 1. Reciprocal glass transition temperature dependent on excipient level within the film. (○, films containing only TEC; △, films containing only Tween® 80; □, films containing TEC plus 8% Tween® 80; —, linear regression of all data; - - -, 95% confidence interval).

was $2.091\times10^{-5}$, which is equivalent to a specific $T_G$-decrease ($T_{G,spec.}$) of $-1.98(K/\%TEC)$.

The addition of Tween® 80 decreased the $T_G$ of Eudragit® RS films in the same way as TEC resulting in a slope of the linear regression of $T_G^{-1}$ versus the Tween® 80 proportion (% w/w) of $1.937\times10^{-5}$ ($r^2=0.9978$), i.e. $T_{G,spec.}=-1.86(K/\%Tween\ 80)$. This result was unexpected, since Felton et al. found no effect of Tween® 80 on the glass transition temperature of Eudragit® L 30D-55 films. However, Bauer [13] observed plasticizing properties of surfactant like polypropylene oxide and polyethylene oxide on various copolymers. Tween® 80, a common wetting agent in film coating, exhibits structural relationship to polyethylene oxide being a mono ester of oleic acid and sorbitan which contains on average 20 mole polyethylene oxide per mole sorbitan ester. Also, Lindholm and co-workers were able to plasticize ethylcellulose films using polysorbate surfactants. Therefore, the influence of Tween® 80 is dependent on the physical properties of the film forming polymer. Eudragit® L 30D, a dispersion of a copolymer containing methacrylic acid (MA) and ethylacrylate (EA) in a ratio of 1:1, could not be plasticized by Tween® 80, while films prepared from the more hydrophobic polymers Eudragit® RS and ethylcellulose could be plasticized by this surfactant. The plasticizing effect seems hence, to be stronger in hydrophobic films like Eudragit® RS and ethylcellulose.

Since, the variances from the linear regressions of both $T_G^{-1}$ versus TEC and $T_G^{-1}$ versus Tween® 80 were homogeneous and both slopes did not differ significantly ($P=0.95$) [14] films containing 8% Tween® 80 and various proportions of TEC (series 3) were prepared. Both excipients were summarized as plasticizer complex (PC).

As expected the linear fit of $T_G^{-1}$ versus the sum of TEC and Tween® 80 led to an identical slope ($P=0.95$) of $2.109\times10^{-5}$ ($r^2=0.9941$), i.e. $T_{G,spec.}=-1.96$ $\left(\frac{K}{\%TEC+\%Tween\ 80}=\frac{K}{\%PC}\right)$ compared to the regression of $T_G^{-1}$ against % TEC or % Tween® 80 alone (Fig. 1).

Since Tween® 80 and TEC alone or in mixture had the same plasticizing impact in Eudragit® RS films an overall calibration curve of $T_G^{-1}$ against all plasticizing excipients and their combinations was calculated (Eq. (2)) in order to determine % PC in leached films using the measured $T_G$.

$$\frac{1}{T_G}=2.079\times10^{-5}\cdot\%PC+0.003 \quad (2)$$

The statistical analysis of the calibration ($R^2=0.9911$) resulted in an overall process standard deviation of 0.7961% PC [14].

While TEC and Tween® 80 decreased the $T_G$ of Eudragit® RS films to the same extent, they did not influence the film formation process in the same way. Eudragit® RS 30D plasticized with TEC resulted in smooth films at concentrations of 10% and higher, while Eudragit® RS 30D plasticized with only Tween® 80 resulted in fissured films at all concentration levels investigated. The films cracked into mosaic like chips upon film formation.

### 3.2. Leaching of plasticizing excipients from the film

Due to the linear relationship between $T_G$ and plasticizer complex (Eq. (2)), the leaching of plasticizer complex during the swelling process could be determined by measuring $T_G$ of swollen films after certain time periods.

The $T_G$ of Eudragit® RS films decreased rapidly and after 30 min an equilibrium was reached at a level of 46 °C (Fig. 2). The remaining PC concentration in the film could then be calculated according to Eq. (3), where $b$ is the $y$-intercept ($K^{-1}$) and $k$ the slope of the linear regression ($\%PC^{-1}\cdot K^{-1}$). The $T_G$ of $46.62\pm1.15$ °C resulted hence,

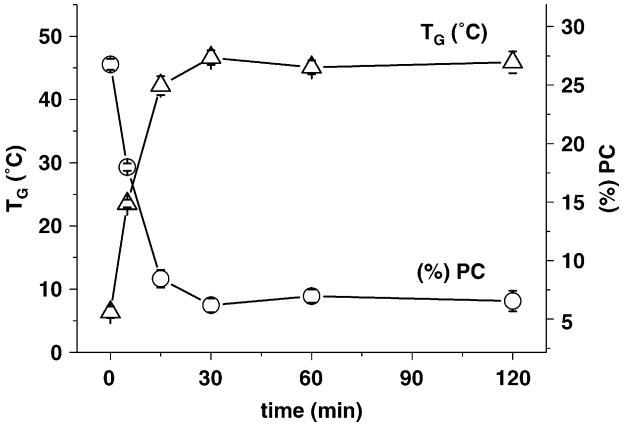


Fig. 2. Glass transition temperature and corresponding (%) PC of Eudragit® RS membranes after swelling in purified water (paddle apparatus, 37 °C, 900 ml, 100 rpm, $n=3$). Error bars representing the 95% confidence interval (△, $T_G$; ○, (%) PC; films containing 20% (w/w) TEC plus 8% (w/w) Tween® 80 prior to the dissolution test).

in 6.08 ± 0.5% PC (Fig. 2).

$$\%\mathrm{PC} = \frac{T_G^{-1} - b}{k} = \frac{T_G^{-1} - 3.0 \times 10^{-3}}{2.079 \times 10^{-5}} \quad (3)$$

That means most of the plasticizer within the membrane leached from the film in the first 30 min.

The plasticizer leaching from Eudragit® RS membranes reported by Bodmeier and Paeratakul [15], however, displayed a much slower kinetic of the TEC leaching from surfactant free films in 500 ml 0.1 M NaCl solution. That might be for the following reasons:

(a) The faster leaching in the present study is due to the better water-soluble surfactant, which should be able to solubilise the TEC and therefore a faster leaching resulted.
(b) Bodmeier and Paeratakul tested the leaching from films cast in aluminium petri-dishes, where leaching took place only from one side of the film, while in the present study the leaching was investigated from the free film hence, diffusion could take place in any direction.
(c) The high salt concentration of the dissolution medium at a level of 0.1 M NaCl solution obstructed the leaching of TEC in the study of Bodmeier and Paeratakul.

The cationic structure of Eudragit® RS (quarternary ammonium groups) enabled an interaction with anion species in the dissolution medium. The original counter ions of the quarternary ammonium groups are chloride ions, which are exchanged by the anion specie of the dissolution medium. The ability of ion exchange of Eudragit® RS films controls the permeability of the membrane [9]. Wagner and McGinity reported on the influence of chloride ion addition on drug release from Eudragit® RS coated pellets. Drug release decreased with increasing chloride concentration. A higher chloride concentration obstructed the permeability of the membrane, i.e. the leaching of the water-soluble drug through the membrane. The same effect may have controlled the plasticizer leaching in the presence of chloride ions at a concentration of 0.1 moles per litre in the investigations of Bodmeier and Paeratakul.

## 4. Discussion

Due to the same effect of the two additives TEC and Tween® 80 with respect to $T_G$ both constituents could be summarized into a plasticizer complex (PC). The linear relationship between $T_G$ and $\mathrm{PC}\left(T_{G,\mathrm{spec.}} = -1.96\frac{K}{\%\mathrm{PC}}\right)$ enabled an easy, nevertheless, precise detection of leached plasticizer amounts from isolated Eudragit® RS membranes which were swollen in dissolution media. However, an identical effect on $T_G$ did not result in the same mechanical properties. With TEC or TEC/Tween® 80 mixtures smooth and continuous films were obtained, while plasticizing with Tween® 80 alone resulted in mosaic like fissured films.

## Acknowledgements

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