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Research paper

Aqueous ethyl cellulose dispersion containing plasticizers of different water solubility and hydroxypropyl methyl-cellulose as coating material for diffusion pellets II: properties of sprayed films[☆]

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Abstract

This study investigates the properties of sprayed films prepared from aqueous ethyl cellulose dispersions (ECD) containing hydroxypropyl methylcellulose (HPMC) and plasticizers of different water solubility in order to clarify the drug release mechanisms of pellets coated with the respective material. It is of special interest to measure the migration of the water soluble components as well as the physical properties of the swollen ethyl cellulose film. Swelling experiments with sprayed films in 0.1 N-HCl at 37°C show that fairly water soluble plasticizers and the pore forming agent (HPMC) migrated rapidly and almost completely out of the films. The water insoluble plasticizers remain predominantly in the film and the migration rate of HPMC is reduced in a release medium of high ionic strength. The glass transition temperature (T_g) and the softening temperature (T_s) of these films after swelling are dependent on the water solubility of the plasticizer. The T_g of ECD films plasticized with triethyl citrate is above the swelling temperature of 37°C after migration of the plasticizer, transforming the polymer in the glassy state. In contrast, dibutyl phthalate-containing ECD films demonstrate a T_g below the swelling temperature, leaving the polymer in the rubbery state. The mechanical properties of dry and wet films are studied as a function of the state of curing of the films and of the swelling temperature. On contact with water, a pronounced shrinkage of ECD/HPMC films plasticized with water insoluble plasticizers is observed. All these results are used to explain the different drug release mechanisms of the coated pellets and to enable the prediction and optimization of drug release-rates from coated pellets.

Keywords: Ethyl cellulose dispersion; Hydroxypropyl methylcellulose; Plasticizers of different water solubility, Films prepared by spraying; Thermal mechanical analysis; Swelling properties; Mechanical properties; Shrinkage

1. Introduction

Aqueous polymer dispersions such as Aquacoat® ECD-30, a 30% aqueous ethyl cellulose dispersion, are applied as coatings for solid oral dosage forms. Theophylline pellets coated with this aqueous ethyl cellulose dispersion (ECD), hydroxypropyl methylcellulose (HPMC) and plasticizers have previously been shown to display three different drug release mechanisms as a function of the water solubility of the plasticizers and the ionic strength of the release medium [1]. Pellet coats plasticized with water soluble or fairly water soluble plasticizers such as triethyl citrate (TEC) or diethyl phthalate (DEP) respectively lead to an approximately zero-order release rate. The drug diffuses through water-filled pores after the migration of the water soluble pore former and plasticizer [2–6]. A two-phase release profile has been discovered in the case of coated pellets plasticized with water insoluble plasticizers such as dibutyl phthalate (DBP) and dibutyl sebacate (DBS) [1,6]. During the first phase, the release is rapid and characterized by drug diffusion through water filled pores after the migration of the pore former. During the second phase, the free volume between the polymer chains is dramatically reduced and therefore the permeability of the coatings decreases. However, a release medium of high ionic strength will reduce the hydration of the water soluble pore former in the coating [1]. Thus, the drug diffuses through a swollen heterogeneous membrane containing EC and HPMC [1,7,8].

These results and hypotheses demonstrate the importance of understanding the properties of coatings before and

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[☆] Dedicated to Prof. Dr. Gerhard Zessin, Halle, on the occasion of his 65th birthday.

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during the drug release process. The properties of coatings in the dry state will be completely different to those of the wet state according to the leaching of the plasticizers and the pore former as well as the hydration of the film forming agent [9,10]. Isolated sprayed films are a suitable model for the examination of the physico-chemical and mechanical properties of swollen and non swollen coatings [11,12]. The thermal mechanical analysis, the swelling experiences with isolated films as well as the puncture tests are methods to explain the physical state of the film forming agent. Free films may also be used to describe the mechanical stability after swelling and to understand the changing film permeability during the swelling process. The objective of this study is to evaluate the properties of dry and wet films in order to predict release mechanisms of coated pellets.

2. Materials and methods

2.1. Materials

2.1.1. Film former

Aquacoat® ECD-30 (FMC Corporation, Philadelphia, USA). Aquacoat® ECD-30 is an aqueous ethyl cellulose dispersion with a solid content of 29–32%. It contains 24.5–29.5% ethyl cellulose, 0.9–1.7% sodium lauryl sulfate, 1.7–3.3% cetylalcohol and small quantities of dimethyl polysiloxane (FMC Corporation, 1985). The resulting films without additives are called ECD films.

2.1.2. Pore former

Hydroxypropyl methylcellulose (HPMC, Pharmacoat® 603 or 606, ShinEtsu Chemical Co., Tokyo, Japan). The viscosity of a 2% aqueous solution at 20°C amounts up to 3 and 6 mPa·s.

2.1.3. Plasticizers

Triethyl citrate (TEC; Boehringer Ingelheim, Ingelheim, Germany; solubility in each case at 20°C in water [13] $c_s = 6.9\%$); diethyl phthalate (DEP, Rhone Poulenc, Frankfurt, Germany; $c_s = 0.15\%$); dibutyl phthalate (DBP, Fluka Chemie AG, Buchs, Switzerland; $c_s = 0.04\%$) and dibutyl sebacate (DBS, Henkel KGaA, Düsseldorf, Germany; $c_s = 0.01\%$). The chemicals were used as received.

2.2. Methods

2.2.1. Preparation of the dispersion

Appropriate quantities of aqueous ethyl cellulose dispersion, plasticizer and HPMC solution were combined and mixed with a glass blade stirrer for 30 min before and after the standing time of 23 h. The pore former HPMC was added as a solution of a maximum concentration of 10% to the aqueous dispersion. The percent of plasticizers refers to the film without HPMC and the percent of pore former refers to the entire film.

2.2.2. Swelling of sprayed films and measurement of extractable components

2.2.2.1. Preparation of the films: The aqueous ethyl cellulose dispersion containing the pore former and/or plasticizers were sprayed with a precision spray gun (Sata Farbspritztechnik GmbH&Co., Ludwigsburg, Germany) onto glass slides, distance from the surface was about 50 cm. The spraying process was alternated with a drying process until a film thickness of 37.5 ± 2.5 μm was reached. The films were dried with a hair drier. The drying temperature was adjusted to 10°C above the minimum film forming temperature, but at least to 40°C, and checked with a thermometer. After the spraying process, the films were cured in an oven for 1 h or 2 h at 70, 80, 90 or 100°C and stored for 24 h over silica gel. High curing temperatures had been used to determine the conditions to reach a constant drug release rate from coated pellets [1].

2.2.2.2. Content of plasticizer: A HPLC assay was used for the analysis of the plasticizer in the films before exposure to the aqueous medium and in the swelling medium after exposure to the aqueous medium. The samples were measured with the HPLC model LC-6A (Shimadzu, Duisburg, Germany) with an automatic sample injector (model SIL-6B), system controller (model SCL-6B), UV-spectrophotometric detector (model SPD-6AV), an integrator (model C-R4AX Chromatopac) and an analytical column (LiChrospher® 100 RP-18, 5 μm particle size, 125 mm length and 4 mm internal diameter; E. Merck, Darmstadt, Germany). The mobile phase consisted of methanol:distilled water 50:50% (v/v) for DEP and acetonitrile:distilled water 70:30% (v/v) for DBP. The volume of injection varied between 20 and 150 μl. The flow rate was 2 ml/min and the UV absorption was measured at 230 nm for both plasticizers. External standards were used for the validation of the method and for the quantitative analysis of the plasticizer concentration.

After the spraying and curing processes, the glass slides with the attached films were transferred into a 300 ml Erlenmeyer flask containing 100 ml of methanol or acetonitrile and were shaken for 24 h in order to measure the residual DEP or DBP content in the films. 1.5 ml samples of the aqueous swelling medium were analysed directly by the HPLC assay. This method offers the possibility to quantitate the amount of plasticizer, that migrated from the films during the swelling period.

2.2.2.3. Swelling: The paddle apparatus was used with 1000 ml of 0.1 N-HCl or 1.5 N-NaCl solution at 20, 37 or 48°C and a stirring speed of 20 or 170 rev./min. The glass slides were placed into the release medium at the bottom of the vessel with the film side faced down. The paddle and the glass slides were additionally separated with a punchplate of teflon. The films were separated from the glass slide after 15 min if they were still adhered to the glass. After predetermined swelling periods, the films were taken out of the swelling medium and surface water was removed placing the films between two filter papers under gentle pressure. The water content of the films (V_w) as well as the extractable components (*Exc*) were calculated from the weight of the wet films (m_s) and the weight of the dry films before and after the swelling m_b and m_a, respectively [6]

$$V_w = \frac{\dfrac{m_s - m_a}{\rho_w}}{\dfrac{m_s - m_a}{\rho_w} + \dfrac{m_a}{\rho_p}} \cdot 100\ (\%(v/v)) \qquad (1)$$

$$Exc = \frac{m_b - m_a}{m_b} \cdot 100\ (\%) \qquad (2)$$

where ρ_w is the density of water, and ρ_p is the density of the polymer.

The swollen films were dried over silica gel until a constant weight was reached. The calculation of the water content assumes that the densities of water and polymer are equal and/or that the extractable components migrate completely out of the films. In order to distinguish the extractable components with reference to the fraction of the pore former and the plasticizer, the plasticizer content was additionally analysed with the HPLC method.

2.2.3. Thermal mechanical analysis (TMA)

A Mettler TA 3000 model (Mettler Instrumente AG, Greifensee, Switzerland) with an integrated TC 10 A processor and a TMA 40 measuring cell was used for the penetration experiments. The glass transition temperature was measured with a small measuring probe, heating rate of 2 K/min, applied force of 0.2–0.5 N and nitrogen as washing gas with a rate of 200 ml/min.

Films of Aquacoat® ECD-30, Pharmacoat® 603 or a mixture of both polymers were casted in petridishes. The film thickness varied between 38 and 208 µm. Sprayed films of plasticized polymers were prepared as described previously (Section 2.2.2.). The glass transition temperature (T_g) and the softening temperature (T_s) of the dry films were measured directly using small parts of the films.

The influence of water on the T_g and T_s were analysed with isolated films after swelling for 24 h in 0.1 N-HCl at 37°C at a stirring speed of 50 rev./min in the paddle apparatus. Films sprayed onto the glass slides were separated from the glass slide after 15 min. The measurement was carried out after removal of the surface liquid.

2.2.4. Mechanical properties of sprayed films

In the tensile test an attached force induces a displacement of length (Δl) of a polymeric film. The following relation exists

$$\frac{\Delta l}{l_0} = \frac{1}{E} \cdot \frac{F}{A} \qquad (3)$$

where Δl is the displacement of length, l_0 is the starting length, E is the elastic modulus (N/m^2), F is the force (N), and A is the area (m^2).From Eq. (3), the elongation $\epsilon(\%)$ can be calculated

$$\varepsilon = \frac{l - l_0}{l_0} \cdot 100\ (\%) \qquad (4)$$

and the tensile strength σ (MPa)

$$\sigma = \frac{F}{A}\ (\text{MPa}) \qquad (5)$$

2.2.4.1. Preparation of films with a spraying apparatus The spray apparatus for the preparation of free films [14,15] consisted of a spray gun with a vertical driving system, a hair drier, a rotary drum (7.5 cm high and 7.5 cm diameter) with a removable teflon sheet and a temperature controlling system. The function as well as the design of the spray apparatus was reported previously [14,15].

The films were prepared under the following conditions: 18 cm distance between the spray gun and the drum, average spray rate of 1 ml/min, spray and dry interval of 5 sec, a drying temperature of 40°C on the drum surface and an inlet air flow of 500 l/min. After the spraying process and an additional curing period of 5 min, the sheets were removed from the drum and cured in an oven for 1 h at 70°C or 2 h at 100°C. Then the polymer film was peeled off the teflon sheet and cut into dumbbelled shaped (tensile test) or rectangular (puncture test) specimens. The mechanical properties were measured directly or after 5 days storage in a desiccator over $CaSO_4$.

2.2.4.2. Mechanical tests: The mechanical properties of the films were evaluated using an Instron model 4201 universal testing apparatus, Instron, Boston (USA).

2.2.4.3. Tensile test method: The test apparatus for measuring the tensile strength consisted of two pneumatic grips and the test procedure is based on the ASTM D822-75d method. The extension speed was 5 mm/min. Film specimens which broke directly at the grips were discarded. The film thickness is given in Fig. 7 and Table 2. The load (kg) and the displacement (mm) at film rupture referred to the cross section area and starting length of the film specimens and were converted to the nominal tensile strength (MPa) at rupture and the nominal elongation (%) at rupture.

2.2.4.4. Puncture test method The Instron model had to be altered for the puncture test method: The two grips were replaced by a film holder and a driving load cell [9,16]. The dry and wet rectangular film specimens (3.5 × 4 cm^2) were positioned between two mounting plates and were fixed with four screws. The plates contain a hole of 22 mm in the center. The driving load cell was driven downwards through the mounted film at a crosshead speed of 5 mm/min. The calculation of the nominal puncture strength and the elongation at rupture is comparable to the tensile test method. However, the elongation is based on the displacement of the radius instead of the length.

2.2.4.5. Swelling The paddle apparatus with 1 l of 0.1 N-HCl at 20, 37 and 48°C and with 50 rev./min was used for the swelling experiments. The mechanical properties were measured after predetermined time periods and removal of the surface water. The polymeric films were put into plastic net-bags in order to prevent the films from folding during the swelling studies.

3. Results and discussion

3.1. Swelling of sprayed films and measurement of extractable components

3.1.1. Volatility of plasticizers

The plasticizer content of films after manufacturing and curing is of great interest. The plasticizer content has been reported to influence the swelling of the film [17]. It is also the basis for the calculation of the extent of the plasticizer migration during the swelling. However, loss of plasticizer can occur after spraying, curing [10,18] and/or after storage under stress conditions [19,20].

DEP has a high tendency to volatilize from the films during the spraying and curing processes. After curing 2 h at 100°C, DEP volatizes almost completely. Nevertheless, the films are mechanically stable and therefore usable for the swelling experiments [18,21]. The plasticizer content in the film decreased to 58% after curing for 1 h at 90°C and stayed constant after curing for 1 h at 70°C. Films prepared with DBP had a reduced plasticizer content of 90 to 98% of the theoretical content after curing for 1 h at 70 or 80°C. DBP was found to volatize only under extreme curing conditions of 2 h at 100°C. The plasticizer content then decreased to approximately 50%. These results are in accordance with volatility measurements of coated pellets [13].

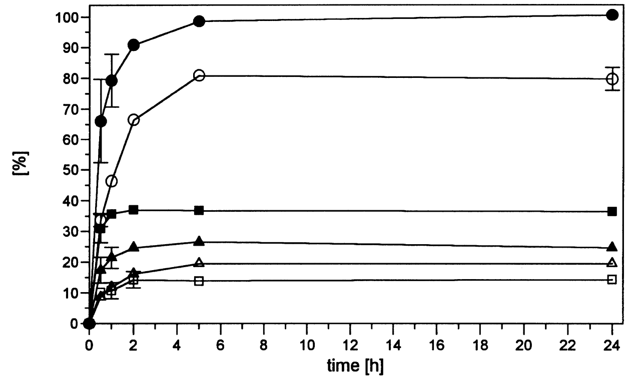

Fig. 1. Leached pasticizer fraction (DEP), extractable components (*Exc*) und water content (V_w) of films with and without pore former as a function of the swelling time. Film: 80% ECD, 20.0% DEP and 90% ECD (20.0% DEP), 10% HPMC. Curing: 1h-70°C; Swelling conditions: 0.1 N-HCl; 37°C; (mean ± SD, $n = 3$). 20.0% DEP: (○) DEP; (△) *Exc*; (□) V_w. 20.0% DEP, 10% HPMC: (●) DEP; (▲) *Exc*; (■) V_w.

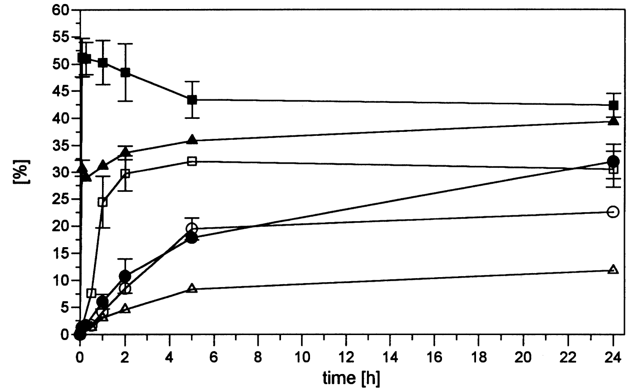

Fig. 2. Leached pasticizer fraction (DBP), extractable components (*Exc*) und water content (V_w) of films with and without pore former as a function of the swelling time. Film: 80% ECD, 20.0% DBP and 70% ECD (20.0% DBP), 30% HPMC. Curing: 1h-70°C; Swelling conditions: 0.1 N-HCl; 37°C; (mean ± SD, $n = 3$) 20.0% DEP: (○) DEP; (△) *Exc*; (□) V_w. 20.0% DEP, 30% HPMC: (●) DEP; (▲) *Exc*; (■) V_w.

3.1.2. Swelling and migration as a function of the additives

Swelling experiments with sprayed films are useful to measure the extractable components and the water uptake. These values are helpful to interpret the permeability of films and to characterize the physical state of the film forming polymer. The aim of these investigations is to enable the prediction of the permeability of coatings and the release mechanism of coated oral dosage forms.

After 24 h of swelling, the extractable components of ECD/20% DEP films without the pore former, and with 10% HPMC amount to 19.5 ± 1% and 24.5 ± 1%, respectively (Fig. 1). The plasticizer and pore former migrate almost completely from the films. In both cases other excipients of the film (see Section 2.1), especially sodium lauryl sulfate may have migrated from the film. Films without the addition of the pore former absorbed 14.3 ± 2% water. The comparable films containing 10% HPMC showed a water content of 36.4 ± 2% (Fig. 1). The water content of 14.3% is nearly equivalent to the amount of leached plasticizer. During and after the migration of the pore former and the plasticizer the films show a disproportional high content of water. Apparently the ethyl cellulose is in the glassy state and contains pores and channels following the migration of the water soluble components.

In contrast, ECD films plasticized with 20.0% DBP and 30% HPMC as additives show a totally different behavior in comparison to the ECD/DEP films. The extractable components reached 11.8 ± 1% in the case of films without HPMC addition and 39.3 ± 1% with 30% HPMC respectively (Fig. 2). These values can be explained by the partial leaching of plasticizer, total migration of the pore former and further film exipients. The water content of the films without HPMC increased up to 30.5 ± 3% after 24 h of swelling

Table 1
Leached plasticizer fraction (DEP or DBP), extractable components (Exc) and water content (V_w) of films as a function of the ionic strength of the swelling medium. Swelling conditions: 1.5 N-NaCl; 37°C; 24 h (mean ± SD, n =3)

Film plasticizer	HPMC	Curing (h-°C)	Plasticizer (%)	Exc (%)	V_w (%(v/v))
11.0% DEP	30	1-90	81.6 ± 4.4	18.9 ± 1.0	38.0 ± 4.1
	30	2-100	90.1 ± 13	13.8 ± 2.0	37.4 ± 7.2
20.0% DEP	0	1-70	79.7 ± 0.9	19.6 ± 0.6	13.2 ± 1.6
	30	1-70	83.0 ± 0.7	25.3 ± 0.6	47.8 ± 1.7
12.5% DBP	30	1-80	8.7 ± 0.9	17.4 ± 0.8	36.2 ± 0.8
	30	2-100	8.3 ± 1.5	13.9 ± 0.6	36.8 ± 3.9
20.0% DBP	0	1-70	5.2 ± 0.3	12.0 ± 2.3	12.9 ± 4.3
	30	1-70	Not analysed	18.6 ± 1.1	40.9 ± 1.4

(Fig. 2). In contrast, the water content of films with 30% HPMC additive increased up to 52.2 ± 4% after 15 min of swelling, but then decreased to a plateau of 43.4 ± 3% during the next 5 h (Fig. 2). Further experiments with ECD films plasticized with 12.5 and 20.0% DBP and 10, 20 or 30% HPMC additive confirm the high amounts of incorporated water after 24 h of swelling in 0.1 N-HCl [13]. One can assume that the plasticizer DBP remaining in the film reduces the glass transition temperature of the swollen ethyl cellulose below the swelling temperature of 37°C. Thus the polymer chains in the rubbery state squeeze out the water after migration of the pore former (Fig. 2) and shrink (Fig. 6) [13,22]. This phenomenon correlates with the decreasing drug release rate of drug containing films and coated pellets respectively prepared from such aqueous polymer dispersions [1,6,23].

3.1.3. Swelling and migration as a function of the ionic strength

It has previously be reported in the literature, that a high ionic strength of the release medium reduces the swelling of polymeric films [24,25]. Table 1 summarizes the properties of HPMC containing ECD films plasticized with DEP or DBP after 24 h of swelling in 1.5 N-NaCl. The fairly water soluble plasticizer DEP migrates almost completely from the polymeric films after 24 h of swelling in 1.5 N-NaCl whereas the poorly water soluble plasticizer, DBP, remains almost completely in the film (Table 1). Surprisingly, ECD films with 11.0% DEP or 12.5% DBP and 30% HPMC as additives show an amount of extractable components of 18.9% and 17.4% respectively (Table 1) and not the expected value of 30–40%. The high ionic strength of the release medium reduced the hydration of the water soluble pore former HPMC and therefore prevents its dissolution and migration from the film. Accordingly, the water contents are comparable between films plasticized with DEP and DBP (Table 1) in contrast to swelling experiments in 0.1 N-HCl (Figs. 1 and 2). The remaining amount of HPMC was the primary determinant for the water uptake. The drug release from pellets coated with EC dispersions, HPMC, DEP or DBP changes from a diffusion mechanism through pores and channels or partitioning, to diffusion through a gel-like membrane [1].

Another interesting aspect is the reduced water content of ECD/20% DBP films containing 20% HPMC from 30.5% (Fig. 2) in 0.1N-HCl to 12.9% (Table 1) in 1.5 N-NaCl. The Na^+ and Cl^- ions apparently take away the swelling water of the ethyl cellulose. The HPMC free ECD films with 20.0% DEP show no loss of water through the high ionic strength of the release medium (14.3% in comparison to 13.2%).

3.2. Thermal mechanical analysis (TMA)

The measurement of the T_g of Aquacoat® ECD-30 films with differential scanning calorimetry (DSC) is difficult because of the slight thermal effects of the ethyl cellulose [26] and because of the melting points of sodium lauryl sulfate and cetylalcohol [27]. Therefore the thermal mechanical analysis is used to measure the glass transition temperature (T_g) and the softening temperature (T_s) [28–30]. The penetration measurement is based on the principle that at the T_g the polymer chain segments are increasingly moving, the free volume increases and therefore the flexibility and penetrability of the films. At T_s the chain mobility

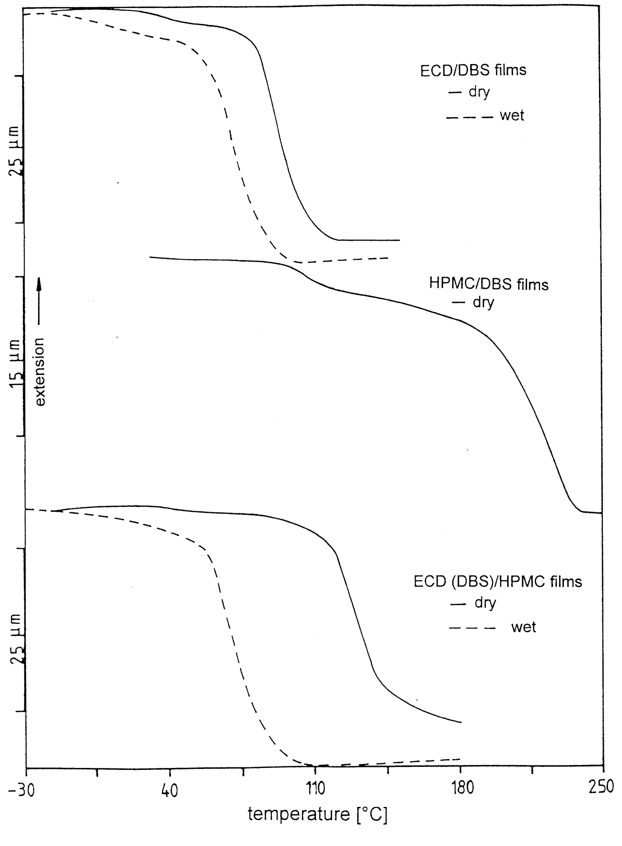

Fig. 3. TMA-curves of dry and wet films. Film: 80% ECD/20.0% DBS; 68.2% HPMC/31.8% DBS and 70% ECD (20.0% DBS)/30% HPMC. Curing: 1h-70°C; Swelling conditions: 24 h; 0.1 N-HCl; 37°C.

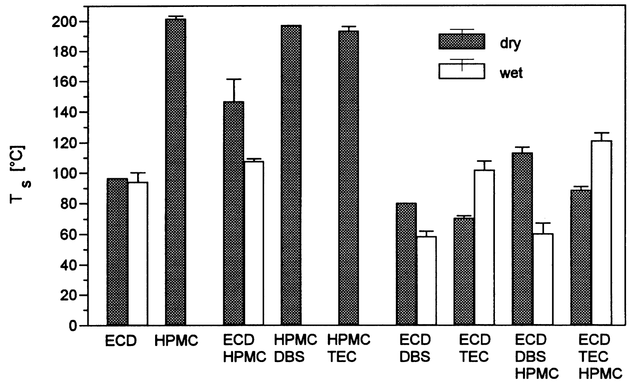

Fig. 4. T_s-values of dry and wet films. Film: 100% ECD; 100% HPMC; 70% ECD/30% HPMC; 68.2% HPMC/31.8% DBS or TEC; 80% ECD/20% DBS or TEC; 70% ECD (20% DBS or TEC)/30% HPMC; Curing: 1h-70°C (100% ECD: 1h-110°C). Swelling conditions: 24 h; 0.1 N-HCl; 37°C; (mean ± SD; $n = 3$).

is so high that the resistance to penetration decreases to a minimum. Inter- and intrasegmental bonds of the polymer chains are strongly reduced.

TMA curves of dry and wet ECD-, HPMC- and ECD/HPMC- films plasticized with DBS are shown in Fig. 3. The first inflection point is taken for the glass transition temperature and the second for the softening temperature. The constant number of two inflection points is evidence for a homogeneous mixture of ethyl cellulose and hydroxypropyl methylcellulose [31]. The curves of the wet films are shifted to lower temperatures in comparison to the dry films (Fig. 3). This does not hold for films with TEC [13].

Fig. 4 illustrates the effect of plasticizing and swelling on the well defined softening temperature T_s of the ECD- and/or HPMC-films. A swelling time of 24 h in 0.1 N-HCl at 37°C does not change the T_s of ECD films. The plasticizers TEC and DBS are only effective for ECD films, the decrease of T_s of HPMC films is insignificant. As expected, after swelling the T_s of ECD/DBS and ECD/HPMC/DBS films are reduced from 80 ± 1°C and 113 ± 4°C to 58 ± 4°C and 60 ± 7°C, respectively. Comparing wet and dry films, it becomes evident that incorporated water acts as an additional plasticizer. However the comparable swollen films plasticized with TEC show T_s values which reach the value of the ECD films. This effect can only be explained by the almost complete migration of the plasticizer and pore former. The more hydrophilic TEC migrates out of the film (Fig. 1), the incorporated water looses its plasticizing effect. Apparently it is only mechanically fixed in pores and channels but not between polymer chains. Nearly the same tendencies as for T_s were observed for the T_g [13]. The T_g of the ECD films plasticized with TEC is above the swelling temperature of 37°C after migration of the plasticizer (84 ± 4°C). In contrast the T_g of the relevant films plasticized with DBS is below the swelling temperature (14 ± 3°C) [13].

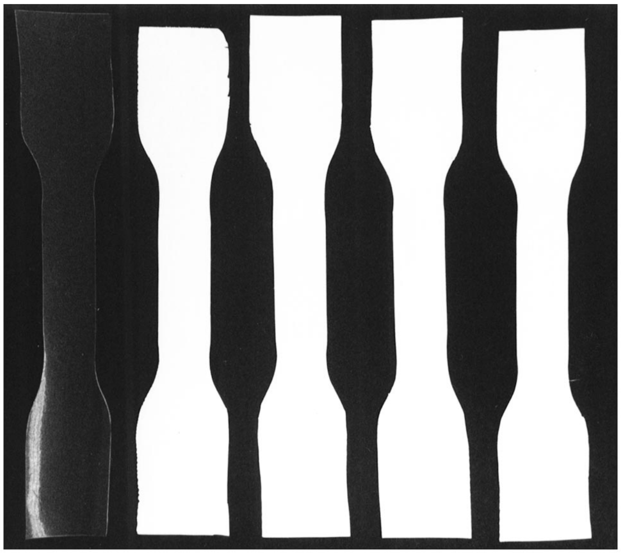

Fig. 5. Shrinkage of ECD-films as a function of the swelling time. Film: 70% ECD (20.0% TEC); 30% HPMC 606; curing: 2h-100°C. Swelling conditions: 0.1 N-HCl; 37°C; time: 0, 0.25, 1, 5 and 24 h.

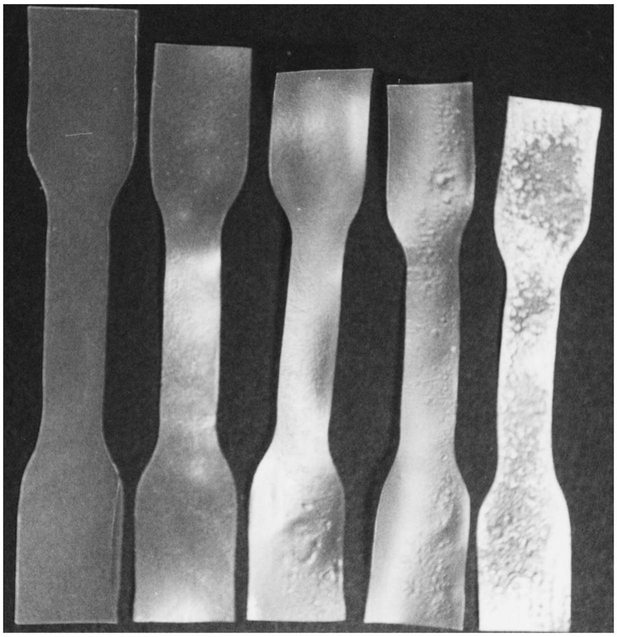

Fig. 6. Shrinkage of ECD-films as a function of the swelling time. Film: 70% ECD (20.0% DBP); 30% HPMC 606; curing: 2h-100°C. Swelling conditions: 0.1 N-HCl; 37°C; time: 0, 0.25, 1, 5 and 24 h.

Summing up these results it becomes evident that the softening temperature as well as the glass transition temperature of non swollen films not only represent the physical and chemical properties of the film forming polymers, but rather these values elucidate the compatibility of different polymers and the effectivity of plasticizers. The thermal transition temperatures of swollen polymeric films reflect the condition of pellet coatings during the release process. The plasticizing effect of water as well as the migration of plasticizer and pore former is documented by this method and related to the release behavior of coated pellets described earlier [1].

An additional interesting aspect is the similarity of the glass transition temperature and the minimum film forming temperature as well as of the softening temperature and the curing temperature for coated pellets to reach a constant and low release rate [13].

3.3. Shrinkage of ethyl cellulose films

Some polymers shrink at temperatures above the glass transition temperature [22]. Extremely high differences in shrinkage are observed in Figs. 5 and 6 with isolated sprayed ECD/HPMC films plasticized with TEC and DBP respectively before and after 0.25; 1; 5 and 24 h of swelling in 0.1 N-HCl at 37°C. These films were prepared for the investigation of the tensile strength (see Sections 2.2.4 and 3.4.). ECD films plasticized with TEC additive do not shrink (Fig. 5) after the migration of the water soluble plasticizer and the pore former (Fig. 1). The ethyl cellulose is in the glassy state (Figs. 3 and 4) and therefore the rather high permeability of the films will not change during the swelling period. In contrast, the DBP plasticized ECD/HPMC films showed a remarkable shrinkage phenomenon (Fig. 6). The poorly water soluble plasticizer mainly remains in the ethyl cellulose (Fig. 2). Thus, the T_g lies below the swelling temperature (Fig. 3 and 4), the film remains in the rubbery state.

The shrinkage of ECD/HPMC films containing almost water insoluble plasticizers such as DBP or DBS correlate to the changing release mechanism of pellets coated with such coatings [1,6]. The permeability of the ECD film coating is distinctly reduced through the shrinkage of the films.

3.4. Mechanical properties of sprayed films

3.4.1. Effect of the curing conditions on the tensile strength of dry films

Usually the physical stability of coated pellets is assessed by drug release studies. The film formation of coatings from aqueous dispersions seems to be optimal when the drug release rates are independent of the curing conditions. At that point, interdiffusion of the polymer chains of dispersion droplets is assumed to be completed. SANS (small angle neutron scattering) offers the possibility to measure directly the interdiffusion of the polymer chains and illustrates that the tensile strength of films increase with increasing interdiffusion of polymer particles until an optimum is reached [31].

With increasing curing temperature and time the tensile strength as well as the elongation of ECD/HPMC films plasticized with TEC or DBP increase (Table 2). These results are in agreement with previous studies with a ready to spray dispersion [32]. The curing effect was more pronounced with TEC. TEC tends to volatilize after curing of 2 h at 100°C (see 3.1.1.). A reduced amount of plasticizer in the polymeric films caused an increasing tensile strength along with a reduction in flexibility [9,11,18]. The described effects can also be observed after five days of storage.

Table 2

Tensile strength (σ_R) and elongation (ϵ_R) as a function of the curing conditions of the sprayed films. Film: 70% ECD (20.0% plasticizer); 30% HPMC 606. Curing: 1h-70°C or 2h-100°C; storage conditions: 0 or 5 days over $CaSO_4$. Film thickness: 120–140 μm ± 10% (mean ± SD, $n = 4$–6)

Plasticizer	Curing h-°C	Storage (days)	σ_R (MPa)	ϵ_R (%)
Triethyl citrate	1-70	0	7.86 ± 0.28	4.80 ± 1.18
	2-100	0	13.12 ± 0.91	11.04 ± 1.85
	1-70	5	11.52 ± 2.50	1.97 ± 0.64
	2-100	5	16.97 ± 1.33	4.48 ± 0.69
Dibutyl phthalate	1-70	0	8.41 ± 0.25	8.64 ± 0.70
	2-100	0	Not analysed	Not analysed
	1-70	5	10.69 ± 0.70	6.34 ± 094
	2-100	5	12.83 ± 0.27	9.12 ± 0.97

Curing conditions of 1 h at 70°C are known as sufficient for pellets coated with aqueous ethyl cellulose containing HPMC and 20% plasticizer [1,2]. If curing for 2 h at 100°C, accompanied by a change in the mechanical properties of the films, influences the permeability of the coating of pellets for drugs, has not been yet investigated.

3.4.2. Effect of the swelling temperature on the mechanical properties of wet films

The investigations of mechanical properties of swollen and non-swollen ECD/HPMC films should reflect the difference of glassy and rubbery state of polymeric films. Fig. 7A,B illustrate the puncture strength and elongation of TEC and DBP containing ECD/HPMC films before and after 24 h of swelling in 0.1 N-HCl at 20, 37 and 48°C, respectively. As expected, after swelling, the puncture strength as well as the elongation of TEC plasticized films significantly decreased from 1.10 to 0.04 MPa and from 0.81 to 0.13 %. The mechanical properties change dramatically after migration of the water soluble plasticizer and pore former. The films were characterized as weak and soft [11,12]. ECD/HPMC films with the addition of DBP show a strong dependence of their mechanical properties on the temperature (Fig. 7A/B). The puncture strength and the elongation decreased after swelling at 20°C but increased again after swelling at 37 and 48°C. The values at 20°C are comparable to the values of TEC containing films. At 37 and 48°C the ethyl cellulose is in the rubbery state. Water acts as a plasticizer and the films attained a better mechanical stability. These results agree with the swelling experiments (Fig. 2) as well as with the measurement of the glass transition temperature (Fig. 4).

Considering the described results, tensile and puncture tests are suitable methods to measure the physical and mechanical properties of dry and wet polymeric films. Thus, it is possible to evaluate the effectivity of plasticizers, the influence of the standing time of the aqueous dispersion, to determine optimal curing conditions, to investigate the

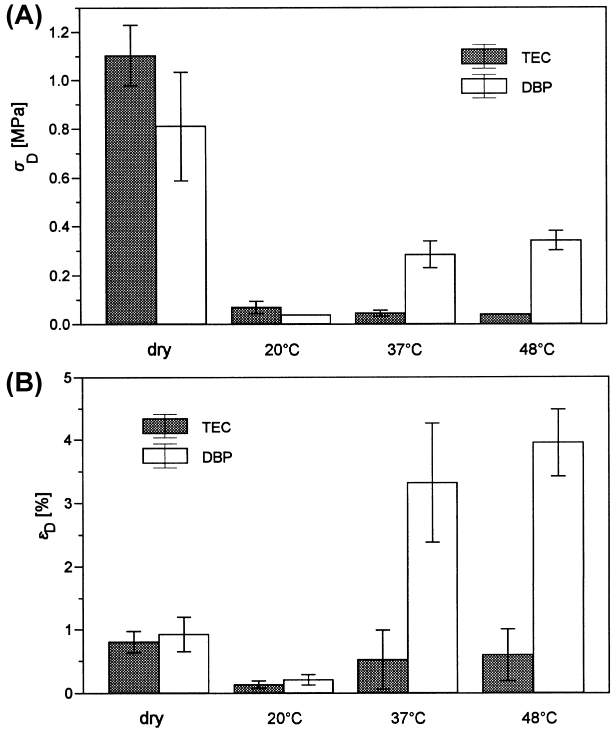

Fig. 7. Puncture strength (σ_D) (A) and elongation (ϵ_D) (B) of the ECD-films as a function of the swelling temperature. Film: 70% ECD (20.0% TEC, DBP); 30% HPMC; curing: 1h-70°C. Storage before swelling: five days over $CaSO_4$; film thickness: 125–135 μm ± 10%; Swelling conditions: 0.1 N-HCl; 24 h (mean ± SD, $n = 3$).

influence of storage conditions and to predict the release mechanism of coated pellets. Even the influence of the standing or stirring time of plasticized dispersions on the resulting film properties, which is observed by a change of the minimum film forming temperature [13,17], will be reflected by the mechanical properties of the films. Sparingly soluble plasticizers cause a clear time dependence to the mechanical properties according to their slow dissolution and partition into the polymer particles [13].

4. Conclusion

Physico-chemical properties of polymer films containing plasticizers and pore forming agents give insight in the behavior of the respective coating of diffusion pellets, especially after contact with 0.1 N-HCl at 37°C. The temperature dependence of the properties elucidates the complex structure of these coatings.

Water soluble plasticizers and HPMC migrate rapidly and almost completely from the films, transferring EC in the glassy state ($T_g > 37°C$). Apparently, the incorporated water does not act as plasticizer, is only mechanically fixed in pores and channels, and enables the high permeability of the films. These films have a relatively low mechanical stability.

In contrast, water insoluble plasticizers mainly remain in the ECD films during swelling in 0.1 N-HCl and migration of HPMC. Thus, EC stays in the rubbery state ($T_g < 37°C$). During migration of the pore forming agent, the polymer chains of EC interact to a higher degree, reducing the free volume and squeezing out water from pores and channels. The films visible shrink. The permeability of the film coatings decreases at this stage. These films, plasticized with the lipophilic plasticizer and water, have a good mechanical stability.

The migration of the pore forming agent HPMC and the water uptake of the films is strongly reduced in a release medium of high ionic strength, irrespective of the type of plasticizer. This correlates with the permeabilities of the film coatings.

The knowledge of these film properties is indispensable for the explanation of the three different drug release patterns of pellets coated with such films. An approximate zero-order release rate is observed with hydrophilic plasticizers, HPMC as pore forming agent. Pellets coated with ECD, HPMC and a poorly soluble plasticizer show a two-phase release profile with a fast release at the beginning and a slow release during the second phase. The third release mechanism at high ionic strength is the drug diffusion through a swollen, heterogenous membrane, with the HPMC partially incorporated in the coating [1].

Knowing the swelling and shrinking behavior, the migration of the additives, and the thermo-mechanically and mechanical features of sprayed films, it seems to be possible to predict the release process of the respective coated pellets. Furthermore, the optimization right from the beginning should be much easier.

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References

[1] M. Frohoff-Hülsmann, A. Schmitz, B.C. Lippold, Aqueous ethyl cellulose dispersions containing methylcellulose as coating material for diffusion pellets I: drug release rates from coated pellets, Int. J. Pharm. 177 (1999) 69–82.

[2] B.H. Lippold, B.K. Sutter, B.C. Lippold, Parameters controlling drug release from pellets coated with aqueous ethyl cellulose dispersion, Int. J. Pharm. 54 (1989) 15–25.

[3] B.C. Lippold, W. Gunder, B.H. Lippold, Drug release from different pellets coated with the aqueous ethyl cellulose dispersion Aquacoat ECD-30 and 20% dibutyl sebacate as plasticizer: partiion mechanism and pore diffusion, Eur. J. Pharm. Biopharm. 47 (1999) 27–32.

[4] L.C. Li, G.E. Peck, Water based silicone elastomer controlled release tablet film coating II: formulation considerations and coating evaluation, Drug. Dev. Ind. Pharm. 15 (1989) 499–531.

[5] P.C. Sheen, P.J. Sabol, G.J. Alcorn, K.M. Feld, Aqueous film coating studies of sustained release nicotinic acid pellets: an in vitro evaluation, Drug. Dev. Ind. Pharm. 18 (1992) 851–860.

[6] W. Gunder, B.H. Lippold, B.C. Lippold, Release of drugs from ethyl

cellulose microcapsules (diffusion pellets) with pore formers and pore fusion, Eur. J. Pharm. Sci. 3 (1995) 203–214.

[7] N.B. Shah, B.B. Sheth, A method for study of timed-release films, J. Pharm. Sci. 61 (1972) 412–416.

[8] R.C. Rowe, The effect of the molecular weight of ethyl cellulose on the drug release properties of mixed films of ethyl cellulose and hydroxypropyl methylcellulose, Int. J. Pharm. 29 (1986) 37–41.

[9] R. Bodmeier, O. Paeratakul, Dry and wet strengths of polymeric films prepared from an aqueous colloidal polymer dispersion: Eudragit RS30D, Int. J. Pharm. 96 (1993) 129–138.

[10] R. Bodmeier, O. Paeratakul, Mechanical properties of dry and wet cellulosic and acrylic films prepared from aqueous colloidal polymer dispersions used in the coating of solid dosage forms, Pharm. Res. 11 (1994) 882–888.

[11] M.E. Aulton, M.H. Abdul-Razzak, J.E. Hogan, The mechanical properties of hydroxypropyl methylcellulose films derived from aqueous systems; Part 1: The influence of plasticisers, Drug. Dev. Ind. Pharm. 7 (1981) 649–668.

[12] M.E. Aulton, Assessment of the mechanical properties of film coating materials, Int. J. Pharm. Technol. Prod. Manf. 3 (1982) 9–16.

[13] Frohoff-Hülsmann, M., Wäβrige Ethylcellulosedispersionen mit Hydroxypropyl-methylcellulose als Überzugsmaterial für Arzneistoffpellets, Dissertation, Heinrich-Heine-Universität, Düsseldorf (1997).

[14] S. Obara, J.W. McGinity, Properties of free films prepared from aqueous polymers by a spraying technique, Pharm. Res. 11 (1994) 1562–1567.

[15] S. Obara, J.W. McGinity, Influence of processing variables on the properties of free films prepared from aqueous polymeric dispersions by a spray technique, Int. J. Pharm. 126 (1995) 1–10.

[16] G.W. Radebaugh, J.L. Murtha, T.N. Julian, J. Bondi, J.N. Bondi, Methods for evaluating the puncture and shear properties of pharmaceutical polymeric films, Int. J. Pharm. 45 (1988) 39–46.

[17] B.C. Lippold, B.H. Lippold, B.K. Sutter, W. Gunder, Properties of aqueous, plasticizer-containing ethyl cellulose dispersions and prepared films in respect to the production of oral extended release formulations, Drug, Dev. Ind. Pharm. 16 (1990) 1725–1747.

[18] C. Bindschaedler, R. Gurny, E. Doelker, Mechanically strong films produced from cellulose acetate latexes, J. Pharm. Pharm. 39 (1987) 335–338.

[19] D. Hutchings, S. Clarson, A. Sakr, Studies of the mechanical properties of free films prepared using an ethylcellulose pseudolatex coating system, Int. J. Pharm. 104 (1994) 203–213.

[20] J.C. Gutiérrez-Rocca, J.W. McGinity, Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers, Int. J. Pharm. 103 (1994) 293–301.

[21] M.A. Winnik, Y. Wang, F. Haley, Latex film formation at the molecular level: the effect of coalescing aids on polymer diffusion, J. Coat. Technol. 64 (1992) 51–61.

[22] J.F. Fuzek, Glass transition temperature of wet fibers - its measurement and significance, in: S.P. Rowland (Ed.), Water in polymers, ASC Symp. Ser. 127, Am. Chem. Soc, Washington, 1980, pp. 515–530.

[23] R. Bodmeier, O. Paeratakul, Evaluation of drug-containing polymer films prepared from aqueous latexes, Pharm. Res. 6 (1989) 725–730.

[24] R.S. Okor, W. Anderson, Swellability of cast films of an acrylate-methacrylate copolymer in aqueous solutions of certain permeants and concentration-dependent permeability, J. Macromol. Sci. Phys. B 25 (1986) 505–513.

[25] B.A. Firestone, R.A. Siegel, Kinetics and mechanisms of water sorption in hydrophobic, ionizable copolymer gels, J. Appl. Polym. Sci. 43 (1991) 901–914.

[26] R. Hyppölä, I. Husson, F. Sundholm, Evaluation of physical properties of plasticized ethyl cellulose films cast from ethanol solutions Part I, Int. J. Pharm. 133 (1996) 161–170.

[27] E. Selinger, C.J. Brine, Use of thermal analysis in the optimization of polymeric diffusion barriers in controlled release delivery systems, Thermochim. Acta 134 (1988) 275–282.

[28] F.C. Masilungan, N.G. Lordi, Evaluation of film coating compositions by thermomechanical analysis I: Penetration mode, Int. J. Pharm. 20 (1984) 295–305.

[29] A.O. Okhamafe, P. York, Studies of interaction phenomena in aqueous-based film coatings containing soluble additives using thermal analysis techniques, J. Pharm. Sci. 77 (1988) 438–443.

[30] K. Johnson, R. Hathaway, P. Leung, R. Franz, Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films, Int. J. Pharm. 73 (1991) 197–208.

[31] K. Amighi, A.J. Moes, Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS30D film-coated sustained-release theophylline pellets, Eur. J. Pharm. Biopharm. 42 (1996) 29–35.

[32] J.N. Yoo, L.H. Sperling, C.J. Glinka, A. Klein, Characterization of film formation from polystyrene latex particles via SANS. 1, Moderate molecular weight, Macromolecules 23 (1990) 3962–3967.