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Time-Dependent Mechanical Properties of Polymeric Coatings Used in Rupturable Pulsatile Release Dosage Forms

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ABSTRACT

The mechanical properties of polymer films used in pharmaceutical coatings of pulsatile drug delivery systems were evaluated in the dry and the wet state by a newly developed puncture test, which allowed the time-dependent measurement of the mechanical properties on the same film specimen. Force, puncture strength, energy at break, modulus, and strain were investigated as a function of water exposure time with respect to the type of polymer and the type and concentration of plasticizer and pore former (hydroxypropyl methylcellulose, HPMC). Eudragit® RS films were very flexible, had a high strain, and broke upon puncture with only small cracks. In contrast, ethylcellulose films were more brittle with a lower strain and showed complete film rupture. Increased amounts of the hydrophilic pore former, HPMC, resulted in a reduced puncture strength and in an increase in water uptake and weight loss of the films. The puncture strength decreased with increasing plasticizer concentration and was lower with the lipophilic dibutyl sebacate than with the hydrophilic triethyl citrate.

Key Words: Ethyl cellulose; Eudragit RS; Hydroxypropyl methylcellulose; Mechanical properties; Polymeric films; Pulsatile release.

INTRODUCTION

Pulsatile drug delivery has gained significant interest in recent years because of a new demand of pharmaceutical products.[1,2] For example, systems have been developed for successive pulse delivery of bioactive agents, or for single pulse release, typically after an initial delay or lag time.

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The mechanisms by which pulsatile delivery can be achieved include pH-sensitivity, ionic sensitivity, mechanical failure, melting, or dissolution of the polymer carrier.[3] Thus, a pulsatile release profile, where the drug is rapidly and completely released after a lag time, could be useful for the delivery of various types of drugs.[4–6] A popular class for pulsatile drug delivery systems is that of rupturable dosage formulations. They consist of a drug-containing core, covered by a swellable layer and an outer insoluble, but water-permeable polymer coating. After exposure to gastro-intestinal fluids, water diffuses through the external polymer coating and hydrates the swellable layer. This causes the development of a swelling pressure, which results in the rupture of the external coating and rapid drug release. The lag-time of such a swelling-controlled dosage form is mainly controlled by the properties of the swelling layer and of the polymer coating, such as its water permeability and mechanical behavior.[7]

Previous contributions described the mechanical properties of polymer films in the dry state with respect to their suitability for controlled-release coatings.[8–10] The coating film should possess a sufficient mechanical strength to avoid damage during manufacturing processes, storage, and transportation. Low elastic moduli were found to be advantageous to prevent the initiation and propagation of cracks and thus reduced the risk of dose dumping.[11,12]

The mechanical properties of coating films change when they are immersed in release media.[13,14] This is due to the uptake of water, which can act as a plasticizer of the polymer film, and also due to the leaching of additives in such films, including water-soluble polymers and plasticizers.[15] Very little has been discussed in the pharmaceutical or polymer literature about the mechanical properties of films with respect to rupturable pulsatile drug delivery systems (DDS). An interesting study on the modeling of pulsatile systems with the identification of the conditions for rupture of the polymer film has been the only effort to accurately describe this rupture phenomenon.[16]

The objective of this study was to develop a puncture test in order to investigate the mechanical properties of polymeric films (henceforth designated also as "wet mechanical properties") as a function of various polymer film parameters and contact time with the release medium. An additional goal was to identify film formulations suitable for rupturable pulsatile DDS.

MATERIALS AND METHODS

The polymers used in this study were: poly(ethylacrylate, methylmethacrylate, trimethylammonioethyl methacrylate chloride) (Eudragit® RS, Röhm GmbH & Co. KG, Darmstadt, Germany), ethylcellulose (EC, Ethocel® Standard 10, Dow Chemical Company, Midland, MI), hydroxypropyl methylcellulose (HPMC, Methocel® E5, Colorcon, Orpington, UK), dibutyl sebacate (DBS), triethyl citrate (TEC) (Morflex, Greensboro, NC). All other reagents were of analytical grade and were used without further purification.

Preparation of Polymer Films

The polymer or mixture of polymers was dissolved in 90% v/v ethanol at a concentration of 10% w/w. The resulting solution was cast on a Teflon plate, $14 \times 14\,cm^2$ and dried for 24 h at room temperature. The film thickness was measured at 5 points with a thickness gauge (Minitest 600, Erichsen, Hemer, Germany).

Mechanical Properties of Polymer Films

Polymer films ($6.5 \times 6.5\,cm^2$) were placed between two custom-made perforated Teflon sheets (hole diameter 10 mm), which were aligned on top of each other (Fig. 1). The mechanical properties of the films were measured with a puncture test (model 4466 Instron® Wolpert, Darmstadt, Germany) ($n = 3$). A metal probe with a hemispherical end (diameter 5 mm,

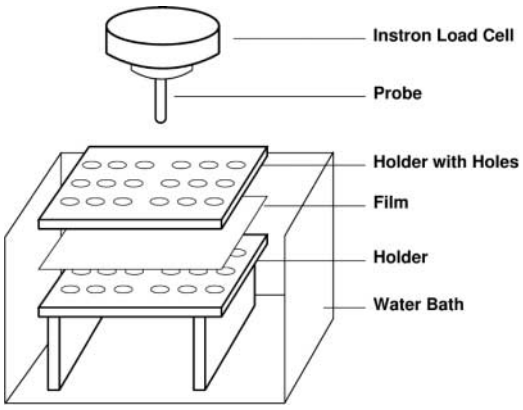

Figure 1. Puncture device as used for the puncture test experiments.

length 15 cm, see Fig. 2) was driven through the dry film at a speed of 5 mm/min. Force vs. displacement curves were recorded with a 50 N or a 500 N load cell. The holder with the fixed film was then immersed in a bath containing a 0.1 N HCl at 37°C and further puncture tests were performed on the same (now wet) film by driving the puncture probe through different holes at different time points. The puncture device therefore allowed the measurement of the time-dependent mechanical properties on the same and not on different film specimens.

Weight Loss and Water Uptake of Polymer Films

Films ($4 \times 4\,cm^2$, $n = 3$) were exposed to 0.1 N HCl at 37°C under constant shaking at 50 rpm. The film samples were removed at predetermined time points, carefully blotted with tissue paper to remove the surface water, weighed with an analytical balance (weight of the wet film, w_w), then dried at 40°C for 12 h and reweighed (weight of the dried film, w_d).

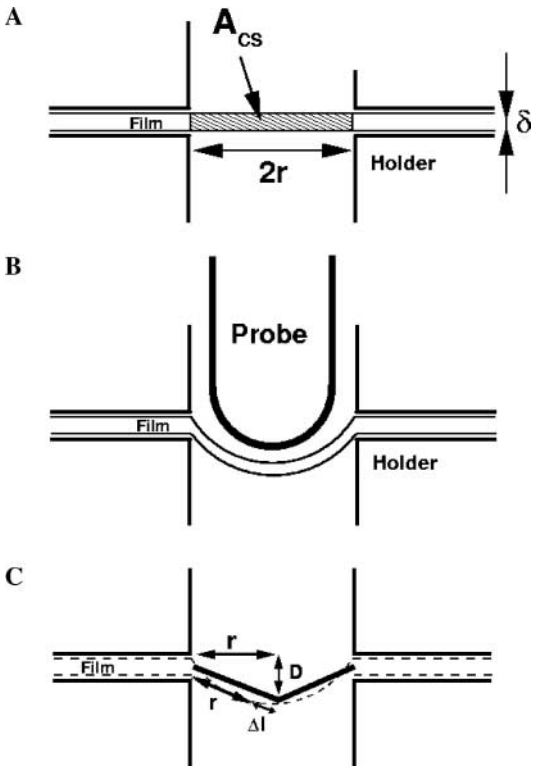

Figure 2. (A) Definition of the area A_{CS}; the radius, r; and the thickness, δ; (B) the metal probe and the film under applied force; (C) definition of displacement D and Δl.

The % weight loss, w_l, was calculated by:

$$w_l = (w_0 - w_d)/w_0 \times 100 \quad (1)$$

Here, w_0 is the initial weight of the film.

The % water uptake, w_u, was calculated by:

$$w_u = (w_w - w_d)/w_d \times 100 \quad (2)$$

RESULTS AND DISCUSSION

Rupturable pulsatile release systems can release the drug after rupture of the outer polymeric coating. Rupture is generally induced by the development of a pressure within the system. The mechanical properties of the polymer coating are therefore very important for the performance of rupturable pulsatile drug delivery systems. Of particular interest are the time-dependent wet mechanical properties of the polymer films in contact with the release medium. A modified puncture test was developed, which allowed the determination of the dry and wet mechanical film properties at predetermined time points after contact with the release medium on the same film specimen (Fig. 1).

Typical force (in N) vs. displacement (in mm) curves are shown in Fig. 3. The force increased as the film was extended due to the application of the puncture probe on the film. These "puncture profiles" were analyzed by the following parameters:[13,17]

The puncture strength, σ_p, was calculated from Eq. (3):

$$\sigma_p = \frac{F_{max}}{A_{CS}} \quad (3)$$

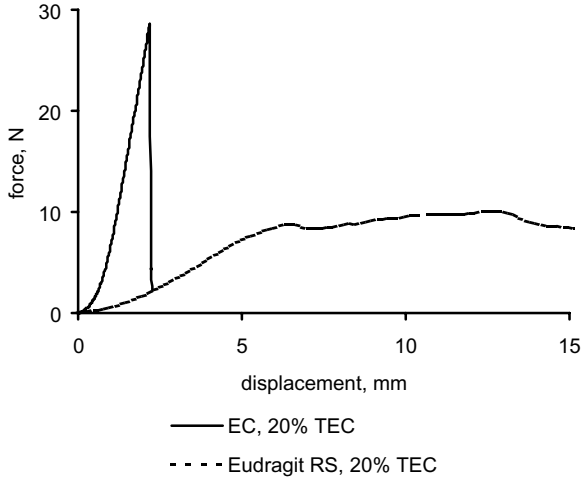

Figure 3. Force-displacement curves of ethylcellulose and Eudragit RS films (20% w/w TEC based on the polymer) in the dry state.

F_{max} is the maximum applied force at film break and A_{CS} is the cross-sectional area of the edge of the film located in the path of the cylindrical hole of the film holder. This area can be approximated by Eq. (4), where r is the radius of the hole and δ is the thickness of the film (Fig. 2A)

$$A_{CS} = 2r \cdot \delta \quad (4)$$

The strain at film break, ε_b, was determined by Eq. (5):

$$\varepsilon_b = \frac{\Delta l}{r} = \frac{\sqrt{r^2 + D^2} - r}{r} \quad (5)$$

where Δl is the linear expansion of the film and D is the displacement of the punch (Fig. 2C). The strain at break can also be expressed in % by multiplying by 100.

The modulus, E, was defined as the slope of the stress-strain curve before film break, with the stress being F/A_{CS}.

The energy at break, ΔE, was

$$\Delta E = F \cdot D \quad (6)$$

Tests were first performed with polymeric films in the dry state (Fig. 3). Eudragit RS [poly(ethylacrylate), methylmethacrylate, trimethylammonioethyl methacrylate chloride] and ethylcellulose (EC), which are two frequently used polymers for extended release dosage forms, were evaluated.

Eudragit RS films were very ductile and flexible, and hence a high displacement of the punch was required for film break. First cracks occurred at a displacement of 6.5 mm, as indicated by a small drop in the recorded force (Fig. 3). The cracks were small and the film did not break completely. The film could be further elongated at a constant force level, indicating the plastic flow of the polymer. These mechanical properties could be advantageous for conventional extended release systems,[12] but are not desirable for a rupturing pulsatile system, where complete rupturing in the form of large cracks or openings is required in order for the drug to be rapidly released after the lag phase. Therefore, Eudragit RS was not a suitable polymer because of the absence of a distinct rupture force and the appearance of only small fissures in the film instead of a complete film rupture.

In contrast to Eudragit RS, ethylcellulose films showed a rupture profile typical of brittle materials[18] with a steep increase in puncture force, resulting in a high modulus. The strain, ε_b, was much smaller than with the Eudragit RS film. Large cracks covering the whole film were observed. Thus, EC was further investigated because of its promising mechanical properties with respect to a rupturable pulsatile DDS.

The wet mechanical properties of various EC/plasticizer/additive films were investigated after different time periods in 0.1 N HCl at 37°C. Typical force/displacement curves are shown in Fig. 4. The shape of the curves remained the same after exposure to the release medium. However, the force at break decreased with increasing exposure time; the curves became flatter (decreased moduli) and the displacement at break increased. This can be attributed to the uptake of release medium by the film.

Plasticizers are often added to polymeric films to improve the film formation and the mechanical film properties. As expected, the puncture strength of EC films decreased with an increasing amount of dibutyl sebacate (DBS), a lipophilic plasticizer (Fig. 5). The puncture strength of films containing up to 10% DBS declined with increasing exposure time in 0.1 N HCl. This decrease in puncture strength could be caused by the uptake of water, which could also act as a plasticizer. The puncture strength of EC films containing 20% w/w DBS was low and did not change at different exposure times.

The puncture strength was also lower for films with the lipophilic DBS than with triethyl citrate (TEC), a hydrophilic plasticizer, at the same plasticizer concentration (Fig. 6). DBS remained in the film during contact with the medium,[15] thus explaining the more flexible character and the lower puncture strength. The puncture strength of TEC plasticized

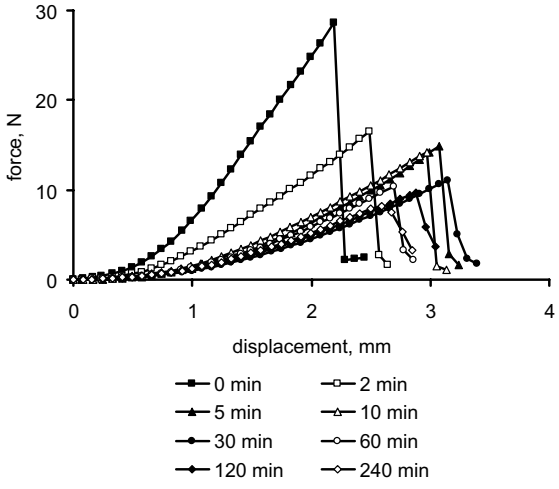

Figure 4. Typical force-displacement curves as a function of the time of exposure to the medium, 0.1 N HCl. Film composition: ethylcellulose:HPMC (80:20 w/w), 20% w/w TEC, film thickness 243.8 μm.

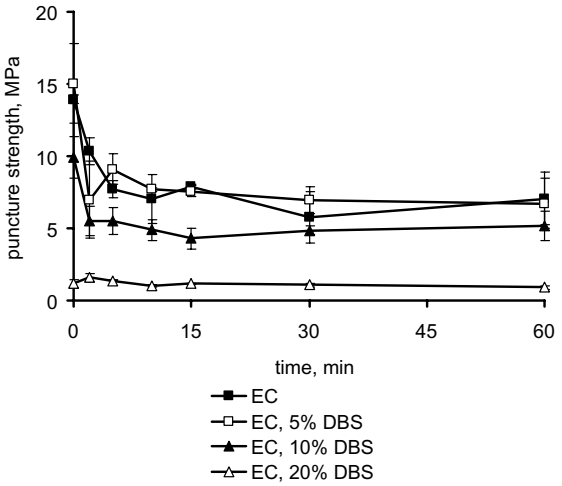

Figure 5. Puncture strength of ethylcellulose films as a function of plasticizer (dibutyl sebacate) concentration ($n = 3 +/- \text{SD}$).

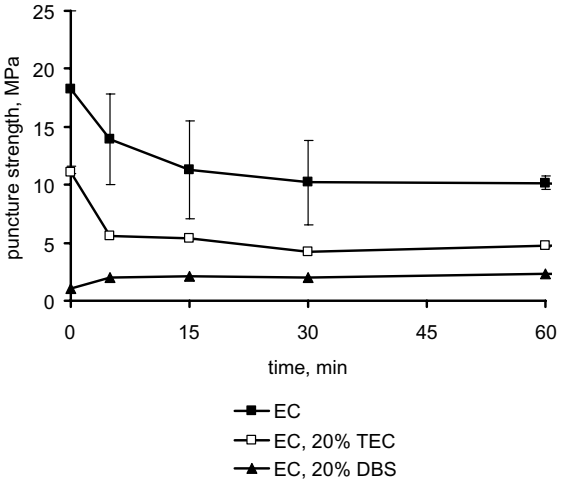

Figure 6. Puncture strength of ethylcellulose films as a function of plasticizer type ($n = 3 +/- \text{SD}$).

films also decreased with time, which implies that the mechanical strength of the film decreased, which would be desired for the rupture of the coating of the pulsatile DDS.

The water permeability of the polymer coating also affects the lag time, because it controls water penetration into the system and therefore the rate of swelling of the swelling layer. The water permeability of EC films can be altered by adding a water-soluble polymer, such as HPMC. Besides its effect on the water permeability of the coating,

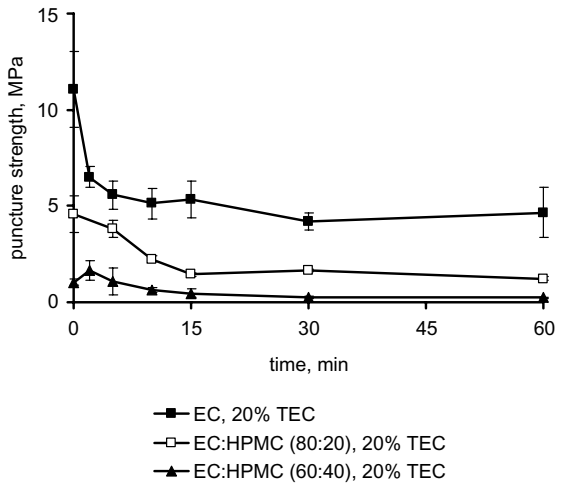

Figure 7. Effect of the addition of HPMC on the puncture strength of ethylcellulose films ($n = 3 +/- \text{SD}$).

HPMC could also affect the mechanical properties. The puncture strength of EC films decreased with increasing amount of HPMC (Fig. 7). HPMC probably leached from the film after contact with aqueous media, thus acting as a pore former. The leaching caused a mechanical weakening of the film, which, in addition to the increased permeability, could shorten the lag time prior to rupture.

The energy at break, which represented the mechanical work necessary to break the film, was highest for the pure EC film. It decreased with plasticized films and was further reduced by the addition of the pore former HPMC (Fig. 8A). The energy at break of the pure EC film decreased with time due to the plasticizing effect of water. In the case of EC film, plasticized with 20% w/w TEC, it decreased due to the leaching of the plasticizer.[15] These data were in good agreement with the associated puncture strength data (Fig. 8B). The energy of EC films plasticized with DBS was already low in the initial state. It did not decrease with time due to the permanence of the lipophilic plasticizer DBS, which did not leach out of the film. EC films containing HPMC showed a low, initial energy value, which decreased further due to the combined effects of water uptake, plasticizer leaching, and HPMC leaching.

The modulus at film break decreased with exposure time, indicating an increasing weakness of the films (Fig. 8C). The sharpest decline in the modulus or the greatest softening of the film was observed for EC/HPMC films because of the high degree of HPMC leaching (Fig. 10) and the high water uptake (Fig. 9).

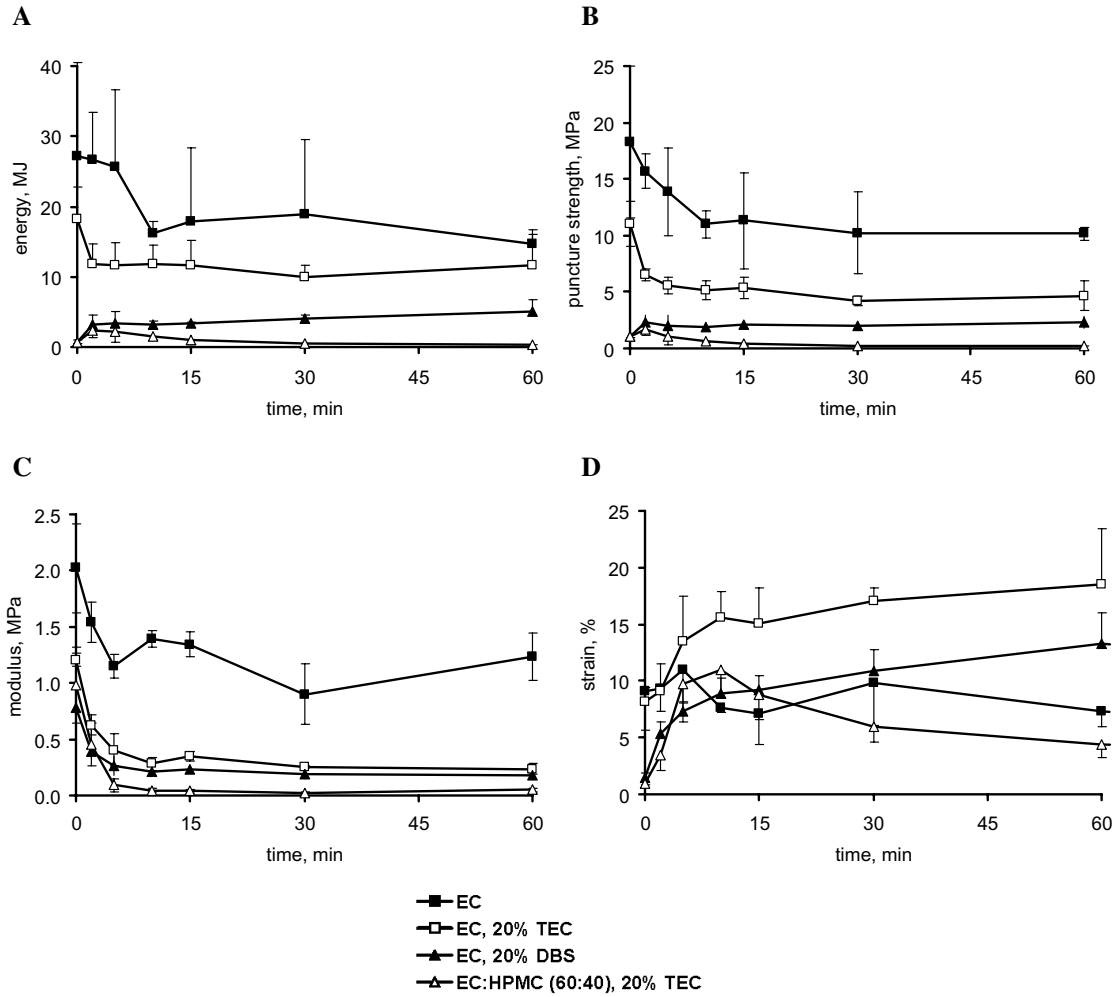

Figure 8. Time-dependent mechanical properties of ethylcellulose films: (A) energy at film break, (B) puncture strength, (C) modulus at film break, and (D) strain ($n = 3 +/- \text{SD}$).

The strain at film break increased within the first minutes of exposure (Fig. 8D), because of the increased flexibility of the film due to the water uptake and temperature increase. The strain of the HPMC-containing film increased in the first 10 min and then declined due to HPMC leaching. The film became very weak and ruptured already at a low probe displacement, resulting in lower strain values. A low strain would be advantageous to ensure a complete rupture in a rupturable pulsatile DDS.

The water uptake of EC films containing HPMC was much higher than for films without pore former (Fig. 9). The reason for the high water uptake was the hydrophilic character of HPMC when compared to EC. The uptake of water from the surrounding medium can explain the change in the mechanical properties upon exposure to the release medium, as water acted as a plasticizer.[15] The maximum force and consequently the resulting puncture strength of the corresponding films were reduced. The lower modulus indicated a softening of the material.

The HPMC-containing films had the highest weight loss (Fig. 10). TEC plasticized EC films also showed a loss in weight, which was attributed to the leaching of the hydrophilic plasticizer TEC, while EC films plasticized with 20% w/w DBS had no measurable weight loss within 240 min (data not shown). The combination of water uptake and loss of film components weakens the film, as seen most dominantly with EC/HPMC films.

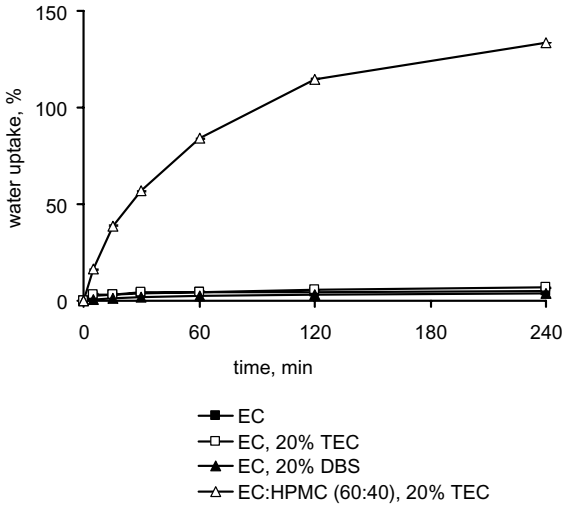

Figure 9. Water uptake of different ethylcellulose film samples.

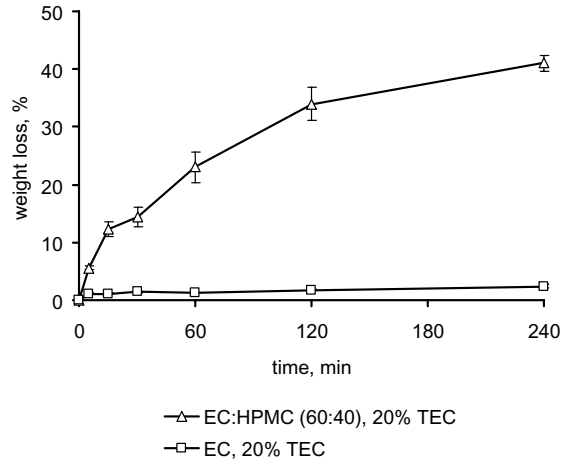

Figure 10. Weight loss of different ethylcellulose film samples.

CONCLUSION

A method was developed to determine the time-dependent mechanical properties of polymer films on the same film specimen, which is the polymer coating in rupturable pulsatile drug delivery systems, where the lag time prior to the drug release phase is mainly controlled by the properties of the coating. The puncture strength, strain, energy at break, and modulus showed a time-dependent change upon exposure of films to release media. These changes were explained by water uptake and leaching phenomena. Ideally, a successful film for use in such pulsatile DDS should have a low modulus but a sufficient high initial mechanical strength, which would then decrease with time to ensure complete rupture behavior. Ethylcellulose with the addition of HPMC as a pore former (ratio EC:HPMC 60:40), plasticized with 20% w/w TEC was a promising composition.

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