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Evaluation of the mechanical properties and drug release of cross-linked Eudragit films containing metronidazole

Nazik Elgindy, Wael Samy*

Faculty of Pharmacy, Department of Industrial Pharmacy, Alexandria University, Alexandria 21521, Egypt

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ABSTRACT

The mechanical properties of casted Eudragit E-100 films were tested for the combined effect of two cohesion promoters (succinic or citric acid) and triacetin as a plasticizer. The prepared films were elastic, self-adhesive, transparent and pale yellow in colour.

Films containing either of the tested cohesion promoters showed a significant reduction in both tensile strength and Young's modulus on increasing triacetin and/or cohesion promoter concentration. Films containing 7% (w/w) succinic acid and 45% (w/w) triacetin gave the highest elongation of the tested films at any given stress with a maximum of 1050% elongation. Optimal bonding to human skin surface (tack) with the highest peel adhesion (588 cN/cm) was observed with these films denoting good self-adhesive properties.

In vitro metronidazole (MN) release from the plasticized Eudragit E-100 films was monitored for the influence of incorporation of cohesion promoters, secondary polymer (Eudragit RL or RS) as well as drug loading. Both cohesion promoters were seen to improve MN release from the films with the maximum drug flux (0.334 mg cm^{-2} h^{-1}) observed with 1.75% (w/w) succinic acid. The tested secondary polymers were also found to improve MN release from the tested films. The highest MN release was observed with 20% (w/w) Eudragit RL which gave 0.77 mg cm^{-2} released after 3 h compared with only 0.34 mg cm^{-2} for plain films. MN release from the films was increased by increasing drug load. Calculating the release rate constant (K_r) showed a linear increase with the increase in drug load.

1. Introduction

Formulation of film-based drug delivery systems involves the optimisation of several factors. The most important of which is the selection of the polymer and testing the physical and mechanical properties of the prepared films (Kotain and Vavia, 2002).

Forming high transparency self-adhesive films, Eudragit E-100 became a very good candidate for TDDS preparation (Data sheet). Adhesive matrices of Eudragit E-100 can be prepared from organic solutions or aqueous dispersions or via hot-melt casting. The produced films are brittle which require the addition of plasticizers to improve their mechanical properties. The properties of the prepared matrix can be also modified by using cohesion promoters (cross-linkers) with free carboxyl groups. Such compounds can enter into ionic interaction with the tertiary amino functions of Eudragit E-100, thus altering the matrix properties (Data sheet).

Generally, cohesion promoters can alter the mechanical properties of the film in different manners. Polydimethylsiloxane (PDMS) pre-polymer was combined with varying concentrations of a cross-linker where the tensile strength was increased from 3.9 MPa to a peak of 10.8 MPa at 5.7 and 14.3% (w/w) cross-linker concentration, respectively. Further increase in the cross-linker concentration led to a reduction in the tensile strength to 4 MPa (Mata et al., 2005).

Polyphosphazenes cross-linked with 2-hydroxyethyl methacrylate (HEMA) or acrylic acid (AA), showed 11 to 17 folds increase in their modulus of elasticity compared to the linear counterpart (Cui et al., 2004). On the other hand, pluronic copolymers showed a decrease in their modulus of elasticity in the presence of ethylene glycol dimethacrylate cross-linker. Pluronic showed an increased cross-linkage, either physical or covalent, with the increasing length of the poly-propylene oxide segments (Bromberg et al., 2004).

A combination of the self-adhesive Eudragit E film with an antibacterial drug-loaded poly(*N*-isopropyl-acrylamide) (PNIPAAm) microgel beads was designed. The result indicates that the tack property of Eudragit E film increased with an increase of the PNIPAAm. In addition, the peel strength of Eudragit E film initially decreased with the addition of PNIPAAm microgel beads, but increased to a maximum value when PNIPAAm microgel beads were added from 4% to 7.6% (w/v), then decreased again after 7.6% (w/v). The optimal concentration of PNIPAAm microgel beads was 7.6%

* Corresponding author. Tel.: +20 3 9533 515; fax: +20 3 4873 273.
E-mail addresses: waelsamy1@hotmail.com, wsamy73@yahoo.com (W. Samy).

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(w/v) which had better tack and peel adhesive properties (Lin et al., 2001).

Fungating tumors, pressure ulcers, and other chronic wounds are frequently the source of offensive odours due to anaerobic bacteria. Such odours may distress patients, family, and healthcare professionals and limit the patients' contact with others causing a negative psychological impact on all concerned. Also, there is widespread agreement among wound care professionals that topical MN is effective in controlling wound odour (Kalinski et al., 2005). The deodorizing effect of MN has been shown to correlate with eradication of anaerobic infection but systemic administration is often associated with adverse events, such as nausea and vomiting (Ashford et al., 1984; Bower et al., 1992; Gomolin and Brandt, 1983; Newman et al., 1989).

Finlay et al. (1996) conducted a multicenter trial that prospectively evaluated MN 0.75% gel on 47 patients with benign and malignant malodorous wounds. Decreased odor was reported on 95% of the patients after 14 days of treatment. There was a significant decrease in anaerobic organism cultured but no significant changes in the growth of aerobic bacteria. Bale et al. (2004) showed a 100% success rate for the MN gel, mostly within 3 days concerning odour control.

The aim of this work is to prepare self-adhesive MN films with optimal properties for controlling anaerobic infections in chronic wounds.

2. Materials and methods

2.1. Materials

Eudragit E-100, RL and RS were supplied by Rhöm Pharma (Germany). Metronidazole (MN) and Triacetin were supplied by Pharco Pharm. Co. (Alexandria, Egypt). Isopropanol, ethyl acetate, citric acid and succinic acid were purchased from Prolabo (EU). Span 85 (Atlas Chem. Co., USA) Spectra/Por® M.W. cut off 10,000 (Spectrum®, USA). DSC 6 Differential Scanning Calorimeter (Perkin Elmer, USA), Lambda 3B Spectrophotometer (Perkin Elmer, USA), Tensile strength tester (Locally made) and USP tablet dissolution rate apparatus (Pharmatest, Germany).

2.2. Preparation of plasticized cross-linked Eudragit films

Eudragit E-100 pellets (10 g) and 0.35 or 0.70 g of either citric or succinic acid as cohesion promoters were soaked in 15 ml of ethyl acetate/isopropanol mixture (2/1). Triacetin was added to the solvent mixture to get a plasticizer concentration of 10, 25 or 45% (w/w) (based on dry polymer weight) for each concentration of the used promoter. The formed solution was then casted over mercury in a 10-cm petri dish and left to dry for 24 h at room temperature (25 °C) in a closed cabinet. The dried films were tested for their mechanical and adhesive properties.

2.3. Evaluation of the mechanical properties of the prepared films

All the prepared films were tested for their thickness, elongation, tensile strength and 180° peel adhesion.

The same procedure and testing parameters were made as previously described by Samy (2007).

2.4. Thermal analysis of the film

The thermal properties of Eudragit E-100 pellets, casted plain (unplasticized) and plasticized films were compared using a Differential Scanning Calorimeter. Samples were weighed and placed into aluminum pans which were then sealed. The samples were held at 35 °C for 1 min under a flow of nitrogen gas and then heated to 200 °C at a rate of 10 °C/min.

2.5. Preparation of the MN-loaded films

Drug-loaded films were individually prepared by dissolving the required percentage of MN (1.88, 3.75 or 7.5 (w/w) based on dry polymer weight) in 5 ml of ethylacetate/isopropanol mixture (2/1) containing 0.3 ml Span 85 and 3.7 g Eudragit E-100 in a 25 ml beaker. Triacetin (45% w/w) was added to the mixture, the beaker was tightly closed with aluminum foil and tape till complete dissolution. The polymer solution was then casted as described before.

The tested cohesion promoters or secondary polymers were incorporated at the specified percentage in the solvent mixture containing 1.88% (w/w) MN before addition to the polymer beads.

The produced films were elastic, transparent, self-adhesive and faint yellow in colour.

2.6. Drug release from Eudragit films

Casted films were cut into circular discs of 9 cm^2 surface area, placed on a plastic support of the same area, covered with the pre-soaked Spectra/Por® membrane and the whole set was fixed together using a plastic ring. The whole set was immersed in 250-ml phosphate buffer saline (PBS) pH 7.4 in a jar of the USP dissolution rate apparatus with the dialysis membrane facing upwards. The paddles were rotated at 40 rpm and the temperature was adjusted at 35 ± 0.5 °C. At predetermined time intervals 5 ml samples were withdrawn and assayed spectrophotometrically for MN content at 317 nm.

None of the used excipients were found to interfere with the drug assay at this wavelength.

3. Results and discussion

3.1. Physico-mechanical properties

3.1.1. Effect of cohesion promoter/plasticizer combinations

At any triacetin concentration, the incorporation of either succinic or citric acid cohesion promoters was shown to reduce both tensile strength and Young's modulus. Increasing succinic acid cohesion promoter concentration resulted in a reduction in these two parameters.

The effect of triacetin concentrations on the mechanical properties of Eudragit E-100 films containing succinic or citric acid cohesion promoters is shown in Figs. 1 and 2, respectively. Increasing both triacetin and succinic acid concentrations gave the highest elongation of the tested films at any given stress. The mechanism through which plasticizers act is based on the "lubrication" of polymer chains thus facilitating chain "slippage" (Samy, 2001). This indicates that the plasticizing action of triacetin and the cross-linkage of succinic acid "augment" together in altering the mechanical properties of Eudragit films. Succinic acid seems to allow the cross-linkage of the polymeric chains into "layers" that "glide" over one another by the action of triacetin. Such performance allows higher elongation at break than that of chain-past-chain "slippage" of uncross-linked polymer (Samy, 2001).

In case of citric acid cohesion promoter, the films showed almost the same pattern of elongation for the two cohesion promoter concentrations. This indicates that citric acid concentration does not significantly affect film elongation causing triacetin to be the predominating factor in controlling film properties.

For succinic acid/triacetin combination, increasing the concentration of either the cohesion promoters or the plasticizer showed reduction in both tensile strength and modulus of elasticity. The least tensile strength (0.98 N/cm^2) and Young's modulus

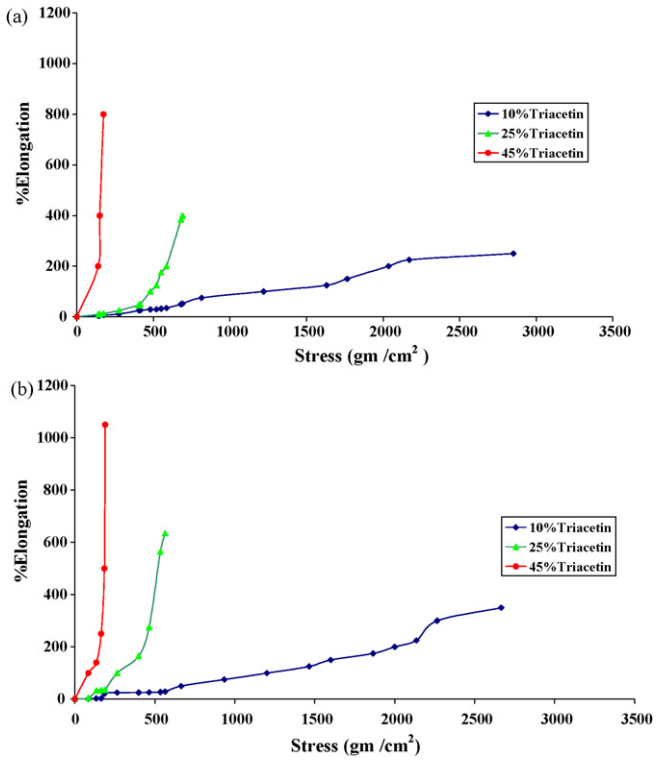

Fig. 1. Effect of different concentrations (%, w/w) of triacetin on the mechanical properties of Eudragit E-100 films containing (a) 3.5% (w/w) and (b) 7% (w/w) succinic acid cohesion promoter.

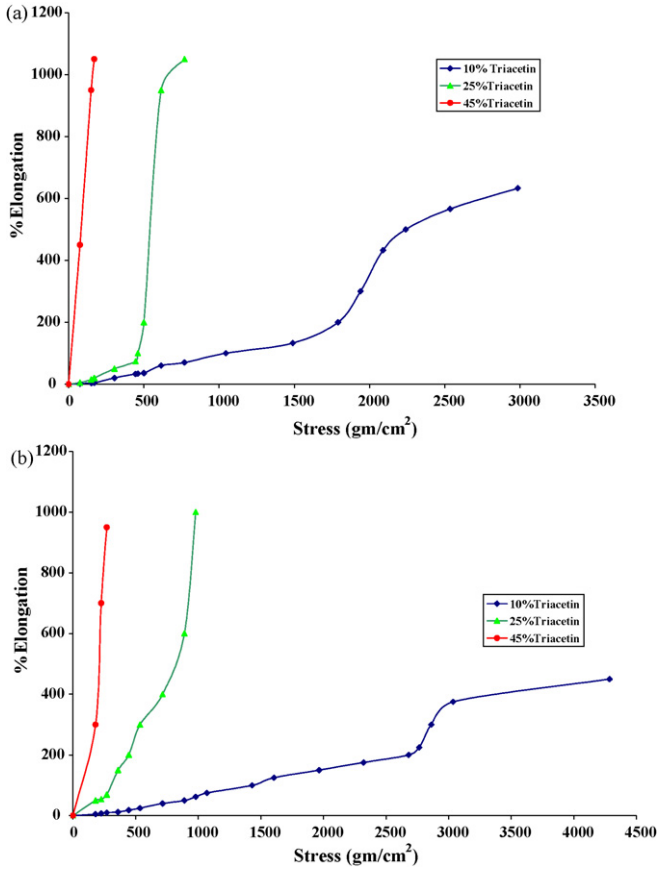

Fig. 2. Effect of different concentrations (%, w/w) of triacetin on the mechanical properties of Eudragit E-100 films containing (a) 3.5% (w/w) and (b) 7% (w/w) citric acid cohesion promoter.

(0.16 N/cm^2) were obtained with films containing 7% (w/w) succinic acid and 45% (w/w) triacetin (Table 1).

In case of citric acid, increasing the promoter concentration seemed to slightly increase both tensile strength and Young's modulus at any given plasticizer concentration. At 25% (w/w) triacetin concentration Young's modulus was increased from 0.75 to 1.06 N/cm^2 on increasing citric acid from 3.5 to 7% (w/w).

3.1.2. Peel adhesion 180°

Citric or succinic acid cohesion promoters were found to increase film adhesion (Table 1) especially at the higher concentration (7%, w/w) which is advantageous for preparing self-adhesive wound dressing.

Lin et al. (2000) tested the adhesive properties of Eudragit films plasticized with triacetin, DBP, DEP or tributyl citrate where film adhesiveness was markedly increased when the plasticizer concentration was greater than 25%.

3.1.3. Thermal analysis of Eudragit E-100 films

Eudragit E-100 films containing 10 or 45% (w/w) of triacetin were examined for their DSC spectra (Fig. 3). The films were compared to Eudragit beads and unplasticized films. The melting enthalpy (ΔH) values revealed a reduction in the ΔH from

Table 1
Effect of triacetin plasticizer concentrations on the mechanical properties of Eudragit E-100 films containing succinic or citric acids cohesion promoters.

Triacetin concentration (%, w/w)	Tensile strength ±SD (N/cm^2)	Young's modulus ±SD (N/cm^2)	Peel adhesion ±SD (cN/cm)
3.5% Succinic acid			
10	26.56 ± 2.40	10.13 ± 1.02	98.00 ± 1.08
25	6.37 ± 0.78	1.85 ± 0.12	196.00 ± 1.37
45	1.57 ± 0.10	0.28 ± 0.01	441.00 ± 2.74
7.0% Succinic acid			
10	25.28 ± 1.20	8.17 ± 0.74	117.60 ± 0.98
25	5.39 ± 0.29	0.90 ± 0.16	274.40 ± 1.18
45	0.98 ± 0.20	0.16 ± 0.01	588.00 ± 4.51
3.5% Citric acid			
10	28.42 ± 1.96	4.54 ± 0.71	98.00 ± 0.88
25	5.68 ± 0.88	0.75 ± 0.03	274.40 ± 1.27
45	1.47 ± 0.10	0.44 ± 0.03	539.00 ± 3.63
7.0% Citric acid			
10	30.38 ± 0.87	9.25 ± 1.06	78.40 ± 0.88
25	6.96 ± 0.29	1.06 ± 0.07	117.60 ± 0.88
45	1.86 ± 0.10	0.30 ± 0.02	470.40 ± 2.35

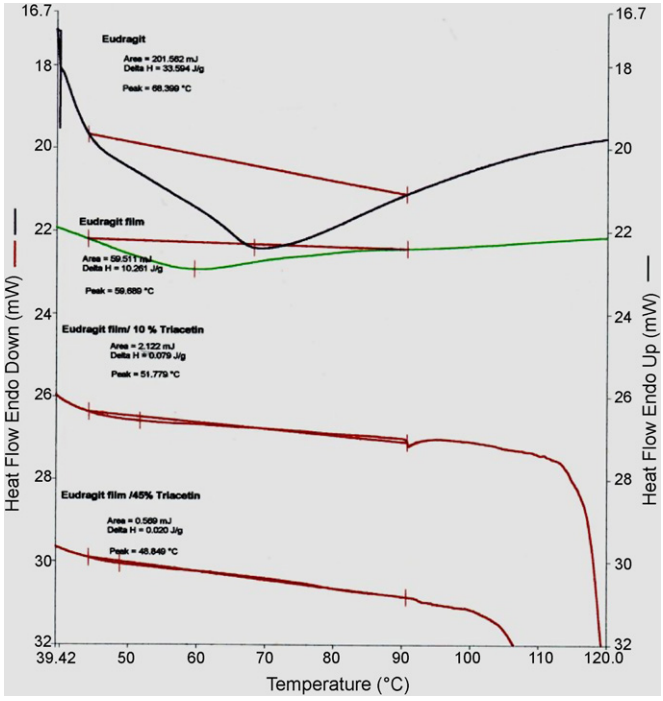

Fig. 3. DSC charts for plain Eudragit films and films containing different triacetin plasticizer concentrations.

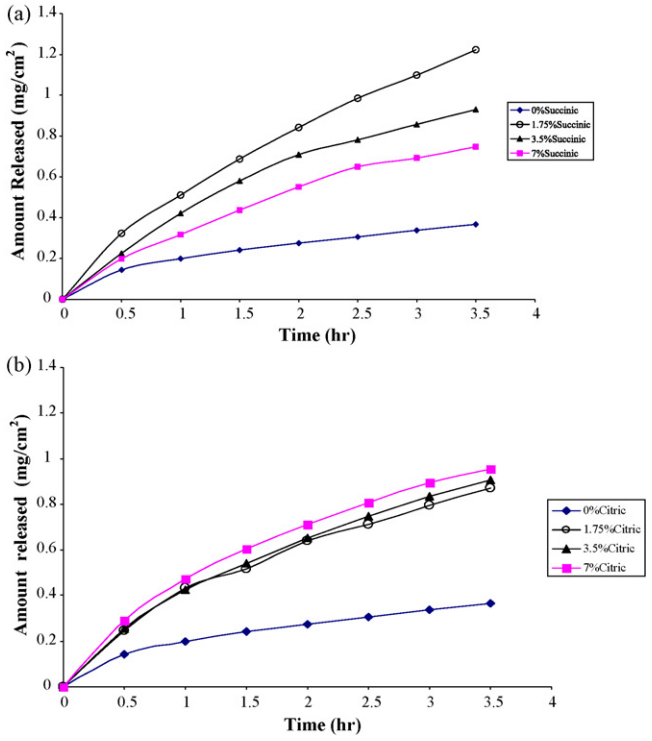

Fig. 4. Effect of cohesion promoter concentration: (a) succinic acid; (b) citric acid on MN release from casted Eudragit films.

33.5 J/g for Eudragit beads to 10.3 J/g for unplasticized films indicating reduced crystallinity. Incorporation of triacetin showed further reduction in the ΔH values to 0.02 J/g at 45% concentration (Table 2). Meier et al. (2004) studied the effect of poly(caprolactone triol) plasticizer on cellulose acetate membranes. They found that the plasticizer decreased the attractive forces between cellulose acetate molecules increasing the chain mobility as manifested by the reduction in the melting enthalpy. This led to the conclusion that poly(caprolactone triol) also reduced polymer crystallinity. Noting that the crystalline region in a polymer matrix hinders solute permeation, the study concluded that the reduction in ΔH suggests significant improvement in solute permeation (Meier et al., 2004). Based on this conclusion, triacetin would be a good plasticizer candidate to improve solute permeation from Eudragit E-100.

3.2. Drug release

MN-loaded films showed the same mechanical properties as the corresponding unloaded films except for the peel adhesion which was seen to be reduced by 5–7% compared with the unloaded Eudragit films.

3.2.1. Effect of cohesion promoter type and concentration

The incorporation of cross-linker in the Eudragit matrix is one of the methods used to modify drug release (Data sheet).

Incorporation of either of the tested cohesion promoters showed an increase in MN release to a variable extent (Fig. 4).

Table 2
DSC values for Eudragit E-100 containing different triacetin concentrations.

Plasticizer (%, w/w)	Area (mJ)	DH (J/g)	Peak (°C)
Solid Eudragit	201.56	33.59	68.4
Plain Eudragit film	59.51	10.26	59.7
10%Triacetin film	2.12	0.08	51.8
45%Triacetin film	0.57	0.02	48.8

Calculation of drug flux (J) and release rate constant (K_r) of MN from the prepared films showed that succinic acid incorporation gave 3.6-folds increase in MN flux at 1.75% (w/w) cohesion promoter concentration whereas a cohesion promoter concentration of 7% (w/w) resulted only in 2.3-folds increase in drug flux. On the other hand, incorporation of citric acid gave MN flux of 2.4, 2.46 and 2.58 mg cm^{-2} h^{-1} for cohesion promoter concentrations of 1.75, 3.5 and 7% (w/w), respectively (Table 3).

MN release rate constant was increased from 0.194 mg cm^{-2} h^{-1} for plain uncross-linked films to a maximum of 0.667 mg cm^{-2} h^{-1} for films containing 1.75% (w/w) succinic acid. Films containing 7% (w/w) succinic acid showed a (K_r) value of only 0.442 mg cm^{-2} h^{-1}. For films containing citric acid cohesion promoter the increase in the calculated values of the release rate constant ranged from 2.5- to 2.7-folds for films containing 1.75 and 7% (w/w) of the promoter, respectively.

Generally, the effect of cohesion promoter on drug release from polymeric matrices is based on their influence on the polymer arrangement within the matrix which indicates that succinic acid can strongly affect Eudragit E-100 arrangement thus significantly affect MN release.

Kankkannan et al. (2004) used succinic acid as a cross-linker in the manufacture of melatonin patches based on Eudragit E-100. The

Table 3
Effect of cohesion promoter on the flux (J) and release rate constant (K_r) of MN release from Eudragit E-100 films containing 1.88% (w/w) MN.

Cohesion promoter (% w/w)	J (mg cm^{-2} h^{-1})	K_r (mg cm^{-2} h$^{-1/2}$)
0% Cohesion promoter	0.093	0.194
1.75 Succinic acid	0.334	0.667
3.50 Succinic acid	0.259	0.524
7.00 Succinic acid	0.210	0.422
1.75 Citric acid	0.240	0.486
3.50 Citric acid	0.246	0.498
7.00 Citric acid	0.258	0.528

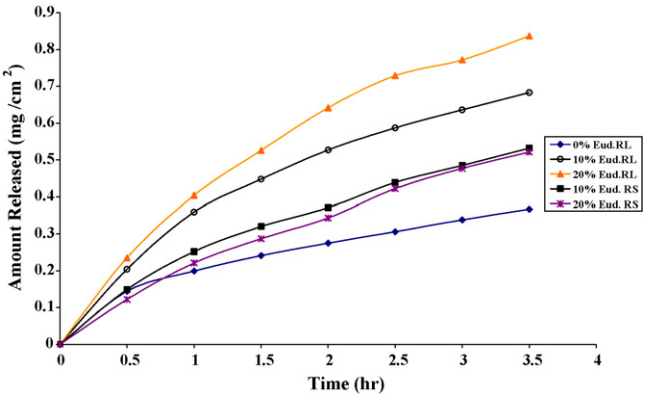

Fig. 5. Effect of a secondary polymer on MN release from casted Eudragit films.

optimized patch composition was found to be the one containing 3.7% (w/w) succinic acid based on dry polymer weight.

El-Gindy et al. (2007) has also shown an improvement in the ex vivo testosterone release from Eudragit E-100-based patches on using succinic acid cross-linker in the polymer matrix.

3.2.2. *Effect of secondary polymer*

Drug release from Eudragit E-100 matrices can be modulated by the use of secondary polymers (Data sheet). So, Eudragit RL-100 or RS-100 was tested for their effect on MN released from Eudragit E-100 films containing 1% (w/w) Span 85 as an enhancer. Both polymers showed an increase in drug release.

Incorporation of Eudragit RL (20%, w/w) gave the highest MN release of 0.77 mg cm^{-2} released after 3 h compared with 0.338 mg cm^{-2} for films without secondary polymers (Fig. 5). Drug flux was also at maximum (0.229 mg cm^{-2} h^{-1}) with 20% Eudragit RL (Table 4). Calculating the release rate constant of MN showed 1.95 and 2.4-folds increase on the incorporation of 10 and 20% (w/w) Eudragit RL, respectively. This increase in the release parameters could be attributed to the disturbance of Eudragit E-100 matrix structure upon the incorporation of Eudragit RL allowing a higher escaping tendency for the drug molecules. In addition, being slightly more hydrophilic than Eudragit E-100, Eudragit RL could allow more hydration of the matrix (Data sheet). The water molecules entering the matrix can thus "leach" more of the drug out of the film. The overall effect of the secondary polymer can be attributed to an equilibration between the "hydrating" and "disturbing" effect of the secondary polymer on the parent Eudragit E-100 matrix (Data sheet). Wong et al. (1999) showed that the incorporation of secondary polymers in Eudragit NE40D-based buccal patches resulted in improving metoprolol tartrate release from the devices. The influence was mainly attributed to the effect of the used hydrophilic polymer on matrix hydration and the formation of "aqueous channels" for drug release. Four out of the six tested secondary polymers showed no direct relation between the rate of drug release and the secondary polymer concentration (Wong et al., 1999).

Table 4
Effect of secondary polymer on the flux (J) and release rate constant (K_r) of MN release from Eudragit E-100 films containing 1.88% (w/w) MN.

Secondary polymer (%, w/w)	J (mg cm^{-2} h^{-1})	K_r (mg cm^{-2} $h^{-1/2}$)
0% Secondary polymer	0.093	0.194
10% Eudragit RL	0.183	0.379
20% Eudragit RL	0.229	0.469
10% Eudragit RS	0.143	0.290
20% Eudragit RS	0.145	0.287

Table 5
Effect of drug loading and dispersion on the flux (J) and release rate constant (K_r) of MN release from Eudragit E-100 films.

Drug loading (%, w/w)	J (mg cm^{-2} h^{-1})	K_r (mg cm^{-2} $h^{-1/2}$)
1.88	0.093	0.194
3.75	0.369	0.741
7.50	0.708	1.406

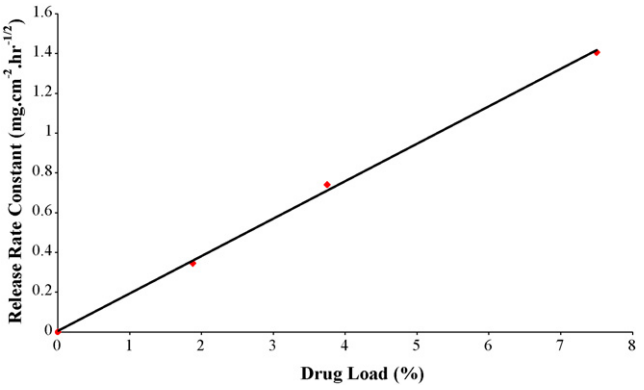

Fig. 6. Effect of drug loading on the release rate constant of MN from casted Eudragit films.

Eudragit RS incorporation resulted in an increase in MN release parameters with both of the tested concentrations giving almost the same values of drug flux and release rate constant (Table 4).

The effect of secondary polymers was also observed in pentazocin release from TDDS containing different ratios of Eudragit RL/Eudragit RS. Pentazocin release was increased on increasing the Eudragit RS increment (Mandal et al., 1994).

3.2.3. *Effect of drug loading*

Plotting the cumulative MN released (μg/cm^2) vs. time or $time^{1/2}$; Fick's and Higuchi's plots, respectively; and calculating their apparent slopes allowed the determination of drug flux (J) and release rate constant (K) of the drug corresponding to each drug load (Table 5). The calculated MN flux was increased from 0.093 mg cm^{-2} h^{-1} at 1.88% (w/w) MN load to 0.708 mg cm^{-2} h^{-1} at 7.5% (w/w) load.

A similar increase in the release rate constant was also observed (Table 5) where the release rate constant was increased from 0.194 to 1.406 mg cm^{-2} $h^{-1/2}$ on increasing MN load from 1.88 to 7.5% (w/w). Plotting (K_r) vs. drug load showed a linear increase (Fig. 6) which is in a good agreement with the results obtained by Yamaguchi et al. (1996) who studied the effect of indomethacin load on its release parameters from gel, hydrophilic ointment, simple ointment and petrolatum ointment.

4. Conclusion

Both of the used cohesion promoters showed improvement in the mechanical properties of the casted Eudragit E-100 films with succinic acid showing better effect especially concerning the self-adhesive properties of the films. Increasing the concentration of either of the cohesion promoter or the plasticizer gave more significant effect on the mechanical properties of tested films. The best combination would be by using 7% (w/w) succinic acid and triacetin (25 or 45% (w/w)). The highest MN flux was obtained at 7.5 % (w/w) drug load and 1.75 % (w/w) succinic acid cohesion promoter. The films are thus good candidates for the fabrication of transparent self-adhesive easy peeling wound dressing containing MN.

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