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Lactic acid-induced modifications in films of Eudragit RL and RS aqueous dispersions

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Abstract

Eudragit RL (ERL) and RS (ERS) are polymethacrylate co-polymers, used in film coating of sustained release dosage forms, possessing some hydrophilic properties due to the presence of quaternary ammonium groups (QAG), where ERL contains more of such groups, hence more permeable, than ERS. However, because these groups ionize in solution, they undergo electrostatic interaction with negatively charged species. This phenomenon was utilized in this study to introduce modification in the film properties of ERL and ERS by interaction with lactic acid (LA). Thermal and mechanical analyses were carried out on polymeric free films. DSC showed a shift in T_g of the film while ^{1}H NMR spectroscopy revealed a significant deshielding in the peak of QAGs protons after interaction with LA. Stress–strain test showed an increase in three mechanical parameters of the new film (containing LA): tensile strength to modulus ratio, relative surface energy and toughness index, indicating an enhancement in the mechanical stress resistance. Tablets coated with LA-containing films showed an increase in the release rate and extent and good stability upon aging, compared to those coated with the original film.

Keywords: Eudragit RL; Eudragit RS; Lactic acid; Acid–polymer interaction; Polymeric free film; Mechanical resistance; Tablet film coating

1. Introduction

Film coating is an integral part of the dosage form development process. Controlled or modified release of drugs is considered one of the most important desired attributes of film coat application (Radebaugh, 1993). This and other end-use properties of the film coating rely on the integrity of the film and sufficient bonding (adhesion) to the substrate to ensure optimum performance (Okhamafe and York, 1987). Aqueous-based polymeric dispersion systems were used in film coating nowadays as an alternative to organic solutions due to the many disadvantages of the later (Hogan, 1982).

Eudragit RL (ERL) and Eudragit RS (ERS) are acrylic and methacrylic acid esters with some hydrophilic properties due to the presence of quaternary ammonium groups (QAGs), where ERL possesses higher amount (50 mEq./100 g polymer) of such groups than ERS (25 mEq./100 g polymer) (Lehman, 1997). They are insoluble in water but swell in digestive fluid independently of the pH and become permeable. They are used mainly in film coating of tablets, granules and other small particles and could be used in matrix formulation (Lehman, 2001).

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It has been reported that QAGs present as chlorides, are completely dissociated in physiological pH range 1–8 (Kibbe, 2000; Rohm Pharm Info Sheets, 2002). These functional groups are cationic in nature and therefore are expected to interact with anionic species in solution, a phenomenon which was thoroughly investigated in literature (Jenquin and McGinity, 1994; Omari, 1995; Khalil and Sallam, 1999; Aceves et al., 2000).

Bodmeier et al. (1996) reported about pH-dependent drug release from beads coated with ERL and ERS aqueous dispersion. The release was attributed to ion-exchange ability (determined by selectivity coefficient) of chloride counterions of QAGs by buffer anions, and not to pH value per se.

Sun et al. (2001) investigated the pH-dependent swelling of ERL/ERS combination films upon interaction with ionic drugs a phenomenon which also determines the drug permeation through the membrane.

In a series of reports, Narisawa et al. (1994, 1995, 1996, 1997) studied the effect of incorporation of organic acids (succinic acid) along with the drug in the core of beads which then coated with ERS. The system was referred to as sigmoidal release system (SRS), due to the release profile shape, resulted from prompt increase in permeability of the film coat upon interaction with the organic acid in dissolution medium.

The effect of interaction of active or inactive ingredients with ERL and ERS on the mechanical properties of the films prepared from these polymers has been studied (Wu and McGinity, 1999; Zelko et al., 2002; Zhu et al., 2002). Among the additives that affecting mechanical properties of the film coating are plasticizers which also enhance film formation by decreasing T_g (and MFT) (Lehman, 1997; Zhu et al., 2002). However, active ingredients per se may play rule in this regard as indicated by Wu and McGinity (1999).

In this study, interaction of lactic acid (LA) with ERL and ERS in aqueous dispersion forms was investigated. The interaction was characterized in the polymer free films (with or without LA) using methods such as FTIR spectroscopy, DSC and NMR spectroscopy. The effect of such interaction on permeation of a model drug (paracetamol) and mechanical properties was assessed. The suitability of the new film for tablet coating was also investigated.

2. Materials and methods

2.1. Materials

Eudragit RL-100, Eudragit RS-100 and triethyl citrate (TEC) (Citroflex®) were purchased from Rohm Pharm (Darmstadt, Germany); Paracetamol, micronized powder (Mallinckrodt chemicals, UK); Lactic acid (E. Merck, Germany); HPMC (Methocel® E5 and E15, Colorcon, UK); Colloidal silicon dioxide (Aerosil® A-200, Degussa, Belgium); Magnesium stearate (Stippil Chim., Malaysia); Maize starch (Rocket, France); PVP (Plasdon® K25, Basf, Germany); Talc (Merk, Germany). Other reagents and solvents were of pharmaceutical grade.

2.2. Preparation of polymer free films

For the preparation of free films of either ERL or ERS, the granules of ERL-100 or ERS-100 were first dispersed in hot water (>80 °C) with high shear stirring (IKA-Labortechnik, GmbH & Co., KG), according to a method reported by Lehman (1986, 1997). In order to ensure sufficient time for plasticization of the polymers, the aqueous dispersion of either ERL (ERL–ADF) or ERS (ERS–ADF) was mixed with TEC (20% of the polymer weight) using magnetic stirrer for at least 1 h. For films containing LA (ERL–LA–ADF, ERS–LA–ADF), the amount of the acid was calculated depending on the alkali values of each polymer (Holgado et al., 1995; Rohm Pharm Info Sheets, 2002), added to the flask (containing polymer and TEC) and mixed, using the same magnetic stirrer, for up to 4 h. The mixture then was caste on a precisely leveled 15 cm × 15 cm Teflon® plate. After water evaporation and film formation the plates (including the films) were cured in an oven at 60 °C for 24 h. Films then were peeled off carefully, examined physically for transparency, cracks or air bubbles, wrapped in double plastic bags and kept for further investigations.

2.3. Differential scanning calorimetry (DSC) analysis

Samples (5 mg) of the free films were precisely weighed in aluminum pan and examined in DSC analyzer (Rheometric Scientific, USA) calibrated with indium. DSC thermograms were recorded under ni-

trogen flow rate of 20ml per minute and heating rate of 20 °C per minute between the temperature range of −20 and 60 °C. Tests were done in duplicates.

2.4. NMR spectroscopy

Film samples were dissolved in a suitable volume of deuterated chloroform in a sample tube. Proton (^{1}H) NMR spectra of the films were recorded using NMR spectrometer (Varian Mercury, USA) operated at 300 MHz with TMS as internal standard.

2.5. Mechanical analysis

This test was carried out with reference to ASTM specifications (ASTM, 1995). Films were cut, using a standard template, into dumbbell-shaped strips. At least five samples were prepared of each film, inspected carefully for any defects, cracks or air bubbles, and any sample containing any of these defects, was discarded. Thickness of film strips was measured, using digital micrometer (Mitutoyo, CD-8, Japan), from a number of places to ensure uniformity. Each strip then was fixed into the flat faced grips of the testing machine (Testometric AXM-350-10, UK) which was operated at constant rate of 10 mm/min. Tensile strength at break, elongation at break and elastic modulus were recorded. Mean values of at least three readings were calculated.

2.6. Permeation tests

The permeability of free films to the model drug (paracetamol) was tested in a paddle dissolution apparatus (Pharmatest PTWS30, Huinburg, Germany) with modifications especially made for this experiment. Film specimen essentially of good thickness homogeneity (200 μm ± 20), was cut and sandwiched in between two pieces of metal screen as a support and attached to the donor cell (2 cm in diameter cylindrical tube) as a part of its punctured cap. The donor cell then was hanged up-side down in the dissolution vessel immersed in the medium. The receptor media was gradient pH-profile corresponding to pH 1.2 (0.1N HCl), pH 5.4 and 6.8 (phosphate buffer) at 37 °C and a paddle rate of 100 rpm. Five milliliter samples were withdrawn, replaced immediately with fresh medium and analyzed spectrophotometrically (Beckman DU-7, USA) at 244 nm. Four replicates of each film were tested and the mean value was calculated.

2.7. Preparation and coating of paracetamol tablets

Tablets were prepared by granulating a certain quantity of paracetamol micronized powder with suitable weight of maize starch in a rotary pan mixer (Erweka, GmbH, Germany) using PVP (10% aqueous solution) as a binder. Granules were dried in fluid bed dryer (Aeromatic AG, Switzerland), passed in between 0.1 and 1 mm sieves, lubricated with 0.5% magnesium stearate and 0.2% Aerosil and compressed into tablets using single-punch tablet machine (Erweka, GmbH, Germany). The average weight of tablets was 570 ± 20 mg containing 500 mg paracetamol. Hardness, friability, weight variation and dimension variation tests were all carried out for the prepared tablets according to APM Co. in house and pharmacopeal (USP XXIV, 2000) specifications.

Film coating of tablets was performed in fluid bed coating machine (Aeromatic AG, Model STREA 1, Switzerland) using bottom spray (Wurster) mode. Tablets (150 g about 300 tablets) were first coated with HPMC (Methocel E5 + E15 in 2:3 ratio) solution (6%), as a subcoat, to a coat-to-core ratio (CCR) of 2%. Tablets then were coated with films of ERL, ERS or their lactate derivatives under the conditions mentioned in Table 1. ERL and ERS films (with or without LA) were applied in CCR of 5 and 1%, respectively. Upon termination of the coating process, tablets were further cured in an oven at 40 °C for 24 h and kept in double plastic bags at room conditions until used.

Table 1
Coating formula and conditions used in tablet coating process

Coating formula	
ERL or ERS (as AD)	25 g (represents 5 g dry polymer)
TEC	1 g (20% of dry polymer weight)
Talc	2.5 g (50% of dry polymer weight)
Water	50 g (for dilution)
Coating conditions	
Nozzle diameter	1 mm
Inlet temperature	50–60 °C
Outlet temperature	40–50 °C
Spray rate	1–3 ml/min
Atomizing air pressure	2 bars
Fluidizing air flow	10–20 m^3/h

LA was added in 1:1 ratio (acid:polymer) as indicated in the text.

2.8. Dissolution of film coated tablets

Drug release from film coated tablets was conducted in 1000 ml of gradient pH-profile dissolution media corresponding to pH 1.2 (0.1N HCl), pH 5.4 and 6.8 (phosphate buffer) using USP paddle method (Pharma Test, Huinberg, Germany), operated at 100 rpm and 37 °C. The change in pH was done in situ by addition of tribasic sodium phosphate salt directly to the medium (Lehman, 2001). Five-milliliter samples were withdrawn and replaced with fresh medium using autosampler (Hanson Research, USA) at predetermined intervals up to 21 h. Samples were then analyzed spectrophotometrically (Beckman DU-7, USA) at 244 nm. Average of six replicates was calculated.

2.9. Accelerated stability study of film coated tablets

An accelerated stability study was carried out by packaging the tablets in PVC blisters and sealed with aluminum foil using a direct heat sealing machine (TEW Electronic Heating Equipment Co., Ltd). Blistered tablets were stored at three different conditions, namely: RT, 40 °C + 75% RH and 50 °C in separate ovens. At the end of the studying period (3 months), tablets were inspected for any physical changes or defects and tested for drug release using the same dissolution apparatus and method mentioned previously. Results were compared to those at zero time.

3. Results and discussion

3.1. Characterization of interaction of LA with ERL or ERS

The basic hypothesis of this study was that the positively charged QAGs of ERL or ERS in aqueous medium are ionizable and able to interact electrostatically with anionic species in the solution (Jenquin and McGinity, 1994; Narisawa et al., 1996). LA is a water soluble carboxylic acid and is expected to undergo such interaction with these polymers. To give enough time for LA molecules to diffuse into polymer dispersion particles, equilibration was continued for several hours according to what has been reported about plasticization time (Lippold et al., 1989; Bodmeier and Paratakul, 1997; Wesseling and Bodmeier, 2001). Also for proper optimization of polymer free films, curing at 60 °C for 24 h was carried out after film formation, in order to allow for complete coalescence (Rohm Pharm Info Sheets, 2002).

The interaction of LA with ERL or ERS was studied on free films using three characterizing techniques: FTIR spectroscopy, thermal analysis (DSC) and NMR spectroscopy. Regarding FTIR spectroscopy and due to the ionic nature of the QAGs, no clear evidence has been obtained from spectra of free films (Silverstein and Webster, 1997).

DSC is considered a fast and valuable method of evaluation for interaction phenomena in which evidence can be derived from appearance, shift or disappearance of peak or variation in enthalpy ΔH (Botha and Lotter, 1990). However, evaluation is only qualitative, that is, it indicates the presence or absence of interaction. Figs. 1 and 2 show DSC thermograms of ERL and ERS films either alone or with LA. From these patterns T_g of the films were calculated as the half of ΔH of each transition curve as reported by Okhamafe and York (1987). Table 2 illustrates T_g values of the tested films and also ΔT_g values which represent the change induced by LA to the original polymer film (i.e. the difference between T_g of the film with LA and T_g of that without). LA decreased T_g of both ERL and ERS films with a higher change in ERL indicating a higher degree of interaction than in ERS. This could be explained by the relative hydrophilicity of the polymers where ERL is considered more hydrophilic, due to higher content of QAGs, and expected to interact with LA to a greater extent.

DSC may also show other events such as those in ERL–LA–ADF thermogram (Fig. 1), where it seems that two transitions occurred. The first transition appeared as a shoulder and could be attributed to the onset of backbone mobility of the plasticized polymer. The second transition which appeared as a broad endothermic peak could be due to intermolecular bond-

Table 2
Glass transition temperatures of aqueous dispersion films of ERL or ERS with or without LA

Films	T_g (°C)	ΔT_g (°C)
ERL–ADF	11.3	
ERL–LA–ADF	6.5	−4.8
ERS–ADF	9.8	
ERS–LA–ADF	9.5	−0.3

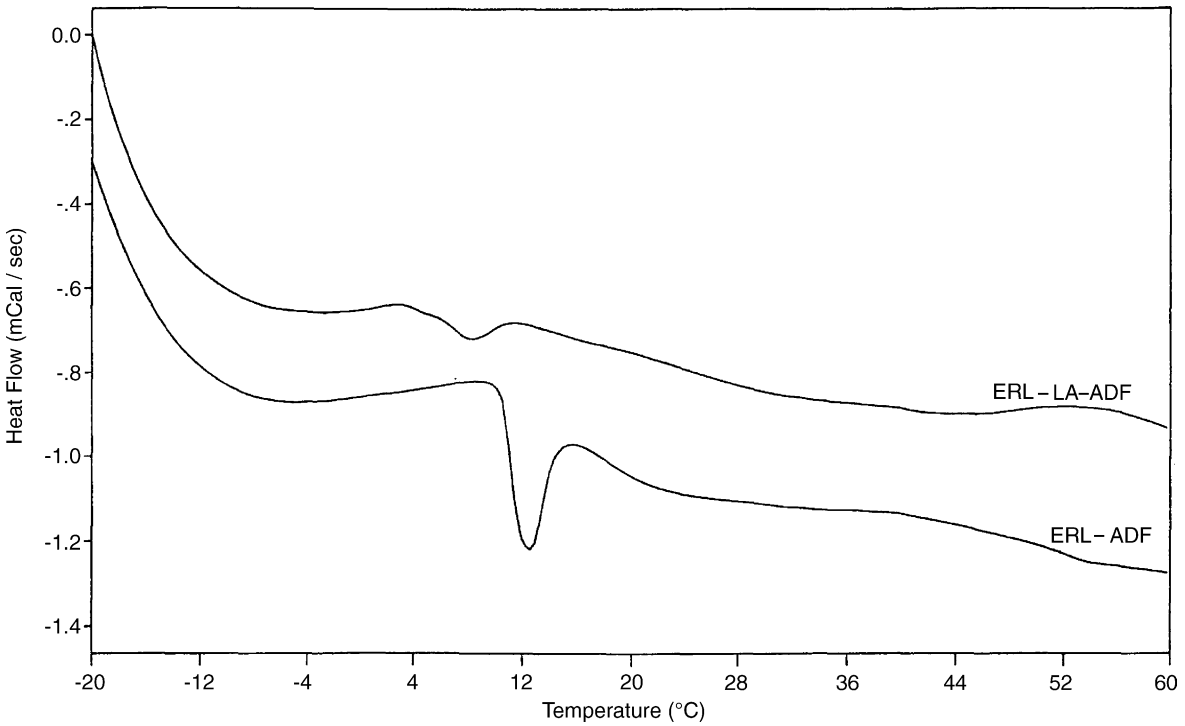


Fig. 1. DSC thermograms of ERL–ADF and ERL–LA–ADF (ordinate is not to scale).

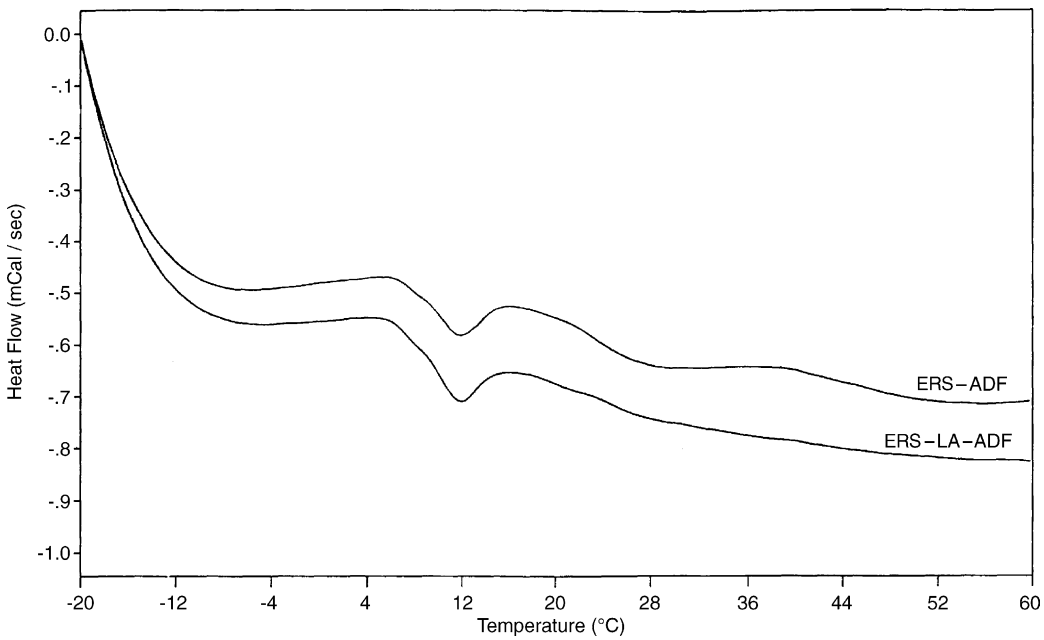


Fig. 2. DSC thermograms of ERS–ADF and ERS–LA–ADF (ordinate is not to scale).

ing associated with the carboxylic groups of LA. Furthermore, the large sharp enthalpy relaxation peak of ERL–ADF (Fig. 1) could be due to the higher mobility of the polymer backbone of ERL after plasticization with TEC, the property which was lost after the interaction with LA.

A stronger support to the above mentioned hypothesis was from NMR spectroscopy. Protons of trimethylamines in QAGs, typically resonate in the range of 3–3.5 ppm (Hanna and Lau-cam, 1985; Silverstein and Webster, 1997). Fig. 3 shows NMR spectrum of ERL–ADF and ERS–ADF. In ERL–ADF spectrum, the peak of concern appeared at 3.408 ppm while in ERS–ADF spectrum this peak did not appear clearly. This is explainable by the fact that QAGs are lower in ERS and could not be detected by the spectrometer. In ERL–LA–ADF spectrum (Fig. 4), the peak appeared at 3.513 ppm which means that a shift of 0.105 ppm has happened. More over, in ERS–LA–ADF (Fig. 4) this peak reappeared at 3.508 ppm.

Interaction of LA-carboxylate anion with positively charged QAGs of the polymers lead to deshielding of protons in trimethylamine groups. Furthermore, the reappearance of the peak in ERS spectrum upon interaction with LA supports this explanation. This could be attributed to LA as a chiral compound, which may induce chirality to the binding moiety, leading to conformational changes and hence allow its detection more clearly (Guther, 1987).

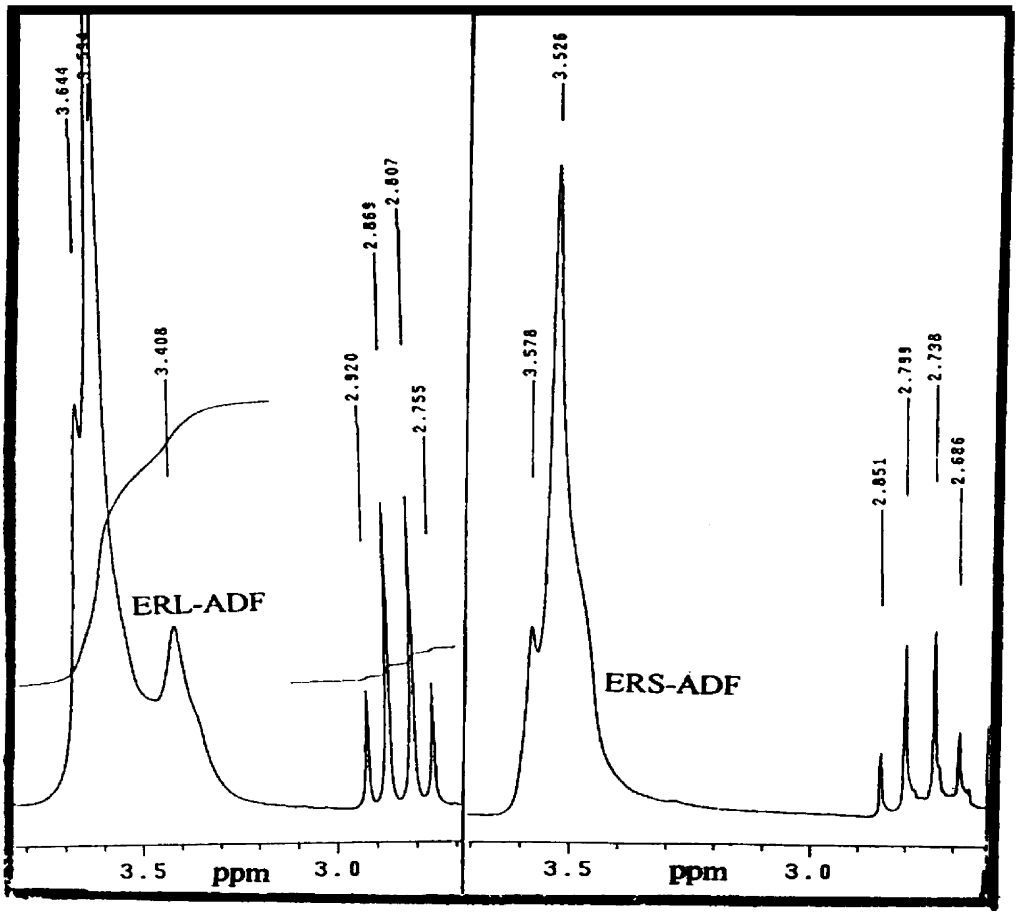


Fig. 3. NMR spectra of ERL–ADF and ERS–ADL.

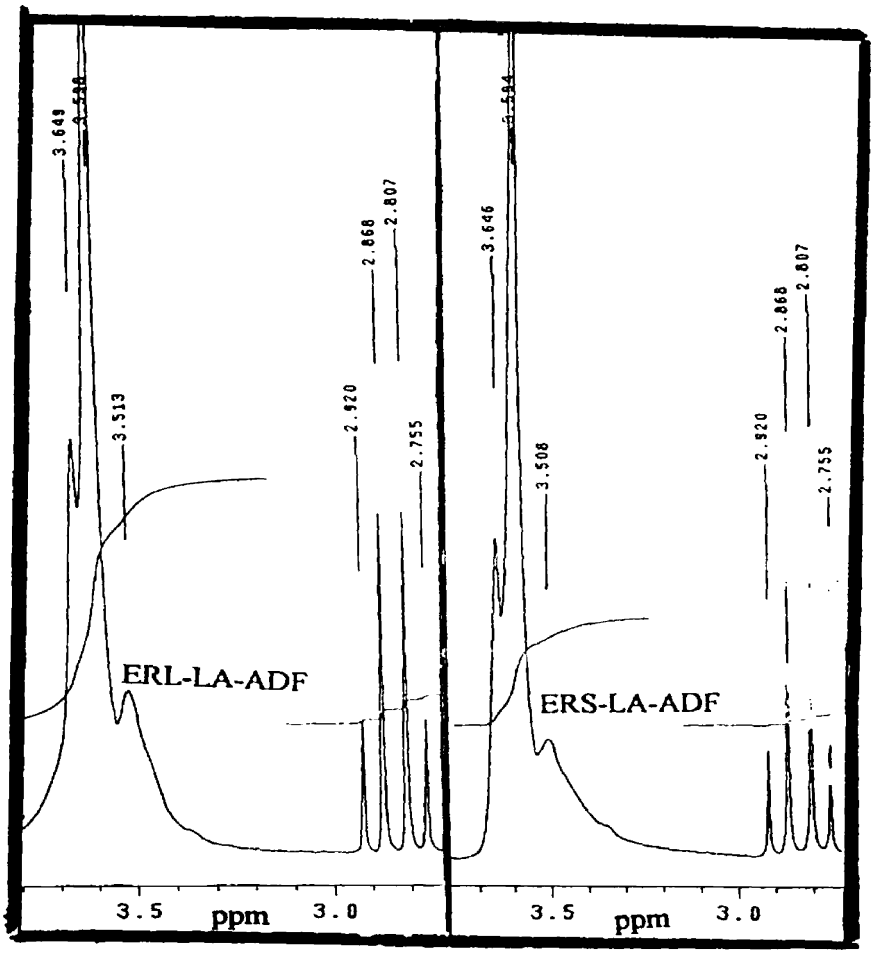
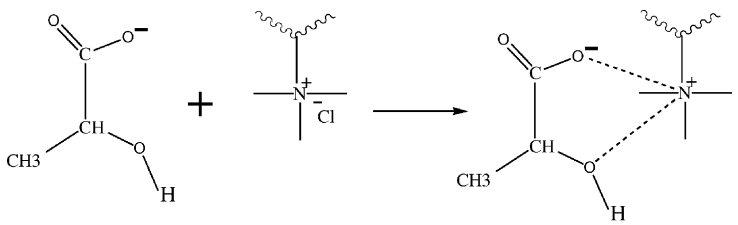


Fig. 4. NMR spectra of ERL–LA–ADF and ERS–LA–ADF.

Other possible explanation is related to the mechanism of interaction of the acid to the polymer. It was supposed that LA with its two functional groups (carboxyl and hydroxyl) can form five membered ring with one of the QAGs as follows:

This complex was thought to be stable by being in planar position. Again this type of interaction might induce change in the electron environment of hydrogen atoms rendering them more detectable by the spectrometer.



LA ERS in teraction complex

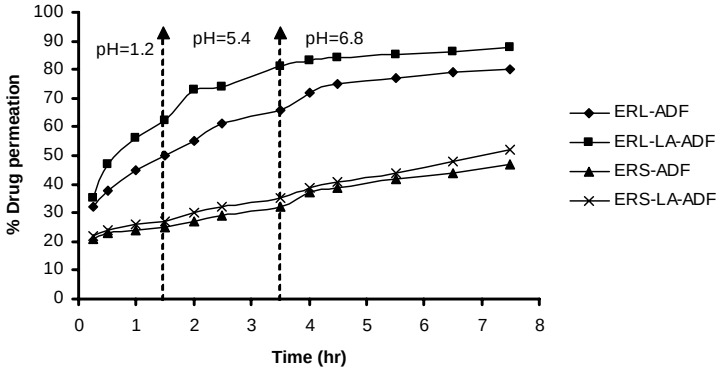


Fig. 5. Paracetamol permeation through free films of ERL and ERS or their LA derivatives in simulated GI media.

3.2. Permeation testing

In controlled drug delivery using film coating, one of the basic functions of the film coat is to control the transport (permeation) of molecules into or out of the dosage form. This process is controlled by diffusion (Okhamafe and York, 1987). In this study, free films of ERL or ERS and their LA-derivatives were tested for permeability using paracetamol as a model drug. This drug is selected due to its somewhat neutral chemical nature and is expected to possess a minimum, if any, interaction with the polymers. Fig. 5 shows the permeation of paracetamol through the four different films investigated here. An increase in permeability due to LA interaction was observed in both polymer films which may be explained by that LA as a hydrophilic molecule, may act as a pore former in aqueous media. However, the effect was again, clearly obvious in ERL but not in ERS films, which is in agreement with the results of DSC and NMR above.

3.3. Mechanical analysis

An ideal film coat with respect to retaining its physical integrity should be hard and tough (Aulton, 1982). This could be determined by assessment of parameters such as tensile strength (σ), strain or elongation (ε) and elastic (Young's) modulus (E) (Aulton, 1982; Okhamafe and York, 1983). The desired hard and tough film should have higher tensile strength, larger elongation (strain) before break and higher elastic modulus (Aulton, 1982).

In this study, the assessment of mechanical properties of films of ERL or ERS prepared with or without LA, was carried out according to ASTM specifications (ASTM, 1995). Results are illustrated in Table 3. From this table, it is apparent that LA had induced changes in the mechanical parameters of ERL and ERS films. However, results were not conclusive: in ERL there was a decrease in two parameters (σ and E) and an increase in the third (ε), while in ERS an increase in all parameters was shown.

For a further evaluation of mechanical properties, other relationships, derived from the above mentioned parameters, were proposed (Rowe, 1981, 1983; Okhamafe and York, 1985). A review of the different formulae used in mechanical evaluation of free films was reported by Okhamafe and York (1985) who decided that the individual parameters (σ, E and ε) are of little practical value as a guide to the actual

Table 3
Mechanical parameters of different aqueous dispersion films of ERL and ERS before and after interaction with LA

Films	Tensile strength (σ) (N/m^2) $\times$ 10^4	Elastic modulus (E) (N/m^2) $\times$ 10^4	Strain (ε) (%)
ERL–ADF	1.67 $\pm$ 0.250	0.610	272 $\pm$ 30
ERL–LA–ADF	1.06 $\pm$ 0.015	0.180	515 $\pm$ 50
ERS–ADF	0.51 $\pm$ 0.070	0.180	455 $\pm$ 61
ERS–LA–ADF	1.11 $\pm$ 0.300	0.330	485 $\pm$ 30

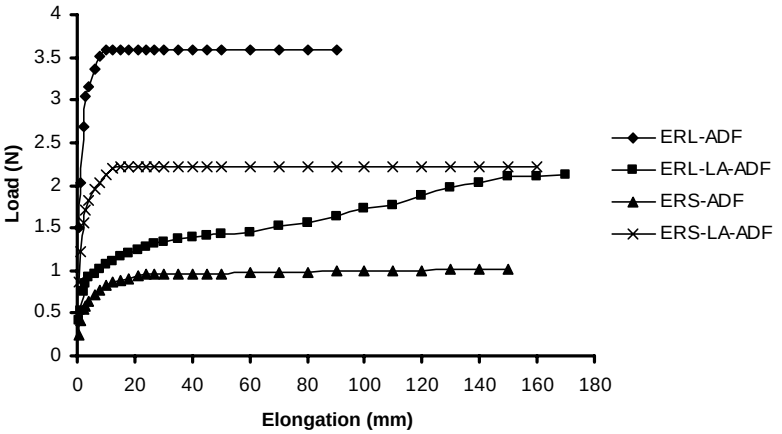


Fig. 6. Mechanical behavior under stress of films of ERL and ERS before and after interaction with LA.

performance of film coatings. They proposed many relationships, three of which were selected to be applied in this study. The first was tensile strength to modulus ratio (σ/E) which serves as a measure of the level of internal stress in the film. The second was relative surface energy as a measure of the resistance of the film to the initiation of the fracture process. The third was toughness index, representing the energy absorbed per unit volume of film under stress. This index is provided by measuring the area under the stress–strain curve where the curve is approximated as quadratic parabola (in this study) (see Fig. 6). The calculations of these derived parameters using data from Table 3 were illustrated in Table 4.

It is evident from Table 4 that LA interaction with the polymers increased all the parameters. These results suggest that such an interaction lead to an appreciable enhancement of the film resistance to mechanical stress. This could be explained as follows: the forces responsible for the mechanical strength of films are the secondary valence forces between adjacent polymer chains rather than the primary forces joining the backbone atoms of single chains (Schott, 1993). It seems that LA, due to its hydrophilic chemical nature, enhance formation of the secondary valence bonds and hence mechanical strength of the film.

3.4. Evaluation of film coated tablets

Tablets containing 500 mg paracetamol were prepared and coated firstly with HPMC aqueous solution (Methocel E5 and E15 in 2:3 ratio) as a subcoat. This step may have advantages such as rounding the tablet edges so better coat uniformity is obtained and that the subcoat acts as an isolating barrier against migration of core constituents to the film (Seitz et al., 1986). HPMC per se has the advantages of being readily dissolved in water and that adhesion of Eudragit polymers to it was reported to be better than to other materials (Cole et al., 2002; Pharma polymers News, 2001).

Tablets then were coated with each of the four different films of ERL and ERS investigated in this work. Talc was added as antitack agent in 50% (w/w) of the dry polymer weight which is the minimum quantity

Table 4
Derived mechanical parameters calculated using data from Table 3 according to mathematical relationships used by Okhamafe and York, 1985

Films	Tensile:modulus ratio (σ/E)	Relative surface energy ($\sigma^2/2E$) (πCN/m^2) $\times$ 10^4	Toughness index ($2/3\sigma\varepsilon$) (N/m^2 $\times$ 10^2)
ERL–ADF	2.7	2.3	3.0
ERL–LA–ADF	5.9	3.1	3.7
ERS–ADF	2.8	0.7	1.5
ERS–LA–ADF	3.3	1.8	3.5

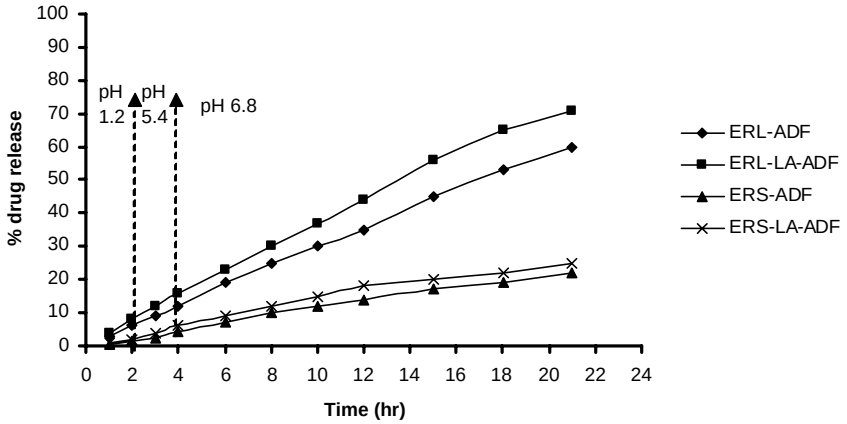


Fig. 7. Release of paracetamol from tablets coated with films of ERL and ERS or their LA derivatives in GI simulated dissolution media.

involved so that a successful coating process with minimum stickiness was obtained. Even though in some other investigations (Maejima and McGinity, 2001) up to 200% talc was used in coating pellets with ERL/ERS 30D mixture, the authors reported a delay in dissolution rate due to this quantity. The effect of such insoluble additives on film coating properties was recently reviewed (Felton and McGinity, 2002).

Film coated tablets were inspected physically for any coating defect and further cured at 40 °C for 24 h in an oven. Dissolution of these tablets was carried out in simulated GI media, as for free film above, to study drug release behavior. Fig. 7 shows release of paracetamol from tablets coated with ERL–ADF and ERL–LA–ADF in coat-to-core ratio of 5% and ERS–ADF and ERS–LA–ADF in CCR of 1%. An increase in release rate and extent was observed in films containing LA in both polymers, and again a higher influence was with ERL films. This result was in agreement with those obtained for free films above.

Release in ERS films was very slow even that film thickness of 1% only was applied. This was due to the effect of the original polymer per se which possesses lower permeability as indicated before. Attempts to reduce thickness to less than 1% were not successful because incomplete film was obtained. With ERL up to 95% release was obtained by decreasing film thickness to CCR of 1.5% (data not shown). Another possible factor for this low permeability, especially in ERS, is the low relative surface area of tablets available for diffusion, which requires more investigation.

The kinetics of drug release was determined with respect to zero and first order release models. Correlation coefficients were illustrated in Table 5. From Table 5, it seems that zero order release behavior was predominant, especially in ERL films; however, first order fitness is also acceptable indicating the importance of drug load effect on release behavior.

Stability of film coating was evaluated by conducting an accelerated stability study on film coated tablets (only those coated with ERL films) under different storage conditions: RT (25 °C), 40 °C + 75% RH and 50 °C. At the end of study period, tablets were sampled out, inspected physically for any film defects or appearance change and tested for their drug release using the same dissolution method as mentioned above. No physical change was observed in any of the tested samples under all conditions. Figs. 8 and 9 show results of dissolution tests of these tablets after stability study along with that obtained at zero time. No significant change in release profile was observed. This

Table 5
Correlation coefficient values of drug release kinetics of tablets coated with aqueous dispersion films of ERL or ERS with or without LA according to zero and first order release models

Films	Zero order model	First order model
ERL–ADF	0.999	0.996
ERL–LA–ADF	0.998	0.990
ERS–ADF	0.994	0.990
ERS–LA–ADF	0.987	0.992

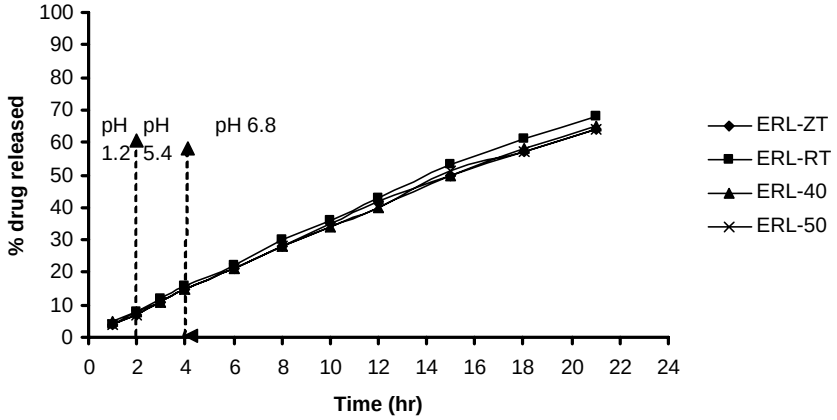


Fig. 8. Release of paracetamol from tablets coated with ERL–ADF after aging at RT, 40 °C + 75% RH and 50 °C compared with results at zero time (ZT).

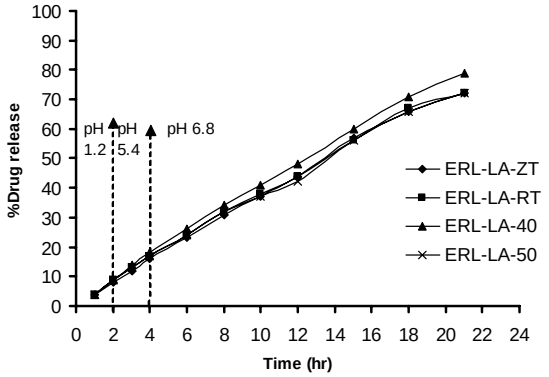


Fig. 9. Release of paracetamol from tablets coated with ERL–LA–ADF after aging at RT, 40 °C + 75% RH and 50 °C compared with results at zero time (ZT).

result, supported by that of physical inspection, suggesting good film coat stability.

4. Conclusion

Ammoniomethacrylate copolymers, Eudragit RL an RS, are mainly used for sustained release preparations as film coat or matrix formulation. The behavior of films of these two polymers was modified by interaction with LA. The interaction was characterized by DSC and NMR spectroscopy. An ionic electrostatic interaction mechanism between the acid and the polymers was proposed. The effect of this interaction on mechanical and permeability properties of polymer free films was evaluated using paracetamol as a model drug. LA enhanced the mechanical resistance of films of both polymers. Paracetamol tablets coated with the modified film showed an increase in release rate and extent, with more effect in ERL films. Also film coated tablets showed good stability upon aging under different storage conditions.

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References

Aceves, J.M., Cruz, R., Hernander, C.E., 2000. Preparation and characterization of furosemide-Eudragit controlled release system. Int. J. Pharm. 195, 45–53.

American Society for Testing and Materials (ASTM), 1995. American National Standard Institute, New York, Designations D882-95a and D6638-95.

Aulton, M.E., 1982. Assessment of the mechanical properties of film coating materials. Int. J. Pharm. Tech. Prod. Mfr. 3, 9–16.

Bodmeier, R., Paratakul, O., 1997. Plasticizer uptake by aqueous colloidal polymer dispersion used for the coating of solid dosage forms. Int. J. Pharm. 152, 17–26.

Bodmeier, R., Guo, X., Sarabia, R.E., Skultety, P.F., 1996. The influence of buffer species on Deltiazem HCl release from beads coated with the aqueous cationic polymer dispersions, Eudragit RS, RL 30D. Pharm. Res. 13, 52–56.

Botha, S.A., Lotter, A.P., 1990. Compatibility study between atenolol and tablet excipient using differential scanning calorimetry. Drug Dev. Ind. Pharm. 16, 1945–1954.

Cole, E.T., Scott, R.A., Connor, A.L., Wilding, I.R., Petereit, H.U., Schminke, C., Becket, T., Cade, D., 2002. Enteric coated HPMC capsules designed to achieve intestinal targeting. Int. J. Pharm. 231, 83–95.

Felton, L.A., McGinity, J.W., 2002. Influence of excipients on film coating systems. Drug Dev. Ind. Pharm. 28, 225–243.

Guther, H., 1987. NMR Spectroscopy. Wiley, New York, pp. 197–205.

Hanna, G.M., Lau-cam, C.A., 1985. A stability indicating proton NMR spectroscopic assay method for succinylcholine chloride injections. Anal. Let. 18, 2183–2194.

Hogan, J.E., 1982. Aqueous versus organic solvent film coating. Int. J. Pharm. Tech. Prod. Mfr. 3, 17–20.

Holgado, M.A., Arevalo, M.F., Fuentes, J.A., Caraballo, I., Llera, J.M., Rabasco, A.M., 1995. Physical characterization of carteolol:Eudragit L binding interaction. Int. J. Pharm. 114, 13–21.

Jenquin, M.R., McGinity, J.W., 1994. Characterization of acrylic resin matrix films and mechanisms of drug-polymer interaction. Int. J. Pharm. 101, 23–34.

Khalil, E., Sallam, A., 1999. Interaction of two diclofenac acid salts with copolymers of ammoniomethacrylate: effect of additives and release profile. Drug Dev. Ind. Pharm. 25, 419–427.

Kibbe, A.H., 2000. Handbook of Pharmaceutical Excipients, 3rd ed. AphA, Washington, pp. 401–406.

Lehman, K., 1986. Acrylic lattices from redispersible powders for peroral and transdermal drug formulations. Drug Dev. Ind. Pharm. 12, 265–287.

Lehman, K., 1997. In: McGinity, J.W. (Ed.), Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, 2nd ed. Marcel Dekker, New York, pp. 101–176.

Lehman, K., 2001. Practical Course in Film Coating of Pharmaceutical Dosage Forms with Eudragit. Pharma Polymer. Darmstadt, pp. 8–10, 144–147.

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

Maejima, T., McGinity, J.W., 2001. Influence of film additives on stabilizing drug release rates from pellets coated with acrylic polymers. Pharm Dev. Tech. 6, 211–221.

Narisawa, S., Nagata, M., Danyoshi, C., Yoshino, H., Murata, K., Hirakawa, Y., Noda, K., 1994. An organic acid-induced sigmoidal release system for oral controlled-release preparation. Pharm. Res. 11, 111–116.

Narisawa, S., Nagata, M., Hirakawa, Y., Ito, T., Yoshino, H., 1995. Drug release in gastrointestinal tract of beagle dogs from multiple unite type rate-controlled or time-controlled release preparations coated with insoluble polymer-based film. J. Cont. Rel. 33, 253–260.

Narisawa, S., Nagata, M., Hirakawa, Y., Kobayashi, M., Yoshino, H., 1996. An organic acid-induced sigmoidal release system for oral controlled-release preparation. 2. Permeability enhancement of Eudragit RS coating led by the physicochemical interactions with organic acid. J. Pharm. Sci. 85, 184–188.

Narisawa, S., Nagata, M., Hirakawa, Y., Kobayashi, M., Yoshino, H., 1997. An organic acid-induced sigmoidal release system for oral controlled-release preparation. III. Ellucidation of the anomalous drug release behavior through osmotic pumping mechanism. Int. J. Pharm. 148, 85–91.

Okhamafe, A.O., York, P., 1983. Analysis of the permeation and mechanical characteristics of some aqueous-based film coating systems. J. Pharm. Pharmacol. 35, 409–415.

Okhamafe, A.O., York, P., 1985. Stress crack resistance of some pigmented and unpigmented tablet film coating systems. J. Pharm. Pharmacol. 37, 449–454.

Okhamafe, A.O., York, P., 1987. Interaction phenomena in pharmaceutical film coatings and testing methods. Int. J. Pharm. 39, 1–21.

Omari, D.M. 1995. The Use of Drug-Excipient Interaction in the Design of Controlled Release Dosage Forms. MSc. Thesis. Jordan University of Science and Technology, Irbid, Jordan, pp. 65–85.

Pharma Polymers News, No 8. Rohm Pharma Polymers, pp. 1–2.

Radebaugh, G.W., 1993. Film Coatings and Film-Forming Materials: Evaluation. In: Swarbrick, J., Boylan, J.C. (Eds.), Encyclopedia of Pharmaceutical Technology, vol. 6. Marcel Dekker, New York, pp. 1–27.

Rohm Pharm Info Sheets, 2002. Rohm Pharm Polymer, GmbH, Darmstadt. Info sheets: O/E 2–4, 7.7/E 1–4, 7.9/E 1–4.

Rowe, R.C., 1981. The cracking of film coatings on film-coated tablets: a theoretical approach with practical implications. J. Pharm. Pharmacol. 33, 423–426.

Rowe, R.C., 1983. A reappraisal of the equations used to predict the internal stresses of film coatings applied to tablet substrates. J. Pharm. Pharmacol. 35, 112–113.

Schott, A., 1993. In: Martin, A., Bustamante, P., Chun, A.H.C. (Eds.), Physical Pharmacy: Physical Chemical Principles of Pharmaceutical Sciences, 4th ed. Lea & Febiger, Philadelphia, pp. 556–594.

Seitz, J.A., Mehta, S.P., Yeager, J.L., 1986. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), The Theory and Practice of Industrial Pharmacy, 3rd ed. Lea & Febiger, Philadelphia, pp. 346–373.

Silverstein, R.M., Webster, F.X., 1997. Spectroscopic Identification of Organic Compounds, 6th ed. Wiley, New York, pp. 200.

Sun, Y., Hsu, S., Lai, J., 2001. Transport properties of ionic drugs in ammoniomethacrylate copolymers membrane. Pharm. Res. 18, 304–310.

Wesseling, M., Bodmeier, R., 2001. Influence of plasticization time, curing conditions, storage time and core properties on drug release from Aquacoat-coated pellets. Pharm. Dev. Tech. 6, 325–331.

Wu, C., McGinity, J.W., 1999. Non-traditional plasticization of polymeric films. Int. J. Pharm. 177, 15–27.

Zelko, R., Orban, A., Suvegh, K., Riedl, Z., Racz, I., 2002. Effect of plasticizers on the dynamic surface tension of Eudragit systems. Int. J. Pharm. 244, 81–86.

Zhu, Y., Shah, N.H., Malick, A.W., Infeld, M.H., McGinity, J.W., 2002. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int. J. Pharm. 241, 301–310.