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Physico-chemical characterization of interactions between erythromycin and various film polymers

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Abstract

In this study the interactions between erythromycin and various polymers (Eudragit L100, shellac, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose acetate phthalate (HPMCP), and hydroxypropyl methylcellulose (HPMC)) were investigated. The polymer films containing drugs were prepared and characterized by the use of infrared spectroscopy, powder X-ray diffraction analysis, thermal analysis, thin layer chromatography, and nuclear magnetic resonance (NMR) spectroscopy. Preliminary studies of pure drug powders recrystallized in various organic solvent systems suggested a mixture of amorphous and crystalline forms whereas those recrystallized in water and organic solvent-water mixture led to the dihydrate form. Erythromycin in drug-polymer mixtures exhibited molecular dispersions in all six polymers studied. The amine salt interaction between the carboxyl group of the acid polymers and N-atom of erythromycin was indicated by the NMR technique. The solid solution of erythromycin in all polymer films studied was physically stable under stress conditions (8°C/3 days and 40°C/3 days for six cycles). © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Drug-polymer interactions; Erythromycin; Anionic polymers; Interaction characterization; Stability studies

1. Introduction

Various film polymers have been widely used to develop sustained release or site-specific release dosage forms of a drug by numerous approaches, which more or less consist of forming matrices with drug or coating of drug-containing core tablets or beads. The matrices may be in the form of tablets, granules, or beads prepared by granulating the drug-polymer blend with solvent(s), or dissolving a drug and polymer in a solvent or solvent mixture and evaporating out thereafter. Interactions between drug and polymers in such intimate contact could lead to improper release characteristics, plasma level fluctuations, and hence failure in desired pharmacological effects.

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In addition, many polymers have been extensively employed in enteric and non-enteric film coating of tablets, pellets, granules, or beads for different purposes. It has previously been suggested by several investigators (Aulton et al., 1983; Simpkin et al., 1983; Okhamafe and York, 1989) that dissolution of a small amount of excipient or drug (contained in a solid dosage form) in a film coating during a coating operation, and/or migration of the excipient/drug into the applied coating over a period of time following the coating application, could occur in practice. Dissolution is particularly likely if the drug or excipient is soluble in the solvent used for the preparation of the coating formulation. The mode of migration could be by drug/excipient dissolution in the residual solvent of the coating or in the moisture penetrating through the coating during storage under high humidity conditions. The undesired presence of a drug or an excipient in an applied film coating may substantially alter the end-use properties of the coating such as mechanical properties, adhesive strength, permeability, appearance, etc.

Physico-chemical characterizations of drug-polymer interactions have been carried out for ephedrine HCl-HPMC, ephedrine HCl-polyvinyl alcohol (Okhamafe and York, 1989), propanolol-Eudragit L (Lee et al., 1991), morphine-Eudragit L30D (Alvarez-Fuentes et al., 1994), verapamil HCl-Eudragit L (Goracinova et al., 1995), carteolol-Eudragit L30D (Holgado et al., 1995), and ketoprofen-HPMC (Mura et al., 1995). The drug-polymer interactions could be any type of chemical interactions caused by redox reaction, acid-base reaction, hydrolysis or the combination of these, and physical interactions caused by change in solubility, phase transition, polymorphic transition, adsorption, etc. It is of interest for this investigation to examine and study the possibility of any molecular interaction between acid polymers commonly used, i.e. Eudragit L100, shellac, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose acetate phthalate (HPMCP), and neutral hydroxypropyl methylcellulose (HPMC), with a basic drug, erythromycin, by employing differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), and nuclear magnetic resonance spectroscopy (NMR) techniques.

2. Materials and methods

2.1. Materials

Erythromycin used in this study was obtained from Hansa Vital, Germany. The six film-forming polymers employed throughout the study were Eudragit L100 (Rohm Chemische Fabrik, Germany), HPMCP (Syntapharm, Germany), CAP (Eastman Chemical Products, USA), shellac (Stroever Schellack 'SSB', Germany), PVAP (Colorcon, Germany), and HPMC (Methocel E5 Premium EP, Colorcon, Germany). Solvents used were isopropanol, acetone, ethanol, methylene chloride (E. Merck, Germany), methanol (J.T. Baker, USA), and dimethylsulfoxide (Aldrich, Germany).

2.2. Recrystallization of erythromycin in various solvent systems

The effects of various solvents on crystalline form of erythromycin were examined by dissolving drug in eight solvent systems, that is, isopropanol, acetone, water, methanol, ethanol, methylene chloride, 1:1-isopropanol:acetone (by volume) and 1:1:2-isopropanol:acetone:water (by volume). The drug solutions in petri dishes were recrystallized by evaporating all the solvents using vacuum oven at room temperature. Recrystallized samples were collected and kept in desiccator at room temperature and protected from light until use.

2.3. Preparation of the drug-polymer mixtures

The drug-polymer mixtures at 1:1 ratio (by weight) were prepared by dissolving erythromycin powder in 2% w/v polymeric solutions (Eudragit L100, shellac, PVAP, CAP, HPMCP in 1:1-isopropanol:acetone (by volume), and HPMC in 1:1:2-isopropanol:acetone:water (by volume)) with constant stirring until clear solutions were ob-

tained. The 30 ml of drug-polymeric solution was put onto a petri dish whose inner surface was covered with Scotch 3M film to allow better peeling off of the cast film after drying, and was placed in a vacuum oven at room temperature set at 200 mbar until the solvent was completely removed. Dried films were subsequently collected, kept in glass containers protected from light, and stored in a desiccator at room temperature until use.

2.4. Physico-chemical characterization of the drug-polymer mixtures

2.4.1. Fourier transform infrared spectroscopy (FTIR)

The KBr discs were prepared by triturating 1–2-mg samples with 300–400 mg of dried, finely powdered potassium bromide, and compressing into 13-mm discs at a pressure of 10 kN for 5 min. The discs were then mounted in FTIR case (FTIR-Spektrometer IFS 66/CS, Bruker-Franzen Analytik, Germany) and scanned from 4000 to 400 cm^{-1}. The measuring conditions were: resolution, 4.0; zero fitting, 2.0; sample scan, 32; acquisition, single sided.

2.4.2. Powder X-ray diffraction analysis (PXRD)

The drug-polymer mixture was put into a sample holder and placed into powder X-ray diffractometer (Stoe & CIE, Germany), the measuring unit of which worked with a rotating anode in transmission technique with the following specifications: Cu $K\alpha_1$ radiation, carbon monochromator, voltage 40 kV, current 200 mA, position scanning detector (PSD), scanning rate 10 s/2θ over a range of 5–50° 2θ.

2.4.3. Differential scanning calorimetry (DSC)

Samples of 10–12 mg were put into standard aluminum pans with covers and scanned using differential scanning calorimeter (DSC 7, Perkin-Elmer, USA) with scanning rates of 20°C/min for a temperature range of 35–250°C under nitrogen gas purge.

2.4.4. Thin layer chromatography (TLC)

Solutions of pure drug, pure polymer, and the drug-polymer mixture in suitable mobile phase (1:2:6:1-cyclohexane: n-butanol: methanol: acetic acid (by volume)) were spotted onto a 0.25-mm silica gel TLC plate with fluorescent indicator (Polygram SIL G/UV_{254}, Macherey-Nagel, Germany) and developed in the solvent chamber. The spots developed on the plates could be visualized by spraying with 2 N sulfuric acid and heated at 80°C for 5–10 min so that the brownish spots appeared.

2.4.5. Nuclear magnetic resonance spectroscopy (NMR)

The ^{1}H-NMR spectra of the samples were recorded using the NMR spectrometer (300 ARX, Bruker-Franzen Analytik, Germany) at 300 K employing dimethylsulfoxide (DMSO-d_6) as a solvent.

2.4.6. Stress test

All drug-polymer mixtures were stressed under six heat/cool cycles (40°C/3 days and 8°C/3 days) and then characterized by PXRD and DSC in order to examine for physico-chemical alterations.

3. Results and discussion

3.1. Effects of various solvent systems on recrystallization of erythromycin

The erythromycin original powder commercially received was in a dihydrate form which was subsequently stored at 110°C for 24 h to transform it into an anhydrous form. This was confirmed by the significant reduction in numerous sharp peaks along the angle of 5–30° 2θ in PXRD pattern of the latter as shown in Fig. 1 and in comparison with the previous report (Murthy et al., 1986). The effects of solvent types on PXRD patterns of recrystallized drug powder are explicitly evident in Fig. 1. Dissolving the drug in organic solvents such as methylene chloride or methanol and evaporating solvent out would lead to PXRD pattern which is difficult to interpret, that is, the baseline shows a halo form indicating

the partially amorphous state of erythromycin. This baseline becomes superimposed by some tiny peaks in the case of isopropanol, acetone, or mixture of isopropanol:acetone, which implies that a certain crystallinity exists. It may be concluded that recrystallization from organic solvents would lead to a mixture of amorphous and crystalline forms. By including water in the solvent the peaks become sharper and appear in the same positions as in the case of erythromycin dihydrate or anhydrous.

The FTIR spectra of erythromycin in various solvent systems are shown in Fig. 2, which reveal differences in three regions (3300–3700, 2900–3000, and 1600–1800 cm^{-1}) as marked by arrows. FTIR spectrum of erythromycin original powder contains a band with many shoulders (3300–3700 cm^{-1}) due to dihydrate form. The bands in this region of both original drug and drug powder after being heated exhibit a little broadening whereas those of drug powders recrystallized from all solvent systems used are extremely broad. This behavior may probably be explained on the basis of semi-crystalline form of drug after recrystallization from solvent systems (as evidenced by PXRD patterns) reflecting a variety in orientations of molecules. It is well known that the variety in orientations of molecules may give rise to the broadening in FTIR spectra. These results are in agreement with the former report (Murthy et al., 1986).

The small shoulder in the region of $\sim$2900–3000 cm^{-1} may be due to the effect of water presented in the molecules on alkane stretching. The difference in intensities of two peaks in the region between 1600 and 1800 cm^{-1} suggests the difference in orientation of carbonyl groups. The low-wavenumber band (representing the ketone carbonyl groups) of erythromycin original as well as that recrystallized from water very much dominates those of drug recrystallized in other solvents as well as being heated, while the high-wavenumber band (representing the lactone carbonyl groups) exerts an opposite effect.

The DSC curve obtained for erythromycin original shows two endothermic peaks at 93 and 199°C which are due to dehydration and melting, respectively, and an exothermic peak at 148°C

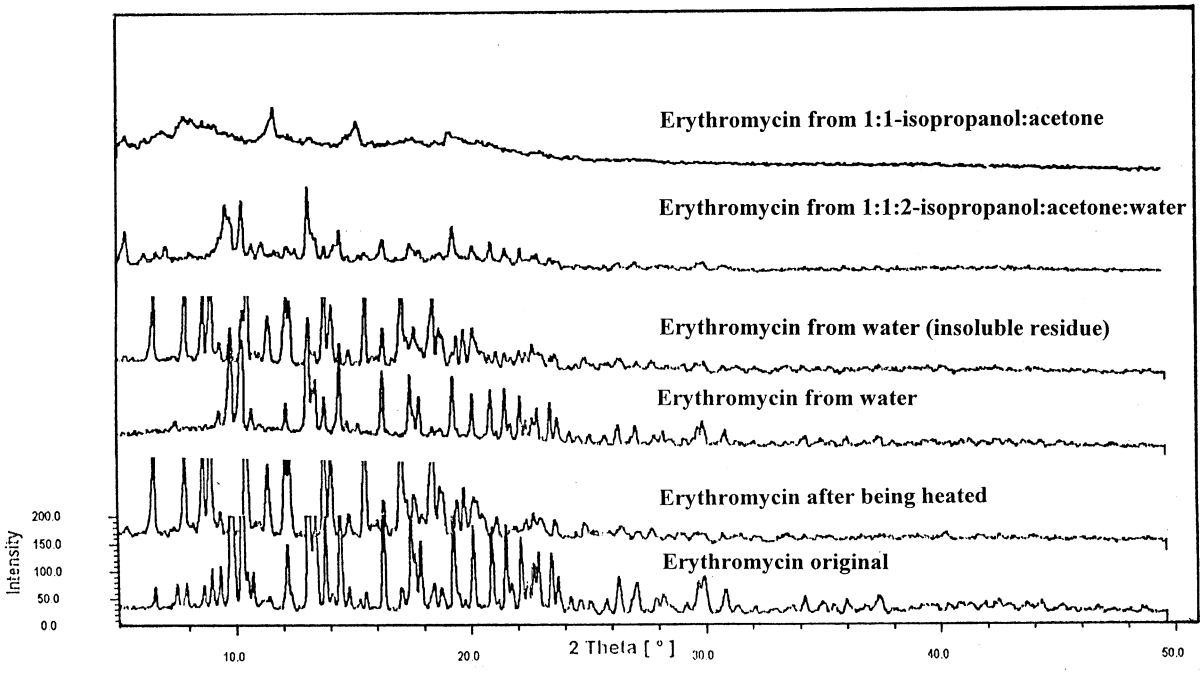

Fig. 1. PXRD patterns of erythromycin powders recrystallized from various solvent systems.

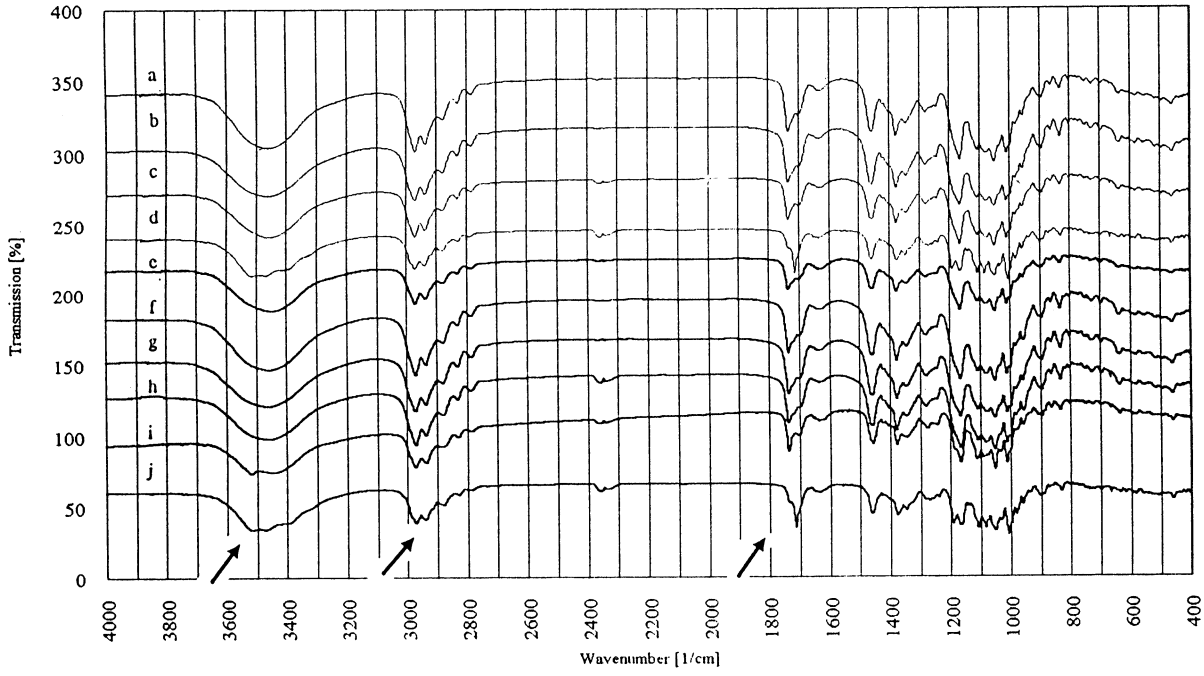

Fig. 2. FTIR spectra of erythromycin powders recrystallized from various solvent systems: a, erythromycin from methylene chloride; b, erythromycin from ethanol; c, erythromycin from methanol; d, erythromycin from water; e, erythromycin from acetone; f, erythromycin from isopropanol; g, erythromycin from 1:1:2-isopropanol:acetone:water; h, erythromycin from 1:1-isopropanol:acetone; i, erythromycin after being heated; and j, erythromycin original.

which is due to recrystallization after dehydration. The DSC process can be clearly demonstrated in the following sequence. Erythromycin original in dihydrate form loses water and becomes amorphous form at 50–115°C, which in turn recrystallizes into anhydrous crystalline form at 137–164°C. The crystalline form melts at 186–203°C into isotropic liquid and then decomposes above 205°C.

Furthermore, the DSC thermogram of erythromycin after being heated (an anhydrous form as indicated by above PXRD results) also shows a sharp endothermic peak at 200.9°C and onset at 196.5°C, which is comparable with the previous report (Murthy et al., 1986). In contrast, those recrystallized from various solvent systems show a broad endothermic peak in the range of 50–130°C without subsequent exothermic and endothermic peaks. This may probably be due to loss of weakly bound surface moisture from nearly amorphous-state samples without recrystallization after dehydration as does the original drug. The samples remain in an amorphous state until degradation occurs with no melting peak.

As a result, 1:1-isopropanol:acetone was subsequently employed as the solvent system in preparing drug-polymer mixtures for all polymers studied except HPMC whose solvent system used was 1:1:2-isopropanol:acetone:water.

3.2. Interaction studies of erythromycin-Eudragit L100 mixtures

The halo patterns of PXRD results (Fig. 3) as well as the DSC thermogram with disappeared melting peak of erythromycin-Eudragit L100 mixtures indicate the amorphous state of drug molecules dispersed in Eudragit L100 film. However, it is interesting to note that the FTIR spectrum of these mixtures in Fig. 4 shows a new band at $\sim 1516–1624\ cm^{-1}$ (marked by an arrow), which may be attributed to an amine salt

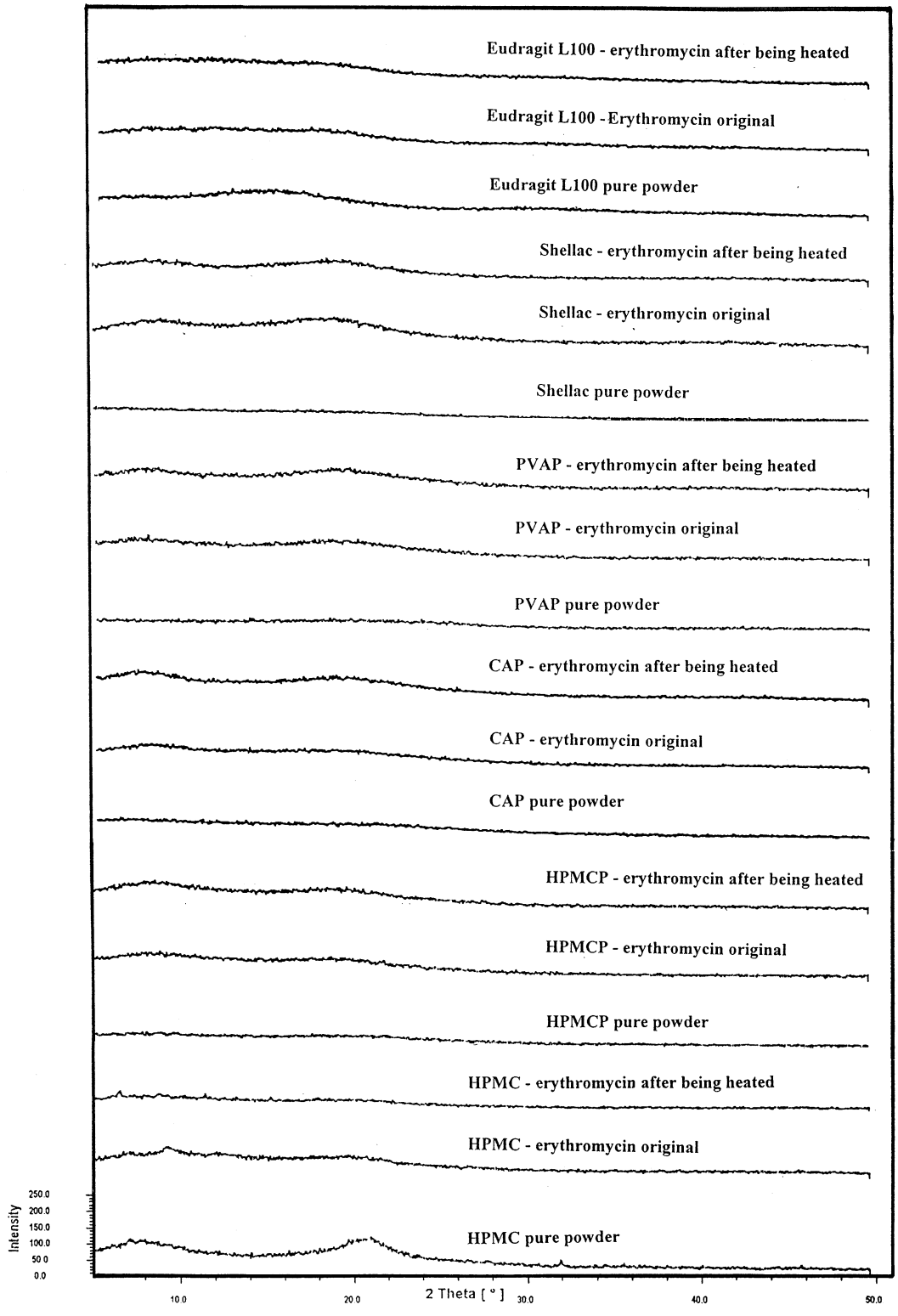

Fig. 3. PXRD patterns of erythromycin-polymer mixtures.

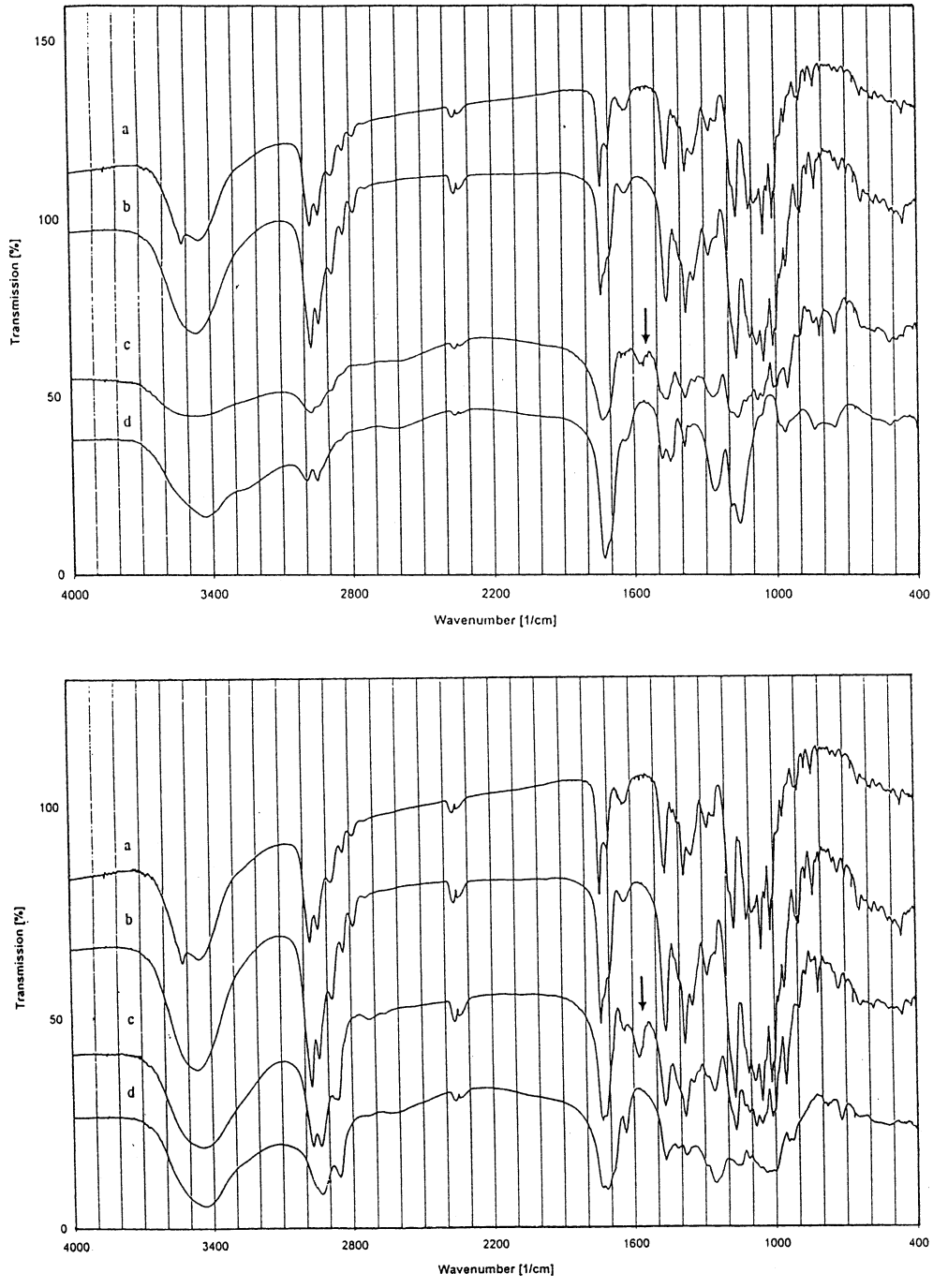

Fig. 4. FTIR spectra of erythromycin-Eudragit L100 mixture (top) and erythromycin-shellac mixture (bottom): a, erythromycin after being heated; b, erythromycin powder recrystallized from 1:1-isopropanol:acetone; c, erythromycin-polymer mixture; d, polymer pure powder.

formation. The carboxylic acid groups of Eudragit L100 could lead to protonation of amine group of erythromycin molecule. Neither new spots nor alterations in R_f value of TLC were however observed, indicating that no degradation of drug was taking place in the mixtures.

3.3. Interaction studies of erythromycin-shellac mixtures

The halo patterns of PXRD results (Fig. 3) as well as the DSC thermogram for erythromycin-shellac mixtures indicate the amorphous state of drug molecules dispersed in shellac film as in the case of Eudragit L100. The FTIR spectrum of this mixture in Fig. 4 shows a new band at a region of 1536–1648 cm^{-1} (marked by an arrow) which may be due to the already mentioned amine salt formation. This postulation is confirmed by the shifting in peak of ^1H NMR spectrum from at $\sim$2.23 ppm in pure erythromycin powder to a region of $\sim$2.35 ppm in erythromycin-shellac mixture as illustrated in Fig. 5. This peak shifting to the higher ppm value reflects the protonation of amine salt (Pretsch et al., 1990). The TLC however indicates no degradation of drug taking place.

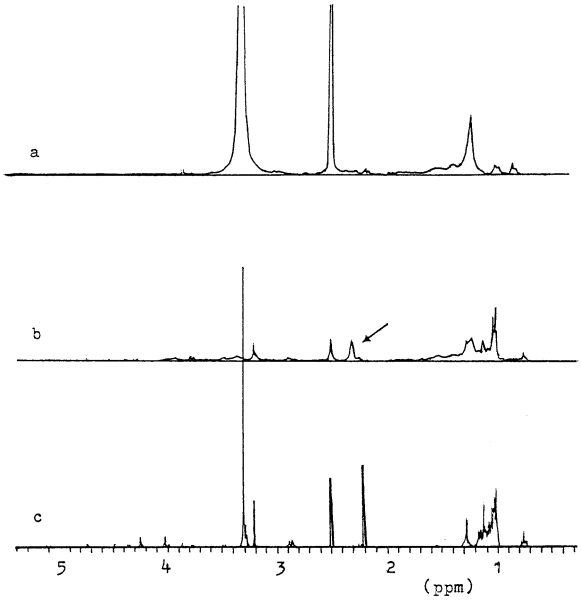

Fig. 5. ^1H-NMR spectra of erythromycin samples dissolved in DMSO: a, shellac pure powder; b, erythromycin-shellac mixture; c, erythromycin powder.

3.4. Interaction studies of erythromycin-PVAP, -CAP, and -HPMCP mixtures

All the mixtures containing PVAP, CAP, or HPMCP and erythromycin (dihydrate and anhydrous) show halo-shape baseline in PXRD as shown in Fig. 3, indicating the amorphous state of drug being dispersed in the films. Moreover, slight difference in FTIR bands for these drug-polymer mixtures could be detected in the region between 1500 and 1600 cm^{-1}, which may be attributed to the polymer chain, but not the protonation of the drug molecule as in the cases of Eudragit L100 and shellac.

3.5. Interaction studies of erythromycin-HPMC mixtures

Both erythromycin dihydrate and anhydrous are molecularly dispersed in HPMC as illustrated by the halo-shape baseline of PXRD patterns in Fig. 3. The FTIR spectrum of the mixture shows no new band, which absolutely differs from those mixtures of anionic polymers discussed above. The only possible interaction between erythromycin molecule and non-ionic HPMC polymer chain would probably be through hydrogen bondings, and protonation of N-group is not the case. The DSC curve obtained for erythromycin-HPMC mixture shows only one endothermic peak at 93.2°C, which is responsible for dehydration, without melting peak. It should be noted that erythromycin was found to be in the state of molecular dispersion in HPMC, and some degree of interactions between the drug molecule and polymer chain would therefore be anticipated.

3.6. Stability studies of erythromycin-polymer mixtures

Fig. 6 shows the PXRD results of erythromycin-polymer mixtures stored under stress

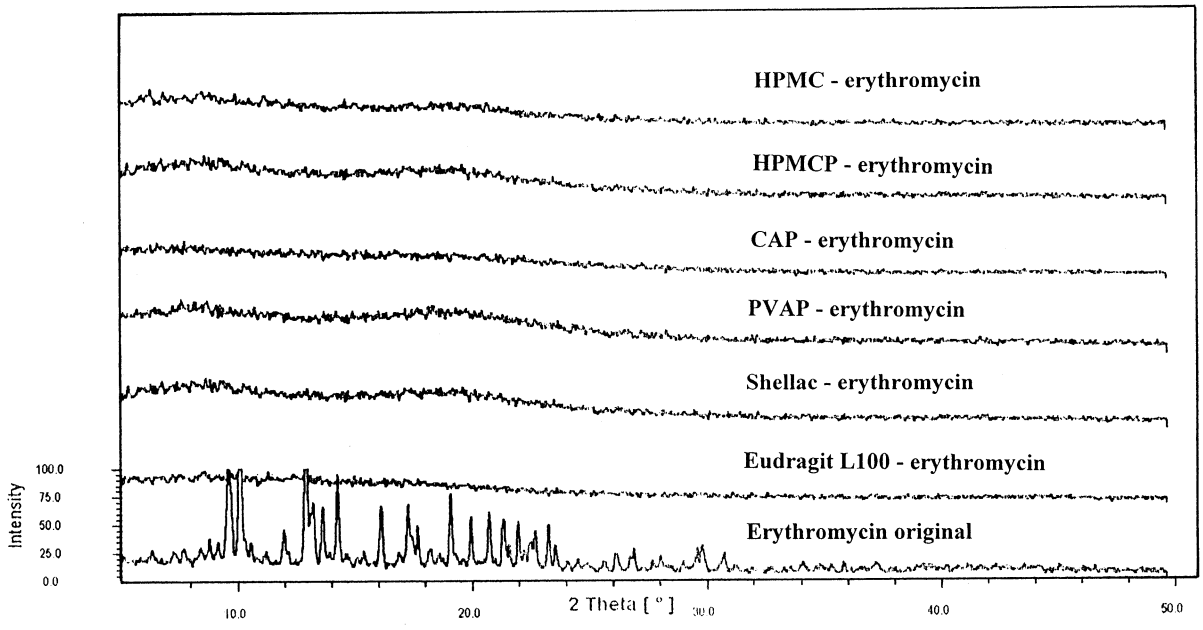

Fig. 6. PXRD patterns of erythromycin-polymer mixtures after stress test (8°C/ 3 days and 40°C/3 days) for 36 days.

conditions (8°C/3 days and 40°C/3 days) for 36 days. It was obviously found that the PXRD patterns of the mixtures showed all halo-form baseline with no alteration after stress test. The solid solution of erythromycin remained stable regardless of the nature of polymer matrices. Crystallization of the drug molecules could not be induced.

4. Conclusion

Erythromycin was found to be dispersed in the form of molecular dispersions in all six polymers studied (Eudragit L100, shellac, PVAP, CAP, HPMCP, and HPMC), which were physically stable under the stress test. The possible interaction between the drug and polymers, which could be characterized by FTIR and NMR spectroscopy, may be explained on the basis of protonation of amine group of erythromycin molecule by the carboxylic acid groups of polymers. There was however no evidence of drug decomposition in the polymer mixtures.

References

Alvarez-Fuentes, J., Fernandez-Arevalo, M., Holgado, M.A., Caraballo, I., Llera, J.M., Rabasco, A.M., 1994. Characterization of morphine polymeric coprecipitates. A biopharmaceutical study. Pharmazie 49, 834–839.

Aulton, M.E., Richards, J.H., Abdul-Razzak, M.H., Hogan, J.E., 1983. Migration of active ingredient between film coats and tablet cores. In: Proceedings of the International Conference on Pharmaceutical Technology held by the Association of Pharmaceutical and galenical Industry (apgi), Rue Jean Baptiste Clement, 92290 Chatenay Malabry, France, vol. III, pp. 154–162.

Goracinova, K., Klisarova, L., Simov, A., 1995. Physical characterization, mechanisms of drug/polymer interactions and stability studies of controlled-release solid dispersion granules containing weak base as active substance. In: Proceedings of the International Conference on Pharmaceutical Technology held by the Association of Pharmaceutical and galenical Industry (apgi), Rue Jean Baptiste Clement, 92290 Chatenay Malabry, France, pp. 283–296.

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

Lee, H.G., Hajdu, J., McGoff, P., 1991. Propanolol: methacrylic acid copolymer binding interaction. J. Pharm. Sci. 80, 178–180.

Mura, P., Mauderioli, A., Bramanti, G., Furlanetto, S., Pinzauti, S., 1995. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. Int. J. Pharm. 119, 71–79.

Murthy, K.S., Turner, N.A., Nesbitt, R.U., Fawzi, M.B., 1986. Characterization of commercial lots of erythromycin base. Drug Dev. Ind. Pharm. 12, 665–690.

Okhamafe, A.O., York, P., 1989. Thermal characterization of drug/polymer and excipient/polymer interactions in some film coating formulation. J. Pharm. Pharmacol. 41, 1–6.

Pretsch, E., Seibl, J., Simon, W., Clerc, T., 1990. Tabellen zur Strukturaufklarung Organischer Verbindung mit Spektroskopischen Methoden. Springer, Berlin, pp. 365–370.

Simpkin, G.T., Johnson, M.C.R., Bell, J.H., 1983. The influence of drug solubility on the quality of film-coated tablets. In: Proceedings of the International Conference on Pharmaceutical Technology held by the Association of Pharmaceutical and galenical Industry (apgi), Rue Jean Baptiste Clement, 92290 Chatenay Malabry, France, vol. III, pp. 163–170.