ELSEVIER

International Journal of Pharmaceutics 202 (2000) 103–112

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Polyoxyethylene-poly(methacrylic acid-co-methyl methacrylate) compounds for site-specific peroral delivery

V. Carelli, G. Di Colo *, E. Nannipieri, B. Poli, M.F. Serafini

Department of Bioorganic Chemistry and Biopharmaceutics, University of Pisa, Via Bonanno 33, 56126 Pisa, Italy

Received 13 December 1999; received in revised form 29 March 2000; accepted 26 April 2000

Abstract

pH-sensitive interpolymer interactions between high molecular weight polyoxyethylene (POE) and poly(methacrylic acid-co-methyl methacrylate) (Eudragit (EUD) L100 or S100) are evidenced and exploited to prepare, from either POE–EUD coevaporates or POE + EUD physical mixtures, both in the 1:1 wt. ratio, compressed matrix tablets, potentially able to deliver the model drug, prednisolone, to sites in the GI tract characterized by specific pHs, such as the jejunum or the ileum. With these devices, drug release is inhibited at pHs lower than the threshold of EUD ionization, whereas at pHs exceeding such a threshold, the matrix undergoes a gradual erosion, which controls the release. A post-compression exposure of tablets to the vapors of appropriate solvents realizes the necessary compaction of matrices, in fact, a high compression force (3 ton) is insufficient, per se, to prevent matrix disintegration in the dissolution medium, whereas such a disintegration is prevented by the treatment with solvent vapors, even with a low compression force (0.3 ton). With the POE + EUD physical mixtures, the exposure to solvent vapors promotes the formation of a layer of POE–EUD complex at the interfaces of the POE and EUD particles in matrix, which inhibits release at pHs lower than that designed for delivery. Both POE and EUD concur to determine the properties of the POE–EUD complex relevant to drug release, indeed, EUD ionization, which elicits matrix erosion and drug release, is favored by the hydrophilic POE. In fact, matrices based on plain EUD exhibit a comparatively low release rate, more suited to an extended delivery to the colon than to a specific delivery to the ileum. Details of the release mechanism are discussed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Polyoxyethylene; Eudragit; Interpolymer complex; Prednisolone; Oral delivery system; Site-specific delivery system; pH-sensitive release system

1. Introduction

Coating solid dosage forms with pH-sensitive polymers to deliver drugs to specific sites of the GI tract is a common practice of the pharmaceutical technology. Methacrylic acid-methyl methacrylate copolymers, registered as Eudragit (EUD) L100 (EUD L) (comonomer ratio 1:1) or Eudragit S100 (EUD S) (comonomer ratio 1:2) are currently used to form coatings soluble as a function of the comonomer ratio and the environ-

---

* Corresponding author. Tel.: + 39-50-24000; fax: + 39-50-43321.

E-mail address: giadic@farm.unipi.it (G. Di Colo).

PII: S0378-5173(00)00429-4

mental pH value. Traditional tablets coated with these polymers dump the dose at the site where the coating dissolves i.e. with EUD L the active ingredient is released at pH values over 6.0 (jejunum), whereas with EUD S the release occurs at pH values over 7.0 (ileum). It would be fruitful to take advantage of the pH-sensitiveness of these EUDs to fabricate, by direct compression, monolithic erodible matrices, able to gradually release the dose to the pre-established site e.g. the jejunum or the ileum. A major advantage of such alternative release systems would be the saving of the time and costs of the coating process. In this paper, the interpolymer interactions between high molecular weight polyoxyethylene and EUD L or S are exploited to prepare compressed matrix tablets endowed with the above release properties. The study was warranted by the following considerations: (i) high molecular weight linear polyoxyethylenes or poly(ethylene glycol)s form interpolymer complexes with polycarboxylic polymers, such as poly(acrylic acid) or poly(methacrylic acid), through cooperative hydrogen bonding and hydrophobic interactions. The complexes are considerably less hydrophilic than the constituent polymers, but dissociate and dissolve at the pH where the polycarboxylic polymer becomes ionized (Bekturov and Bimendina, 1981; Kharenko and Kemenova, 1995; Haglund, et al., 1996; Ozeki, et al., 1998); (ii) a semi-interpenetrating polymer network (semi-IPN) of EUD L and crosslinked polyoxyethylene forms an interpolymer complex via hydrogen bonding. In water or acidic media, the semi-IPN equilibrium swelling is comparatively low, whereas in neutral buffer the complex dissociates, due to ionization of the EUD, and the swelling increases markedly (Buonaguidi, et al., 1997; Carelli, et al., 1999).

The main scopes of the present study have been (i) producing evidence of intermacromolecular interactions between linear polyoxyethylene (POE) and EUD in POE–EUD coevaporates, and (ii) evaluating and comparing the release characteristics, in simulated GI fluids, of matrix tablets obtained by direct compression of the drug powder with POE–EUD coevaporates, or physical mixtures of POE and EUD, or plain POE or EUD. Prednisolone has been chosen as a model of poorly water-soluble drugs.

2. Materials and methods

2.1. Materials

The following commercially available materials were used as received. Prednisolone (PDN) (Carlo Erba, Milan, Italy), polyoxyethylene (POE), M_w 400 kDa (POE 4), and M_w 4000 kDa (POE 40)(Aldrich Chimica, Milan, Italy), EUD L and S (gifts from Rofarma Italia S.r.l., Milan, Italy), Tegiloxan 300 000T (TEG)(gift from Goldschmidt Italia S.r.l., Cremona, Italy). TEG is a liquid silicone having a kinematic viscosity of 3×10^5 cStokes.

2.2. Preparation of POE–EUD coevaporates as films

Coevaporates composed of POE 4-EUD L, POE 40-EUD L, POE 4-EUD S, or POE 40-EUD S, each in the 1:1 or 1:2 wt. proportion of the two polymers, were obtained as films of around 0.1 mm thickness by casting a methanol-chloroform 3:1 v/v solution, containing a total polymer concentration of 29 mg/ml, onto a Teflon Petri dish. To prepare the solution, the POE was first suspended in 1 volume of methanol, then it was dissolved by adding 1 volume of chloroform to the suspension. The resulting solution was added with a solution of EUD in 2 volumes of methanol and the mixture was stirred until an apparently homogeneous solution was obtained. In order to gain an insight into the POE–EUD interaction in the coevaporates, the weight loss of a film, composed of POE 40-EUD L 1:1 w/w, following extraction with water, was determined. To this purpose, the film was first equilibrated in a calcium chloride dessiccator, up to a constant weight (sensitivity, 10^{-5} g), then immersed in excess water, at ambient temperature, for 3 days, after which it was dried and kept over calcium chloride up to a constant weight. A weight loss of 40.5% resulted. Then, the film was immersed in water again for further 6 days, after which no further weight loss was evidenced. This result will be discussed in the light of the change of the IR spectrum of the film following extraction with water.

2.3. Preparation of POE–EUD coevaporates as powders

POE 4-EUD L, POE 40-EUD L, POE 4-EUD S, and POE 40-EUD S compounds, each in the POE–EUD 1:1 wt. ratio, were obtained in the form of powders by the following coevaporation procedure. An 18-ml volume of a solution of 0.25 g each of POE and EUD in methanol-chloroform 3:1, prepared as described above, was dispersed portionwise, by levigation, into 5 g TEG, under an air stream to favor solvent evaporation. After dispersion of the last portion, the mixing was continued up to a constant weight of the resulting suspension. The coevaporate powder was collected by dissolving the TEG with an excess of petroleum ether, decanting the liquid, repeatedly washing the powder with petroleum ether up to complete TEG removal, and finally, air drying the powder, followed by vacuum drying. The powder particles were essentially in the 25–50 μm size range, as measured by an optical microscope.

2.4. IR spectroscopy

IR spectra of thin films of POE, EUD and POE–EUD compounds, obtained by casting polymer solutions in chloroform, methanol and methanol–chloroform 3:1, respectively, onto a Teflon Petri dish, were recorded with a Mattson 3000 FTIR spectrophotometer.

2.5. Differential scanning calorimetry (DSC) measurements

A Mettler TA 3000 thermal analysis system, consisting of a TC-10 TA processor, DSC 20 measuring cell and printer-plotter, was used. Samples of 8–10 mg were scanned in sealed aluminum pans in the 0–100°C temperature interval, at a heating rate of 10 K/min. The measuring cell worked in a freezer.

2.6. Preparation of matrices

Cylindrical matrices of 50 mg weight and 6 mm diameter, containing 10 or 20% PDN, were prepared by compressing, by means of a Perkin–Elmer hydraulic press, the commercial drug, mixed with the POE–EUD 1:1 w/w coevaporate powders, or with physical mixtures of commercial POE and EUD in the 1:1 wt. ratio. Before processing, all powders were passed through a 106 μm sieve. For preparing each matrix, the ingredients were weighed, with a 10^{-5} g sensitivity, thoroughly mixed with a spatula, and compressed by a force of 3 ton or, in some cases, 0.3 ton. In order to prevent matrix disintegration during the subsequent dissolution experiments, the welding of the polymer particles in the tablets was strengthened by keeping the tablets 15 min in an air-tight glass chamber saturated with the vapors of a methanol–chloroform 1:1 mixture. The tablets rested on a wire mesh fixed at a small distance over the solvent surface. Then, the solvent was completely removed from the matrices by air drying at 55°C, up to a constant weight.

2.7. Release experiments

For the measurement of the drug release kinetics, the matrix was placed into a stainless steel wire mesh bag, formed by joining together the four corners of a wire mesh square of 1.5 cm side. The bag was fastened to a stainless steel hook, fixed to the shaft of a glass paddle stirrer, in such a way that the matrix was held under the impeller, at a 1.2 cm distance from the paddles. The impeller diameter and paddle width were 4.9 and 1.5 cm, respectively. At time $t = 0$, the stirrer, with attached matrix, was immersed in 200 ml of dissolution medium, contained in a jacketed beaker (internal diameter, 6.5 cm; internal height, 9.0 cm) thermostated at 37 ± 0.1°C, in such a way as to position the matrix at the center of the receiving phase, and stirring at 60 rpm was initiated by means of a synchronous motor. The apparatus described above was designed to ensure a strict hydrodynamic control of the matrix environment. At intervals, a measured volume of receiving phase was withdrawn and replaced by an equal volume of fresh, pre-thermostated dissolution medium. The volume withdrawn and the time intervals were appropriate to maintain sink conditions in the receiving phase throughout the release experiment. At pre-established times, the receiving phase was completely replaced by a medium of different pH, in order to simulate matrix transit across the GI tract. If not otherwise indicated, the matrices were eluted with simulated GI fluids, consisting of the following solutions: hydrochloric acid 0.04 M, pH 1.2, made isotonic with sodium chloride; phosphate buffer pH 6.8, 0.13 M, made isotonic with sodium chloride; and phosphate buffer pH 7.4, 0.13 M, isotonic. Such solutions were used in sequence. The elution with the solution at pH 1.2 and that with the solution at pH 6.8 lasted 2 h each; the elution with the solution at pH 7.4 lasted until the end of the experiment. The receiving phase was analyzed spectrophotometrically for the drug, at 246.5 nm. Blank runs showed the absence of significant interference with the spectrophotometric measurements. For purposes to be specified, the percent weight loss of matrix following a given elution time was determined by removing from the dissolution apparatus the wire mesh bag, with the undissolved matrix residuum in it, then drying and weighing. The matrix weight loss was computed, knowing the initial dry matrix and the bag weights.

3. Results and discussion

3.1. Properties of the POE–EUD coevaporates

All films composed of POE–EUD 1:1 w/w appeared clear, whereas those made of POE–EUD 1:2 w/w appeared non homogeneous, with separate clear and opaque zones, indicative of a segregation of the polymer mix into its constituents. In fact, films of plain POE 4, or POE 40, looked homogeneously opaque, whereas films of plain EUD L, or EUD S, looked uniformly clear. The POE 40-EUD L 1:2 w/w system required several months to segregate, probably due to a very low mobility of the POE 40 macromolecules. On the other hand, all of the POE–EUD 1:1 w/w systems have remained clear for more than a year now since their preparation. This points to the 1:1 wt. ratio as the more favorable to POE–EUD interpolymer interactions. Surprisingly enough, mixed films containing an EUD wt. proportion in excess of 50% appeared non-homogeneous, even though plain films of EUD were clear. Apparently, such an EUD excess weakened the POE–EUD with respect to the EUD-EUD interactions, thus favoring mixture segregation. On the other hand, an absence of segregated macroscopic POE domains in the POE–EUD 1:1 w/w films was deduced both by visual inspection and by a lack of tack of such films, when hydrated with distilled water, knowing that the plain POE forms an adhesive gel following hydration. Conversely, the POE–EUD 1:1 w/w films became adhesive and gradually dissolved, when hydrated with pH 7.4 buffer, reasonably because the ionization of the EUD carboxyls by the buffer would disrupt the POE–EUD interactions, dissolve the EUD and set the POE free to exert its adhesiveness at the dissolution front.

Since POE is a semi-crystalline polymer, a lowering of the POE's crystallinity degree by EUD could be taken as a proof, as well as a measure, of the POE interaction with EUD. The enthalpy of fusion of POE crystallites was measured by DSC for the POE–EUD 1:1 w/w coevaporates and compared with the values for plain POE samples. The measurements were enabled by the absence of EUD signals in the fusion interval of the POE crystallites. Some time after complete removal of solvent was required by POE to attain the crystallinity degree corresponding to thermodynamic equilibrium. In fact, constant fusion enthalpy values could not be obtained before 10–15 days from the drying of the coevaporates. In Table 1, the relative crystallinity degree, RCD, of POE in the

Table 1
DSC data and relative crystallinity degree (RCD) for POE–EUD 1:1 w/w coevaporates and pure polymers

Material	$T_p \pm$ SD ($n=3$), °C	ΔH ± SD ($n=3$), J/g	RCD
POE 4-EUD L	68.4 ± 0.1	73.2 ± 12.2	0.40
POE 40-EUD L	60.0 ± 2.3	71.8 ± 6.2	0.42
POE 4-EUD S	65.2 ± 1.0	108.1 ± 7.5	0.58
POE 40-EUD S	65.2 ± 4.2	101.1 ± 3.7	0.58
POE 4	73.9 ± 0.7	185.0 ± 0.0	1
POE 40	74.3 ± 1.8	172.7 ± 0.5	1

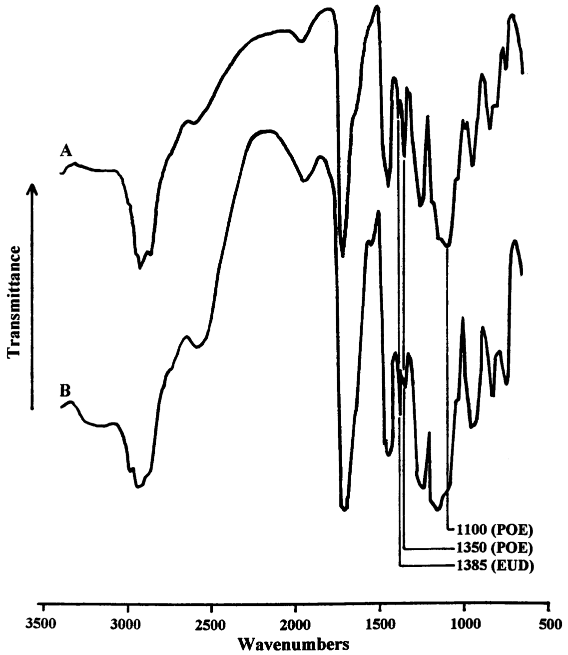

Fig. 1. Comparison of IR spectra of a POE 40-EUD L film. A, before extraction with water; B, after extraction with water.

POE–EUD coevaporates is reported as the ratio of the enthalpy of fusion per unit POE mass for the POE–EUD coevaporates to that for the correspondent pure POE. All of the RCD values for the coevaporates are indeed lower than unity and, in particular, the values for the systems containing EUD L are lower than those for the systems containing EUD S, indicating a stronger POE interaction with EUD L. On the other hand, similar RCD values for the systems comprising the same EUD type and different molecular weight POEs indicate that the POE–EUD interaction is virtually uninfluenced by the POE molecular weight, at least in the 400–4000 kDa range.

The effect of water on the POE–EUD interaction was investigated by equilibrating a POE 40-EUD L 1:1 w/w film with an excess of distilled water, at ambient temperature, then determining the film weight loss, and comparing the IR spectra of the film before and after the equilibration. A comparison, in Fig. 1, between the IR spectra for the insoluble residuum and the initial film shows that the absorption peaks at 1350 and 1100 cm^{-1}, typical of POE, are still present in the spectrum of the residuum, although their intensity is considerably decreased with respect to the EUD peaks. This is best verified by referring to the peaks at 1350 and 1385 cm^{-1}, typical of POE and EUD, respectively. Then, water reduces the POE–EUD ratio in the insoluble residuum, probably by dissolving a less strongly interactive POE portion, but is unable to completely split the polymer compound into its constituents, the water soluble POE and the water insoluble EUD, due to the presence in the residuum of a strongly interactive POE portion. This is confirmed by a weight loss of the film, following water extraction, of only around 40%.

3.2. Release studies

3.2.1. Matrices based on coevaporates

The notation POE 4 (or 40)-EUD L (or S) will henceforth refer to a coevaporate containing the specified POE and EUD in the 1:1 wt. ratio. Fig. 2 shows data on PDN release from matrices based

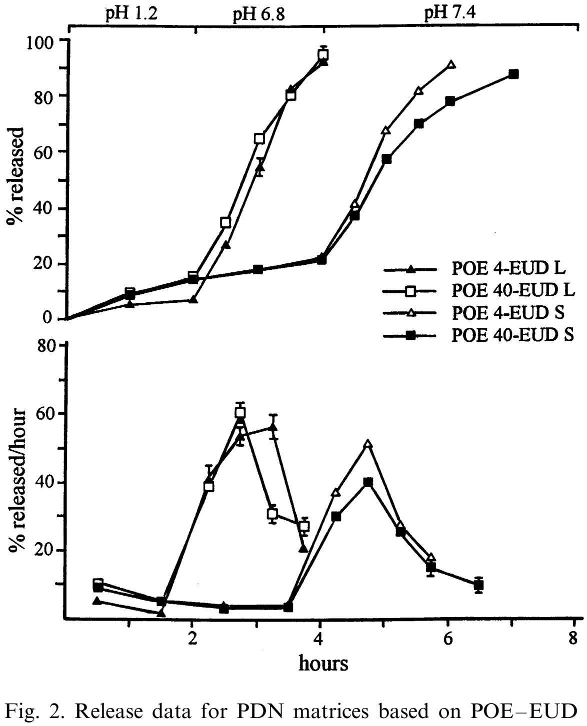

Fig. 2. Release data for PDN matrices based on POE–EUD coevaporates, loaded with 10% drug. Data points are the means and SD of triplicate runs.

Table 2
Percent dose released (PDR) from matrix and percent weight loss (PWL) of matrix, during consecutive elution periods (EP) at increasing pH, for representative matrices based on POE–EUD coevaporates, loaded with 10% drug[a]

Coevaporate	pH 1.2	pH 6.8	pH 7.4
POE 4-EUD L	EP = 2 h PDR = 7.3 ± 0.1 PWL = 11.3 ± 0.0	EP = 1 h PDR = 49.8 ± 3.5 PWL = 50.8 ± 4.3	
POE 40-EUD S	EP = 2 h PDR = 10.0 ± 0.3 PWL = 13.0 ± 0.0	EP = 2 h PDR = 6.8 ± 0.1 PWL = 17.4 ± 0.0	EP = 1 h PDR = 40.7 ± 0.7 PWL = 40.3 ± 3.2

[a] The data are the means ± SD of three matrices.

on POE 4-EUD L, POE 40-EUD L, POE 4-EUD S and POE 40-EUD S, containing 10% drug. Each data point of the release rate vs. time plot represents the drug fraction released in the time interval Δt after time t, and is placed at time $t + 0.5\ \Delta t$. It appears from the figure that the release essentially occurs at the pH where the commercial EUD is known to dissolve, namely, pH 6.8 with the systems containing EUD L, or pH 7.4 with those containing EUD S. In fact, an erosion of the respective matrices was visually evident at these pH values, which was not visible at lower pHs. In order to gain insight into the release mechanism, matrices composed of POE 4-EUD L or POE 40-EUD S were taken as representative, and the percent dose released (PDR) and percent weight loss (PWL) during each of consecutive elution periods at increasing pH were determined for these matrices. The PDR, or PWL, value for any elution time interval, $\Delta t = t_2 - t_1$, was computed as the difference between the PDR, or PWL, values determined for matrices eluted, according to the usual pattern of increasing pH, up to time t_2 or t_1. The data, listed in Table 2, show, for the 2 h elution interval at pH 1.2, some weight loss from both matrices. Such a loss is not due to drug release only, which should imply: PDR > PWL, nor to surface erosion of matrix, which should give: PDR = PWL. In fact, PDR is smaller than PWL, indicating that some polymeric material is extracted from inside the matrices, during elution. According to the results of the extraction of a POE 40-EUD L film with water, discussed before, the extracted polymer should be POE. Such an extraction could occur via hydration and swelling of the polymer compound, allowing POE to migrate through the swollen system by reptation. Drug release in this stage is rather slow and probably occurs via dissolution-diffusion in the matrix. During the next elution interval, at pH 6.8, the two matrix types behaved differently, depending on the different solubility, at this pH, of EUD S compared to EUD L. It is seen, in Table 2 that, for the matrix containing EUD S, the PDR is decreased with respect to the preceding elution period at pH 1.2, and is much lower than the corresponding PWL. These data suggest that the drug release and polymer dissolution phenomena are much the same as in the preceding elution period at pH 1.2, although the increased PWL value points to some EUD S ionization weakening the interpolymer interaction. On the other hand, the PDR and PWL values for the POE 4-EUD L matrix in a 1 h elution interval at pH 6.8, found in Table 2, are comparatively high and virtually equal. This is in accord with a rapid ionization of EUD L at this pH, eliciting matrix surface erosion and an erosion-controlled release. A similar process appears, from the data in Table 2, to occur with the POE 40-EUD S matrix during elution at pH 7.4. Fig. 2 shows that, for the matrices containing EUD L, the release rate in the erosion-controlled stage, at pH 6.8, is virtually uninfluenced by the POE molecular weight. This suggests that, with these matrices, the erosion is rather controlled by the ionization of EUD L, which is believed to be independent of the POE molecular weight, than by the disentanglement of the POE chains, which would depend on molecular weight. Reasonably, then, the EUD L ionization would break the interpolymer interaction and set the EUD and POE macromolecules free in the dissolved state. On the other hand, Fig. 2 shows, for the matrices containing EUD S, a significantly, although slightly, slower release for the higher compared to the lower molecular weight POE, in the matrix erosion stage at pH 7.4. This suggests that some entanglement of the POE 40 chains persists after EUD S ionization, and the disentanglement of such chains is the final step of matrix erosion, in this case. The above data interpretation is in accord with the stronger interaction with POE of EUD L compared to EUD S, shown before.

3.2.2. *Matrices based on pure polymers*

We have shown before that the physicochemical properties of the POE–EUD coevaporates are different from those of the constituent polymers. A comparison of data in Fig. 3 with those in Fig. 2 shows profound differences also in drug release properties, between polymer compounds and component polymers. Indeed, the release profiles for matrices based on the plain POEs, seen in Fig. 3, are apparently uninfluenced by pH and depend strongly on the POE molecular weight. It is known that drug release from matrices based on high molecular weight linear POEs is controlled, in a first phase, by polymer swelling and, subsequently, by surface erosion of the swollen hydrogel. Both processes are pH-independent, but depend profoundly on the macromolecule size (Apicella, et al., 1993). On the other hand, the erosion rate of the POE–EUD matrices is mainly determined by EUD ionization, which depends on pH and is independent of POE molecular size. Nevertheless, the presence of POE of whichever molecular size in the coevaporates is determinant to the matrix erosion rate. Indeed, the release rate, at pH 7.4, for the matrix based on plain EUD S, which is undoubtedly determined by EUD S ionization and matrix erosion, is seen in Fig. 3 to be much lower than that for either the POE 4-EUD S or POE 40-EUD S matrix, at the same pH, seen in Fig. 2. Apparently, then, the POE in the POE–EUD compound facilitates EUD ionization, probably by carrying water and buffer ions into the matrix. On the opposite, water is unable to diffuse into the matrix of plain EUD S, therefore, the erosion-controlled release from this matrix, at pH 7.4, is too slow to be considered ileum-specific, but rather, the matrix is potentially apt to provide a sustained release to the colon. Data on drug release from a matrix of plain EUD L could not be obtained, because the matrix disintegrated in the dissolution medium, despite the treatment with solvent vapors.

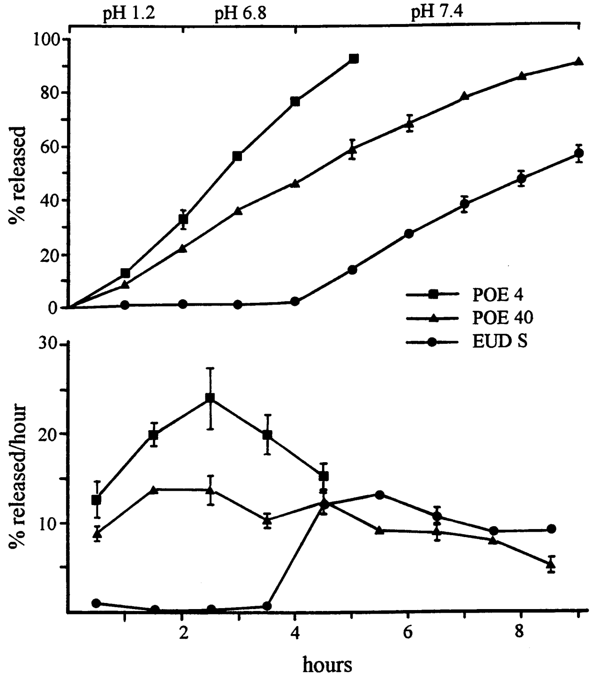

Fig. 3. Release data for PDN matrices based on POE 4, POE 40 or EUD S, loaded with 10% drug. Data points are the means and SD of triplicate runs.

3.2.3. *Matrices based on physical mixtures*

Data on drug release from matrices based on physical mixtures of POE and EUD powders are presented in Fig. 4. The notation POE 4 (or 40) + EUD L (or S) will henceforth refer to a physical mixture of the specified POE and EUD, in the 1:1 wt. ratio. Drug release from these matrices appears as pH-specific as with the matrices based on the POE–EUD coevaporates, however, a comparison of relevant data in Fig. 4 and Fig. 2 shows that, in the erosion-controlled phase, the release with the POE + EUD matrices depends more strongly on the POE molecular size than it does with the POE–EUD systems. The release properties of the POE + EUD matrices depended strictly on the treatment of the compressed tablets with solvent vapors, as described in Section 2.6. Indeed, a POE 40 + EUD S matrix

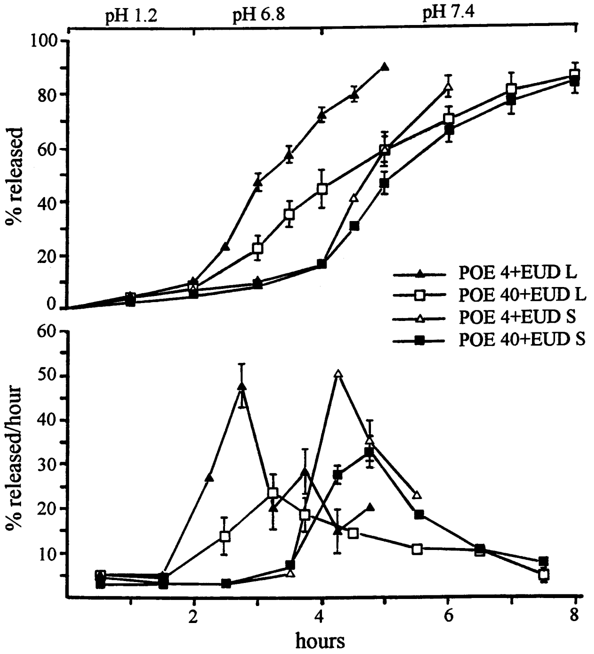

Fig. 4. Release data for PDN matrices based on POE + EUD physical mixtures, loaded with 10% drug. Data points are the means and SD of triplicate runs.

not treated with solvent vapors showed a pH-independent release profile (not reported), quite similar to that for the plain POE 40 matrix, seen in Fig. 3. Such a similarity can be explained by the absence of POE–EUD interpolymer interaction in the matrix under discussion, allowing the formation of a rate-controlling POE 40 hydrogel mass since the start of the release experiment. On the other hand, the exposure of the POE + EUD compressed tablets to solvent vapors caused interpenetration of POE and EUD macromolecules at the interfaces of the POE and EUD particles in matrix, with formation of interfacial POE–EUD interpolymer complex, which prevented the POE particles from joining into a continuum hydrogel mass, as long as the elution medium pH was below the value for EUD dissolution. When this value was exceeded, the interfacial POE–EUD complex dissolved, allowing the formation of a continuum POE hydrogel mass, the erosion of which controlled drug release to a rate depending on the POE molecular mass.

3.2.4. Relevance of drug load

We have shown before that the insignificant release at pHs below the threshold of EUD dissolution, and hence, the pH-specific release from the present matrices, is due to the barrier function of the POE–EUD interactive system. Reasonably, then, in order for such a barrier function to be retained, the drug load should not exceed the percolation threshold. We have studied the effect of doubling the load, from 10 to 20%, on the release characteristics of matrices based on POE–EUD or POE + EUD. The 20% load must still be below the percolation threshold, so far as the release data obtained with all these matrices (not reported) were similar to those for the POE–EUD matrices, loaded with 10% drug, seen in Fig. 2. This similarity suggests that, with 20% load, the erosion of the POE + EUD matrices was mainly controlled by the same mechanism as that for the POE–EUD matrices i.e. the ionization and dissolution of EUD. However, it has been shown, in section 3.2.3, that the release profile for POE + EUD matrices containing 10% drug was different from that for POE–EUD matrices containing the same load, in fact, for the former matrices the erosion of a continuum POE hydrogel phase was suggested as the rate-controlling step of release. Thus, with the POE + EUD matrices, the increase of drug load caused a change of release mechanism, from POE-erosion to EUD-dissolution-controlled. Probably, with the higher load, the drug particles concentration in the POE hydrogel, left behind by EUD dissolution, exceeded the percolation threshold and the drug was free to dissolve in the percolating elution medium.

3.2.5. Relevance of compression force

The matrices discussed so far were compressed with a force of 3 ton. In order to assess the relevance of the compression force, representative matrices, based on POE–EUD or POE + EUD, loaded with 10 or 20% drug, were prepared at a compression force of 0.3 ton, and release data for these matrices were obtained by the usual procedure. No important differences were observed between such data (not reported) and those for the correspondent matrices compressed at 3 ton. Such an irrelevance of compression force suggests that the actual compaction degree of matrices depended on the welding action of the solvent vapors to which the compacts were exposed following compression, as described in Section 2.6.

3.2.6. Relevance of buffer molarity

It has been stated in the foregoing discussion that the ionization of EUD carboxyls by the buffer anions is a fundamental step of the release process. In order to assess the relevance of the buffer molarity to the release rate, release data for representative matrices, based on POE–EUD and POE + EUD, were obtained using receiving buffers of a molarity reduced from 0.13 to 0.032 M. A comparison of the data in Fig. 5, relative to POE–EUD systems, with the relevant data in Fig. 2, shows that the release, in the erosion-controlled phase, is slowed down significantly by a substantial reduction of the buffering strength of the elution medium, in accord with an EUD-ionization-controlled matrix erosion. Such a buffer molarity effect on release appears, from a comparison of relevant data in Fig. 6 and Fig. 4, to be still present with the POE 4 + EUD L matrix whereas it is virtually absent with the POE 40 + EUD S matrix, probably because, in this case, the EUD ionization and dissolution was, with either buffer molarity, faster than the erosion of the POE 40 hydrogel.

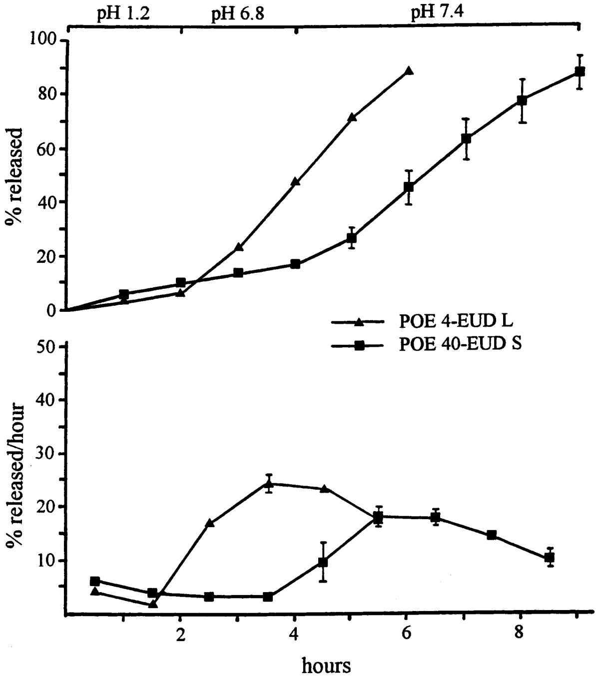

Fig. 5. Release data for PDN matrices based on POE–EUD coevaporates, loaded with 10% drug, eluted with phosphate buffers 0.032 M. Data points are the means and SD of triplicate runs.

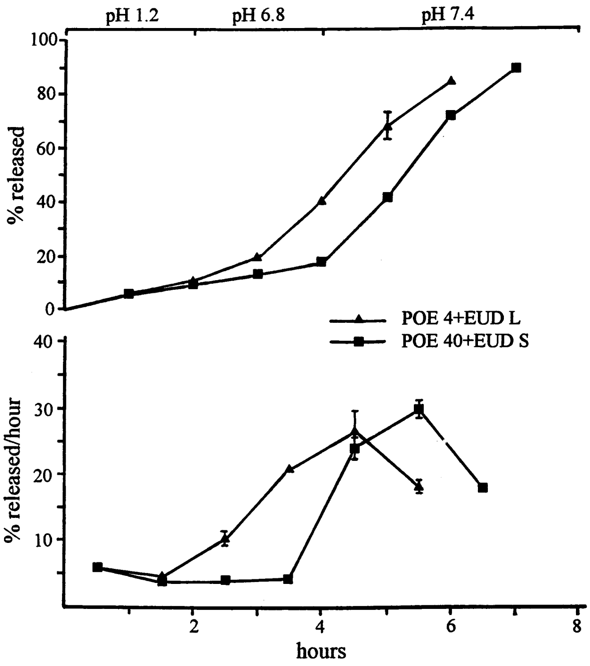

Fig. 6. Release data for PDN matrices based on POE + EUD physical mixtures, loaded with 10% drug, eluted with phosphate buffers 0.032 M. Data points are the means and SD of triplicate runs.

4. Conclusions

We have shown that POE and EUD, in the 1:1 wt. ratio, undergo pH-sensitive interpolymer interactions, which could be exploited to prepare compressed matrix tablets, potentially able to deliver the drug to sites in the GI tract characterized by specific pHs, such as the jejunum or the ileum. A post-compression exposure of tablets, prepared from either the POE–EUD coevaporates or the POE + EUD physical mixtures, to the vapors of appropriate solvents is essential to realize the necessary compaction of matrices, in fact, even as high a compression force as 3 ton is insufficient, per se, to prevent matrix disintegration in the dissolution medium, whereas such a disintegration is prevented by the treatment with solvent vapors, even when the compression force is as low as 0.3 ton. In the case of direct compression of POE + EUD physical mixtures, the exposure to solvent vapors serves to promote the formation of a layer of POE–EUD complex at the interfaces of the POE and EUD particles, which is expected to inhibit drug release to the GI zones preceding the site designed for delivery. On an industrial scale, the treatment with solvent vapors might be carried out e.g. in a Wurster apparatus. Both POE and EUD concur to determine the properties of the polymer compound relevant to drug release, indeed, the pH-specific EUD ionization and dissolution process, which elicits matrix erosion and drug release, is favored by the hydrophilic POE. In fact, matrices based on plain EUD S exhibited a comparatively low release rate, more suited to an extended delivery to the colon than to a specific delivery to the ileum. The pH-specific release properties of the present matrices are retained when the drug load is increased from 10 to 20%, reasonably because the higher load is still below the percolation threshold. Where the release is governed by matrix erosion, it is expected to be profoundly influenced by the hydrodynamics of the matrix environment, and where the erosion is controlled by EUD ionization, it depends strongly on the buffering strength of such an environment. Therefore, the present release data are valid so far as they depict release patterns, suggest release mechanisms and evidence differences among them, but cannot be taken as reproductive of the actual release rates in the GI tract, since the in vivo hydrodynamics and mechanics, and environmental buffering strength, were not reproduced by the in vitro experiments. Anyway, some advantages of the present devices over the traditional EUD-coated tablets can be anticipated, such as (i) the replacement of the coating process by the simpler treatment with solvent vapors, and (ii) a gradual delivery of the dose to the designed site which, for many drugs and therapies, is more suitable than the dose dumping, typical of the traditional dosage forms. On the other hand, potential disadvantages of the present matrices should be recognized, such as (i) the necessity of a drug load not exceeding the percolation threshold, and (ii) an incomplete inhibition of release in the protected GI zones, due to some drug diffusion in the hydrated matrix. The importance of such an unwanted diffusive release depends on the drug physicochemical properties. It must be stressed, in this respect, that the model drug used in the present work is only representative of sparingly water-soluble drugs. Further study with more soluble drugs would extend the information on the present delivery systems.

Acknowledgements

Rofarma Italia is thanked for donating the Eudragits. Goldschmidt Italia is thanked for donating Tegiloxan 300 000T. This research was supported by a grant from Ministero dell'Università e della Ricerca Scientifica e Tecnologica.

References

Apicella, A., Cappello, B., Del Nobile, M.A., La Rotonda, M.I., Mensitieri, G., Nicolais, L., 1993. Poly(ethylene oxide) (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials 14, 83–90.

Bekturov, E.A., Bimendina, L.A., 1981. Interpolymer complexes. Adv. Polym. Sci. 41, 99–147.

Buonaguidi, M., Carelli, V., Di Colo, G., Nannipieri, E., Serafini, M.F., 1997. Evaluation of a pH-sensitive semi-interpenetrating polymer network for control of GI drug delivery. Int. J. Pharm. 147, 1–10.

Carelli, V., Coltelli, S., Di Colo, G., Nannipieri, E., Serafini, M.F., 1999. Silicone microspheres for pH-controlled gastrointestinal drug delivery. Int. J. Pharm. 179, 73–83.

Haglund, B.O., Joshi, R., Himmelstein, K.J., 1996. An in situ gelling system for parenteral delivery. J. Controll. Release 41, 229–235.

Kharenko, A.V., Kemenova, V.A., 1995. Controlled release from oral formulations based on interpolymeric polymethacrylic acid–polyethylene glycol complex. Proceed. Inter. Symp. Controll. Release Bioact. Mater. 22, 232–233.

Ozeki, T., Yuasa, H., Kanaya, Y., 1998. Mechanism of medicine release from solid dispersion composed of poly(ethylene oxide)–carboxyvinylpolymer interpolymer complex and pH effect on medicine release. Int. J. Pharm. 171, 123–132.