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International Journal of Pharmaceutics 269 (2004) 343–351
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Polymers–gamma ray interaction. Effects of gamma irradiation on modified release drug delivery systems for oral administration

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Received 26 April 2003; received in revised form 5 September 2003; accepted 12 September 2003

Abstract

The aim of this work is to verify the efficiency of two kinds of matrix tablets formulations containing PEO or PVA as retarding polymer. Moreover, since in the last years the exposure to ionizing radiation is a more and more used method to reduce bacterial charge in pharmaceutical products, the effects of gamma irradiation on these two kinds of polymers has been evaluated. The study is performed on matrix tablets containing diltiazem HCl, as model drug, and polyethylene oxides (PEO) of two different molecular weights or polyvinylalchool (PVA) of medium degree of hydrolysis, as drug release modulators. Dissolution of the matrices, release of diltiazem and morphological behaviour of the samples, before and after exposure to increasing doses of gamma irradiation, are investigated in order to verify their stability.

The results show that the ionizing radiation does not modify significantly the dissolution trend of the PVA samples; on the contrary, the dissolution and the morphological behaviour of the PEO matrices is strongly affected by the radiation dose received. In particular, the dissolution rate of the irradiated PEO tablets dramatically increases as a function of the irradiation dose and the swelling process, which characterised the non-irradiated PEO samples, was replaced by a rapid erosion process responsible for the quickly dissolution of the matrices. The changes of the dissolution and morphological PEO tablets performances could be explained by a breaking of the polymeric chains (shown by EPR studies) as a consequence of the exposure to gamma rays. These chemical–structural modifications of the polymers are responsible for the reduced efficacy of the PEO systems in controlling the drug release rate.

Keywords: Polyethylene oxide; Polyvinylalcohol; Controlled drug release; Matrix tablets; Gamma irradiation

1. Introduction

Matrix systems, composed of an active drug dispersed in a hydrophilic soluble polymer, are the most commonly used extended release dosage forms for oral administration.

During dissolution, matrix tablets containing these kinds of polymers swell upon contact with the dissolution medium and form a gel layer at their surface (Hogan, 1989). The gel layer, its texture and thickness controls the drug release process. The characteristics of the layer depend on the solvent penetration rate, on the degree of swelling and on the erosion rate of the matrix. Among the hydrophilic polymers employed in the preparation of matrix type oral dosage forms, hydroxypropylmethylcellulose (HPMC) is the

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doi:10.1016/j.ijpharm.2003.09.027

most commonly used. Recently it has been demonstrated that also polyethylene oxide (PEO) can be used as retarding polymer in the formulation of oral drug delivery system (Maggi et al., 2000). This is a good candidate for the use in matrix tablets (Kim, 1995, 1998): PEOs have good hydration and swelling properties, are not affected by the pH of the gastrointestinal tract, thanks to the non-ionic properties of the polymer, and the drug release process is independent from the environmental pH (Polyox, Technical Bulletin).

The drug release kinetics from PEO matrix tablets is strongly related to the polymer molecular weight. The release mechanism can be governed by swelling and drug diffusion or by swelling and polymer erosion depending upon the percentage and on the molecular weight of the PEO used. Generally, for low molecular weight products the prevailing mechanism of drug release is the polymer erosion rate, whereas, for high molecular weight, swelling of the polymeric material is the dominant step in controlling release kinetics (Apicella et al., 1993; Cappello et al., 1994).

Polyvinylalcohol (PVA) is used in the form of crosslinked hydrogel in a large number of biomedical applications (such as contact lenses, implants and artificial organs). Recently, this polymer has been used as a drug release modulator in the formulation of hydrophilic matrix tablets (DiLuccio et al., 1994; Quintanar-Guerrero et al., 1999; Möeckel and Lippold, 1993). PVA is a swellable polymer; its swelling behaviour depends on the degree of hydrolysis of the corresponding polyvinylacetate precursor. In fact, if the polymer is completely hydrolysed, it acts as a disintegrant because in water it swells but does not form a gel layer because of intra- and inter-molecular hydrogen bonds between polymer hydroxyl groups. But, the presence of acetate groups in the polymer weakens the inter-molecular hydroxyl bonds and the polymer is able to gelify.

The aim of this work is to verify the efficiency of two kinds of matrix tablet formulations, containing PEO or PVA (characterised by a degree of hydrolysis of 88 mol%) as retarding polymers. Moreover, since in the last years the exposure to ionizing radiation is a more and more used method to reduce bacterial charge in food, cosmetic and pharmaceutical products, the stability of these two kinds of polymers after gamma irradiation has been evaluated.

The study is performed on matrix tablets, containing diltiazem hydrochloride, as model drug, and polyethylene oxide (PEO) of two different molecular weights or polyvinylalcohol (PVA) of medium degree of hydrolysis, as drug release modulators. The dissolution and morphological behaviour of the matrices, before and after exposure to increasing doses of gamma rays, are investigated in order to verify their stability.

In a recent work Maggi et al. (2003) investigated the chemical stability of diltiazem HCl to gamma irradiation. The EPR analysis showed the presence of degradation products, but the HPLC measures revealed that no significant differences were found in the drug content of the HPMC tablets before and after irradiation at the maximum level (50 kGy). This indicates that the DTZ degradation products formed (and detected by EPR) were present only on traces and drug content of the dosage forms is unchanged. Starting from the assumption that this drug is stable to gamma rays, the aim of the present work is to investigate if gamma radiation may be responsible for the alteration of the characteristics of the polymer employed as carrier able to control the drug release from the dosage form. EPR studies are carried out to define the possible modifications of the polymers induced by this high-energy radiation. Moreover, if any modification is detected, the polymer viscosity was measured before and after gamma irradiation.

2. Materials and methods

2.1. Materials

Polyethylene oxide (Polyox WSR of molecular weights 2×10^6 and 7×10^6) was kindly donated by Union Carbide (Danbury, CT, USA) and diltiazem hydrochloride by Profarmaco S.p.A. (Milan, Italy). Polyvinylalcohol (Erkol W40-140) with a degree of hydrolysis of 88.7 mol% was supplied by Erkol-Acetex Chimica s.r.l. (Milan, Italy). A 4% (w/v) aqueous solution of PVA has a viscosity of 40 cps, Hoppler viscosity at 20 °C (values as stated by the supplier).

2.2. Methods

PEO and PVA matrices were prepared mixing the polymer and the active compound (diltiazem HCl) for

30 min (Turbula T2A, Bachofen, Basel, CH) and then tableting the powder mixtures using a single-punch machine (Kilian, Coln, D) instrumented with piezoelectric load washer (Kistler, Winterthur, CH) for force compression measurements (Conte et al., 1972), equipped with flat punches of 9.5 mm in diameter. The compression force was adjusted at 25 kN.

Batches of the three types of tablets (X2, X7 and W40) were exposed to three different doses of gamma irradiation (7.5, 25 and 50 kGy). The irradiation dose of 25 kGy is generally suggested for sterilising pharmaceutical products, although each product needs a validation procedure, while lower doses are used to reduce bacterial charge (US Pharmacopoeia XXIV, 2000; The European Pharmacopoeia, 3rd Edition, 2001). The irradiation of the samples for the dissolution test was performed at room temperature (25 °C, 60% R.H.) in air. The exposure to gamma radiation was performed in a ^{60}Co source at a dose rate of 1.1 kGy/h. The samples for the EPR measurements, sealed under vacuum in quartz tubes, were irradiated at the liquid nitrogen temperature with total doses of about 15 kGy. For the viscosity measurements, pure PEOs were irradiated for short times (from 0 to 8.8 kGy), because their viscosity decays very strongly after irradiation. As the tablets containing PVA do not show any significant modification in their dissolution behaviour after the exposure to the ionizing radiation, the viscosity tests were not performed.

Drug release profiles were performed using the apparatus 2 (USP XXIV) with the paddle rotating at 100 rpm in 1000 ml of distilled water at 37 °C. At predetermined time intervals, samples were assayed for diltiazem release at 236 nm by UV detection (Spectracomp 602, Advanced Products, Milan, Italy). To verify the morphological behaviour of the dosage forms during the release process, the matrices were placed in dissolution media, in the same conditions as previously detailed, and their modifications (hydration, swelling, gelling and erosion) were analysed at time intervals. A digital video-camera connected to a proper software allows measuring the total dimensions of the tablet and of its solid or swollen phases. At predetermined time intervals, the samples were withdrawn from the dissolution fluid, they were sectioned and the photos of the matrices were taken. The images were recorded using a digital video-camera (SV Micro^{TM}, Sound Vision Inc., Taunton, MA, USA) equipped with a 50 mm C-mount lens. Then, the dimensions of the whole tablet, of its solid phase and of the gel layer were evaluated using the software provided for the image analysis (CV9000, Version 4.0, FKV S.r.l., Sorisole, BG, Italy).

The viscosity measurements on pure PEOs were performed at 35 °C in 0.2% (w/v) water solution using an Ubbelhode viscosimeter. The reduced viscosity is evaluated according to the equation:

$$\eta_{\text{red}} = \frac{[(t/t_0) - 1]}{c} \tag{1}$$

where t is the time flow of the water polymeric solution, t_0 is the time flow of pure water and c is the concentration of the sample.

The EPR analysis on PEO powder was carried out to determine the possible chemical–structural modifications induced by gamma rays on the polymeric material. Using a Bruker 300 spectrometer in the temperature range 123–340 K using an automatic temperature control system and the Bruker data acquisition system. The computer simulation was performed using the Hamiltonian including the Zeeman electron and nuclear terms and the hf interaction:

$$H = \beta \bar{g} \vec{B} + \sum_i S\overline{A_i} I_i - \sum_i \beta_n \vec{I}_i \vec{B} \tag{2}$$

where β and β_n are electron and nuclear magnetons, g is g tensor, B is the magnetic field vector, A_i is the hyperfine tensor and S and I_i are electron and nuclear spin vectors.

The visible spectra of trapped electrons were obtained using polyethylene glycol as model compound since it has the same structure as PEO with repeating units –O–CH_2CH_2– but is a liquid at room temperature because of the lower molecular weight (∼5000 Da). Transparent ‘lenses’ of glassy polyethylene glycol were prepared by fast quenching the viscous fluid in liquid nitrogen kept within a removable walls aluminium container. The ‘lenses’ were then irradiated at 77 K with gamma doses of 3–5 kGy. After the irradiation the samples were located under liquid nitrogen into a dewar equipped with suprasil windows and their UV-Vis spectra were recorded on an HP diode UV-Vis spectrometer.

At the end, to confirm that the exposure to γ irradiation is the sole cause of the PEO matrices dissolution and morphological modifications, a stress test

was carried out (ICH Guidelines, 2001). X2 and X7 samples (non-irradiated) have been kept under storage condition of 40 °C and 75% R.H. for 6 months. After this time, a dissolution test was carried out.

3. Results and discussion

The data from dissolution tests performed on the three formulations (W40, X2 and X7) were analysed with the empirical equation (Ritger and Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \tag{3}$$

where M_t/M_∞ is the fraction of drug released; k is a constant characteristic of the system and n is the exponent for the release kinetics. For $n = 0.5$ drug release follows a Fickian transport mechanism, $0.5 < n < 1$ represents an anomalous diffusion and $n = 1$ a zero order release kinetic. A linear regression analysis of the logarithmic form of the Eq. (3) was carried out and a correlation coefficient $R^2 = 0.999$ was obtained in all cases.

For the PEO matrices the drug release rate is controlled by a combination of drug diffusion and polymer swelling, in fact the mechanism of the drug release process is anomalous ($n_{X2} = 0.771$, $n_{X7} = 0.767$). On the contrary PVA samples yield a square root of time kinetics (Higuchi, 1963): in fact, the release kinetics exponent n is 0.569 and it indicates a prevailing diffusive mechanism for drug release process.

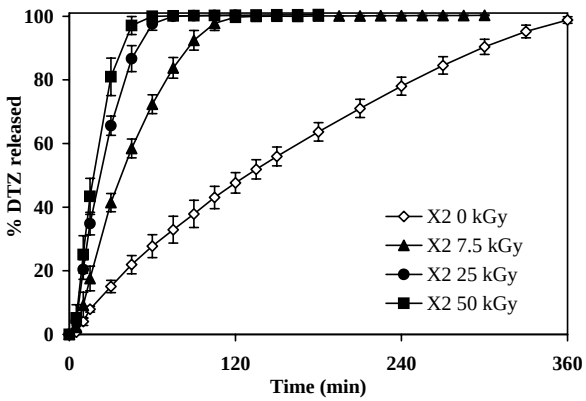

Fig. 2. Release profiles of diltiazem from the matrices containing PEO of lower molecular weight (X2) compared to the release profiles of X2 matrices gamma irradiated with doses of 7.5, 25 and 50 kGy.

By comparing the DTZ release profiles of the polyvinylalcohol tablets before and after gamma irradiation, no changes were observed (Fig. 1): the ionizing radiation does not significantly modify the dissolution trend of the dosage form.

On the other hand, the diltiazem release trends of the PEO tablets exposed to increasing doses of gamma irradiation show quite different behaviour compared to the original PEO matrices: the drug release rate was strongly affected by the radiation dose received. In particular, the dissolution rate of the irradiated samples dramatically increases as a function of the irradiation dose (Figs. 2 and 3). After exposure to the

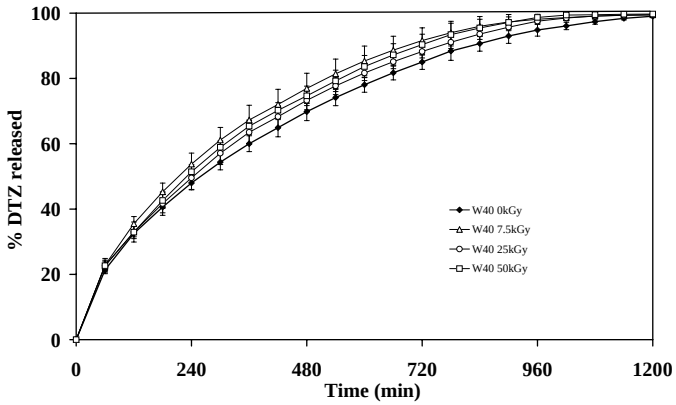

Fig. 1. Release profiles of diltiazem from PVA matrices (W40) before and after exposure to gamma radiation.

Table 1
Times needed to release 90% of drug content ($t_{d90\%}$) of the two PEO formulations (X2 and X7) before and after exposure to increasing doses of gamma rays

Dose of gamma-rays formulation	0 kGray $t_{d90\%}$(min)	7.5 kGray $t_{d90\%}$(min)	25 kGray $t_{d90\%}$(min)	50 kGray $t_{d90\%}$(min)
X2	300	86	50	38
X7	369	63	38	39

lowest dose of radiation (7.5 kGy), for both X2 and X7 tablets, the efficacy of the system in controlling and modulating the drug release is dramatically reduced. This reduction is confirmed by the $t_{d90\%}$ value, that is the time at which 90% of the drug is released (Table 1). This effect is already evident at the lowest dose of gamma irradiation; then the X2 and the X7 matrices irradiated to 25 and to 50 kGy completely loose their ability to control drug delivery, in fact the active compound is completely dissolved in less than 1 h or even in few minutes.

This extreme release performance can be explained by a dramatic difference in the dissolution behaviour of the PEO tablet after irradiation (compared to the original matrix tablet). A comparison of the photos of X2 samples during dissolution (before irradiation and irradiated with the lowest dose), at different time intervals, is reported in Fig. 4. The original tablets (non-irradiated) slowly hydrate, swell and give rise to a thick gel layer, which is responsible for controlling the drug release process. On the contrary, the X2 matrices irradiated even at the lowest dose, does not show any firm gel layer. A strong erosion/dissolution of the matrix is evident thus the system is no longer able to modulate the drug release process causing a marked increase in drug dissolution rate. For example, the X2 matrices after 30 min in dissolution show a solid core (in the photo dull and opaque) and a visible thick gel layer (transparent and glossy). The samples exposed to a dose of 7.5 kGy, on the other hand, after the same time in dissolution, show only a bulky core without any gel phase. The ephemeral gel layer formed at the tablet surface is not able to maintain its structural

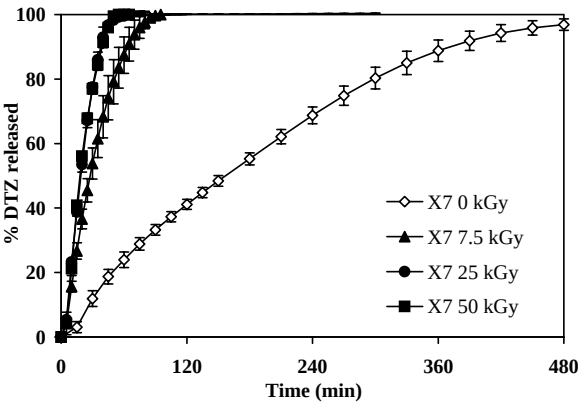

Fig. 3. Release profiles of diltiazem from the matrices containing the PEO of higher molecular weight (X7) compared to the release profiles of X7 matrices gamma irradiated with doses of 7.5, 25 and 50 kGy.

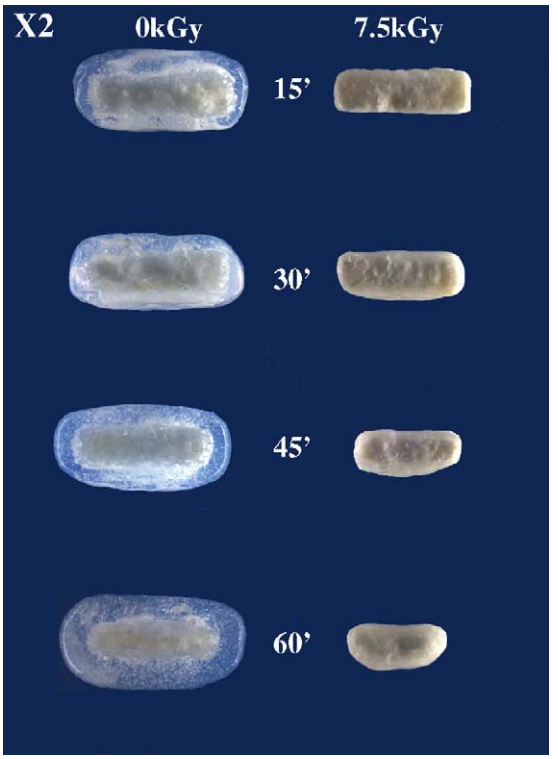

Fig. 4. Photographs of the X2 tablets during dissolution: first column before irradiation, second column samples exposed to 7.5 kGy of irradiation. From top to bottom: after 15, 30, 45 and 60 min of dissolution test.

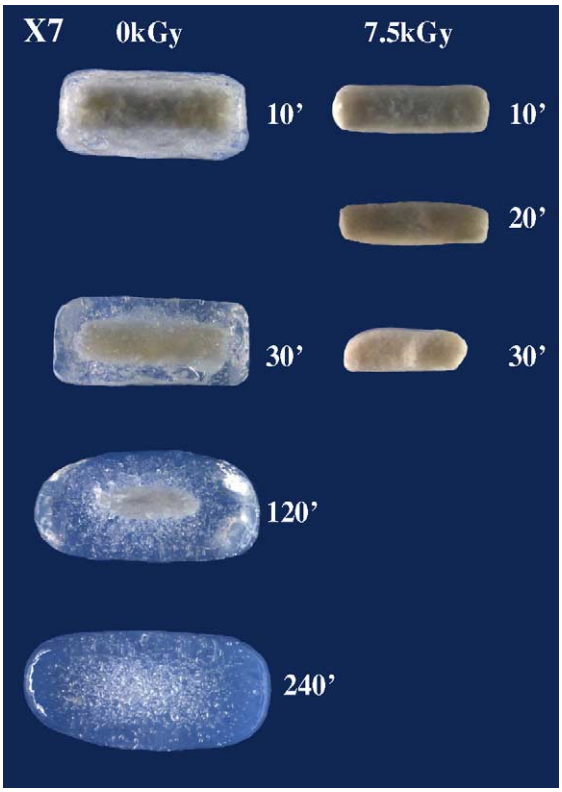

Fig. 5. Photographs of the X7 matrices during dissolution: first column before irradiation, (from top to bottom: after 10, 30, 120 and 240 min of dissolution test); second column samples irradiated with a dose of 7.5 kGy of gamma irradiation (from top to bottom: after 10, 20 and 30 min).

integrity and is rapidly removed by the dissolution fluid. As a consequence of this process the irradiated tablets dissolve rapidly and their dimensions decrease quickly compared to the references. The same behaviour can be observed in X7 formulation and as they contain a higher molecular weight PEO, the morphological differences between the irradiated and the not irradiated samples are more marked (Fig. 5). In the case of PVA samples no significant differences can be detected in the dissolution behaviour of the tablets before and after exposure even to the highest dose of radiation (50 kGy). In fact, by observing the photos of the original matrices and of the irradiated ones (Fig. 6), it is evident that their morphological behaviour is practically comparable. In both cases the tablets swell and form a gel layer, which controls the drug release process. The results of the swelling studies are reported also in Fig. 7, obtained by plotting the matrices volume percent modification versus the matrices gel layer increase. Observing this graph, it is easy to identify the process that characterized the matrices dissolution behaviour: when a swelling behaviour prevails, a continuous and contemporary increase of tablets volume and gel layer thickness can be observed (trends towards right side of the graph). On the other hand, if the erosion rate prevails on swelling, a volume decrease is coupled to a very thin and constant gel layer formation (Conte et al., 1993). PVA tablets, whether exposed to gamma rays, show a volume increase and simultaneous gel thickness increase, which are indicative of the presence of a swelling process that characterises the dissolution behaviour of the samples for a given time, then the systems start to dissolve when the erosion process prevails (trend elbow). X2 and X7 tablets show a swelling behaviour only before exposure to the radiation; after gamma irradiation the swelling process is replaced by a fast

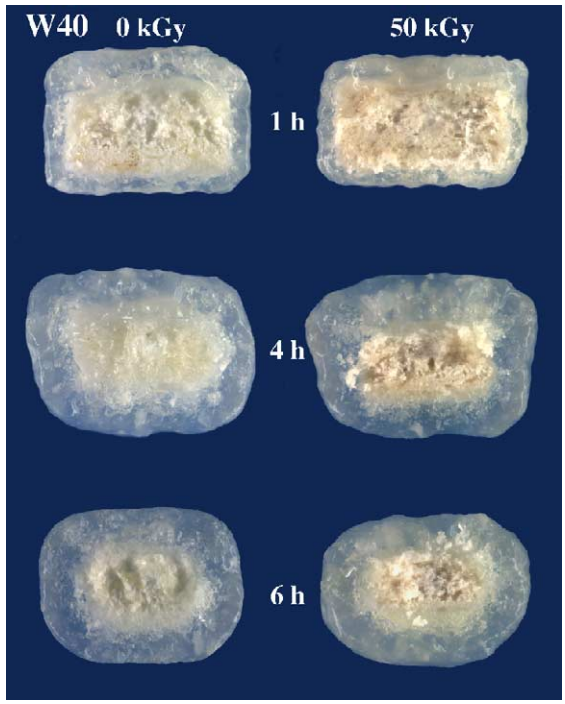

Fig. 6. Photographs of the W40 tablets during dissolution: first column before irradiation, second column samples exposed to the higher dose of irradiation (50 kGy). From top to bottom: after 1, 4 and 6 h.

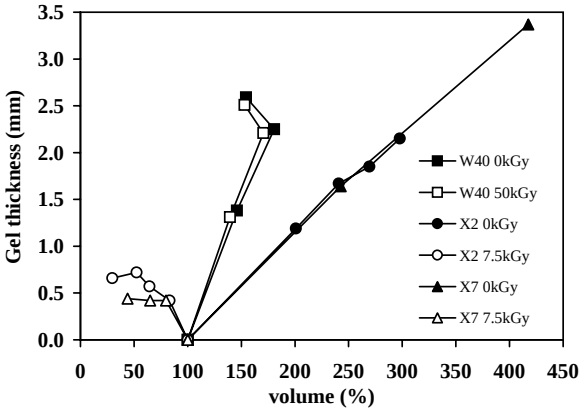

Fig. 7. Volume percent modification vs. gel layer thickness measured on matrices made with the three different hydrophilic polymers (PEO MW = 2×10^6, PEO MW = 7×10^6 and PVA). The gamma irradiation doses reported are 7.5 kGy for PEO samples and 50 kGy for PVA samples.

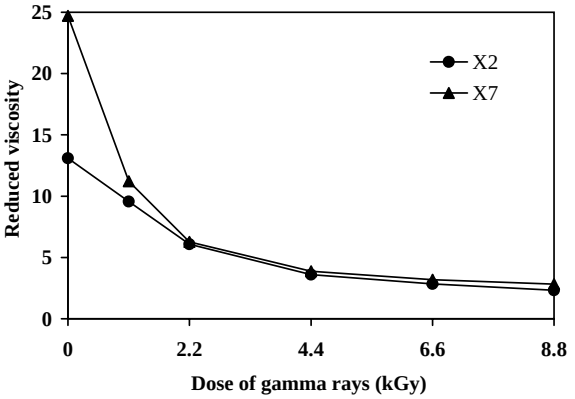

Fig. 8. Effect of the gamma dose on the reduced viscosity of PEO X2 and PEO X7 having different average molecular weight.

erosion process. In fact, Fig. 7 shows clearly how, soon afterwards the exposure to the very lowest dose of radiation, the volume of the samples does not increase very much and the gel layer grows thinner and then it is maintained constant by erosion at the surface of the X2 and X7 tablets. The very soft gel layer is not able to withstand the action of the dissolution medium and it is continuously removed. The erosion process is responsible for the rapid reduction of the dimensions of the irradiated tablets and for their quick dissolution.

The changes of the dissolution and morphological behaviour of PEO matrices could be explained by the polymeric chains rupture caused by the exposure to gamma rays. This breaking determines a reduction of PEO molecular weight that could be the determining factor of the reduced ability of the polymer in controlling and modulating the drug release process. These assumptions can be confirmed by the viscosity tests (Fig. 8).

A rapid decrease of viscosity of the polymer (in water solutions) is seen after gamma irradiation. Even after the exposure to the very lowest dose of gamma rays (1.1 kGy), whether PEO X2 and particularly PEO X7 show a rapid and drastic reduction of the viscosity, followed by a more slow decrease with increasing the irradiation dose. In fact, when pure PEO is irradiated in the solid state, chain scission is prevalent leading to a continuous decrease of the reduced viscosity with increasing radiation dose (Dole, 1972).

A rationale of this degradation process is obtained when considering the nature and evolution of the paramagnetic intermediates in the radiolysis process as detected by EPR spectroscopy (Fig. 9). The initial spectrum recorded at 123 K after irradiation at 77 K is mainly a triplet of about 15 G average peak to peak separation centred at $g = 2.0033$. On warming at 173 K a significant enhancement of the resolution occurs presumably because of the decay of triplet signals due to radical couples. According to the computer simulation this latter signal can be accounted for in terms of the interaction of one α-proton with coupling of 15.4 G and two non-equivalent β-protons of 11.0 and 3.8 G as expected for the radical $–CH_2CH^{\bullet}O–$.

The computer simulation is also compatible with the presence of a minor amount of a second species, the chain scission radical $–OCH_2^{\bullet}$ whose relative abundance, however, does not exceed ca. 10%.

Further warming to 298 K causes the progressive build up of a novel signal consisting of a doublet of 15.6 G having the centre shifted toward low field with respect to the free electron value ($g = 2.0056$) (Fig. 9). These hf features are safely reckoned with the aldehydic radical of formula:

$–O–CH^{\bullet}–CH(=O)$

The ionization of PEO is expected to afford cation radicals with the unpaired spin centred on the oxygen atoms. The intra or inter-molecular proton transfer to

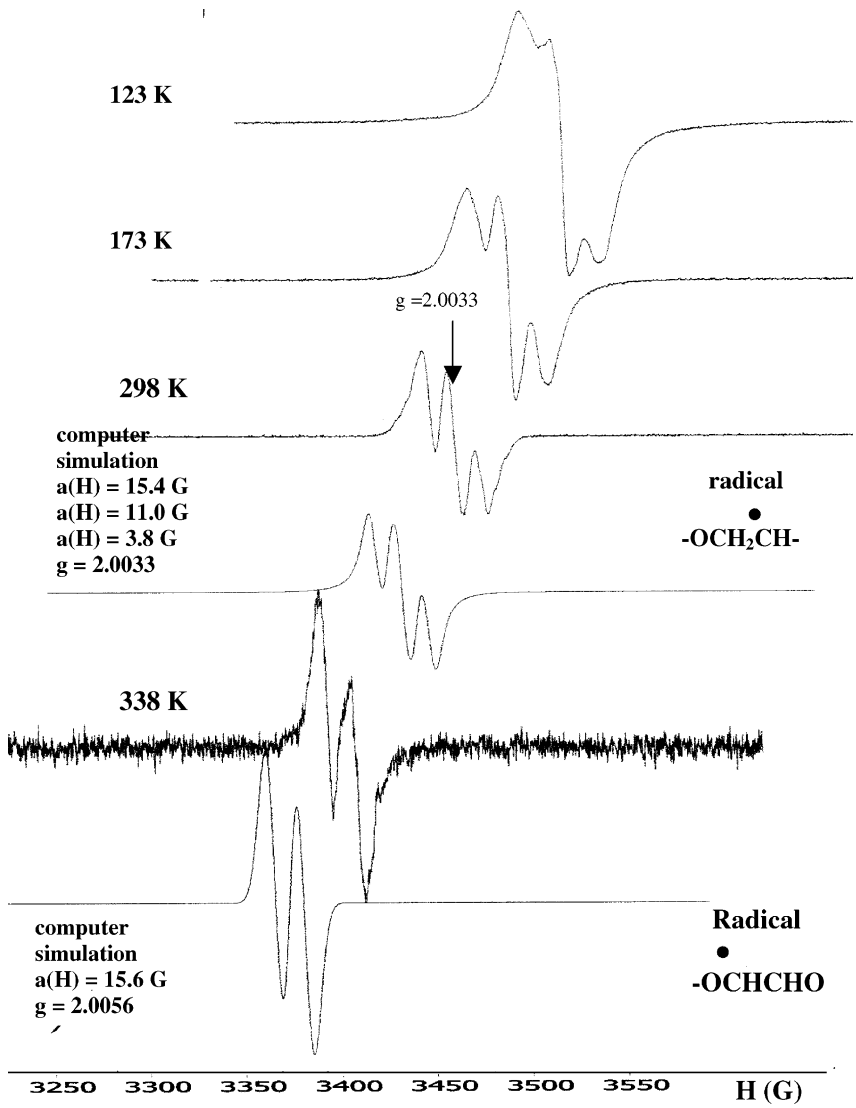

Fig. 9. EPR spectra of the radiolytic intermediates obtained from PEO samples after gamma irradiation at 77 K under vacuum followed by the progressive warming to room temperature. Gamma dose: 15 kGy.

the charged oxygen would then result in the formation of the hydrogen abstraction radicals $–CH_2CH^{\bullet}–O–$ and protonated diamagnetic ether units. The charge neutralization of this latter species with the ejected electrons can afford H atoms which in turn are expected to contribute other $–OCH_2CH^{\bullet}O–$ radicals and molecular hydrogen.

The coupling of the secondary radicals $–OCH_2CH^{\bullet}O–$ leads to the formation of crosslinks. However, such species are thermally unstable and near room temperature undergo β-scission thus causing chain scissions and forming aldehydic chain ends $–CH_2C(=O)H$. The formation of the aldehydic units in close proximity with the chain radical $–OCH_2^{\bullet}$ can favour the H abstraction with formation of the aldehydic radicals $–CH^{\bullet}CH(=O)$. The detection of $–CH^{\bullet}CH(=O)$ radicals can thus be considered a direct EPR evidence of the chain scission events.

4. Conclusions

The exposure to increasing doses of gamma irradiation has different effects on the polymers employed in this work as drug modulators: PVA tablets are not affected by this kind of radiation and are able to guarantee a good control of the drug release process even after irradiation with higher dose level. On the other hand, PEO matrices are strongly affected by gamma irradiation and their ability to control drug release fails. Before and after irradiation, a different dissolution and morphological behaviour is evidenced. The swelling-gelling process, which controls the drug release from the original PEO matrices, is replaced by a quick erosion behaviour in the case of the irradiated samples and this causes the rapid dissolution of the tablets.

The different dissolution and morphological behaviour of the PEO matrices before and after exposure to gamma irradiation can be explained by polymeric chain rupture to which polyethylene oxides undergo after irradiation in the solid state. The breaking of the polymeric molecules is responsible for the reduction of polymer molecular weight (EPR study) and thus of polymer viscosity. As a consequence, the efficacy of the PEO drug delivery systems in controlling the drug release is lost.

Acknowledgements

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (COFIN 2002) and by the University of Pavia (Progetto di Ateneo).

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