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European Journal of Pharmaceutics and Biopharmaceutics 55 (2003) 99–105

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Photostability of extended-release matrix formulations

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Received 11 October 2001; accepted in revised form 29 August 2002

Abstract

The photostability of drugs has been widely studied while less attention is devoted to the possible modifications that UV light may induce on the excipients of a dosage form, in particular, on the functional polymers used to modulate drug delivery. In this work we have evaluated the effect of UV light on the release characteristics of extended-release matrix tablets containing hydroxypropylmethylcellulose (HPMC) or polyethylene oxide (PEO) as retarding polymers. Two different model drugs have been used: nifedipine (insoluble and photolabile drug) and diltiazem (soluble and photostable drug). Photodecomposition of nifedipine was evaluated and the formation of the photoproducts was followed during the dissolution process. Regarding the dissolution stability, the matrix tablets containing HPMC exposed to UV light have not shown significant differences in drug release profiles compared to the same non-irradiated formulation, while the matrix tablets containing PEO and exposed to the same conditions of UV light have shown a remarkable increase of drug release rate within the first minutes of the dissolution test (burst effect) which is particularly critical because it can cause the loss of the desired therapeutic control.

Keywords: UV light; Photostability; Extended release; Matrix tablet; Nifedipine; Diltiazem; Polyethylene oxide; Hydroxypropylmethylcellulose

1. Introduction

Preformulation studies of a new dosage form include chemical and physical stability testing of the drug alone and/or in presence of excipients. Heat and moisture have been commonly used as environmental factors in stress testing. But in the last years, many studies have demonstrated the effect of light on the physical chemical stability of some drugs, and light is also considered as an environmental factor to be evaluated in preformulation studies [1]. The ICH Harmonized Tripartite Guideline considers that light testing should be an integral part of stress testing and recommends evaluation of the photostability of a drug to demonstrate that light exposure does not result in unacceptable changes [2].

Although the photostability of drugs has been widely studied whether in solid state [3], in solutions [4] or in dosage forms [5], there are no reports concerning the effect of UV light on the excipients used for drug formulation, in particular, on the efficiency of the functional polymeric materials used to prolong drug release in extended-release formulations. In this work, we have evaluated the effect of UV light on the stability of the drug and also on the stability of two polymers used frequently to prolong drug release from extended-release dosage forms. In fact, possible changes of the dissolution behaviour of controlled-released matrix tablets could cause undesired effects because the dosage form is designed to provide a precise delivery rate of the drug.

Nifedipine (NIF) was used as model drug because it is highly sensitive to photodegradation whether in solution or in solid state. Upon exposure to ultraviolet light, NIF degrades to dimethyl 4-(2-nitrosophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate [2] (nitroso derivative) and dimethyl 4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate [3] (nitro derivative) [6]. On the basis of this information, the photostability of NIF present in the extended-release formulations was evaluated by an HPLC method.

Two extended-release formulations containing NIF were prepared using two different drug-delivery modulators: hydroxypropylmethylcellulose (HPMC) and polyethylene oxide (PEO). High-viscosity HPMCs are the most commonly used polymers for the preparation of extended release matrices [7,8]. More recently, high molecular weight polyethylene oxides have been proposed as drug-release modulators [9,10] but no information is available about

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doi:10.1016/S0939-6411(02)00126-1

the effect of UV irradiation on the molecular structures of both polymers, which are responsible for the release mechanism of the delivery device.

NIF is insoluble in water, thus its dissolution rate was enhanced using a previously tested technique [11], and the drug was thoroughly mixed with a superdisgregant and formulated in a hydrophilic swellable matrix, using either HPMC or PEO. For these reasons the drug release process does not depend only on the retarding polymer used, but is strongly influenced by other formulation excipients. Thus, to evaluate the effect of UV light exposure on the release characteristics of the two polymers considered without the interference of other excipients, simple matrix tablets containing only a soluble drug and HPMC or PEO were prepared and exposed to the same irradiation conditions used for NIF formulations. Diltiazem hydrochloride (DTZ) was chosen as second model drug because it is freely soluble in water [12], and photostable to UV light in the solid state [13].

2. Materials and methods

2.1. Materials

Industria Chimica Italiana S.p.A., Milan, Italy supplied nifedipine (NIF), while diltiazem hydrochloride (DTZ) was obtained from Profarmaco S.p.A., Milan, Italy. Cross-linked sodium carboxymethylcellulose (ACDISOL) was supplied by FMC Corp., Philadelphia, PA, USA. Hydroxypropylmethylcellulose (Methocel K15M $\eta = 15\,000$ cP and Methocel K100M $\eta = 100\,000$ cP) (K15M and K100M) were kindly donated by Colorcon, Orpington, UK. Polyethylene oxide (Polyox WSR N60K molecular weight = 2 000 000) (PEO) was supplied by Union Carbide, Danbury, CT, USA. Additionally the following excipients were used: polyvinylpyrrolidone (Povidone K30, ISP, Wyne, NY, USA), colloidal silicon dioxide (Syloid 244, Grace GmbH, Worms, Germany), magnesium stearate, and talc (Carlo Erba, Milan, Italy).

2.2. Tablet preparation

The tablet compositions containing NIF are reported in Table 1.

NIF is practically insoluble in water; for this reason, cross-linked sodium carboxymethylcellulose (SCMC) was used as hydrophilic carrier to enhance NIF dissolution. The drug was previously mixed with SCMC in a Turbula mixer (Type T2A, Bachofen, Basel, CH) for 2 h. For the preparation of NIF prolonged-release tablets, the drug-carrier system was mixed with the retarding polymers: K15M for NFUV1 formulation, or PEO for NFUV2 formulation. Both mixtures were then moistened with a 20% polyvinylpyrrolidone ethanolic solution. The wet mass was forced through a 25-mesh sieve (710 μm). The granules were dried at 40 °C until a constant weight was achieved and then calibrated through the same sieve. The lubricants were added to the dry granules, and mixed for 15 min in the Turbula apparatus.

For both formulations, tablets were prepared with 60 mg of drug content corresponding to 240 mg of total weight (Korsh EK0, Berlin, D, 10 mm punches). The crushing strength of the NFUV1 and NFUV2 formulations were 130 and 120 N, respectively. The tablets were not coated with a light-protective film, with the aim of evaluating the effect of UV light on the overall delivery device.

DTZ matrices were prepared by simply mixing 63.5% of DTZ and 36.5% of K100M (DTZUV1) or 36.5% of PEO (DTZUV2) in the Turbula apparatus. The two different mixtures were compressed with a single-punch tableting machine equipped with flat punches of 9.5 mm in diameter (Kilian, Cologne, Germany). DTZ tablets contain a dose of 180 mg of drug corresponding to 283 mg of total weight. The crushing strengths of DTZUV1 and DTZUV2 formulations were 230 and 90 N, respectively.

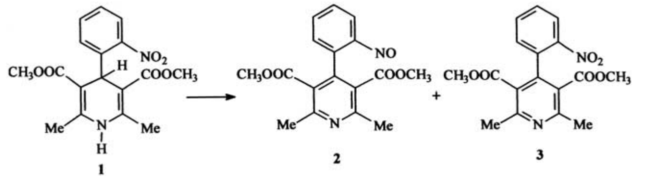
2.3. Irradiation conditions

The tablets prepared as above were irradiated in a photostability cabinet fitted with 2 × 20 W phosphor-coated lamps (λ_{max} 366 nm) at 12 cm distance. The light flux was measured by means of a calibrated radiometer and found to be 1.2 ± 0.1 mWcm^{-2}. Tablets were reversed at half time and sampled at 20 h, 40 h, 4 days, 12 days and 25 days for NIF tablets or 20 h, 12 days and 25 days in the case of DTZ matrices. Non-irradiated tablets and irradiated tablets were submitted to a dissolution test as well as to the assay of residual nifedipine content and photoproducts formed.

Samples of pure K15M and PEO were spread in very thin

Table 1
Composition (%) of the two extended-release formulations containing nifedipine

Components	NFUV1 (%)	NFUV2 (%)
Nifedipine	25	25
Cross-linked sodium carboxymethylcellulose (ACDISOL, FMC)	30	30
Hydroxypropylmethylcellulose (Methocel K15M)	30	–
Polyethylene oxide (Polyox WSR N60K)	–	30
Polyvinylpyrrolidone (Povidone K30)	9	9
Talc	4	4
Magnesium stearate	1.5	1.5
Colloidal silicon dioxide (Syloid Al 1)	0.5	0.5



Scheme 1. Nifedipine (**1**) and photoproducts: nitroso derivative (**2**) and nitroderivative (**3**).

layers and irradiated for 20 h, 4 days, 12 days and 25 days at the same conditions as above and then the viscosity of the their aqueous solutions was determined.

2.4. Dissolution tests

The dissolution tests of tablets containing NIF were performed using the USP apparatus 1 (basket, 100 rpm), in 1 l of distilled water containing 0.75% of sodium lauryl sulphate at 37 °C. The dissolution tests of matrix containing DTZ were performed in 1 l of distilled water, at 37 °C, with the USP apparatus 2 (paddle) at 100 rpm. The amount of drug released was assessed by UV detection at 237 nm (for NIF) and 236 nm (for DTZ) (Spectracomp 602, Advanced Products, Milan, Italy). During the dissolution tests of NFUV1 and NFUV2 formulations some samples of the dissolution medium were taken at 2, 4, 7 and 24 h to evaluate the concentration of the possible photoproducts formed during the release process. All the dissolution equipment was protected from light exposure.

2.5. Determination of NIF and its degradation products

The assays of residual NIF content in the tablets, and photoproducts formed after irradiation, were carried out by dispersing the tablets in methanol (500 ml/tablet for NIF determination and 50 ml/tablet for photoproduct determination) filtering and analysing the solution by HPLC (Purosphere RP18, 5μ column, 250-4, 30:70 water/methanol mixture as the eluant, 0.5 ml/min, detection at 238 nm). The retention times of NIF, nitroso derivative and nitro derivative were 10, 8.6 and 7.8 min, respectively. NIF and its photoproducts were measured on the basis of suitable calibration curves.

2.6. Viscosity measurements of aqueous solutions of polymers

Aqueous solutions of K15M (2% w/w) and PEO (4% w/w) were prepared from non-irradiated polymers and from 20-h-, 4-day-, 12-day- and 25-day-irradiated samples of polymers. The viscosity of these solutions was determined using a rotational viscometer (Viscotester VT7 R, Haake, Karlsruhe, Germany) with a TR9 spindle, in the shear rate range of 0.68–17 s^{-1}. All the solutions were tested at 23 °C and only the data obtained at 1.7 s^{-1} are reported (average of three runs). Solutions prepared from 12-day- and 25-day-irradiated PEO were not measured because to low and their viscosity was out of the determination range of the apparatus

3. Results and discussion

The irradiation of nifedipine (**1**) contained in the tablets causes a partial conversion into dimethyl 4-(2-nitrosophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**2**) and dimethyl 4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (**3**) (Scheme 1). The data are reported in Table 2 for NFUV1 and Table 3 for NFUV2. The results show that the photodecomposition of **1** is limited, though clearly above the error limits. For NFUV1, the limit of 7% conversion of **1** is reached at 5 days of UV irradiation and does not increase significantly afterwards (25 days). Correspondingly, the amount of photoproducts formed increases only slowly after 5 days (the main product **2** reaches ca. 4% level, with ca. 0.3% of the minor compound **3**). Together, the identified products **2** and **3** account for 75–85% of the converted NIF for both formulations. These are the same products obtained by irradiation in solution and also the ratio found is similar (unpublished results from the author's laboratory). Apparently, the reaction occurs in the same way also in the crystals, which is not unexpected since it involves intramolecular attack of the nitro group onto the neighbouring benzyl hydrogen atom, reasonably not hindered by the rigidity of the crystal lattice.

Table 2
Conversion of nifedipine and formation of photoproducts from NFUV1 tablets after UV irradiation

Irr. time	Nifedipine **1**		Photoproduct **2**[a]			Photoproduct **3**[a]		
	mg	% converted	mg	% of initial amount	% of converted NIF	mg	% of initial amount	% of converted NIF
Before irr.	60.0	–	–	–	–	–	–	–
20 h	58.5	2.5	1.5	2.6	106	0.2	0.3	13.5
40 h	57.5	4.2	1.6	2.8	70	0.2	0.3	8.1
4 days	56.5	5.8	1.9	3.3	58	0.3	0.5	8.7
5 days	56.0	7.0	2.1	3.7	55	0.2	0.3	5.0
25 days	55.5	7.5	2.8	4.9	66	0.4	0.7	8.9

[a] Percentages of 2 and 3 were calculated with reference to initial amount of NF converted after irradiation.

Table 3
Conversion of nifedipine and formation of photoproducts from NFUV2 tablets after UV irradiation

Irr. time	Nifedipine **1**		Photoproduct **2**[a]			Photoproduct **3**[a]		
	mg	% converted	mg	%of initial amount	% of converted NIF	mg	% of initial amount	% of converted NIF
Before irr.	63.0	–	–	–	–	–	–	–
20 h	61.0	3.2	1.9	3.2	99.8	0.10	0.16	5.0
40 h	59.0	6.3	2.8	4.7	73.6	0.15	0.24	3.8
4 days	59.0	6.3	2.9	4.9	76.2	0.20	0.32	5.0
5 days	59.5	5.6	2.9	4.8	88.4	0.20	0.32	5.8
25 days	59.0	6.3	2.9	4.9	76.2	0.20	0.32	5.0

[a] Percentages of 2 and 3 were calculated with reference to initial amount of NF converted after irradiation.

The limited amount of drug reacting is due to the limit in light penetration in the sample. In accordance with this postulate, the results of the analysis of photodegradation products carried out during the dissolution test of NFUV1 show that tablets irradiated for 25 days release the whole amount of the photoproducts within 4 h (Fig. 1) when less than half of the dose of NIF has been released (Fig. 1). Similar behaviour was found for NFUV2 tablets.

The light absorbed in 20 h corresponds to the dose prescribed by the ICH Guideline for Photostability for confirmatory test [2]. The amount of photodegradation product **2** formed at this time exceeds the allowed limits indicated in USP 24 for NIF capsules (<0.5% relative to the Nifedipine content) [14].

The extended-release formulation containing NIF and HPMC (NFUV1) is able to deliver the drug over a prolonged time at a constant rate. The exposure to UV light does not significantly modify the dissolution trend of the dosage form (Fig. 2).

Using PEO of very high molecular weight, slower release rate can be obtained from NFUV2 compared to the NFUV1 formulation. In fact, NFUV2 matrices are able to deliver the drug in about 16 h, and a linear trend is maintained (Fig. 3). By comparing the dissolution behaviour of non-irradiated NFUV2 tablets and after 20 h or 4 days of UV exposure, similar profiles were obtained. But in the case of 25-day-irradiated NFUV2 tablets, a faster drug release was found in the first minutes of the dissolution test (burst effect) compared to the same non-irradiated tablets (Fig. 3). The burst release caused by UV-irradiation produces a displacement of the dissolution profile, advancing the whole dissolution process by about 4 h. Therefore, 25-day-irradiated NFUV2 tablets release the dose within 12 h, while non-irradiated tablets deliver the whole dose within 16 h. Although we have verified that the course of the drug photoreaction is the same in both extended-release formulations, the influence of UV-irradiation on the dissolution profile is clearly different with very little effect in NFUV1 and a marked increase of the drug dissolution rate in NFUV2. UV light exposure produces an increase in the delivery rate during the first phase of the dissolution test, but does not influence the ability of the polymer inside the matrix to retard the drug release. In accord with this rationalization, the percentage of drug released within 30 min for NFUV2 before irradiation is about 2% while this percentage increases progressively to about 12% for tablets exposed for 25 days to UV light (Fig.4). In the case of 20-h- or 4-day-irradiated tablets, this burst effect (in terms of drug released within 30 min) is rather small and does not show a relevant influence on the rest of the dissolution profile. In the case of NFUV1 (tablets containing HPMC) the percentage of drug released within 30 min is comparable for non-irradiated tablets and for 20-h-, 4-day- and 25-day-irradiated tablets.

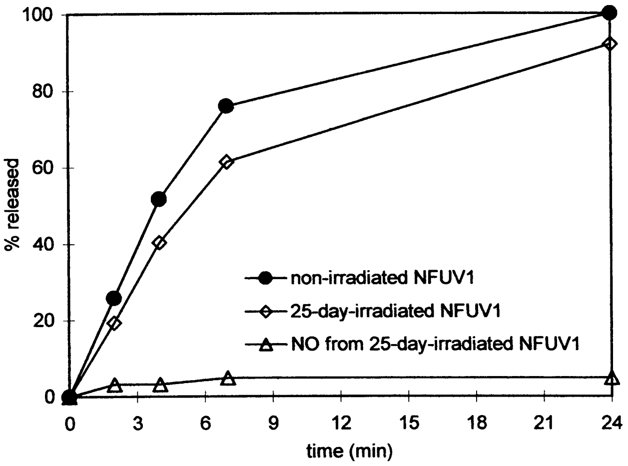


Fig. 1. Dissolution profile of NIF from NFUV1 before and after 25 days of UV irradiation, and dissolution profile of nitrosoderivative **2** (NO) from NFUV1 tablets irradiated for 25 days.

In comparison, the dissolution tests performed on the DTZ:polymer matrices (DTZ:K100M or DTZ:PEO) exposed to the same irradiation condition used for NIF tablets have shown that in matrices containing DTZ and K100M (DTZUV1) the drug is delivered within 16 h. The exposure to UV light does not significantly modify the release rate of DTZ from the device (Fig. 5); the small difference in the dissolution profile of the 25-day-irradiated tablets is within the standard deviation. In a previous study we verified that HPMC used to modulate drug-delivery rates could be altered when exposed to high-energy radiation, (γ rays) [15]. Instead, the low-energy irradiation (UV-VIS) used in this study does not significantly affect the release

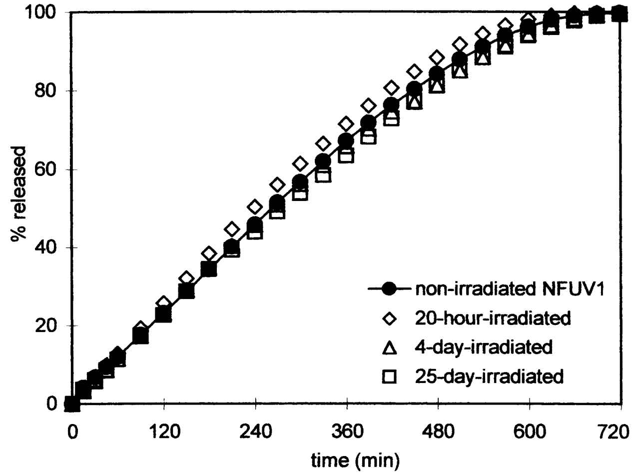


Fig. 2. Dissolution profiles of NFUV1, before and after UV irradiation.

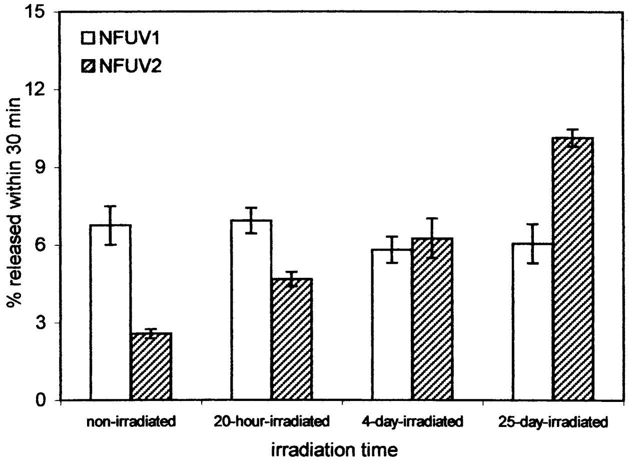


Fig. 4. Percentage of NIF released after 30 min from NFUV1 and NFUV2 as a function of irradiation time.

characteristics of the formulations prepared with this kind of polymer.

For DTZ matrices containing PEO (DTZUV2), the exposure to UV light for 20 h does not modify the release trend of the drug, while 12- and 25-day-irradiated tablets showed a dramatic increase of the burst effect: it means that the polymer when exposed to UV light for a prolonged time, is no more able to control the drug release (Fig. 6), the increase of the burst effect strongly depends on the exposure time to UV-irradiation. In fact, the percentage of drug released within 30 min for non-irradiated DTZUV2 was about 15% and this parameter was not significantly changed when tablets were irradiated for 20 h, while this percentage increased progressively to about 30 and 55% when tablets were irradiated for 12 and 25 days (Fig. 7).

The viscosities of the solutions prepared with non-irradiated and UV-irradiated K15M are very similar, and no changes in the release mechanism for this polymer were detected from the dissolution tests. On the other hand, PEO solutions prepared from irradiated polymer show a remarkable decrease in viscosity compared to the starting material (Fig. 8). This decrease is strictly related to UV light exposure time. After 12 or 25 days of UV-irradiation, the polymer solutions at 4% concentration were too low and out of the range of detection of the viscometer. For this polymer, the damage caused by UV-irradiation on the macromolecular chain evidenced by the viscosity decrease can explain the loss of efficiency in the control of drug release (burst effect).

The damage to the retarding polymer occurs only on the surface exposed to the light. This damage may cause a lowering of the molecular weight, therefore a lowering of the viscosity and the ability of the polymer to control drug release from the matrix surface.

The above results show that high molecular weight PEO is sensitive to light independently of the drug incorporated and of the additives present. The linear chain structure of this polymer makes it more susceptible to radical initiated degradation and it is conceivable that under irradiation, particularly in presence of oxygen, radicals are formed. It

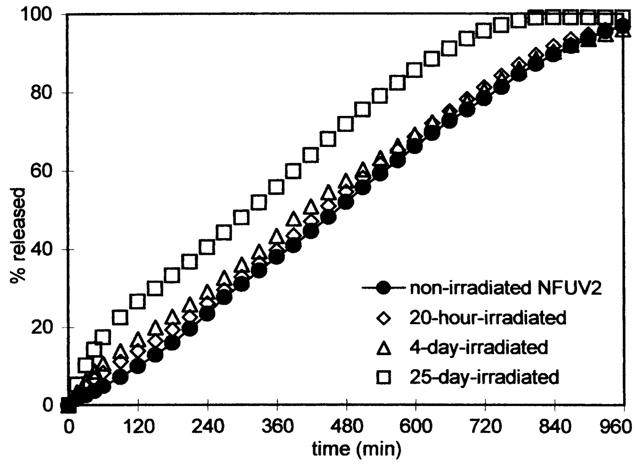


Fig. 3. Dissolution profiles of NFUV2, before and after UV irradiation.

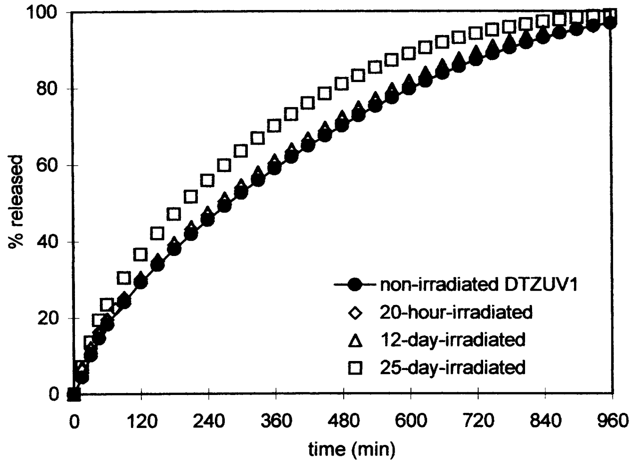


Fig. 5. Dissolution profiles of DTZUV1, before and after UV irradiation.

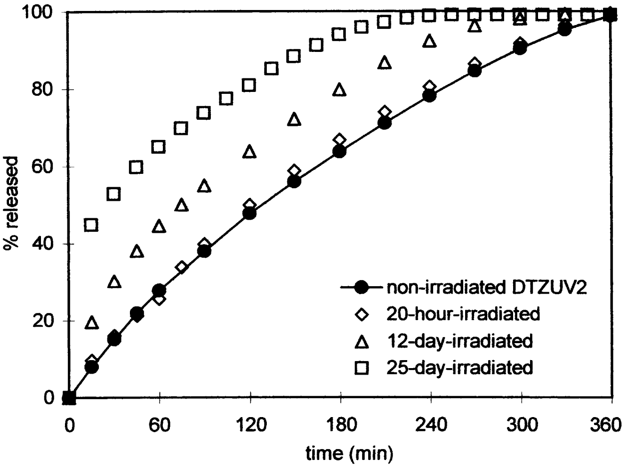


Fig. 6. Dissolution profiles of DTZUV2, before and after UV irradiation.

should be noted, however, that this effect is noticeable only after prolonged irradiation (25 days), much above the recommended dose for confirmatory studies of photostability.

4. Conclusions

As expected, in the tablets containing NIF, without proper light protection and exposed to the dose prescribed for confirmatory test, the level of photoproducts formed exceed the accepted limits. However, under the more severe conditions of a stress test, the photodecomposition of NIF increases more gradually because, as is generally observed, the UV irradiation does not penetrate below the first molecular layers. The confirmatory test does not reveal significant differences in the dissolution trend of the extended-release formulation tested, while the release profiles of tablets made of PEO show a remarkable loss of drug control efficacy after more prolonged UV-irradiation. Although such stress tests have no immediate bearing on the evaluation of these matrices for quality assurance purposes, they do point to a possible failure of the release characteristics of dosage forms. It may be that such a failure occurs more rapidly under different conditions and this certainly warrants further studies. These data, albeit preliminary, suggest that the photoinduced changes in the matrix (in particular of polymeric material whose physical properties are drastically altered even by a limited chemical decomposition) should be evaluated in parallel with the change of the drug component in preformulation studies, since changes in dissolution behaviour as those observed in this study can cause the loss of the desired therapeutic effect.

Further experiments are in progress to deepen the knowledge of the effect of UV light on retarding polymers used to prolong drug release from matrix-tablet formulations.

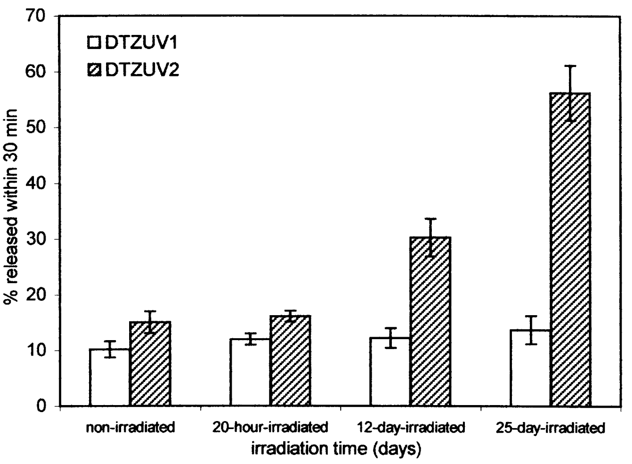


Fig. 7. Percentage of DTZ released after 30 min from DTZUV1 and DTZUV2 as a function of irradiation time.

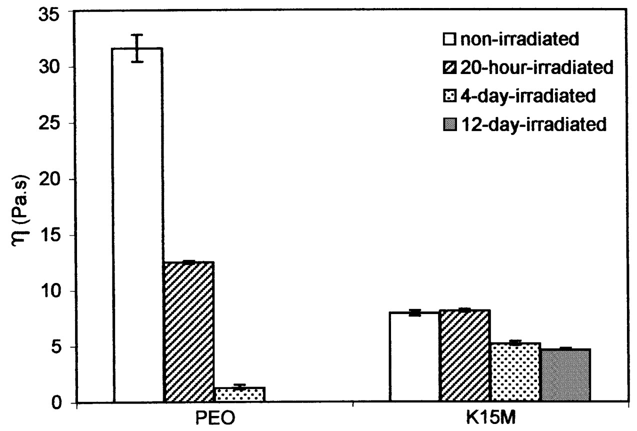


Fig. 8. Viscosity values at a shear rate of 1.7 s^{-1} of PEO and K15M solutions prepared from non-irradiated and irradiated polymers.

Acknowledgements

This work was partially supported by 'Progetto di Ricerca di Ateneo' University of Pavia, and by 'Programma di Ricerca Scientifica di Rilevante Interese Nazionale' MM03228583-2000.

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