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Effect of UV light exposure on hydrophilic polymers used as drug release modulators in solid dosage forms

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The effects of UV light on hydrophilic polymers used as drug release modulators in matrix-tablets are evaluated. Three different polymers were chosen for this study: hydroxypropylmethyl cellulose (HPMC), polyethylene oxide (PEO) and polyvinyl alcohol (PVA). Diltiazem hydrocloride, a well-known photostable molecule, was chosen as model drug. When matrix tablets prepared with PEO or with HPMC of higher viscosity grade were exposed to UV irradiation, displacements of the drug release profiles were observed compared to the dissolution profile of the non-irradiated samples. In the case of PVA tablets, the exposure to UV light did not modify the dissolution profile of the matrices. The polymers that showed to be affected by UV irradiation, were then subjected to viscosity measurements. The rheological analysis indicates that viscosities of solutions prepared with irradiated PEO were much lower compared to the solution prepared with non-irradiated polymer. The same results, but less evident, were found for HPMC.

Keywords: Hydroxypropylmethyl cellulose – Polyethylene oxide – Polyvinyl alcohol – UV irradiation – Matrix tablets – Dissolution test – Viscosity.

High molecular weight HPMC, PEO and PVA are hydrophilic polymers well known for their ability to swell and to form a gel in aqueous medium. For these reasons these polymers are used for the preparation of extended-released matrix tablets.

It is known that most polymers are liable to photodegradation to some degree and many studies on this topic are available in the literature. However, the effect that unwanted exposition to light may have on the pharmaceutical properties of modified released oral dosage forms has received little attention. Therefore, we decided to explore the modification on hydrophilic polymers used as drug release modulators under UV-A light, similar to that present in the environment, and following the UV irradiation conditions recommended by ICH guidelines [1].

As for previous literature, HPMC is a cellulose ether widely used in food and pharmaceutical industry. HPMC has many pharmaceutical applications as coating agent, emulsifier, viscosant and drug release modulator. HPMC is the first choice for the formulation of hydrophilic matrix systems, providing a reliable mechanism for the slow release of drugs from oral solid dosage forms.

In a previous work [2], it has been shown that extended-release matrices prepared with HPMC and irradiated with gamma rays showed alterations in the drug release profiles compared to the non-irradiated matrix, and it was demonstrated that the molecular structure of HPMC could be modified by gamma rays. In another publication, extended-release matrix formulations containing HPMC were exposed to UV light: no differences in drug release rate were found in the irradiated formulation compared to non-irradiated formulation, even after prolonged exposure time [3]. A work published in 1972 [4] demonstrated that it was possible to induce light degradation in aqueous HPMC solutions by the addition of sodium nitrite and rheological analysis indicated that chain scission was the primary process of polymer degradation. However, this was due to the action of peroxides formed in the photolysis of nitrite.

PEO is a non-ionic hydrophilic polymer with several industrial and biomedical applications. In pharmaceutical field, PEO is used as drug release modulator in extended-release solid formulations [5]. Although this kind of polymer should not absorb low wavelength radiation, the oxygen bridges, present in the PEO chain, make it susceptible to light degradation [6]. The photoreactions of such polymer are induced by structural defects, impurities or additives [6]. In recent years, the photo-oxidative degradation of PEO in presence of transition metal salts was studied [7]. The results of the research showed that even in absence of the metal salts the polymer undergoes chemical and physical changes due to UV irradiation.

PVA is a partially acetylated polymer, whose properties depend on the degree of polymerisation and on the percentage of free alcohol present in its chain. In the pharmaceutical field, PVA is used in topical formulations, particularly in ophthalmic products [8], it is also used in the preparation of microparticles, nanoparticles, hydrogels and matrix tablets for controlled release formulations [9]. PVA is negligibly photosensitive. The presence of a catalyst, like titanium dioxide, is necessary to produce photodegradation of the polymer [10]. Bravar *et al.* [11] mentioned that even prolonged exposure of PVA to UV irradiation did not produce alterations in the molecular structure of the polymer. Although the photostability of PVA has been previously demonstrated, it is used in this work to verified its photostability at the UV irradiation conditions used in this work.

To evaluate the possible modifications that UV light could produce on the polymer ability to modulate drug release rate, some matrices containing a physical mixture of a soluble model drug and one of the three polymers were prepared. The matrices were subjected to various UV light exposure times, and were

then evaluated by means of a dissolution test. Diltiazem hydrocloride was chosen as model drug because it is photostable in the solid state [12].

At the same time, accelerated stability tests were conducted in a dark room at 45°C and 75% HR for six months to verify whether the matrix tablets were stable in absence of light, but under stressed conditions of temperature and humidity. Moreover, the chemical stability of diltiazem HCl in the matrices exposed to stress conditions (light, heat and humidity) was verified by a specific HPLC method able to separate the possible products of degradation of diltiazem hydrochloride (13).

The rheological behaviour of the polymers before and after UV irradiation was evaluated by measuring the viscosity of aqueous polymer solutions prepared with the non-irradiated and irradiated polymer powders.

I. MATERIALS AND METHODS

1. Materials

Hydroxypropylmethylcellulose (Methocel K4M η = 4,000 cP and Methocel K100M η = 100,000 cP) (K4M and K100M) were kindly donated by Colorcon, Orpington, United Kingdom. Polyethylene oxide (Polyox WSR N60K, molecular weight = 2,000,000 and Polyox WSR 303, molecular weight = 7,000,000) (X2 and X7) were supplied by Union Carbide, Danbury, CT, United States. Polyvinyl alcohol (Erkol W40-140: degree of hydrolysis of 88.7 mol%) (PVA) was obtained from Erkol-Acetex Chimica s.r.l., Milan, Italy. Diltiazem hydrocloride (DTZ) was supplied by Profarmaco S.p.A, Milan, Italy. Acetic acid glacial and triethylamine analytical grade were supplied by Carlo Erba Reagents, Milan, Italy. Methanol and acetonitrile for chromatographic analysis were HPLC grade and obtained from Carlo Erba Reagents, Milan, Italy. Water used for solutions and buffers was HPLC grade.

2. Matrix tablets preparation

DTZ matrices were prepared by simply mixing 63.5% of DTZ and 36.5% of HPMC or PEO (DTZK4M, DTZK100, DTZX2, DTZX7). For the preparation of matrices containing PVA, 63.5% of polymer and 36.5% of DTZ (DTZPVA) were used. The different mixtures were compressed with a single-punch tabletting machine equipped with flat punches of 9.5 mm in diameter (Kilian, Coln, Germany) thickness of 3.15 ± 0.05 mm for HPMC and PEO matrices, and 5.30 ± 0.05 mm for PVA matrices. All DTZ matrices contained a dose of 180 mg of drug.

3. Irradiation conditions

The samples (polymer powders or matrix tablets) were irradiated in a dark photostability cabinet fitted with 2 x 20 W phosphor-coated lamps (λ = 366 nm). The intensity of incident light was measured by means of a calibrated radiometer and found to be 0.95 ± 0.1 mWcm^2. The distance between the light source and the sample was 12 cm. Irradiated matrix tablets were reversed at half time and sampled at 20 h, 4, 12 and 25 days. Samples of pure K100M, X2 and X7 powders were spread in very thin layers (about 1 mm) in large transparent containers and irradiated for 20 h, 2, 4, 12 and 25 days. To evaluate the effect of oxygen on the possible photodecomposition of the polyethylene oxide molecule, an additional experiment in absence of oxygen was conducted. DTZX2 matrix tablets were kept under vacuum in a UV transparent container and irradiated in the same conditions as above for 25 days. PVA and Methocel K4M powders were not tested.

4. Accelerated stability test

The matrices were stored in closed polyethylene bottles and maintained at 40°C and 75% of relative humidity in a standard testing atmosphere chamber protected from light, for 6 months.

5. Dissolution test

Non-irradiated and irradiated matrix tablets were tested using the USP dissolution apparatus 2 (paddle) at 100 rpm [14]. The dissolution medium was distilled water, at 37°C. The amount of drug released was assessed by UV detection at 236 nm (Spectracomp 602, Advanced Products, Milan, Italy). The determinations were made in triplicate (SD ≤ 3%).

6. Drug content

The DTZ content of the tablets was assessed just after production, on tablets irradiated for 25 days and on the samples after 6 months of accelerated stability test. For the determination of the drug content an HPLC method able to separate the drug from its degradation products was used. The tablets were dissolved in distilled water, HPLC grade, and diluted with TEA acetate buffer (pH 4) to final volume. The TEA acetate buffer was prepared by adding acetic acid to 0.01 M triethylamine aqueous solution up to the desired pH value. The solution was filtered off and analysed using a Hypersil BDS C18 column and 70:30 TEA acetate buffer:acetonitrile mixture as eluant, with a flux of 1 ml/min. The drug was assessed at 240 nm with a UV detector. The determinations were made in triplicate.

7. Viscosity measurements

The amount of polymer required was dispersed in distilled water with continuous stirring, further water was added to adjust the volume and stirred until obtaining a homogeneous solution. The concentration of the K100 solution was 3% w/w. For X7 and X2 solutions the concentrations were 3 and 4% w/w, respectively. All the samples were allowed to equilibrate overnight before the rheological evaluation.

The viscosity of the solutions was determined with a rotational viscometer (Viscotester VT7 R, Haake, Karlsruhe, Germany) equipped with a recirculating water bath for temperature control (23°C). Rheological measurements were done in the range of 0.1-27 s^{-1} values of shear rate, in triplicate (SD ≤ 2%). The solutions prepared with PEO X2 irradiated for 12 and 25 days, and the solution prepared with 25-day-irradiated X7 powder could not be measured because their viscosities were too low and out of the range of the apparatus.

II. RESULTS AND DISCUSSION

1. Drug content

The drug content of the matrices prepared with HPMC or PEO was tested with a specific HPLC method. No significant differences were found in the overall amount of diltiazem content