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Photostabilization of uncoated tablets of sorivudine and nifedipine by incorporation of synthetic iron oxides

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Summary

The synthetic iron oxides are strong absorbers of radiation wavelengths below 400 nm. They also have great hiding power due to their high refractive indices and high tinctorial capacity. These properties of iron oxides were utilized in photostabilization of two light-sensitive drugs, sorivudine (BV-araU) and nifedipine. Light stability studies on 10 mg potency aqueous wet granulated uncoated tablets of sorivudine and nifedipine formulated with or without 0.2% w/w yellow iron oxide were performed by exposing them directly to room light and/or light of 400 foot candle intensity. Subsequent to exposure, they were assayed for loss in potency and increase in level of degradants due to photodecomposition. Uncoated tablets containing 0.2% w/w yellow iron oxide were found to be more light stable than those without it. The effect of incorporation of 0.2% w/w yellow iron oxide in the tablet core on photolytic degradation was also compared with that of a film coated tablet. Inclusion of 0.2% w/w yellow, red, or black iron oxide into uncoated tablets provided more light protection than 11% w/w coating with Opadry® white. Furthermore, inclusion of a combination of 0.05% w/w red and 0.04% w/w yellow iron oxides into uncoated tablets gave them more light protection than the inclusion of either 0.2% w/w yellow or red iron oxide alone.

Introduction

Photostabilization effects of various additives on light sensitive drugs have been extensively reported (Matsuda et al., 1978; Nyqvist and Nicklasson, 1982; Asker and Harris, 1988; Teraoka et al., 1988; Tonnesen and Karlsen, 1988; Asker and Habib, 1991). However, utility of synthetic iron oxides for this purpose has not been adequately investigated. Iron oxides are not only strong absorbers of radiation wavelengths below 400 nm, but also have great hiding power due to their high refractive indices and high tinctorial capacity (Rowe, 1984). These properties of iron oxides were utilized in photostabilization of uncoated tablets of a new antiviral agent, sorivudine (BV-araU). Sorivudine is susceptible to photolytic degradation. The main degradation product, the *Z*-isomer (Scheme 1), is less active against HSV-1 than sorivudine (Declercq et al., 1984); therefore, such photolytic degradation is undesirable. In order to prevent such degradation, synthetic iron oxides were included in uncoated tablets of sorivudine. Stability was then monitored upon

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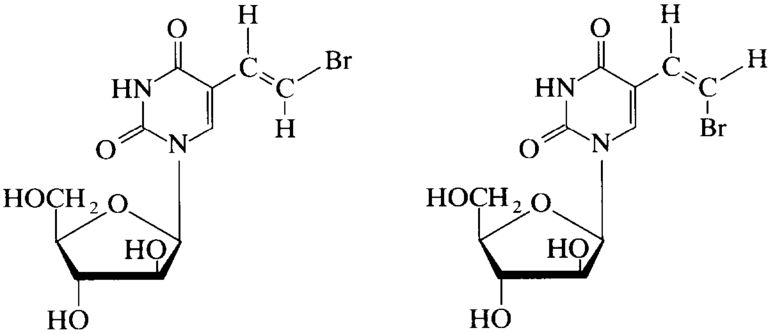

Scheme 1. Structural formulae of sorivudine and its *Z*-isomer.

exposure to different light sources. The photostabilization effect of iron oxides in uncoated sorivudine tablets was also compared to the protection that can be provided by a film coating, a routine method for protection from light. In addition, the photostabilization effect of iron oxides was also studied on another light-sensitive compound, nifedipine. In the presence of light, nifedipine degrades into two major degradants, nitrophenylpyridine and nitrosophenylpyridine (Berson and Brown, 1955). To study photostabilization effects of synthetic iron oxides on nifedipine, yellow iron oxide was selected and included in uncoated tablets of nifedipine, and then stability was monitored upon exposure to a light source.

Materials and Methods

Materials

The following ingredients were used as received from the suppliers: sorivudine (Yamasa Shoyu Co., Choshi, Japan), standards for sorivudine and its *Z*-isomer (Bristol–Myers Squibb's 'in-house' standards), nifedipine (Sigma Chemicals, St. Louis, MO), standards for nifedipine, nitrophenylpyridine and nitrosophenylpyridine (USPC, Washington, DC), lactose hydrous (Foremost Whey, Baraboo, WI), pregelatinized starch (Starch® 1500) (Colorcon Inc., Indianapolis, IN), microcrystalline cellulose (Avicel® PH 101) (FMC Corp., Newark, DE), magnesium stearate (Mallinckrodt, St. Louis, MO), iron oxides (Crompton & Knowles Corp., Fairlawn, NJ), and Opadry® White YS-1-7003 (Colorcon Inc., West Point, PA).

Equipment

The following apparatus were obtained from the indicated sources: Hobart planetary mixer (Hobart Manufacturing Co., Troy, OH), tray oven (Shampaine Scientific Co, Roselle, NJ), F-press (Stokes–Pennwalt, Warminster, PA), beta press (Manesty, U.K.; distributed in the U.S. by Thomas Engineering Co., Chicago, IL), Carver laboratory press-model C (Fred S. Carver Inc., Menomonee, WI), Driacoater® 500 (Driam U.S.A., Spartanburg, SC), light source for 110 foot candle light (flourescent room light), light cabinet for 400 foot candle light (Hotpack, Philadelphia, PA), light cabinet for 900 foot candle light (Shampaine Scientific Co, Roselle, NJ), and AEMC lightmeter model 814 (AEMC Corp., Boston, MA).

Preparation of granules

The formulation composition of the granules used for the manufacture of the tablets used in this study is given below:

Ingredient	% in formulation (w/w)
Sorivudine or nifedipine	10.0 or 12.5
Lactose hydrous [a] approx.	68.8 or 66.3
Microcrystalline cellulose, pregelatinized starch, and magnesium stearate totalling	21.0
Iron oxide (yellow, red, or black)	0.2
Purified water [b]	q.s.
Total	100.0

[a] Amount of lactose was adjusted based on concentration of active ingredient.
[b] Not present in the final product, removed by drying.
Batch size: 3.0 kg.

The active ingredient (sorivudine or nifedipine) and lactose were screened separately using a no. 20 mesh screen into a 12 quart Hobart bowl and to this was added pregelatinized starch. Iron oxides were screened separately through a no. 30 mesh screen and were mixed with microcrystalline cellulose for 5 min in a 5 quart Hobart bowl. This mixture was then added to the bowl containing the active ingredient, lactose, and pregelatinized starch. The contents of the bowl were then mixed for 5 min at slow speed and granulated using purified water. The wet mass was screened through a no. 8 mesh screen and dried in a tray oven at 50°C. The resulting dried granules were screened through a no. 24 mesh screen and mixed with no. 30 mesh screened magnesium stearate for 3 min in a Hobart bowl. Granules without the colorants were made in a similar manner to make tablets which could serve as controls. In place of colorant(s), the lactose content was increased appropriately.

Compression of granules into tablets

Sorivudine granules were compressed into 100 mg round tablets of 10 or 12.5 mg potency on a Beta Press using Holland-McGinley 1/4 inch round concave tooling. Nifedipine granules were compressed into 100 mg round tablets of 10 mg potency on the F-press using 1/4 inch round concave tooling.

Coating of tablets

A 12.5% w/w coating dispersion of Opadry® white in purified water was prepared by mixing the required amount of Opadry® white with water for at least 30 min after all of the Opadry® powder was added. Mixing was continued during the coating process. The coating dispersion was applied to the compressed tablets using a Driacoater® 500 coating pan using the following parameters: inlet air temperature, 60–65°C; atomizing pressure, 4.0 bar; dispersion spray rate, 20–30 g/min; air volume, 73–75 Pa; and pan speed, 12 rpm. The amount of coating applied was 3, 6, or 11% w/w. The amount of coating was determined by an increase in weight of the tablets.

Light stability studies

Tablets placed in a petri dish as a single layer were exposed to either fluorescent room light (110 foot candle), 400, or 900 foot candle light. Every 24 h, each tablet was turned over to maximize its area of light exposure. Light intensity in the different light exposure cabinets was measured at different time intervals using a lightmeter and adjusted if necessary. The control for study was set up by wrapping up the petri dish containing the tablets with aluminum foil and placing them along with the light exposed tablets. Samples were withdrawn at suitable time intervals and analyzed for loss in potency of the active ingredient and increases in the concentrations of the photodegradants using stability-indicating HPLC assays.

Preparation of samples for HPLC analysis

Each of 10 tablets required for assay was placed into a 1000 ml amber volumetric flask containing 200 ml of water at room temperature and sonicated for 10 min. Following that 600 ml of 15% v/v acetonitrile/water solution which was heated to 40°C was added into the flasks. The flasks were insulated with cotton sheets and shaken on a rotary shaker at 350 rpm for about 30 min. The insulation was removed and the contents of each flask was allowed to cool to room temperature before bringing them to volume with acetonitrile/water. A small portion of the solution was placed in a small test tube and clarified by centrifugation for 10 min before injecting the clear solution into the HPLC system.

HPLC analysis

The HPLC conditions for the assay of both drugs and their degradants are given below.

Sorivudine and its degradant Z-isomer Stationary phase, Lichrosorb 5 μm/60 Å RP18 (150 mm × 4.6 mm); mobile phase, 15% v/v acetonitrile, 85% v/v 0.01 M TEAA buffer, pH 7.0; flow rate, 1.0 ml/min; UV detection wavelength, 254 nm; retention time, *Z*-isomer of sorivudine, 3.4 min; sorivudine, 5.5 min.

Nifedipine and its degradants nitrophenylpyridine and nitrosophenylpyridine Stationary phase, Supercosil 3 μm/100 Å LC-18-DB (150 mm × 4.6 mm); mobile phase, 20% v/v acetonitrile, 30% v/v methanol, and 50% v/v 0.01 M TEAA buffer, pH 5.0; UV detection wavelength, 270 nm; flow rate, 1.0 ml/min; retention times: nitrophenylpyridine, 9.5 min; nitrosophenylpyridine, 11.2 min; and nifedipine, 12.5 min.

The typical chromatograms for both drugs and their major degradants are given in Fig. 1.

Results and Discussion

As outlined in Materials and Methods, degradation of nifedipine and sorivudine uncoated tablets with and without iron oxide(s) was monitored by measuring loss in potency and increase in concentration of their respective degradants following their exposure to different light sources.

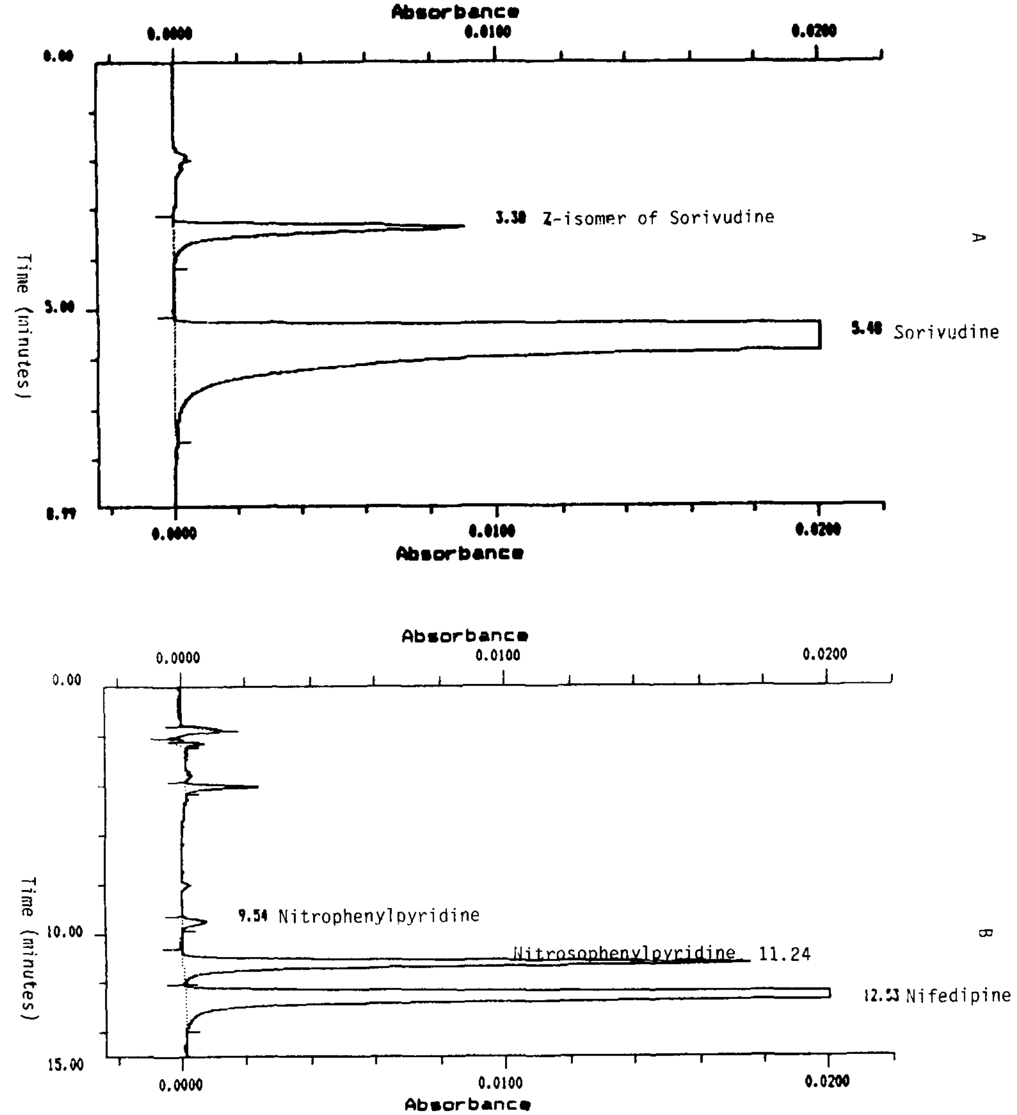

Fig. 1. A typical chromatogram of (A) sorivudine and its Z-isomer and (B) nitrophenylpyridine, nitrosophenylpyridine, and nifedipine.

TABLE 1

Mean % of initial nifedipine remaining and % of nitrosophenylpyridine and nitrophenylpyridine formed in 10 mg potency nifedipine uncoated tablets without yellow iron oxide and uncoated tablets containing 0.2% w / w yellow iron oxide, exposed to 400 foot candle light for up to 14 days

Light exposure time	Without iron oxide				With 0.2% w/w yellow iron oxide			
	% of initial nifedipine remaining	Nitrosophenyl-pyridine formed (%) [a]	Nitrophenyl-pyridine formed (%) [a]	Unknown formed (%) [b]	% of initial nifedipine remaining	Nitrosophenyl-pyridine formed (%) [a]	Nitrophenyl-pyridine formed (%) [a]	Unknown formed (%) [b]
Initial	100.0	2.8	0	0.6	100.0	2.4	0	0.3
1 day	86.2	14.2	0.5	2.4	91.4	8.9	0.4	1.6
3 days	75.2	25.1	0.9	2.1	85.1	15.5	0.6	1.3
7 days	63.2	35.7	1.1	2.5	79.2	21.1	0.8	1.6
10 days	57.5	39.6	1.4	3.2	77.6	22.7	0.9	1.8
14 days	56.8	40.5	1.5	3.4	75.2	24.4	0.9	2.0

[a] Based on peak area ratio, corrected for differences in absorbances.
[b] Based on peak area ratio, not corrected.

TABLE 2

Mean % of initial sorivudine remaining and % of Z-isomer of sorivudine formed [a] *in 10 mg potency sorivudine uncoated tablets without yellow iron oxide and uncoated tablets containing 0.2% w / w yellow iron oxide, exposed to 400 foot candle light for up to 14 days*

Light exposure time	Without iron oxide		With 0.2% w/w yellow iron oxide	
	% of initial sorivudine remaining	Z-isomer of sorivudine formed (%) [a]	% of initial sorivudine remaining	Z-isomer of sorivudine formed (%) [a]
Initial	100.0	< 0.10	100.0	< 0.10
1 day	99.2	0.71	99.2	< 0.10
3 days	96.9	1.78	99.6	0.45
7 days	96.2	3.73	98.8	0.74
10 days	95.8	4.48	98.3	0.95
14 days	94.1	5.75	98.2	1.10

[a] Based on peak area ratio, corrected for differences in absorbances.

TABLE 3

Mean % of initial sorivudine remaining and % Z-isomer of sorivudine formed in 10 mg potency sorivudine uncoated tablets without iron oxide or containing 0.2% w / w red or black iron oxide, exposed to 400 foot candle light for up to 14 days

Light exposure time	Without iron oxide		With 0.2% w/w red iron oxide		With 0.2% w/w black iron oxide	
	Sorivudine remaining (%)	Z-isomer formed (%) [a]	Sorivudine remaining (%)	Z-isomer formed (%) [a]	Sorivudine remaining (%)	Z-isomer formed (%) [a]
Initial	100.0	< 0.10	100.0	< 0.10	100.0	< 0.10
1 day	99.2	0.71	100.0	< 0.10	99.6	< 0.10
3 days	96.9	1.78	99.7	0.54	99.3	0.55
7 days	96.2	3.73	98.8	0.83	98.1	0.98
10 days	95.8	4.48	98.6	1.03	98.1	1.20
14 days	94.1	5.75	98.6	1.27	97.8	1.47

[a] Based on peak area ratio, corrected for differences in absorbances.

TABLE 4

Mean % of initial sorivudine remaining and % Z-isomer of sorivudine formed in 10 mg potency sorivudine uncoated tablets without iron oxide or containing 0.2 or 0.5% w/w yellow iron oxide, exposed to 900 foot candle light for up to 27 days

Light exposure time	Without iron oxide		With 0.2% w/w yellow iron oxide		With 0.5% w/w yellow iron oxide	
	Sorivudine remaining (%)	Z-isomer formed (%) [a]	Sorivudine remaining (%)	Z-isomer formed (%) [a]	Sorivudine remaining (%)	Z-isomer formed (%) [a]
Initial	100.0	< 0.10	100.0	< 0.10	100.0	< 0.10
5 days	94.1	6.42	99.1	1.11	99.1	1.00
12 days	90.3	9.98	98.1	1.76	98.4	1.45
19 days	87.7	12.01	97.4	2.31	98.0	1.85
27 days	87.5	12.34	96.8	2.49	97.8	2.09

[a] Based on peak area ratio, corrected for differences in absorbances.

Nifedipine tablets of 10 mg potency, with or without 0.2% yellow iron oxide, were exposed to 400 foot candle light for up to 14 days. After 14 days exposure, only 57% of the initial nifedipine potency was retained in the tablets not containing any iron oxide whereas in tablets with iron oxide, 75% of the initial nifedipine potency was detected (Table 1). Moreover, the degradant concentrations were higher in the nifedipine tablets without iron oxide compared to those with iron oxide indicating that iron oxide reduced the photolytic degradation of nifedipine (Table 1).

Likewise, sorivudine tablets containing 0.2% w/w yellow iron oxide were also more stable to 400 foot candle light than those without iron oxide (Table 2). A smaller amount of the photodegradant, the *Z*-isomer of sorivudine, was formed in tablets containing 0.2% w/w yellow iron oxide compared to that formed in tablets without iron oxide (Table 2). Similarly, sorivudine tablets containing 0.2% w/w red or black iron oxides were also found to be more light stable than tablets without iron oxides (Table 3).

Of the two light-sensitive drugs discussed above, sorivudine was selected for further studies. When the concentration of yellow iron oxide in the tablet was increased from 0.2 to 0.5% w/w, the photostabilization effect also increased slightly (Table 4). Even though iron oxides in higher concentrations probably can give more protection to photolabile active ingredients, their use as colorants is limited in the U.S.A. to a maximum ingestion of 5 mg of elemental iron per day (Handbook of Pharmaceutical Excipients, 1986).

Iron oxides are gaining importance as mineral colorants as a result of recent limitations affecting many synthetic organic dyestuffs (Drake, 1975; Hess and Schrank, 1979). Iron oxides are available in four colors, namely, red, brown, yellow, and black. These iron oxides can be combined to generate different shades. For the photostabilization effect of iron oxides, incorporation of a combination of two iron oxides into tablets proved to be more beneficial than that of a single iron oxide. As shown in Table 5, after two weeks exposure of the tablets to room light, less *Z*-isomer was found in sorivudine tablets containing a combination of 0.05% w/w red and 0.04% w/w yellow iron oxides than those containing either 0.2% w/w red or yellow iron oxide alone.

The results presented in Tables 1–5 demonstrate the photostabilization effect of iron oxides.

TABLE 5

Percent Z-isomer of sorivudine formed [a] in 10 mg potency sorivudine uncoated tablets containing red or yellow iron oxide or a combination of red and yellow iron oxides, exposed to fluorescent room light (110 foot candles) for up to 14 days

Light Exposure time	% *Z*-isomer of sorivudine formed [a]		
	With 0.2% w/w yellow iron oxide	With 0.2% w/w red iron oxide	With 0.05% w/w red and 0.04% w/w yellow iron oxides
Initial	< 0.10	< 0.10	< 0.10
7 days	< 0.10	< 0.10	< 0.10
14 days	0.19	0.17	< 0.10

[a] Based on peak area ratio, corrected for differences in absorbances.

As mentioned in the Introduction, the photostabilization effect of iron oxides is largely due to their capacity to absorb light below 400 nm wavelengths. Sorivudine has absorption maxima at two wavelengths, 239 and 283 nm. and nifedipine has maxima at 237 and 360 nm (Majeed et al., 1987). Based on the principle of photoprotection by spectral overlapping (Thoma and Klimek, 1991), photoprotection of a light-sensitive drug can be achieved by finding suitable stabilizers whose absorption spectra overlap that of the light-sensitive drug. It is hypothesized, therefore, that because iron oxides are strong absorbers of UV light below 400 nm, they absorb wavelengths of light responsible for the photolytic degradation of sorivudine and nifedipine. Furthermore, when different color iron oxides are physically mixed together, their absorption wavelength range probably increases significantly, resulting in better photoprotection effect as was seen with the combination of yellow and red iron oxides (Table 5).

The photostabilization effect of iron oxides on sorivudine tablets was compared with a traditional light protective method such as film coating. Sorivudine tablets were coated with 3, 6, and 11% w/w Opadry® white (which contains hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, and polysorbate 80) and exposed along with uncoated tablets to fluorescent room light (110 foot candle) for up to 7 days. These tablets were analyzed for increase in the concentration of the photodegradant, i.e., *Z*-isomer of sorivudine. Increase in the *Z*-isomer concentration was detected in uncoated tablets after 1 day of exposure, while in all coated tablets, the concentration of *Z*-isomer did not increase above the detection limit after 1 day exposure (Table 6). After 3 days exposure, there was an increase in *Z*-isomer concentration in uncoated tablets as well as in the coated tablets. The concentration of *Z*-isomer was lower in all of the coated tablets than in the uncoated tablets, indicating a protective effect of film coating on sorivudine tablets against photolytic degradation. This protective effect of film coating increased up to 6% w/w coating level. However, an increase in coating level from 6 to 11% w/w did not decrease *Z*-isomer concentration significantly (Table 6).

The photostabilization effects of different iron oxides and film coating on sorivudine white uncoated tablets are compared in Fig. 2. Without the protection of iron oxides or coating, a significant amount of the *Z*-isomer of sorivudine was formed in the core tablets (Fig. 2). The amount of *Z*-isomer formed in uncoated tablets containing 0.2% w/w yellow, red, or black iron oxide was less than that detected in 11% w/w Opadry® white film coated tablet after their exposure to fluorescent room light. Thus, the photostabilization effect of iron oxide on sorivudine uncoated tablets was better than that of a film coating. Analogies can be drawn between film coating and physical sunscreen agents (such as zinc oxide or titanium dioxide) and between iron oxides and chemical sunscreen agents (such as *p*-aminobenzoic acid) with regard to photoprotection effects. Like the physical sunscreens, which block up to 99% of UV and visible light by reflection and scattering (Larson and West, 1991), the photostabilization effect of film coating arises from its

TABLE 6

Mean % of Z-isomer of sorivudine formed [a] *in 12.5 mg potency sorivudine uncoated tablets and 3, 6, and 11% w/w Opadry* ® *white coated tablets exposed to fluorescent room light (110 foot candle light) for up to 7 days*

Light exposure time	% Z-isomer of sorivudine formed [a]			
	Uncoated tablets	3% w/w Opadry white coated tablets	6% w/w Opadry white coated tablets	11% Opadry white coated tablets
Initial	< 0.10	< 0.10	< 0.10	< 0.10
1 days	0.11	< 0.10	< 0.10	< 0.10
3 days	0.28	0.16	0.13	0.12
7 days	0.68	0.52	0.24	0.21

[a] Based on peak area ratio, corrected for differences in absorbances.

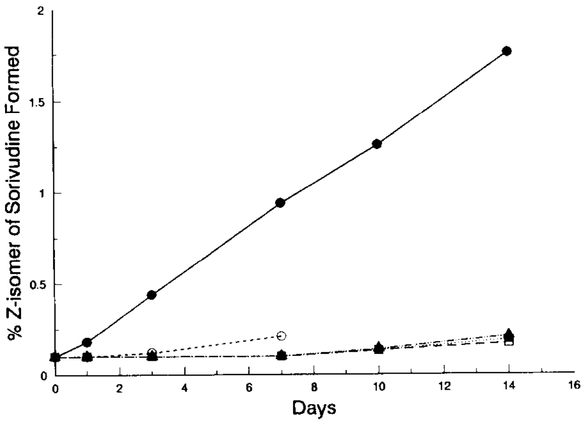

Fig. 2. Increase in concentration of Z-isomer in uncoated 10 mg potency sorivudine tablets containing (●) no colorants, (▲) 0.2% w/w yellow iron oxide, (□) 0.2% w/w red iron oxide, or (■) 0.2% w/w black iron oxide, and (○) tablets without any iron oxide but 11% w/w coating of Opadry® white, after 14 days exposure to fluorescent room light (110 foot candle light).

ability to block light from reaching a photolabile active ingredient. On the other hand, iron oxides, like chemical sunscreens, provide photoprotection by absorbing harmful wavelengths of light.

As shown above, the photostabilization effect of iron oxide is much better than that of film coating. Coating is costly and time consuming, since it is an extra step in the manufacturing of tablets. By including iron oxides in uncoated tablet formulations of a light-sensitive drug, coating can be avoided. Moreover, combinations of iron oxides in an uncoated tablet formulation can impart desired colors on tablets for trade dress.

Conclusions

Iron oxides were used in uncoated tablet formulations of light sensitive drugs sorivudine and nifedipine to reduce their photolytic degradation. The photostabilization effect of 0.2% w/w iron oxides on sorivudine tablets was found superior to that of 11% w/w of coating with Opadry® white. Moreover, combination of different color iron oxides in an uncoated tablet formulation had a better photostabilization effect than that of a greater amount of a single iron oxide. The photostabilization effect of iron oxides can be very useful in protecting a photolabile drug during manufacture and subsequent storage.

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