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Film coating: effect of titanium dioxide concentration and film thickness on the photostability of nifedipine

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Summary

The opacity of film coatings is of particular importance for the stabilization of photosensitive drugs and can be defined by means of a contrast ratio. Films having contrast ratio values of 33% to > 99% were evaluated using a photolabile compound, nifedipine, as a model drug. Titanium dioxide was used as the pigment to impart film opacity and was added at 9.5–29.5% (dry film) levels to HPMC 6 cP films plasticized with PEG 3350 (20%). Films were sprayed onto nifedipine 20 mg tablets at 2–15% weight gains using a Wurster column with a bottom spray configuration. The film thicknesses were evaluated by scanning electron microscopy. The cores and coated tablets were introduced into a light cabinet and exposed to 4.4 klux fluorescent light (Cool White, General Electric) over 21 days. The tablets were sampled at predetermined time points and assayed by HPLC (UV detection at 230 nm) for percent nifedipine remaining. Control samples were also introduced into opened containers and stored in total darkness. The results showed that the film thickness values ranged over 24–145 μm. The films that had contrast ratios values of above 98% imparted good light protection. This was achieved by using a coating that contains 29.5% titanium dioxide with a thickness of 145 μm.

Introduction

Many drugs used in therapeutics can be degraded by ultraviolet and visible light. In addition, these chemical changes generally influence the physical appearance of tablet dosage forms producing discoloration of the surface. The usual approach utilized to protect light-sensitive drugs is to use a light-resistant package. However, an obvious and more effective means is to apply a film coating onto a tablet. If film coatings could be formulated to be totally opaque to radiant energy, the formulator would not have to rely on the packaging material any more as a means to protect drugs from light. Curiously, data pertaining to the effect of coating formulation variables upon the photostabilization of drugs are not readily available from the pharmaceutical literature.

The opacity of film coatings is of particular importance for the stabilization of photosensitive drugs. The paint industry has defined the degree

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of opacity by means of a contrast ratio. The contrast ratio is defined as the ratio of the reflectance of an incident light when a film is placed on a black substrate over the reflectance obtained on a white substrate (Mitton, 1973). Films that produce 'complete hiding' are defined as having 98% contrast ratio values. Contrast ratios of pharmaceutical coating formulations containing various pigments have been determined (Rowe, 1984a). The effects of pigment type and concentration on the contrast ratios were assessed. It was found that titanium dioxide and iron oxides imparted the highest contrast ratio values to hydroxypropyl methylcellulose (HPMC) films. It was also found that high pigment concentrations as well as small particle size were related with the high contrast ratio films. In order to produce opaque films, pigments must have high indices of refraction as well as high extinction coefficients over a wide range of wavelengths. Other reports (Rowe, 1984b,c) studied the quantitative relationships between titanium dioxide concentration and film thickness on the opacity of HPMC films. It was found that opaque films, i.e., having a 98% contrast ratio, could be produced, for example, by using 29.5% (% w/w dry film) titanium dioxide concentration in films of about 90–100 μm thicknesses. The practical relevance of these papers was high, since titanium dioxide and HPMC have been used as ingredients in aqueous coating formulations for many years. However, the definition of complete hiding employed in the paint industry and its significance on the actual photostabilization of a drug are unknown.

Nifedipine was used as a model drug because it is extremely photosensitive and is degraded into many photodecomposition products by exposure to daylight and UV light (Teraoka et al., 1988; Matsuda et al., 1989; Matsuura et al., 1990; Thoma and Klimek, 1991). This means that the drug must be protected from both UV and visible light. The photodegradation depends on the spectral energy distribution of the light source. Nifedipine is stable down to wavelengths of 475–500 nm (Matsuda et al., 1989; Thoma and Klimek, 1991) where photolysis starts. The molecule is stable below 290 nm. The region of instability coincides with the absorption band of nifedipine. The degradation rate of the solid neat drug as well as the relative proportion of degradates is also a function of the wavelength and it appears that the rate of formation is most rapid at about 380 nm (Matsuda et al., 1989). This study describes the effect of titanium dioxide concentration and film thickness on the chemical stability of nifedipine coated tablets exposed to high light intensities.

Materials and Methods

Manufacture of nifedipine tablets

Nifedipine (Sigma, MO) was used as the model compound. Each tablet contained 20 mg of nifedipine, 100 mg of microcrystalline cellulose (Avicel PH102, FMC Corp., PA), 48.3 mg pregelatinized starch (Starch 1500, Colorcon, PA) and 1.7 mg of magnesium stearate. Tablets were manufactured using a direct compression procedure. Microcrystalline cellulose and pregelatinized starch were added to a twin shell blender. Then, nifedipine was passed through a no. 30 mesh (U.S.) screen and added to the other ingredients. The mixture was blended for 5 min at 35 rpm. Magnesium stearate was passed through a no. 60 mesh (U.S.) screen, added to the powder blend and the mixture lubricated for 3 min at 35 rpm. Tablets were compressed at a 170 mg weight on a Korsch PH106 (Korsch Tableting Inc., NJ) rotary press fitted with one set of 9.0 mm round standard concave tools. Tablet weight and hardness (Model HT300, Key Int. Inc., NJ) were determined and the tablets were finally stored in a desiccated amber glass container.

Film coating formulation and coating process

HPMC 6 cP (Pharmacoat 606, Shin Etsu, Japan) was used as the polymeric material. Polyethylene glycol 3350 (Carbowax 3350, Union Carbide, CT) was used as the plasticizer and was added at a 20% level (% of polymer). Anatase titanium dioxide (Whittaker, Clark & Daniels, Ontario) was added as the pigment at 9.5, 17 and 29.5% (% of dry film) levels. Contrast ratio values for these film compositions were taken from the

TABLE 1

Coating process parameters for nifedipine 20 mg tablets

Batch size: 720 g placebos and 30 g nifedipine 20 mg tablets
Inlet air flow: 80–85 scfm
Inlet air dew point: 13–15°C
Inlet air temperature: 55°C
Atomizing pressure: 30 lb/inch^2
Spray rate: 8–10 g/min
Amount of dispersion to spray: 150–1125 g
Outlet temperature: 48–50°C
Drying: 10 min at 40 scfm

scfm, standard cubic feet per min.

literature (Rowe, 1984b). Clear films did not contain any titanium dioxide. The aqueous coating dispersions contained 10% solids. The pigment was dispersed in approximately half of the water using a homogenizer (Model L4R, Silverson Machines Inc., MA) equipped with a disintegrating head. The pigment concentrate was then added and mixed with the plasticized polymer.

Coating trials were carried out using a 10 cm Wurster-type column with a bottom spray configuration. Process parameters are given in Table 1. Nifedipine tablets were coated at five weight gain/film thickness levels: 2, 4, 6, 10 and 15%. After coating, tablets were stored in desiccated polyethylene bottles. Film thicknesses were assessed by scanning electron microscopy (Model JSM 820, Jeol, MA) on tablets that were cut in half with a scalpel blade.

HPLC determination of nifedipine

Chromatographic conditions A binary HPLC system (Hewlett-Packard, Model 1090) equipped with an autosampler, a diode array UV spectrophotometer and a Hewlett-Packard Chemstation was used throughout the experiment. The UV detector was set at 230 nm. Chromatographic separation was achieved with a 5 μm (25 cm $\times$ 4.6 mm i.d.) reversed-phase column (Beckman Ultrasphere ODS, Mandel Scientific, Ontario, Canada) thermostated at 40°C. The mobile phase consisted of 48% water in methanol and the flow rate was set at 0.8 ml/min.

Sample preparation A tablet containing 20 mg nifedipine was pulverized and transferred quantitatively to a 25 ml volumetric flask and sonicated for 10 min with 5 ml deionized distilled water. A 20 ml aliquot of methanol was then added to the aqueous suspension and mixed vigorously. The combined mixture was cooled to room temperature and adjusted to 25 ml with methanol. A 1 ml aliquot of the final sample solution was transferred to a polypropylene vial and centrifuged for 20 min at $1000 \times g$. The supernatant was transferred to an amber vial and 10 μl injected directly into the HPLC.

System suitability The precision and accuracy of the method were determined by repeated injections ($n = 10$) of the nifedipine standard solutions (1 mg/ml) on different days ($n = 5$). Nifedipine (Sigma, MO) standards were prepared fresh each time and protected from light. The within- and between-day coefficient of variation of the peak area from the repeated injections is no more than 2%. The resolution between nifedipine and nitrosonifedipine is greater than 2, the efficiency of the column calculated using the nifedipine peak is more than 25 000 plates/m and the asymmetric factor was less than 1. A separate calibration curve was constructed for nifedipine, nitroso- and nitrophenyl USP standard derivatives (A&C Chemicals Ltd, Quebec). A concentration range from 0.01 to 1 mg/ml was used for nifedipine and from 0.005 to 0.1 mg/ml for the degradation products. The sensitivity of the detector was determined such that 2 μg/ml will give a signal-to-noise ratio of greater than 10:1. The recovery of nifedipine from the extraction of tablets was found to be 100% ($\pm$1).

Calculations The concentration of nifedipine in each sample was quantified using the calibration curve generated on the same day the samples were analyzed. Nifedipine amounts (A_0 and A_t) were calculated from the concentration of nifedipine $\times$25 ml. A_0 and A_t are the amounts of nifedipine for time zero and time t, data points, respectively. The percentage of nifedipine remaining as a function of time was calculated from $(W_t \times A_0)/W_0 = Z$ and $A_t/Z \times 100$ where W_0 and W_t are the tablet weights at time zero and time t, respectively.

Light exposure studies

Cores and coated tablets (with and without pigment) were put onto a glass petri dish and introduced into a light cabinet (Model 3890, Forma Scientific, OH) equipped with 12×15 W cool white fluorescent tubes (F15-T8-CW, General Electric, Ontario). Fluorescent lamps are a low-pressure gas discharge source, in which light is produced by fluorescent powders activated by UV energy generated by a mercury arc (Kaufman, 1981). The color and the spectral energy distribution produced by a fluorescent lamp depend on the blend of fluorescent material covering the walls of the tube. UV radiations generally represent less than 1% of the total energy. All fluorescent lights have a combination of continuous and line spectra. Cool white tubes (Kaufman, 1981) have line emissions at about 440, 410 and 360 nm. Tablets were exposed to 4.4 klux (6.6 J/s m^2 or 6.6 W/m^2) over 21 days. The temperature and relative humidity were respectively 28–30°C and 30–50% throughout the experiments. Tablets were sampled at predetermined time intervals and assayed for remaining nifedipine. Plots of % nifedipine remaining as a function of time were then constructed. Coated tablets having a 10% weight gain were used as controls and were placed in opened containers stored in total darkness at ambient temperature and relative humidity.

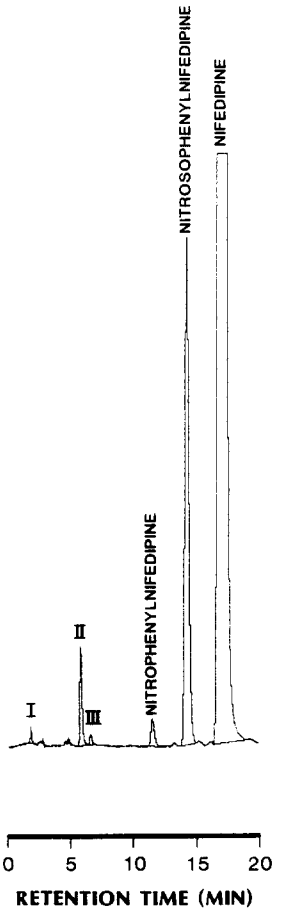

Fig. 1. Chromatogram of a nifedipine sample extracted from a tablet coated with 2% weight gain (17% titanium dioxide). The sample had been exposed for 3 days under 4.4 klux light intensity.

Results and Discussion

Nifedipine uncoated tablet weight and hardness were respectively 174 ± 1.6 mg (mean $\pm$ S.D., $n = 20$) and 10.7 ± 1.4 kP (mean $\pm$ S.D., $n = 20$).

HPLC determination of nifedipine

The chromatogram shown in Fig. 1 was obtained from a sample of nifedipine exposed to intense light. The chromatogram exhibited five extra peaks. The major photolytic products were found to be nitrosophenyl and nitrophenyl nifedipine. Additional isolation would have to be performed in order to identify the degradation products I–III. These findings are in agreement with previously reported data (Matsuda, 1989). The sample preparation required minimal manipulation and extraction recovery from tablets was found to be complete with low variability. The system suitability was performed on each time point and was found to be very consistent with relative standard deviations less than 1%. The method is specific for nifedipine.

Effect of pigment concentration and film thickness on nifedipine stability

Tables 2 and 3 show film thickness and contrast ratio (taken from Rowe, 1984b) values for TiO_2/HPMC films used in this study, respectively. Film thicknesses ranged over 24–145 μm and contrast ratios extended from about 33%

TABLE 2

Film thickness values (μm) [a]

Weight gain	TiO_2			
	0%	9.5%	17%	29.5%
2%	26 (1)	24 (2)	25 (5)	28 (8)
4%	48 (5)	51 (12)	50 (12)	48 (7)
6%	68 (3)	63 (7)	61 (8)	57 (8)
10%	–	–	–	102 (11)
15%	–	–	–	145 (13)

[a] Mean (S.D., $n = 5$).

(clear films) to > 99%. Based on the data listed in Tables 2 and 3, films of at least 100 μm thickness and containing 29.5% titanium dioxide would have to be utilized in order to be opaque, i.e., having a 98% contrast ratio. Below these values, poor light protection is expected. Film coating formulations developed for taste masking or color applications are generally applied to tablets at weight gains of about 2–4%, which typically produce films of less than 50 μm in thicknesses. The pigment concentration is generally limited to a value of about 30% (dry film) because very high levels can compromise the film formation during the coating process.

The effect of film thickness and level of titanium dioxide on the chemical stability of nifedipine is shown in Figs 2–6. Except for films that provided good light protection, all profiles were biphasic with high initial degradation rates that extended over about 48 h. Similarly, high initial degradation rates were observed for the photodegradation of dyes at tablet surfaces (Lachman et al., 1960, 1961, 1962; Swartz et al., 1961). It was postulated that surface degradation was mainly responsible for the high initial degradation rate. The change in reaction rate was attributed to many contributing factors such as the

TABLE 3

Contrast ratio values (%) for TiO_2 / HMPC films [a]

Weight gain	TiO_2		
	9.5%	17%	29.5%
2%	75	83	91
4%	83	91	95
6%	87	93	96
10%	–	–	98
15%	–	–	> 99

[a] Taken from Rowe (1984b). 0% TiO_2 is 33%.

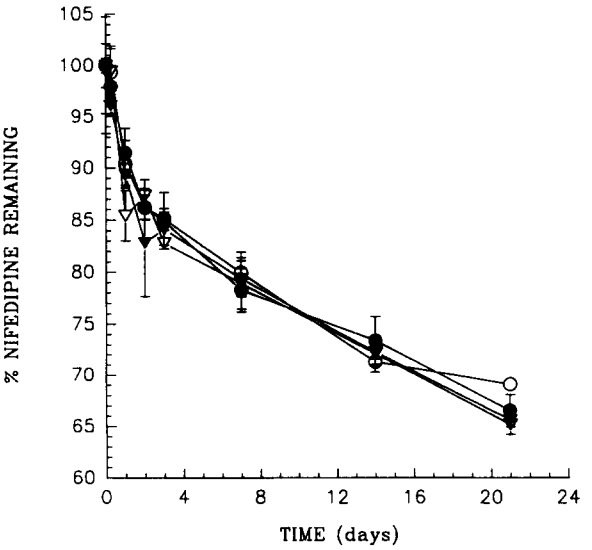

Fig. 2. Plots of % nifedipine remaining as a function of time in tablets coated with clear films. Cores (○); 2% (●); 4% (▽) and 6% (▼) weight gains. Mean ± S.D. ($n = 3$).

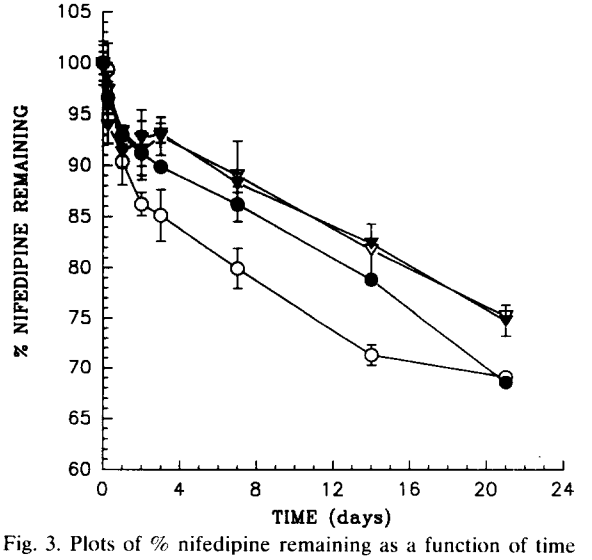

Fig. 3. Plots of % nifedipine remaining as a function of time in tablets coated with films containing 9.5% titanium dioxide. Cores (○); 2% (●); 4% (▽) and 6% (▼) weight gains. Mean ± S.D. ($n = 3$).

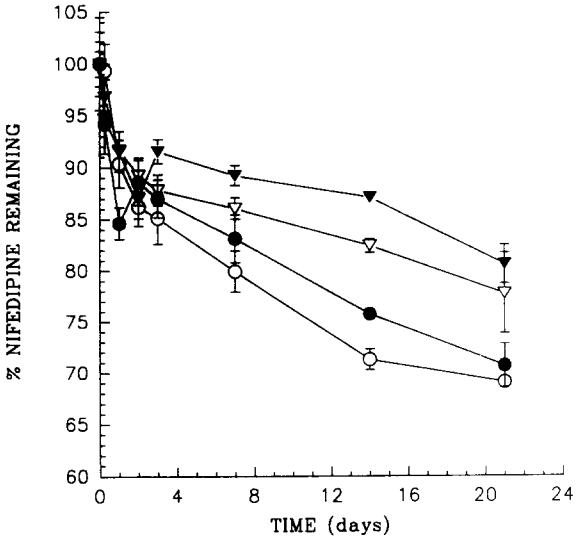

Fig. 4. Plots of % nifedipine remaining as a function of time in tablets coated with films containing 17% titanium dioxide. Cores (○); 2% (●); 4% (▽) and 6% (▼) weight gains. Mean ± S.D. ($n = 3$).

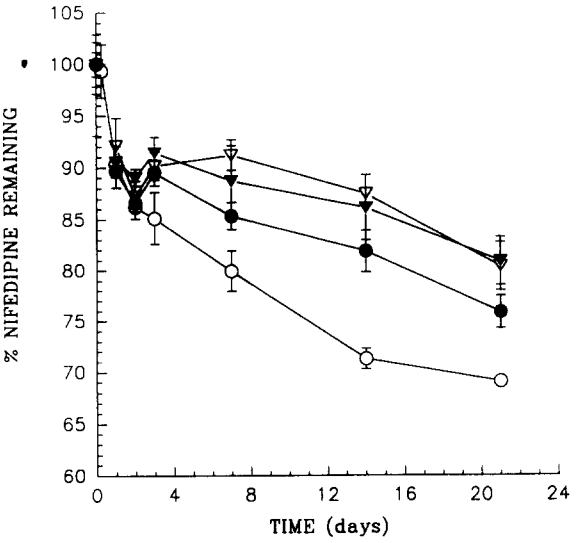

Fig. 5. Plots of % nifedipine remaining as a function of time in tablets coated with films containing 29.5% titanium dioxide. Cores (○); 2% (●); 4% (▽) and 6% (▼) weight gains. Mean ± S.D. ($n = 3$).

light opacity of the tablet surface itself and the possible involvement of secondary reactions.

Clear coats with thicknesses of 26–68 μm (2–6% weight gains) did not offer any light protection when compared to cores exposed to the same conditions. All degradation profiles were superimposable. Between 12 and 22% of nifedipine was degraded after 2 days and 30–35% after 3 weeks. This correlates well with the low values of film contrast ratios obtained for these compositions. The addition of titanium dioxide to 24–68 μm films did not improve the light protection (Figs 3–5), even though a contrast ratio value of 96% was achieved with a 57 μm film containing 29.5% titanium dioxide. The nifedipine degradation rate was as fast as for the core tablets in the early phase, i.e., for the first 2–3 days. However, in the second portion of the degradation profiles, the film thickness appeared to be a key variable. The amounts of nifedipine degraded were less for thicker films. Nevertheless, there was still 15–25% of drug degraded after 21 days. In order to protect the nifedipine from UV and visible light, films of 145 μm (15% weight gain) containing 29.5% titanium dioxide had to be applied to tablets (see Fig. 6). Under these conditions, % nifedipine remaining with time profiles were similar to those of tablets stored in total darkness.

The results shown in this study clearly indicate that film coatings having contrast ratio values of

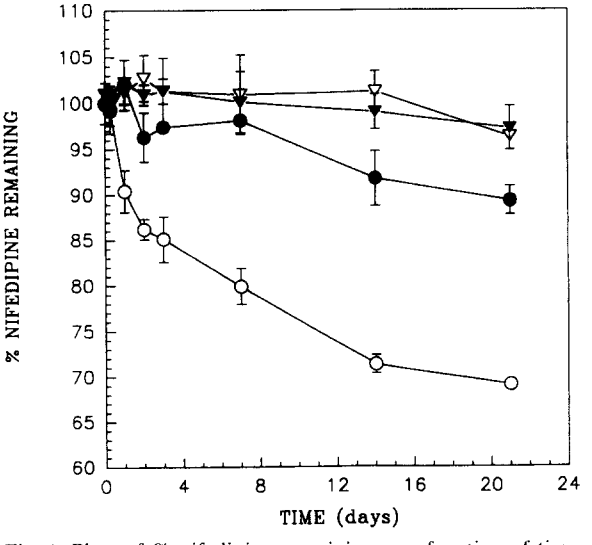

Fig. 6. Plots of % nifedipine remaining as a function of time in tablets coated with films containing 29.5% titanium dioxide. Cores (○); 10% (●); 15% (▽) and 10% (opened container, total darkness) (▼) weight gains. Mean ± S.D. ($n = 3$).

less than 98% are not adequate for the light protection of nifedipine. Titanium dioxide concentrations up to 29.5% in films of 24–68 μm, a thickness range typically used in conventional pharmaceutical applications such as taste masking or coloring, were not enough to protect the drug from light degradation. The use of higher levels of titanium dioxide has little interest since it could compromise the film formation during the coating process. The film thickness was a key variable at high coating levels since 145 μm containing 29.5% titanium dioxide provided good light protection. The potential effect of such a high level of coating on the dissolution/bioavailability of a drug would have to be determined before such an approach be envisaged.

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