J. Pharm. Pharmacol. 1988, 41: 293–297
Received July 28, 1988

Quantitative Design for Photostabilization of Nifedipine by using Titanium Dioxide and/or Tartrazine as Colourants in Model Film Coating Systems

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Abstract—The photostabilization of nifedipine by using film coating has been investigated in model systems in which a drug sample, dispersed on a glass plate, was covered with a free film and exposed to intensive light of mercury vapour lamp. The light transmission properties of films containing titanium dioxide or tartrazine alone as colourant were not always satisfactory. The tartrazine system exhibited superior light transmission properties to the titanium dioxide system at all additive concentrations. However, in combination both colourants gave much better light protection than did the colourants separately.

The film-coated drug degraded following apparent first-order kinetics. The degradation rate constant decreased as both colourant concentration and film thickness increased; thus photostabilization was almost completely achieved by applying a film (thickness: 60 μm) of the binary mixture system containing only 0·7% of each of these colourants. The protective effectiveness of a film could be quantitatively evaluated by plotting the degradation rate constant against CL value of film formulation (C: concentration of colourant; L: film thickness). The degradation rate constant showed a good linear correlation with the average percent transmittance of a film in the wavelength range relating to the photolytic degradation of the drug. The average percent transmittance was thus proved to be an important and useful parameter for estimating the photostability of film-coated drugs.

To protect against photolytic degradation, photo-sensitive preparations have usually been packed in light-resistant coloured glass or opaque containers. Blister packaging using coloured plastic films have also been used widely for tablets or capsules. Previously, we have demonstrated that coating with a polymer film containing a UV absorber can be used satisfactorily as a method to protect a photosensitive drug from light (Matsuda et al 1978). In that during investigation a film coating was shown to be effective in minimizing the discoloration and photolytic degradation of drug. The light protection of tablets achieved by film coating with some inorganic pigments has been evaluated and a numerical convolution method has been applied to predict their discoloration (Nyqvist et al 1982; Nyqvist & Nicklasson 1984). The opacity of tablet film coating containing titanium dioxide has also been analysed to see if it can be used to evaluate the relative opacity of different film formulations (Rowe 1984a, b, c). Although film coatings have been applied to enhance the physical or chemical stability of solid dosage forms, there have been no quantitative studies dealing with the effect of light transmission properties of films on photostability of film-coated drug except for our previous paper (Matsuda et al 1978). The purpose of the present investigation is to establish a precise phamaceutical design for stabilizing nifedipine, which is photo-labile and which degradation by light has been already elucidated (Matsuda et al 1988).

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Materials and Methods

Materials and irradiation test

A drop (100 μL) of 1 w/v% chloroform solution of nifedipine was spread on a glass plate (38 × 26 mm) with a microsyringe, and recrystallized according to Matsuda et al (1988). The glass plate was mounted on the back of the same sample holder as used earlier (Matsuda et al 1978), and the fine crystals dispersed discretely on the glass plate were irradiated at room temperature (25°C) by the same mercury vapour lamp as that employed by Matsuda et al (1988). The other irradiation conditions were the same as those in the previous investigation.

Preparation and application of free films

Hydroxypropyl methylcellulose (TC-5R; Shin-Etsu Chemical Co. Ltd., Japan) (40 g), as a film former was dissolved in 460 mL of a cosolvent of water and methanol (1 : 1 v/v), then either or both tartrazine (FD & C Yellow No. 5) or titanium dioxide (anatase form; $\bar{D}_p = 0{\cdot}19$ μm by helium gas adsorption method) were added (as colourant or opacificient), and dissolved or dispersed with a homogenizer. An amount of solution or suspension was injected with a syringe into a polyvinyl chloride ring (8 cm i.d.) placed on a horizontal glass plate, and dried at 25°C for 24 h. The resultant transparent or opaque films were peeled from the plate, and free films of 3 × 3 cm were prepared.

The thickness of films, which was varied from 20 to 100 μm by adjusting the amount of solution or suspension injected, was represented by the mean of the values measured at five fixed points on a film using an electro-magnetic thickness meter (model VL-30B, Kett Co., Japan). The thicknesses at these points were within the range of the mean ± 2 μm for any

formulation. The concentrations of colourants were 0·1–1·0% of the weight of a dried film. The light transmission curve of a film was read with a multi-purpose spectrophotometer (model MPS-50L; Shimadzu Co., Japan). The film was fixed to the front of the described holder as a model system of film-coated dosage forms.

HPLC analysis

The chromatograph employed and the analytical conditions for unchanged nifedipine were the same as those reported by Matsuda et al (1988), except for the treatment of the sample after exposure. Thus, after irradiation on the glass plate, the sample was washed several times with chloroform, then 70 μL of an antipyrine solution (800 μg mL^{-1}) as an internal standard, was added, and the mixture evaporated to dryness under vacuum. The residue was dissolved in 1 mL of ethyl acetate and 2·0 μL of this was injected into the chromatograph to determine the concentration of unchanged drug.

Results and Discussion

Light transmission properties of films

The light transmission curves of hydroxypropyl methylcellulose films without colourant proved to be almost transparent over the wavelength 290–450 nm, relating closely to the photodegradation of nifedipine (Matsuda et al 1988): transmittances were >86(80 μm-thickness)—93% (20 μm-thickness) at 380 nm. Fig. 1 shows the transmission curves of films containing either 0·5% of tartrazine or titanium dioxide, or both at 0·5% of colourants. Although the films containing tartrazine effectively excluded most of the light at 370–480 nm, corresponding to its absorption band (λ_{max}=428 nm), they did not exclude most of the UV light, suggesting poor protective effectiveness in the ultraviolet. In contrast, the films containing titanium dioxide exhibited a good shielding effect to UV light, not a satisfactory shielding in the visible region. Improvement of the protective effectiveness of the films over a wide range of wavelengths (290–450 nm) may be possible by the combination of these colourants. The percent transmittances of films containing 0·5% each of the colourants were much lower, especially in the ultraviolet region, than those of any other film having the same film thickness, in which a single colourant had been incorporated. The percent transmittance fell uniformly, at any wavelength, with increasing film thickness of each film. It is therefore expected that the protective effectiveness of a film of 60 μm-thickness on degradation would be almost complete for the binary mixture system.

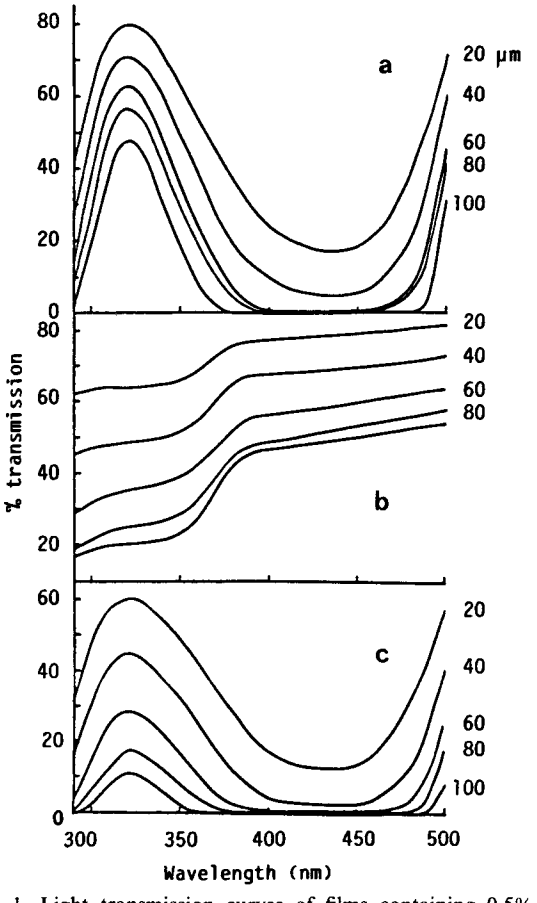

FIG. 1. Light transmission curves of films containing 0·5% of tartrazine (a), titanium dioxide (b), and each 0·5% of these colourants (c).

To quantitatively evaluate the overall transmission properties of films, the average percent transmittance was obtained by calculating the area under the transmission curve within the wavelength range of 290–450 nm. This is a purely empirical way of quantifying the opacity of the films. The amount of light energy transmitted should be a function of the physicochemical nature and thickness of films. The logarithmic values of average transmittance are plotted against film thickness in Fig. 2. The values decreased with the increase of either film thickness or concentration of colourant. The average transmittance was much lower in the tartrazine system than in the titanium dioxide system for any colourant concentration, thus suggesting tartrazine to be superior to titanium dioxide in its shielding effect. A good linear relationship was established between both variables for any colourant system over the whole range of film thickness investigated.

Photostabilization of nifedipine by film coating

Fig. 3 shows the timecourse changes in percent remaining of nifedipine coated with the same films as those in Fig. 2. The plots gave a good linear relationship for all formulation systems, suggesting that the film-coated nifedipine also apparently followed the first-order degradation kinetics as previously (Matsuda et al 1988). It is clear from Fig. 2 that, although no appreciable protective effect of the films without colourant was found even in the greater film thickness, the photodegradation could be inhibited depending on the film thickness. Even after the 8-min intensive irradiation, more than 95% nifedipine still remained for the film of 100 μm thickness in the binary mixture system, indicating it to be almost photostable. However, the drug decomposed rapidly, only 31 percent remaining after the same irradiation time, when the drug was coated by a film of the same thickness without colourant. The values of degradation rate constant calculated from the slope of regression line are plotted against film thickness for all formulation systems in Fig. 4. Tartrazine exhibited a more marked effect on the inhibition of degradation rate than did titanium dioxide even at lower concentrations. It can be considered that the protection was

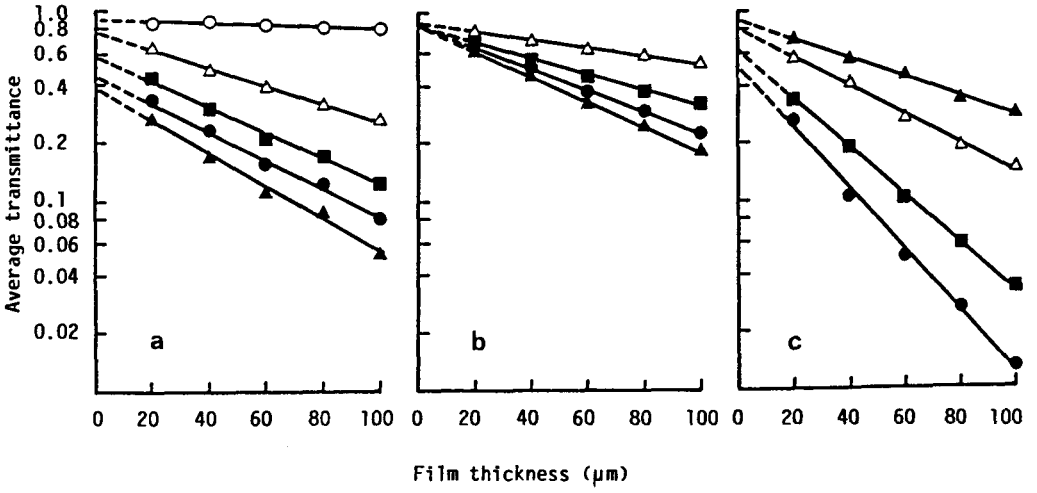

FIG. 2. Semi-logarithmic plots of average transmittance (290–450 nm) of film against film thickness in tartrazine (a), titanium dioxide (b), and binary mixture (c) systems. Concentration of colourants: (○), 0%; (△), 0·2%; (■), 0·5%; (●), 0·7%; (▲), 1·0% in system a and b. (▲), 0·1%; (△), 0·2%; (■), 0·5%; (●), 0·7% in system c.

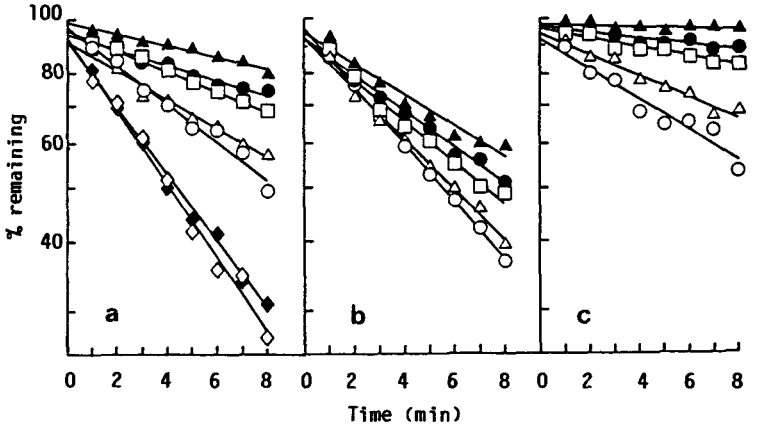

FIG. 3. First-order kinetic plots for photodegradation of nifedipine coated with film containing 0·5% of tartrazine (a), titanium dioxide (b), and 0·5% of each of these colourants (c). Film thickness: (◇), 0%, 20 μm; (◆), 0%, 100 μm; (○), 20 μm; (△), 40 μm; (□), 60 μm; (●), 80 μm; (▲), 100 μm.

achieved almost completely by using a film of 80 μm thickness, which contained only 0·7% of each of these colourants.

The degradation rate constant was controlled by both colourant concentration and film thickness (Fig. 4). It is therefore more rational to introduce another overall parameter for more direct evaluation of the protective effect of a film. Although the different colourant concentrations (C) and film thicknesses (L) were used in a film formulation, the film having the same CL value (C × L) should show a similar protective effectiveness since the amount of colourant incorporated in a unit area of a film was equal. Fig. 5 represents the semi-logarithmic plots of the degradation rate constant against CL value calculated from data shown in Fig. 4. Irrespective of the formulation and film thickness, a good linear relationship also existed between these variables for every colourant system, as well as in Fig. 4. This result strongly suggests that the protective effectiveness of a film can be satisfactorily evaluated by using this parameter without consideration of the light transmission properties of a film. The CL value rarely affected the degradation rate constant in the titanium dioxide system, and the protective effectiveness still remained the poorest. The greater the CL value, the more evident was the superiority of the other two systems to the titanium dioxide system, and the binary mixture system afforded the best protective effectiveness. Such a good correlation of degradation rate constant to CL value must affect the relationship between the degradation rate constant and average percent transmittance of a film, since the same CL value should give the same average percent transmittance in a colourant system. The plots of the degradation rate constant against average percent transmittance are depicted in Fig. 6 for all colourant systems. All the data (n = 66), including that obtained without film coating, were well regressed by a straight line which passed through the origin, thus indicating that irrespective of the kinds of formulations, the degradation rate constant was proportional to the average transmittance. It was also shown that

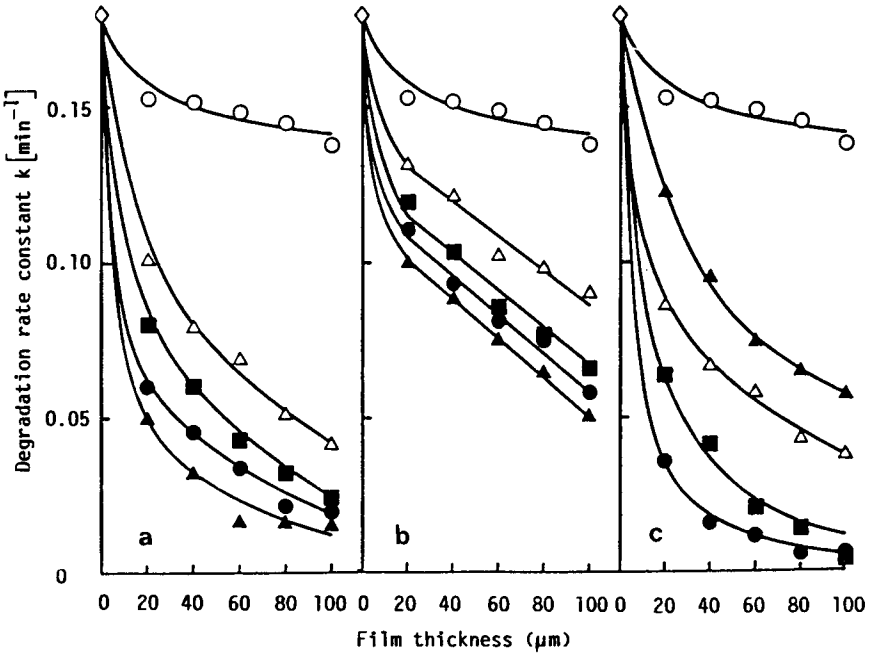

FIG. 4. Effect of film thickness on the degradation rate constant of nifedipine in tartrazine (a), titanium dioxide (b), and binary mixture (c) systems. Concentration of colourants: (○), 0%; (△), 0·2%; (■), 0·5%; (●), 0·7%; (▲), 1·0%; in systems a and b. (○), 0%; (▲), 0·1%; (△), 0·2%; (■), 0·5%; (●), 0·7% in system c.

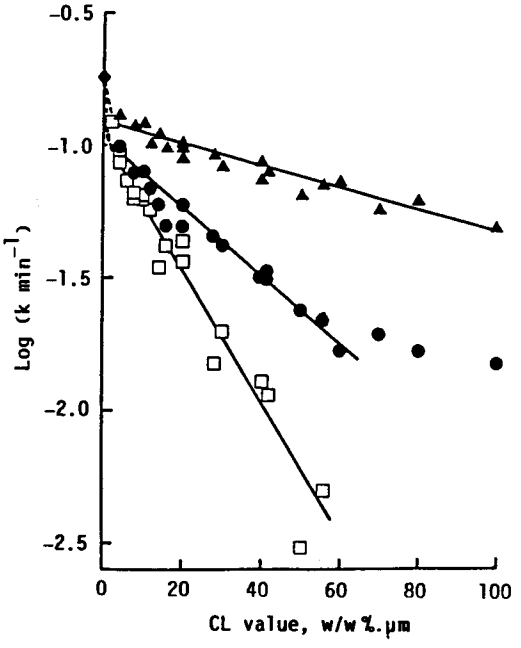

FIG. 5. Relationship between degradation rate constant of nifedipine and CL value of film in three formulation systems. Key: (◆), without film; (●), tartrazine system; (▲), titanium dioxide system; (□), binary mixture system.

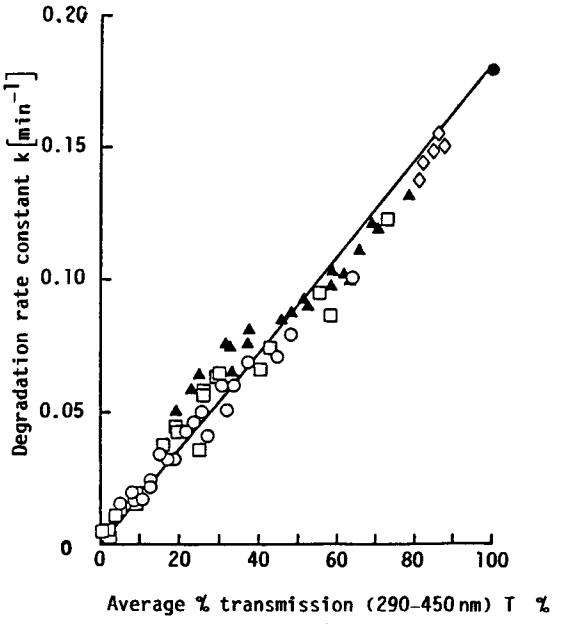

FIG. 6. Relationship between degradation rate constant of nifedipine and average percent transmission of film in three formulation systems. Key: (●), without film; (○), tartrazine system; (▲), titanium dioxide system; (□), binary mixture system; (◇), without colourant.

the colouration rate constant of a drug in model gelatin capsules was directly controlled only by the average percent transmittance of capsule shell (Matsuda et al 1980). This result strongly suggests that the average percent transmittance of a film is the decisive parameter to quantitatively estimate the photostability of the film-coated drug.

In conclusion, it was proved that film coating by combining both titanium dioxide and tartrazine in a film formulation could sufficiently assure the photostability of nifedipine in the ordinary range of film thickness (50–100 μm) being applied to commercial dosage forms. It is necessary for reliable protection to characterize the light transmission properties of films over the wavelength range relating to the photostability of encapsulated drug. The

average transmittance, in this respect, may be a useful parameter to evaluate the protective effectiveness against photodegradation.

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