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Influence of lag-time between light exposure and color evaluation of riboflavin in the solid state

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The lag-time between sample light exposure and evaluation of the samples strongly influences the observed change in surface color of riboflavin bulk substance and tablets. The decrease in total color change (ΔE^*ab) as a function of time after exposure is ascribed to a change in the surface moisture content of the samples during storage. Our results emphasize the need for a standardization of the lag-time between light exposure and sample evaluation in the photostability testing protocol of drug substances and products.

Photostability testing should be an integral part of the studies undertaken to elucidate drug stability characteristics. Photostability testing is addressed in a separate official ICH document (ICH Q1B) and applies to both the drug substance and the drug product. The design of a testing protocol is not specifically covered in the document and is left to the applicant's discretion. The guideline allows for alternative approaches, assuming that these are scientifically sound. The design of the testing protocol is of great importance because the testing program can affect many of the decisions made throughout the drug development process. In most cases the main emphasis will be on the selection of an appropriate radiation source and exposure time, and the presentation of the samples within the test chamber. The lag-time between sample exposure and sample evaluation is often considered of less importance. In the present work we have demonstrated that this lag-time strongly influences the results and as a general rule should be standardized. Riboflavin is a photolabile compound. A discoloration of riboflavin bulk substance or tablets is often observed, even after a low radiation dose. Evaluation of the solid surface color is therefore a useful tool in addition to quantitative analysis to estimate the shelf-life of the product because discolored tablets are likely to be discarded by the user. In the present work we have used the change in surface color as an indicator for pass/fail of bulk substance and tablets after light exposure. The surface color was determined by means of the CIELAB color space system ($L^*a^*b^*$ values) (Minolta CM-3500d spectrophotometer). Both riboflavin bulk substance and tablets were exposed in a Suntest CPS$^+$ (Atlas) chamber according to Option 1 in the ICH Guideline. The surface color was recorded at fixed exposure levels. The samples were then either put directly back into the Suntest CPS$^+$ chamber for further exposure or stored in the dark for 24 hours and re-measured before further exposure. The results for a representative series of bulk sample is presented in Fig. 1. The tablets showed similar curves. Above a radiation dose of 450 kJ/m^2 the total color change (ΔE^*ab) keeps nearly constant when the color is determined directly after exposure and the samples are put back into the Suntest CPS$^+$ immediately after the color measurements. A large fluctuation in color change is however, observed when the samples are measured directly after exposure and re-measured after 24 hours before further exposure. A steady decrease in ΔE^*ab values as a function of time is confirmed in samples exposed to a radiation dose of 1400 kJ/m^2 followed by storage in the dark for 24 hours and measured at frequent intervals (Fig. 2). The fluctuations in ΔE^*ab values can be reduced if the samples are kept in a sealed container in the presence of dried silica. From DSC and moisture analysis it is apparent that the bulk substance contains loosely adsorbed water (up to 15% at high RH). Water molecules initially adsorbed on the surface may form a monomolecular layer and increase the van der Waals forces, thereby increasing the interactions between the molecules and smooth out surface microirregularities

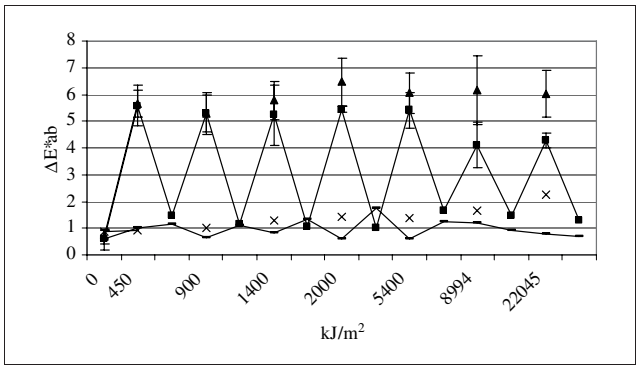

Fig. 1: The total color change (ΔE^*ab) of riboflavin bulk substance as a function of continuous exposure or exposure following 24 hours intervals in the dark. Control samples are wrapped in aluminum foil during exposure.
▲ Sample exposed, measured directly and further exposed without delay (n = 3)
■ Sample exposed, measured directly, re-measured after 24 hours in the dark and further exposed (n = 3)
× Dark control, continuous exposure
– Dark control, 24 hours intervals

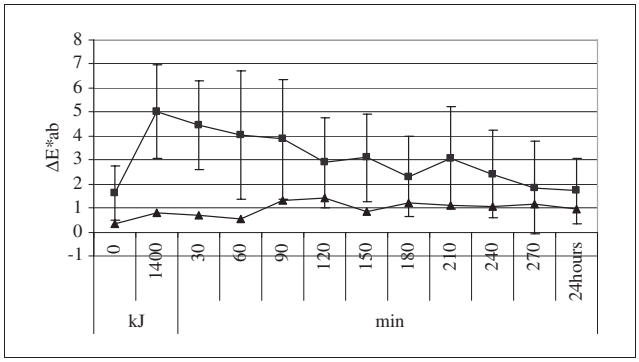

Fig. 2: Total color change (ΔE^*ab) of riboflavin bulk substance as a function of the lag-time between light exposure (1400kJ/m^2) and detection of surface color. The control sample was wrapped in aluminum foil during exposure.
■ Exposed sample (n = 3)
▲ Dark control

that might influence the wavelength distribution of the reflected light (Nokhodchi and Javadzadeh 2007). The presence of water molecules can also change the polarity of the microenvironment which may leads to solvatochromism (Gordon and Gregory 1987). Adsorbed water can further influence the reactant conformation, intra- and intermolecular hydrogen bonding properties or facilitate hydrogen atom abstraction. All these parameters are important for photochromism (i.e. reversible color change upon exposure to light) (Nokhodchi and Javadzadeh 2007). The sample surface temperatures will, however, increase during exposure and this can lead to evaporation of the moisture on the sample surface (Tønnesen and Baertschi 2004). Moisture can be re-adsorbed from the atmosphere when the samples are cooled in an open container. This might explain the large fluctuations in the total color change as a function of lag-time. In the case of RF the lag-time will have a large impact on whether the sample should pass the test or be discarded. A color tolerance limit of ΔE^*ab in the range 1.5–2 would be reasonable for many pharmaceutical preparations (Tønnesen et al. 2007). According to this criterion the samples would only pass the photostability test (i.e. total exposure 22045 kJ/m^2) in cases where the color evaluation was made at a certain lag-time after exposure, assumed that the samples are stored under ambient conditions in the dark.

To our knowledge this aspect of the photostability testing protocol has not previously been addressed. Our results may possibly be valid for many photolabile, (slightly) hygroscopic substances and emphasize the need for a standardization of the lag-time between exposure and analysis in order to achieve maximum reproducibility and representative results.

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Influence of pre-systemic modifications on the drug performance

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Influences of technological and other pre-systemic modifications on the drug performance play a pivotal role in drug development and optimization. The paper evaluates these influences within a framework of the sensitivity theory. Deviations of the drug performance that were caused by modified pre-systemic parameters are predicted and compared with those obtained *in vivo*. A close correspondence between them demonstrates feasibility of the approach presented and its usability as an alternative or suplementary means of the *in vitro-in vivo* correlation analysis.

Novel principles and technologies used in drug manufacturing and optimisation call for effective means that could analyse influences of pre-systemic modifications on a given performance measure, e.g. the concentration-time profile, area under the concentration curve etc. In the approach presented here the direct influences of modified pre-systemic parameters on the concentration profile are expressed and predicted explicitly. Both the magnitudes and directions of the influences are displayed though continuous functions of time rather then by a single value. The approach is applicable regardless of the dosage forms and relating kinetics (linear-nonlinear). It is also discriminating enough, able to assess influences of virtually all technological and/or pre-systemic processes, like disintegration, dissolution and absorption. This means a significant enrichment of the knowledge the designer has on her/his disposal when designing a new or modifying an already manufactured dosage form. Explicitly expressed sensitivities of the concentration profile to any modifications of pre-systemic parameters allow singling out their influences. Besides, the sensitivities provide valuable information about the "degree of belief" to which the *in vitro* dissolution test may be considered as a waiver of bioequivalence studies.

It is worth mentioning that sometimes an opinion appears, advocating the possibility *to predict* the fate of a drug in the body by pharmacokinetic modeling. A problem is that such a model can predict nothing at all, but reflects a specific real process the model is tuned to. Hence, it lacks generalization abilities. In fact the actual behaviour of a